Studies on Peroxidation and Rearrangement Reactions toward the Synthesis of Heterocyclic Scaffolds under Batch/Continuous Flow

A Thesis

Submitted in Partial Fulfillment of the Requirements

for the Degree of

Doctor of Philosophy in Chemistry

By

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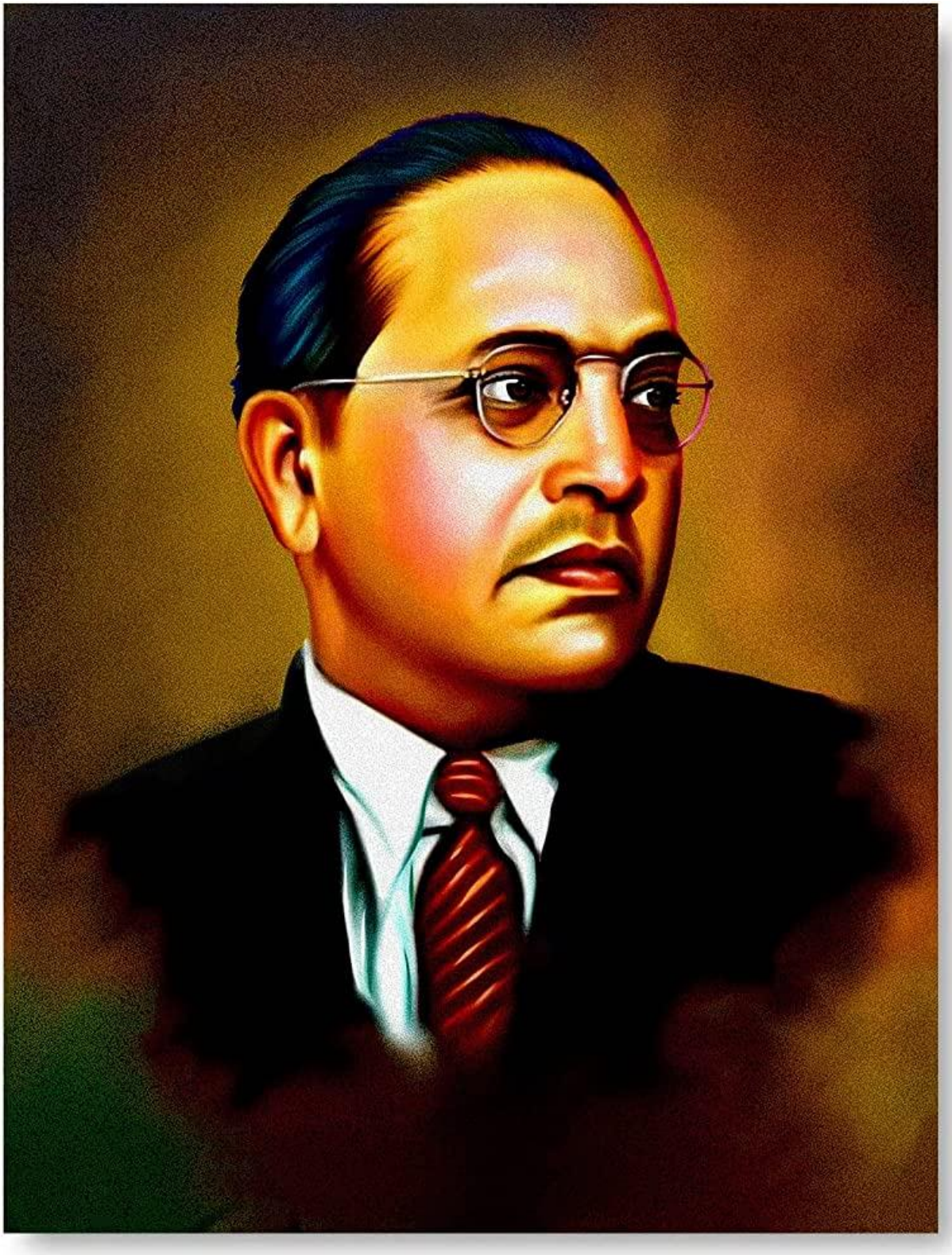
This Thesis is Dedicated to

Dr. B. R. Ambedkar



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CERTIFICATE

This is to certify that the work incorporated in this thesis entitled (***"Studies on peroxidation and rearrangement reactions toward the synthesis of heterocyclic scaffolds under batch/continuous flow"***) submitted by **Akash Shahu Ubale**, has been carried out by the candidate under my supervision at the Indian Institute of Science Education and Research, Pune. The work presented here or any part of it has not been included in any other thesis submitted previously for the award of any degree or diploma from any other university or institution.

(Supervisor)

Dr. Boopathy Gnanaprakasam

(Associate Professor, Chemistry)

Date: 29/08/2023

Place: Pune

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Akash Shahu Ubale

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LIST OF ABBREVIATION

ACN	Acetonitrile	h	Hour (s)
Ac	Acetyl	Hz	Hertz
Ar	Aryl	TLC	Thin layer chromatography
Atm	Atmospheric	IR	Infra-red
Aq	Aqueous	J	Coupling constant in NMR
Ac	Acetyl	L	Ligand
Bn	Benzyl	EI	Electron impact
bs	Broad singlet	M	Molar (mol L^{-1})
Bu	Butyl	m/z	mass to charge ratio
bpy	Bipyridyl	m	multiplet (in NMR)
bs	Broad singlet	Me / Et	Methyl / Ethyl
$CDCl_3$	Deuterated chloroform	MS	Mass spectroscopy
calcd.	Calculated	Mp	Melting point
conc.	Concentrated	mg	Milligram
DTBP	Di-tert-butyl peroxide	mmol	Millimoles
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene	MsOH	Methanesulfonic acid
DCM	Dichloromethane	NMR	Nuclear magnetic resonance
DCE	Dichloroethane	OAc	Acetate
THF	Tetrahydrofuran	Ph	Phenyl
DMF	*N, N*-Dimethyl formamide	PTSA	*Para*-toluenesulfonic acid
DEPT	Distortionless enhancement by polarization transfer	pybox	(2,6-Bis[(*4S*)-(−)-isopropyl-2-oxazolin-2-yl]pyridine)
DMSO	Dimethyl sulfoxide	° C	Degrees Celsius
DMSO-d_6	Deuterated dimethyl sulfoxide	rt	Room temperature
dr	Diastereomeric ratio	Sn	Tin
ee	Enantiomeric excess	*tert*	Tertiary
equiv.	Equivalents	ESI	Electron spray ionization
EtOAc	Ethyl acetate	TBHP	*tert*-butyl hydroperoxide
ESI TOF	Electrospray ionization time-of-flight	Ts	4-Toluenesulfonyl
FTIR	Fourier-transform infrared spectroscopy	t_R	Residence time (in Continuous flow)
g	gram(s)	TMS	Tetramethyl silane
GC	Gas chromatography	THF	Tetrahydrofuran
GC-MS	Gas chromatography-mass spectrometry	HRMS	High-resolution mass spectroscopy

PREFACE

Peroxide (R-O-O-R) is a ubiquitous functional group in organic chemistry and a key pharmacophore in drug discovery. Structurally discrete peroxides exhibited anticancer, antimalarial, anthelmintic, antiviral properties, etc., and their omnipresence in natural products and drugs. For instance, Artemisinin constituting cyclic peroxide has been used in curing malaria. The existence of reactive (O−O) bonds ($\Delta H°_{298}$ = 158−194 kJ mol^{-1}), which are readily cleaved by heat, light, and metals, leads to the formation of reactive oxygen species (ROS) such as superoxides, hydroperoxyl radicals, and hydroxyl radicals. Furthermore, these versatile intermediates are used in radical chemistry, rearrangement reactions, and several organic transformations, such as the oxidation process. Additionally, the migration of the aryl or alkyl group toward the electron-deficient oxygen atom has been widely studied for the Baeyer−Villiger oxidation and Criegee solvolysis of peresters. These reactions showcase the diverse reactivity of peroxides and their potential in organic transformations. Despite the fact that several peroxidation reactions can be achieved using metal and metal-free conditions, its synthesis during scalable is associated with safety hazards. In this context, developing safer and more scalable methods for synthesizing peroxides is undoubtedly an important aspect of their application. Balancing reactivity with safety is a common challenge in chemistry. The present investigation of this thesis is to find operationally simple and scalable routes for peroxide synthesis and its study under different reaction conditions, such as Lewis/Brønsted acid or base for novel biological active heterocyclic scaffolds by skeletal rearrangements reaction. This not only contributes to safer synthesis practices but also opens up opportunities for more widespread use of peroxides in various fields.

This thesis describes the research finding ***"Peroxidation and rearrangement reactions toward the synthesis of heterocyclic scaffolds under batch/continuous flow,"*** which comprises five chapters.

Chapter 1: Introduction to Peroxidation and Rearrangement Reactions

At the outset, the brief introduction of peroxides and rearrangement is described. We have discussed different types of reagents used to synthesize peroxidation and its transformations through various approaches such as rearrangement, construction of heterocycles, alkylation/arylation, and alkoxylation/amination. Further, selected examples for

various peroxidation and rearrangements are presented. Then, the aim and rationale of the thesis are described.

Chapter 2: Manganese-Catalyzed Synthesis of Quaternary Peroxides: Application in Catalytic Deperoxidation and Rearrangement Reactions

In this chapter, we have presented a manganese-catalyzed highly efficient, selective, and direct C−H peroxidation of 9-substituted fluorenes and 2-oxindoles derivatives, The sterically hindered bis-peroxidation of different substituted arylidene-9*H*-fluorene/arylideneindolin-2-one derivatives is also effectively promoted by this method, providing highly selective bisperoxides with high selectivity over oxidative cleavage of the C=C bond, which typically forms ketone and aldehyde. Furthermore, we have demonstrated the synthetic application of 9-substituted peroxides toward the synthesis of (*Z*)-6-benzylidene-6*H*-benzo[*c*]chromene *via* rearrangement and by using Pd-catalyst successfully achieved de-peroxidation. Here, we have covered all literature backgrounds, rationale, optimization studies, substrate scope, and mechanistic studies.

Chapter 3: Peroxidation and Skeletal Rearrangement for the Synthesis of Dioxole-2-carboxamide Derivatives under Continuous-Flow Condition

In this chapter, we have studied another protocol which is catalyst-free peroxidation and skeletal rearrangement for the synthesis of dioxole-2-carboxamide derivatives under continuous-flow conditions. This includes the optimization of reaction conditions for peroxidation in batch/continuous flow. Furthermore, the broad substrate scope is demonstrated. Moreover, the synthesized peroxide has been successfully converted into the bioactive 3-hydroxy-3-phenylbenzofuran-2(3*H*)-one and 1,2-naphthoquinone. According to the mechanistic analysis, C-O coupling is a free radical-mediated process that drives the reaction.

Chapter 4: Sequential Oxidative-Fragmentation and Skeletal Rearrangement of Peroxides for the Synthesis of Quinazolinone Derivatives

In continuation of the previous chapters 2 and 3, we have investigated rearrangement reactions using these synthesized peroxides. For instance, peroxyoxindole was treated under the basic condition that forming isocyanate as a critical intermediate that accelerates novel oxidative-skeletal rearrangement using amino alcohol or primary amine to synthesize exo-olefinic-substituted oxazoloquinazolinone or quinazolinone. The broad substrate scope is demonstrated with various primary amine nucleophiles at room temperature in excellent yield. In the presence of secondary amine, this oxidative fragmentation generates a variety of unsymmetrically substituted functionalized urea. Furthermore, with double nucleophilic

scaffold such as amino alcohols, this reaction proceeded a sequential oxidative fragmentation and nucleophilic addition followed by intramolecular nucleophilic attack on tertiary alcohol, resulting in a variety of tricyclic quinazolinone derivatives as a diastereomeric mixture in one step. Trapping investigations and spectroscopic data have supported the generation of isocyanate as an important step that accelerates rapid oxidative-skeletal rearrangement.

Chapter 5: Transition-Metal-Free Alkylative Aromatization of Tetralone Using Alcohol/Amino Alcohol towards the Synthesis of Bioactive Naphthol and Benzo[*e/g*]indole Derivatives

In the final chapter 5, we studied the versatile and environmentally friendly approach to synthesize valuable naphthol and benzo[*e*/*g*]indole derivatives using readily available starting materials and reagents. The fact that it is transition-metal-free and does not require inert conditions could make it particularly attractive for large-scale synthesis and industrial applications. The generated water and hydrogen peroxide byproducts also align with green chemistry principles. Demonstrated a wide substrate scope and showed exclusive regioselectivity. Finally, based on preliminary experimental results and previous literature studies, a plausible mechanism was proposed for the alkylative aromatization of tetralone.

The outcomes obtained in the current investigations are highlighted in the conclusion section. The references section includes the literature references cited in the background, results, discussion, and experimental sections. The Appendix section illustrates the proton and carbon NMR spectra of selected compounds that are provided at the end of each chapter. Finally, closer to the end of the thesis, it provides a list of publications resulting from the current studies.

Chapter 1

Introduction to Peroxidation and Rearrangement Reactions

1. Introduction to Peroxidation and Rearrangement Reactions

1.1. Abstract

In the present chapter, the synthesis and applications of peroxidation and its rearrangement reactions in synthetic chemistry have been briefly discussed. In organic chemistry, peroxidation and rearrangements of electron-deficient oxygen-related reactions are important since they are widely used in the research laboratory, manufacturing, and biological processes. Moreover, the definitions and general overview of peroxidation and the classical electron-deficient oxygen rearrangements involving peroxides as intermediate have been described. The rearrangements of organic peroxides have been covered in hundreds of publications and reviews in the literature. The definition of peroxides, their structural characteristics, and other well-known name rearrangements of electron-deficient oxygen are all included in this chapter, along with a comparison of the reaction's mechanisms and also discussion of their potential uses in organic synthesis. The selected representative examples of peroxidation and rearrangement reactions are also summarized in this chapter. Finally, the aim and rationale for the thesis work are described.

1.2. Introduction to peroxidation and its structural properties

Peroxide is an organic compound that includes the peroxo unit (O_2^{2-}). The chemistry of organic peroxides has a history of over a hundred years. The organic peroxide is a class of chemical compounds in which a single covalent bond connects two oxygen (R-O-O-R) atoms. This is a ubiquitous functional group in organic chemistry and a key pharmacophore in drug discovery. It has the omnipresence of various biological activities such as anticancer,[1] anti-HIV,[2] anthelmintics,[3] antimalarial,[4] etc. pharmaceuticals, natural products, and drugs (Figure 1.2.1.). Conferring to the World Health Organization (WHO), malaria is a widespread disease. About 3.2 billion people persist at risk of malaria, and 214 million cases and 438 thousand deaths from malaria were reported in 2015.[5] The discovery of effective antimalarial and antihelminthic drugs is a significant challenge in the medicinal chemistry of peroxides. For instance, the naturally occurring peroxide artemisinin constituting cyclic peroxide was first discovered in the 1970s from the sweet wormwood plant. Nowadays, it has been used worldwide for treating malaria.[6] The central biologically active core of these compounds[51] includes six-membered 1,2-dioxane,[7] 1,2-dioxene,[8] 1,2,4- trioxane,[9] five-membered cyclic 1,2,4-

trioxolane,[10] and 1,2-dioxolane[11] compounds (Figure 1.2.1.). We are motivated to create bioactive peroxy compounds because of the complex structures known that are bioactive.

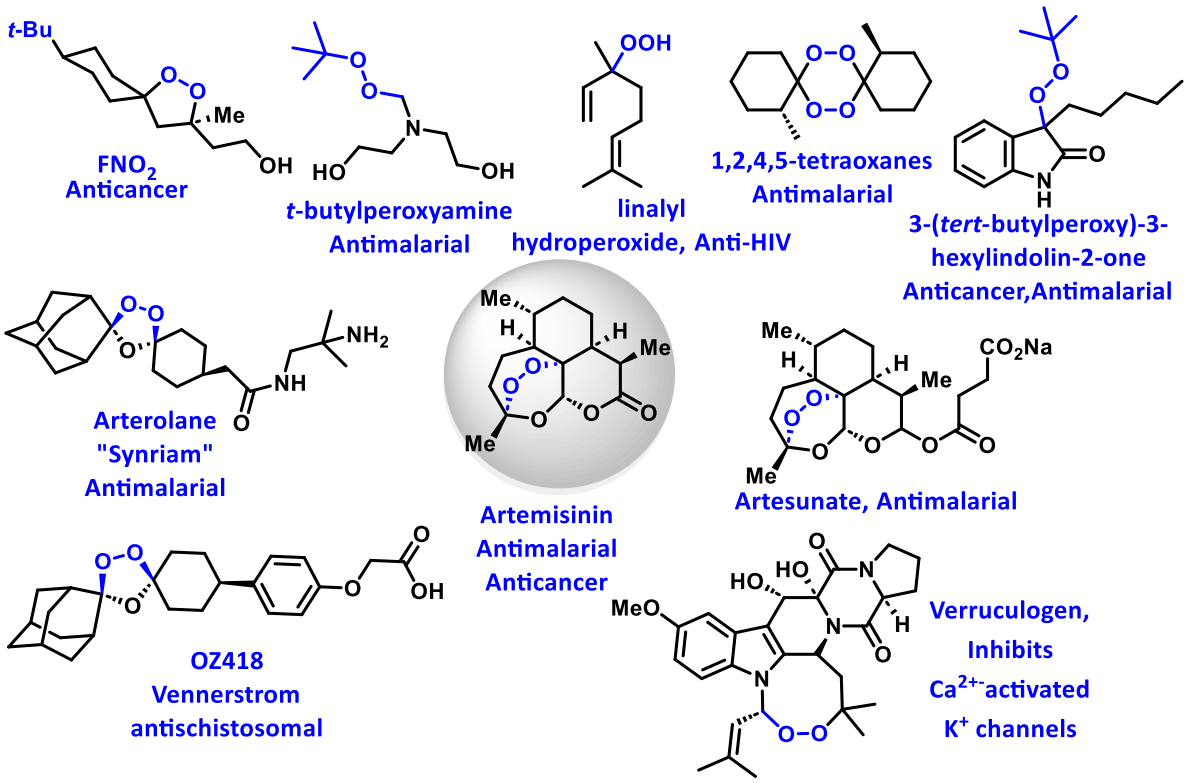


Figure 1.2.1. Bioactive molecules display peroxide linkage

The existence of reactive (O–O) bonds ($\Delta H°_{298}$ = 158–194 kJ mol^{-1}),[12] which are readily cleaved by heat, light, and metals, leads to the formation of reactive oxygen species (ROS) such as superoxides, hydroperoxyl radicals, and hydroxyl radicals.[13] Furthermore, these versatile intermediates are used in radical, rearrangement reactions, and several organic transformations for the construction of heterocycle, alkylation/arylation, and alkoxylation/amination reactions (Figure 1.2.2.).[14]

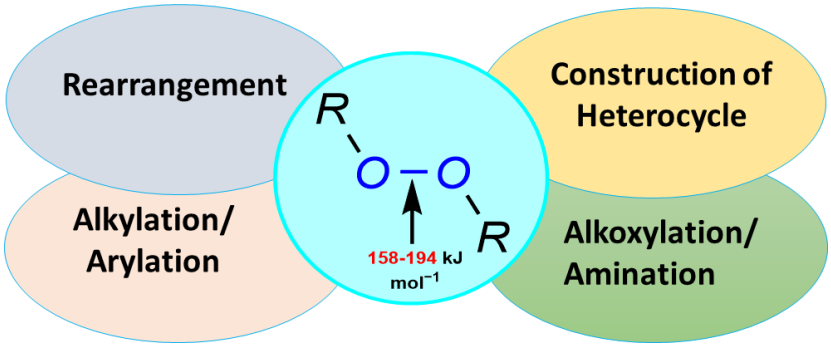
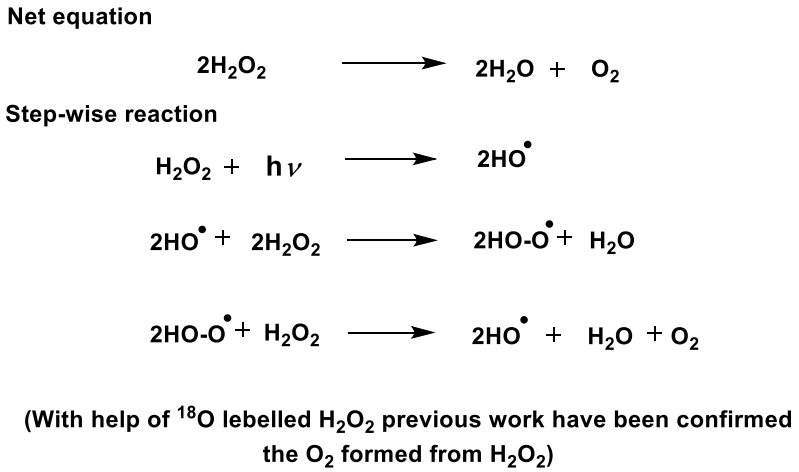


Figure 1.2.2. An important application of peroxide in synthetic chemistry

Additionally, the migration of the aryl or alkyl group toward the electron-deficient oxygen atom has been widely studied for the Baeyer–Villiger oxidation[15] and Criegee solvolysis of peresters.[16] These

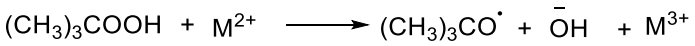
transformations fall under peroxidation, oxygen insertion, or oxygen (O_2) involvement by rearrangement reactions.

The best-known example of a peroxide is hydrogen peroxide **1b** (Figure 1.2.1.) which includes the peroxo unit. The versatile use of peroxide-containing peroxo units is demonstrated by the variety of oxidation potentials and pH ranges in which it can act as an oxidizer. Peroxide is a reasonable oxidant but becomes strong when catalyzed with metal. Similar to all other peroxides, hydrogen peroxide (H_2O_2) contains a comparatively weaker (O−O) bond that is sensitive to light or heat. In the presence of UV light, the net reaction proceeds through the decomposition of hydrogen peroxide (H_2O_2) spontaneously into water and oxygen (Scheme 1.2.1.).[17]



Scheme 1.2.1. Photodissociation and photodecomposition of H_2O_2

The organic peroxide is thermally unstable; at particular temperatures, it will self-react. Thermally unstable must be stored at frigid temperatures, while some can be stored at room temperature without any safety issues. However, alkyl hydroperoxides are reacted with transition metals to form alkoxy radicals, whereby the metal undergoes a redox-like reaction (Scheme 1.2.2.).[18] Peroxides are the reactive intermediates that react violently with metals to form metal hydroxides and alkylperoxo metal species.



Scheme 1.2.2. The reaction of metal with peroxide

1.3. Overview of peroxidation

1.3.1. Peroxidation

The peroxidation is produced by oxidation process by adding oxygen. Various reports are available for peroxidation, and most of them use atmospheric oxygen or reagents as an oxidant. There

are several regents used for oxidation, including peroxidation, such as oxygen **1a**, hydrogen peroxide **1b**, *tert*-butyl hydroperoxide (TBHP) **1c**, *tert*-butyl perbenzoate **1d**, di-*tert*-butyl peroxide (DTBP) **1e**, *meta*-chloroperbenzoic acid (*m*-CPBA) **1f**, dibenzoyl peroxide **1g,** and cumene hydroperoxide **1h** (Figure 1.3.1.). Peroxidation with an oxidant or regents could result in more applicant ring expansion *via* oxygen insertion.[15,16] Although there are several reports available, some of the literature reports are presented. Thus, in this chapter, we have described a few pioneering examples of peroxidation in which peroxide regents have been used along with metal and metal-free catalysts and their further rearrangement reactions.

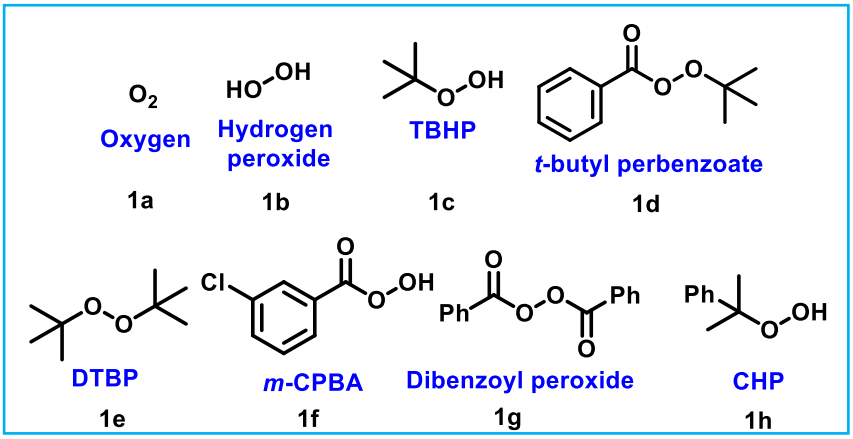
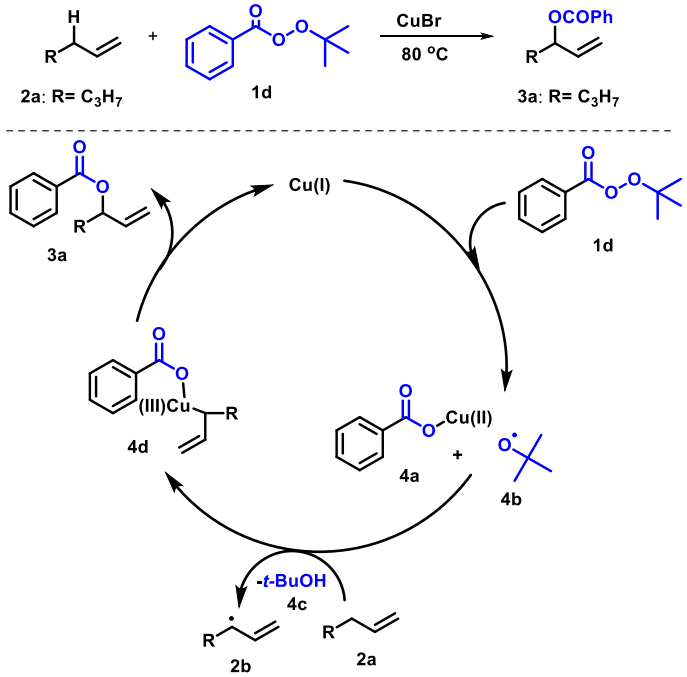


Figure 1.3.1. Commonly available reagents for peroxidation reactions

1.4. Literature background on peroxidation

The Kharasch-Sosnovsky's reaction was discovered for the first time in 1958.[19a]

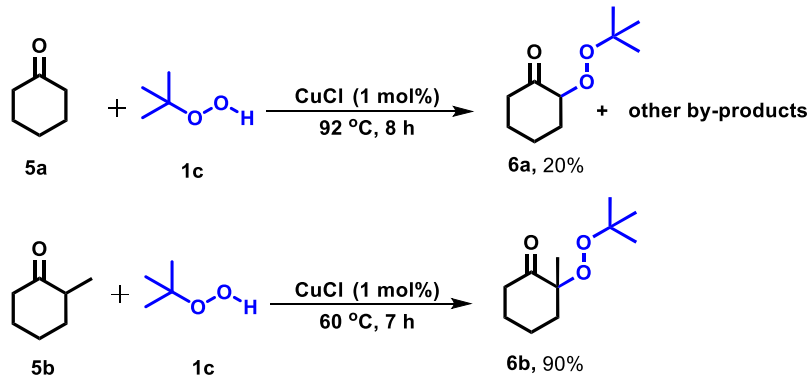


Scheme 1.4.1. Kharasch and Sosnovsky's reaction

This pioneering work uses the copper catalyst and *tert*-butyl benzoperoxoate **1d** for the peroxidation reaction of allylic olefin by a radical mechanism.

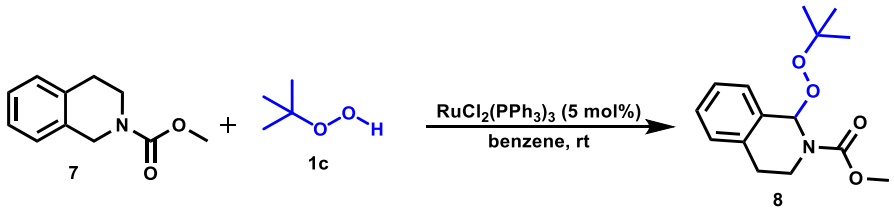
In this transformation, peroxide *tert*-butyl benzoperoxoate **1d** was used as an oxidant as well as a reagent. The mechanism of this reaction follows a radical pathway. Initially, the metal salts react with peroxides *tert*-butyl benzoperoxoate **1d**, giving the alkoxy radical and Cu-complex by oxidation **4a**. Next, the alkoxy radical **4b** affords allylic radical **2b** by abstracting hydrogen from olefin. Finally, the recombination of Cu-complex **4a** and allylic radical **2b** gives the final product **3a**, and the catalyst is regenerated for the next catalytic cycle. By using this strategy, several reports were established for the peroxidation reaction (Scheme 1.4.1.).[19a]

Likewise, Kharasch and Sosnovsky's also reported the peroxidation of carbonyl compounds **5** in the presence of CuCl as a catalyst and TBHP **1c** upon heating conditions (Scheme 1.4.2.).[19b]



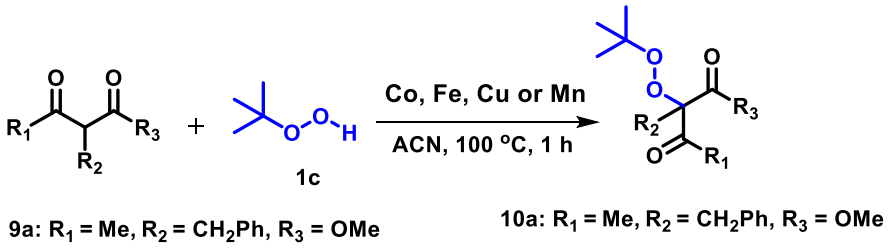
Scheme 1.4.2. Kharash-Sosnovsky's approach for the peroxidation of carbonyl compounds

In this context, the peroxidation of heterocyclic compound **7** using 5 mol% of ruthenium catalyst ($RuCl_2(PPh_3)_3$) and TBHP **1c** was achieved by Murahashi and co-workers.[20]



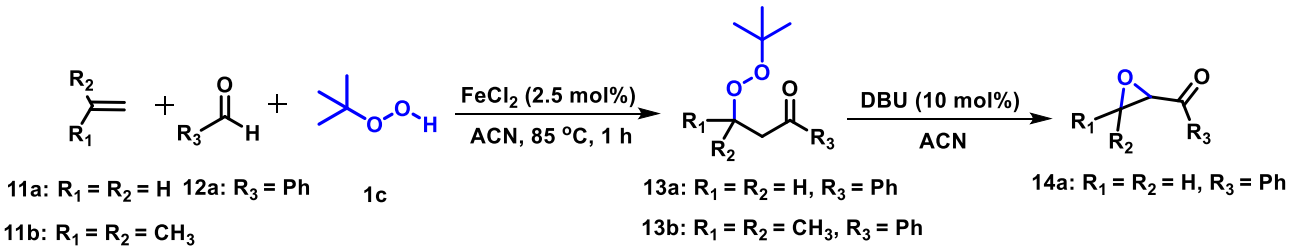
Scheme 1.4.3. Peroxidation of heterocyclic compound **7** by Murahashi research group

Similarly, the peroxidation of *β*-diketones, *β*-keto esters, or diethyl malonate **9** was reported by Terent'ev and co-workers by using the transition metal (Cu, Fe, Mn, Co) catalyst and *tert*-butyl hydroperoxide **1c**.[21]



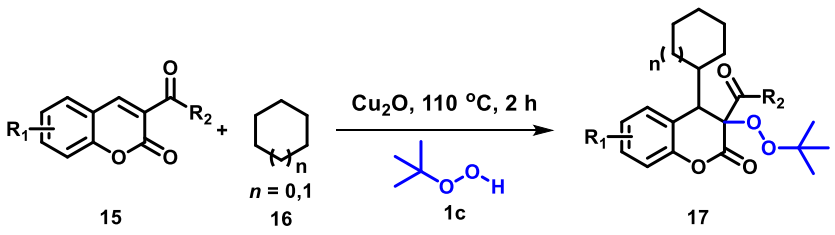
Scheme 1.4.4. Peroxidation of di-carbonyl compounds **9** by Terent'ev research group

Remarkably, Li and co-workers reported peroxidation-carbonylation of olefins **11** by using aldehyde **12a**, TBHP **1c,** and Iron-catalyst ($FeCl_2$) *via* a radical pathway.[22] In this method, a variety of substrate scopes for the difunctionalization, such as alkylation-peroxidation **13,** has been demonstrated. Furthermore, the synthesized peroxides were transformed into epoxides **14a** by using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base in the presence of ACN as a solvent.



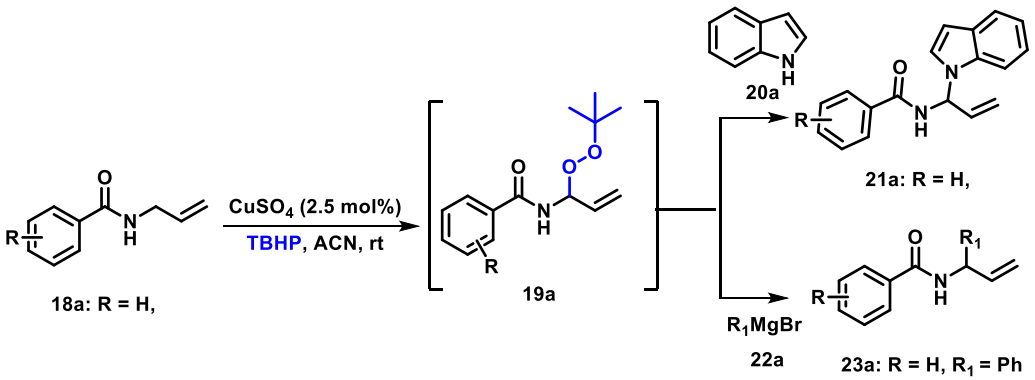
Scheme 1.4.5. The di-functionalization of an alkene by Li et al.

Likewise, Patel and co-workers demonstrated the cycloalkylation-peroxidation of coumarins **15** by using cycloalkanes **16** and *tert*-butyl hydroperoxide (TBHP) **1c** in the presence of Cu_2O as a catalyst.[23] This procedure creates two stereocenters, establishing C-O and C-C bonds over sp^3 C-H functionalization.



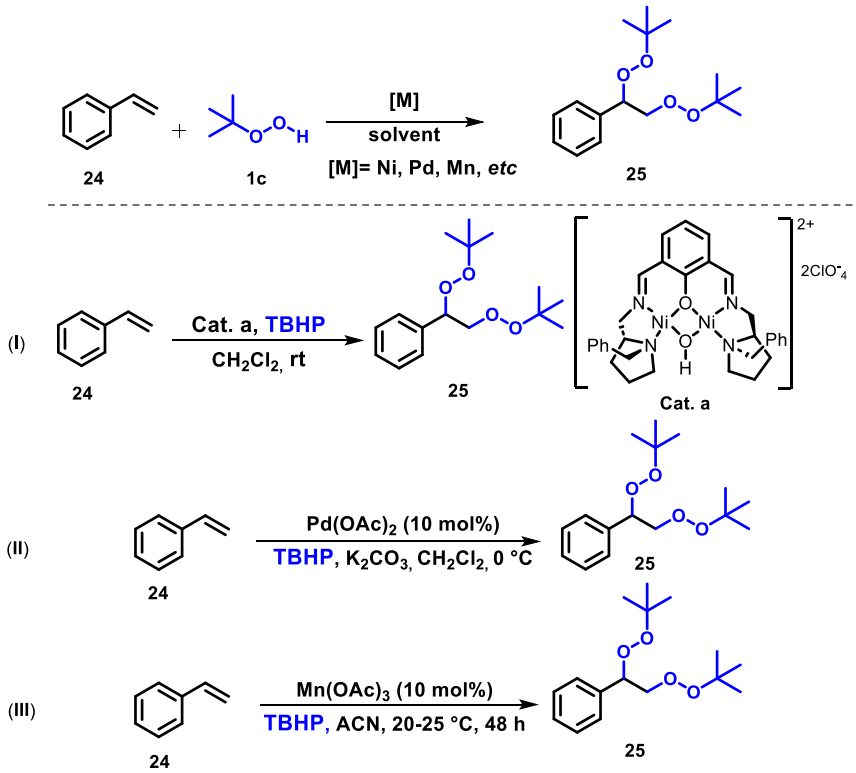
Scheme 1.4.6. Cycloalkylation-peroxidation of coumarins by Patel et al.

Furthermore, Krishna and co-workers reported the C-N and C-C bond construction by using *N*-allylbenzamides **21a** with indole **20a** in the presence of a copper catalyst ($CuSO_4$) and TBHP **1c** as an oxidant *via* peroxides of *N*-allylbenzamides intermediate **19a**. Further, the Grignard reagent **22a** was used as a reagent for the synthesis of α-substituted *N*-allylbenzamides **23a**.[24]



Scheme 1.4.7. Krishna's approach for the C-H bond functionalization of *N*-allylbenzamides

In 1996, the Feringa group reported the vicinal bisperoxidtion of styrene derivatives **24** in the presence of TBHP **1c** and nickel catalyst when attempting to epoxidate styrene derivatives (Scheme 1.4.8. (I)).[25] Similarly, in 2002, Corey and co-workers reported the bisperoxydation of styrene **24** in the presence of TBHP **1c**, $Pd(OAc)_2$, and K_2CO_3 in DCM at 0 °C (Scheme 1.4.8. (II)).[26]



Scheme 1.4.8. Bisperoxidation of styrene **24** using a metal catalyst

Although these reports provide good yields, it has some limitation, such as the use of expensive catalysts, and some multi-steps were also required for the bisperoxidation. To overcome these limitations, Terent'ev and co-workers reported the $Mn(OAc)_3$-catalyzed bisperoxidation of alkenes derivatives in excellent yields (Scheme 1.4.8. (III)).[27] Manganese catalysts with oxidation states 2, 4, and 7 also effectively catalyze this reaction.

1.5. Overview of rearrangement of peroxides

Rearrangement is the movement of an atom or group of atoms from one atom to another within the same molecule (Figure 1.5.1.).[28] The migration group may entirely separate from the molecule during migration and then reattach at a different reactive site of the molecule (intermolecular rearrangement). However, in some cases migration group doesn't leave the molecule through migration (intramolecular rearrangement). The most frequent atoms to migrate are carbon or hydrogen, while halogen, oxygen, sulfur, and nitrogen migration are also widely recognized. The 1,2-shift of the alkyl or aryl group is one of the most significant rearrangement reactions in which an atom or group moves from one atom to a nearby atom with a pair of electrons.[29]

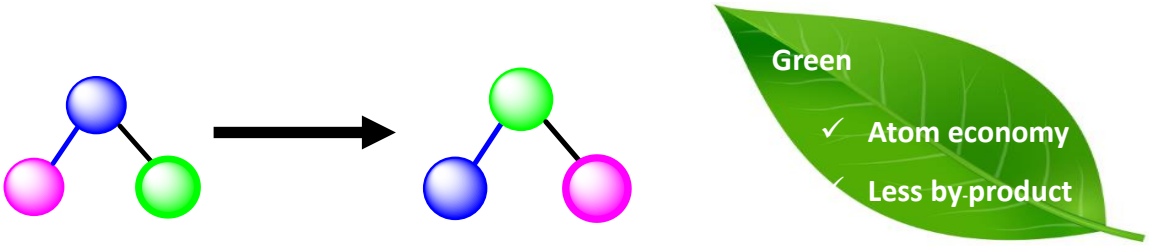


Figure 1.5.1. Graphical representation of rearrangement reaction

The most commonly found rearrangement in the organic chemistry listed below:[29]

(A) Migration of carbon: Rearrangement involving migration to electron-deficient carbon: The movement of carbocation from an unstable state to a more stable state through structural rearrangement. For example: Wagner–Meerwein, Pinacol Pinacolone, Wolff, Benzil–benzilic acid rearrangement. Carbocation rearrangements have two different types: hydride shift and alkyl shift. The molecules can also go through unimolecular substitution (S_N1) or unimolecular elimination (E1) processes when they are rearranged.[30]

(B) Migration of heteroatoms: (a) Rearrangement involving migration to electron-rich carbon: The rearrangement of electron-rich carbon included the Favorskii, Steven's, Sommelet-Hauser Witting, and Neber rearrangement; (b) Rearrangement involving migration to electron-deficient nitrogen: The rearrangement of electron-deficient nitrogen atoms such as Beckmann, Hofmann, Curtius, Loseen, and Schmidt includes nitrene/isocyanate intermediate for the synthesis of amide or primary amines *via* migration of a group from nearby carbon to the nitrogen.[31] (c) Rearrangement involving migration to electron-deficient oxygen: A peroxide or corresponding derivatives such as R-O-O-H or R-O-X is the most basic precursor of an oxa cation. It is energetically unfavorable to remove the hydroxide anion from a hydroperoxide as long as it is first transformed into a better-leaving group, exactly how alcohol substitution reactions make it possible. A tricoordinate oxonium cation is formed when strong acids

protonate the divalent oxygen atom of alcohols and ethers. However, the structure of the initial molecule is altered during the rearrangement of organic peroxides to create an isomeric product without the peroxy group.[32] For example: Baeyer-Villiger oxidation, Hydroperoxide rearrangement, Dakin reaction. Various other rearrangement reactions exist, often named after the chemist who discovered them or the specific substrates involved.

The rearrangement typically includes cleaving or moving peroxide groups within an identical molecule. Subsequently, stability is responsible for the different pathways of the process.

Rearrangement is decisive with essential elements of sustainable development and is still fully compatible with all green chemistry concepts, including the atom economical since it produces fewer byproducts. Rearrangement reactions offer an alternative route for the synthesis of complex building blocks.[33,14] The different types of rearrangement reactions of peroxides, such as acid or base or radical catalyzed, are reported in the literature (Figure 1.5.2, and Figure 1.5.3.).[14]

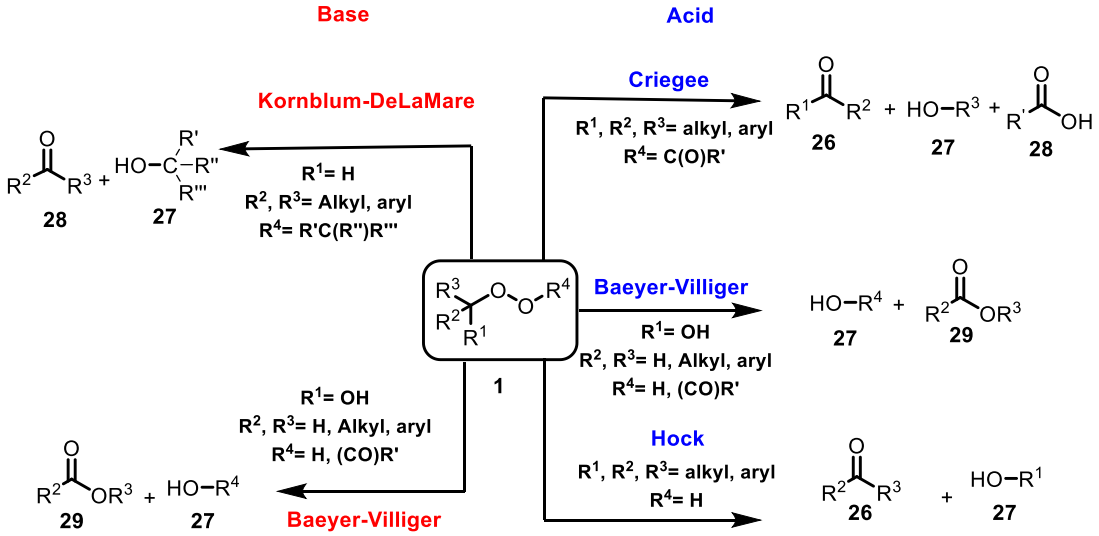


Figure 1.5.2. Acid/Base catalyzed rearrangement of peroxides

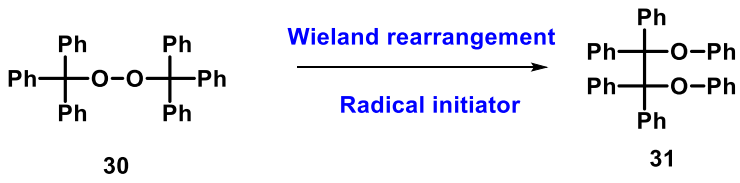


Figure 1.5.3. Radical rearrangement of peroxide

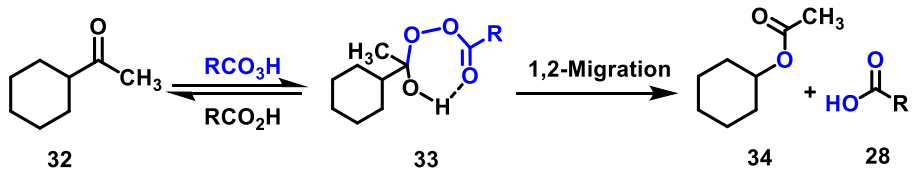
Apart from these, lipid peroxidation in biochemistry is a significant research area; therefore, attractive to the scientific community from across several disciplines. Hydroperoxide lyase (HPL) transforms fatty acid hydroperoxides toward hemiacetal derivatives by way of Hock-type

rearrangement enzymatically that spontaneously decomposes to the aldehydes in oxylipin metabolism.[34]

Organic peroxides and their rearrangements play a significant role in the chemistry of oxidation processes. Thus, *tert*-butyl hydroperoxide **1c** is the critical reagent in the Sharpless epoxidation of allylic alcohol[35] and the production of propylene oxide in the Prilezhaev reaction.[36] The rearrangement of cumene hydroperoxide for synthesizing phenol and acetone by the Hock process, which is used in the industry for its production. In 2003, more than 95% phenol was produced by the Hock process.[37] An additional important application of organic peroxides is the Baeyer–Villiger oxidation for synthesizing lactones from cyclic ketones. The synthesis of caprolactone from cyclohexanone with peracetic acid is also one of the commercially essential methods for its synthesis.[38]

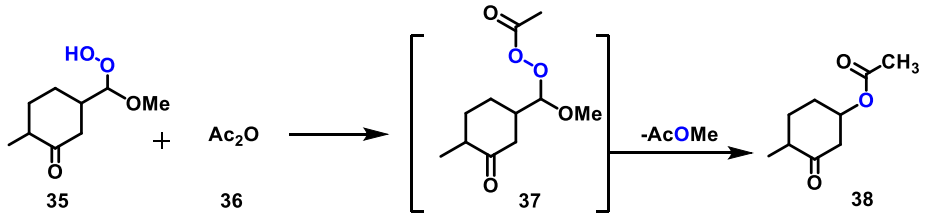
1.6. Literature background for the rearrangement of peroxides

The ketone **32** to ester **34** transformation was reported by Baeyer and Villiger in 1899, using peracids *via* 1,2-migration. Today, this is one of the greatest reactions extensively studied because of its several applications in synthetic chemistry (Scheme 1.6.1).[15]



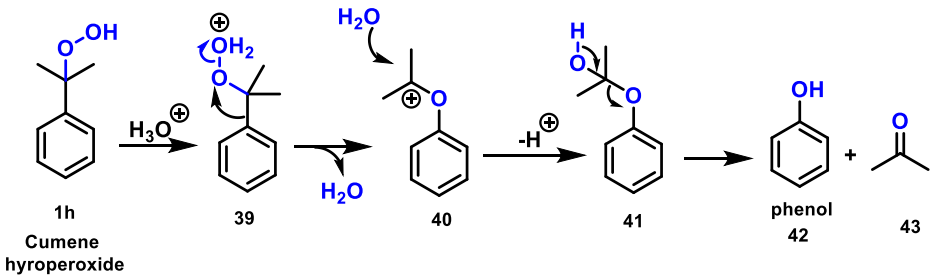
Scheme 1.6.1. Baeyer-Villiger rearrangement

Afterward, the mechanism of the Criegee reaction is similar to the Baeyer-Villiger reaction. The Criegee rearrangement includes the conversion of hydroperoxide **35** into perester intermediate **37**, which is called a Criegee intermediate. Furthermore, perester intermediate **37** upon rearrangement to forms the respective ester **38** (Scheme 1.6.2).[16]



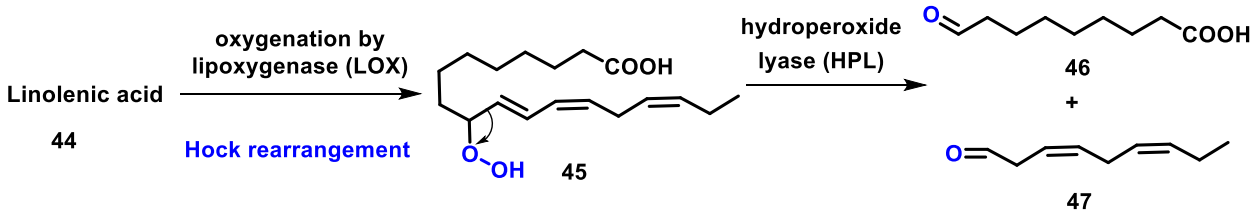
Scheme 1.6.2. Criegee rearrangement

In the Hock rearrangement, cumene hydroperoxide **1h** decomposes into phenol **42** and acetone **43** in the presence of an acidic source. Due to the commercial production of acetone and phenol, Hock rearrangement has great importance in the industry (Scheme 1.6.3).[33]

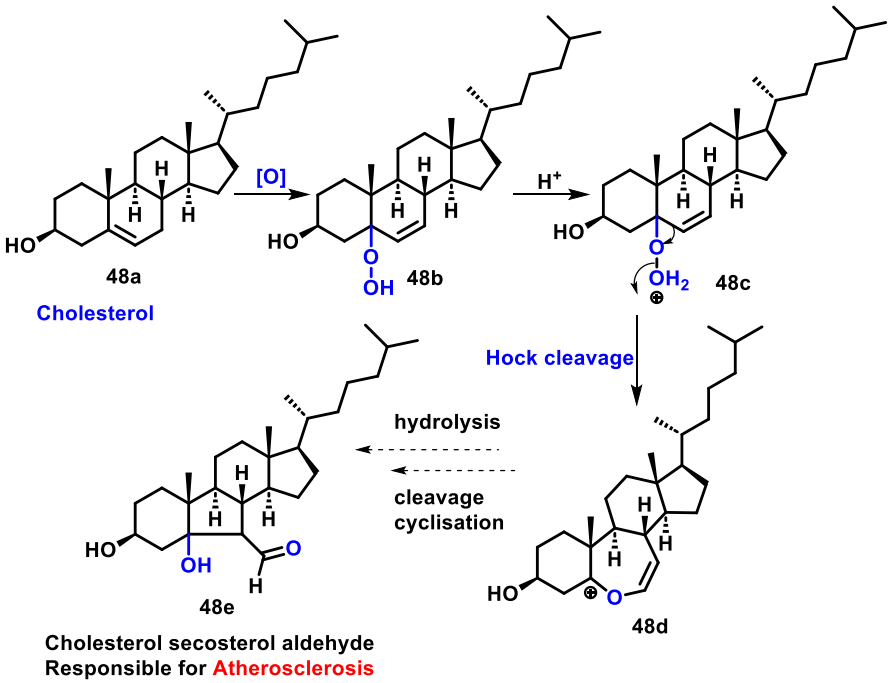


Scheme 1.6.3. Hock rearrangement

Remarkably, in plant metabolism, Hock rearrangement has been found. Lipoxygenase's oxygenation of linoleic acid **44** initiates the enzymatic oxylipin metabolism. Then, upon Hock rearrangement of (10*E*,12*Z*,15*Z*)-9-hydroperoxyoctadeca-10,12,15-trienoic acid **45** (hydroperoxide) to form the desired products 9-oxononanoic acid **46** and (3Z,6Z)-nona-3,6-dienal **47** (Scheme 1.6.4.).[34,39,14]



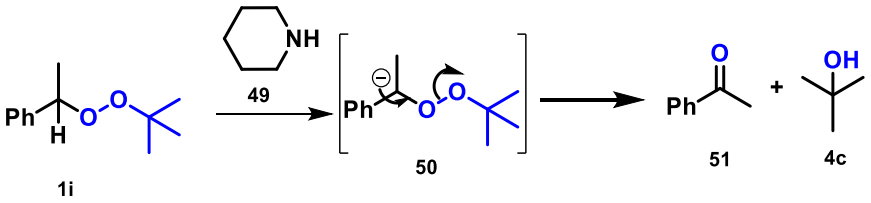
Scheme 1.6.4. Enzymatic rearrangement: Oxylipin metabolism in plants



Scheme 1.6.5. Enzymatic Hock rearrangement in cholesterol

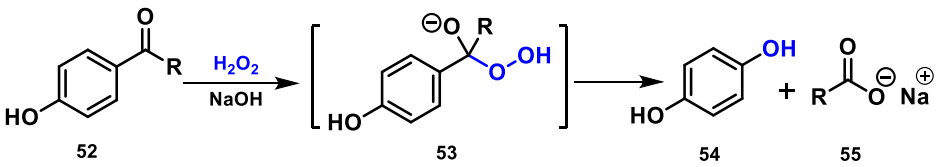
Next, secosterol aldehyde is responsible for Atherosclerosis. The formation of secosterol aldehyde from cholesterol by the Hock rearrangement, which is an important aspect of this rearrangement. In this reaction, initially the cholesterol undertakes peroxidation by oxygen to from the peroxy compound (3S,8S,9S,10R,13R,14S,17R)-5-hydroperoxy-10,13-dimethyl-17-((R)-6-methylheptan-2-yl)-2,3,4,5,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-ol **48b**. Further, treatment of peroxy compound **48b** with acid to afford the ring expansion intermediate Hock rearranged product **48d**. Finally, upon cyclization of **48d** produces secosterol aldehyde 4**8e,** through hydrolysis and aldol condensation of **48d** (Scheme 1.6.5.).[24, 39,14]

In 1951, Kornblum and DeLaMare reported the base-catalyzed rearrangement of peroxides, which involves the rearrangement of (1-(*tert*-butylperoxy)ethyl)benzene **1i** to afford acetophenone **51** and *tert*-butanol **4a** (Scheme 1.6.6).[40]



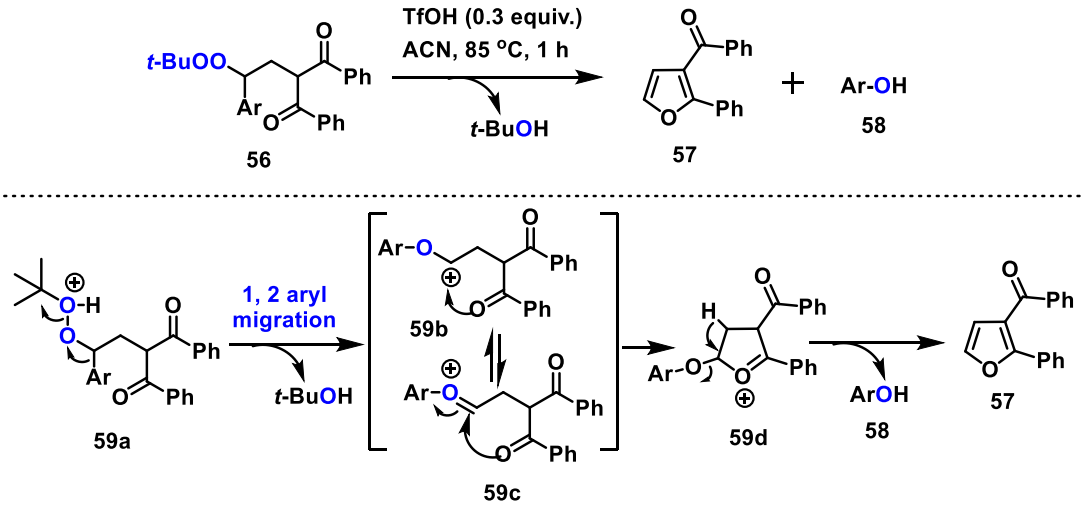
Scheme 1.6.6. Kornblum and DeLaMare Rearrangement

Dakin oxidation reaction for the synthesis of phenol is similar to the Baeyer–Villiger oxidation. This reaction involves the ketone **52** reacts with hydrogen peroxide **1b** in the presence of a base to afford desired products benzenediol **54** and carboxylate **55** *via* the tetrahedral intermediate **53** (Scheme 1.6.7.).[41]



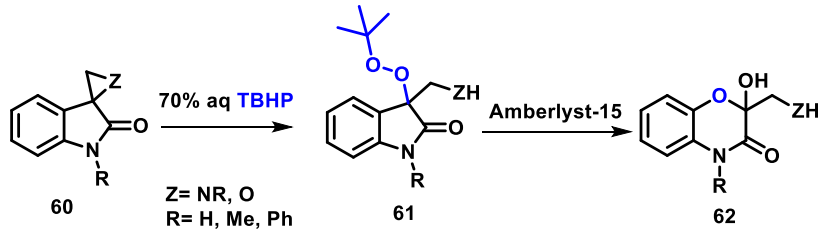
Scheme 1.6.7. Dakin Reaction

Apart from the famous rearrangement reactions, several unnamed reactions are documented in the literature. Few research groups have carried out other rearrangements using different heterocyclic peroxides. For instance, the rearrangement of *tert*-butylperoxides to the synthesis of 2,3-disubstituted furans **57** *via* 1,2-aryl group migration in the presence of acid reported by the Li and co-workers (Scheme 1.6.12.).[42]



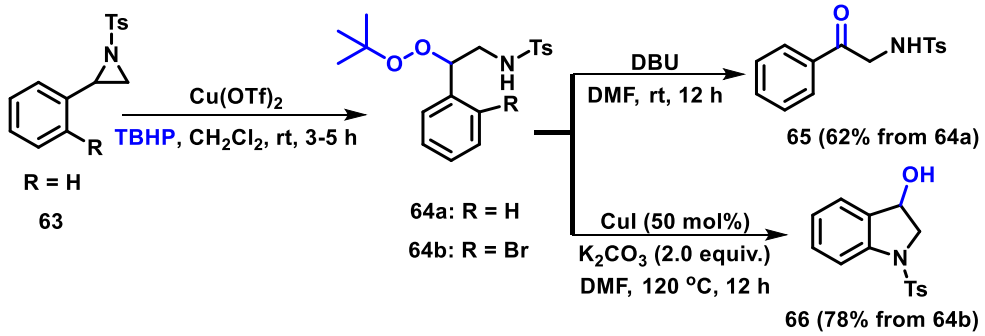
Scheme 1.6.12. The rearrangement of peroxides to synthesize furan derivatives by Li research group

Furthermore, Hajra and co-workers reported the C3-ring opening by regioselective reaction of spiro-aziridine or spiro-epoxy oxindoles using 70% aqueous *tert*-butyl hydroperoxide **1c'** at room temperature under metal or catalyst-free conditions. This method delivered a widespread 3-peroxy-3-substituted oxindoles **62** (Scheme 1.6.13.).[43]



Scheme 1.6.13. Rearrangement of peroxides by Hajra research group

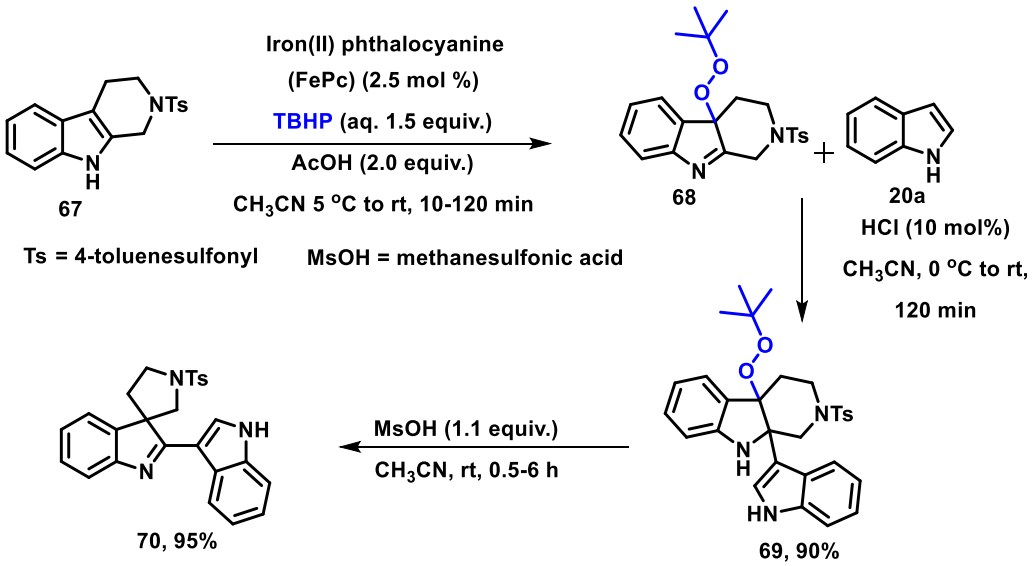
Further, the synthesis of site-selective bond polarization of two classes of aziridines under two Lewis acid-activation conditions has been reported by Saha and co-workers.



Scheme 1.6.14. Synthesis of *β-N*-peroxy compounds by Saha research group

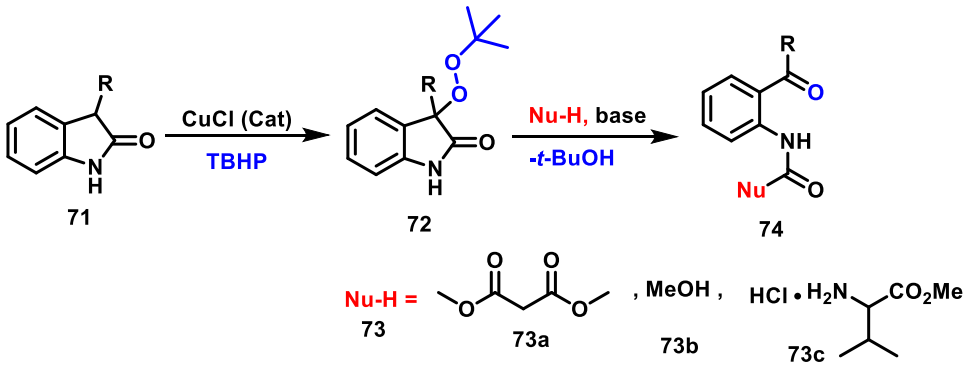
This method is valuable for preparing the variety of substrate scope, *N*-(*α*-/*β*-peroxy)-linkage, and similar pharmacophores. Next, the *β*-*N*-peroxy compounds were subjected to the synthetic application, where aminoketone **65** is produced *via* base-mediated Kornblum and DelaMare rearrangement of **64a**. Additionally, the synthesis of 3-hydroxyindoline derivative **66** by using intramolecular *N*-arylation from the *β*-*N*-peroxy compounds **64b** (Scheme 1.6.14.).[44]

Next, Chen and co-workers reported the synthesis of tetrahydro-*β*-carbolines (THβCs) and tetrahydro-*γ*-carbolines (THγCs). Further, these compound (THβCs)/ (THγCs) treated with *t*-BuOOH **1c** afforded 3-peroxyindolenines, which upon rearrangement by using HCl in the presence of indole **20a** to form surprising 2-indolyl-3-peroxyindolenines **69** in good to excellent yields (Scheme 1.6.15.). Next, rearrangement has been shown by using these 2-indolyl-3-peroxyindolenines **59** with methanesulfonic acid (MsOH) to afford spiroindolenines **70** in good to excellent yields.[45]



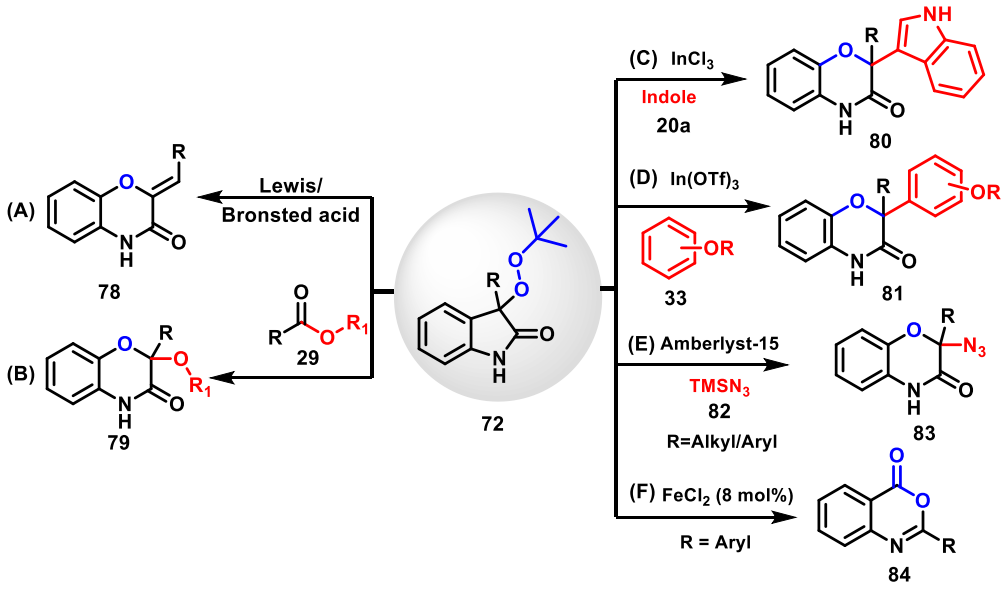
Scheme 1.6.15. Rearrangement of 3-peroxyindolenines towards 2-indolyl-3-peroxyindolenines by Chen

Later, Stoltz and co-workers reported peroxidation and rearrangements of 2-oxindole **71** by Cu catalyst followed by base-mediated fragmentation (Scheme 1.6.16.).[46]



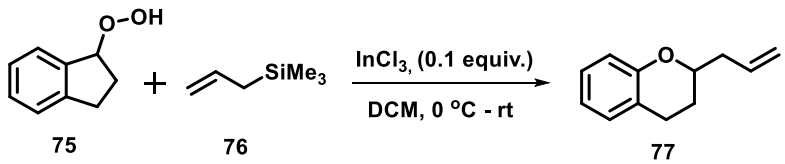
Scheme 1.6.16. Base-mediated fragmentation of 2-oxindole peroxide by Stoltz research group

Subsequently, Lewis acid and Brønsted acid were used by Gnanaprakasam and co-workers for rearrangement of C3-substituted 2-oxindole peroxide towards the construction of biologically active 1,4-benzooxazin-3-one **77** and substituted-2*H*benzo[*b*][1,4]oxazin-3(4*H*)-one **78** derivatives (Scheme 1.6.17. (A, B)).[47a,b] Furthermore, a few more rearrangement reactions have been reported by the same group in the presence of Lewis acid/Brønsted acid and nucleophiles such as indole (**20a**), phenols (**42**), $TMSN_3$ (**82**), for the synthesis of C3-substituted 1,4-benzooxazin-3-one derivatives (**80-83**) (Scheme 1.6.17. (C-E)).[47c-e] Similarly, for the synthesis of 1,3-benzooxazin-2-ones **84**, a rearrangement reaction has been performed with the help of aryl peroxyoxindoles in the presence of $FeCl_2$-catalyst (Scheme 1.6.17. (F)).[47f]



Scheme 1.6.17. Rearrangement for the C3-substituted 1,4-benzooxazin-3-one derivatives

Recently, a tandem process involving a Hock or Criegee oxidative cleavage and a nucleophilic addition upon the oxocarbenium species using $InCl_3$ catalysis is described by Bastien and co-workers which involved in the Hosomi-Sakurai-type allylation. (Scheme 1.6.18.).[48]



Scheme 1.6.18. Hosomi-Sakurai-type allylation by Bastien research group

1.7. Aim and rationale of thesis work

The peroxidation of fluorenes, 2-oxindoles, naphthols, and benzofuranones are an attractive and challenging scaffold among the various functionalities owing to their important biological properties and their existence in natural products. These compounds are pharmacophores, easily

available, and less explored towards direct C-H peroxidation. Despite the fact that several peroxidation reactions can be achieved using metal and metal-free conditions, its synthesis during scalable is associated with safety hazards. However, the functionalization of such types of moieties requires special reagents, stoichiometric amounts of additives/oxidants, and high temperatures, which limits their utilization in several organic transformations. Furthermore, the unique structure of peroxide and its reactive properties toward constructing heterocyclic scaffolds inspired us to develop an operationally simple and scalable route for their synthesis and rearrangements. In this context, organic chemists are on the virtue of the development of a sustainable, efficient, and elegant approach for the C-H peroxidation of fluorenes, 2-oxindole, naphthols, and benzofuranone and its rearrangement toward the synthesis of heterocyclic scaffolds under batch/continuous flow.

Hence, this thesis work focused on the developments of peroxidations of fluorenes, 2-oxindoles, naphthols, and benzofuranones and further its rearrangement reactions towards the synthesis of novel and biologically important heterocyclic scaffolds (Figure 1.7.1.).

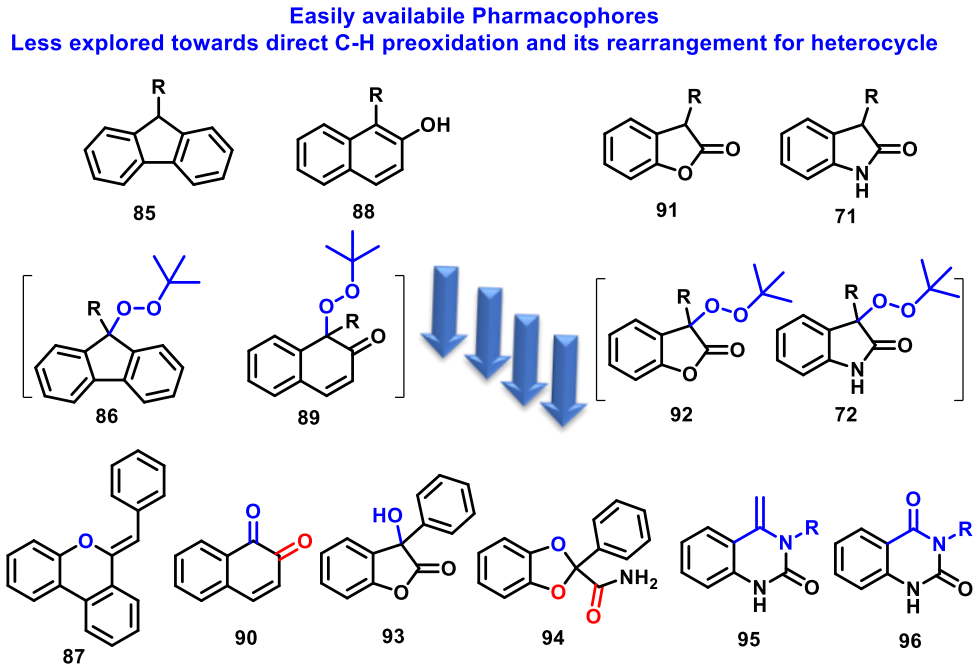


Figure 1.7.1. Heterocyclic scaffolds can be achieved by commercially available pharmacophores

1.8. Objectives of the thesis

1.8.A. Synthesis of Quaternary Peroxides: Application in Catalytic Deperoxidation and Rearrangement Reactions

The design of a new catalytic system for the selective oxidative C−O bond formation is a formidable and long-standing goal in synthetic chemistry. Organic peroxides are privileged scaffolds, and the existence of a reactive O−O bond makes them versatile intermediates in radical chemistry and

many chemical syntheses. Thus, we anticipated the safe, green, and mild protocol for C-H peroxidation using an earth-abundant metal catalyst in batch/flow. The peroxidation reactions preceded smoothly using an Mn catalyst. To our delight, the synthesized quaternary peroxides exhibited good anticancer and antimalarial activities and could be synthesized on-demand on a large scale with a shorter duration using continuous flow. Furthermore, we have investigated the synthetic application of 9-substituted peroxides toward rearrangement and de-peroxidation.

1.8.B. Catalyst-Free Peroxidation and Skeletal Rearrangement for the Synthesis of Dioxole-2-carboxamide Derivatives under Continuous-Flow Conditions

Peroxidation is one of the important chemical reactions in organic synthesis and has been used to insert oxygen *via* skeletal rearrangement reactions. This functionality has also important in natural products and drugs. Transition-metal has played an important role as a catalyst to promote peroxidation reactions. Notably, Fe, Cu, Co, and Mn catalyst has been primarily used for C-H peroxidation. However, recently oxidative peroxidation that can lead to the dearomatization of aromatic compounds has been demonstrated using metal-catalyst. However, catalyst-free organic reactions are desirable in synthesis since they can avoid the metal-traces in the product purity. However, minimal reactions were explored for the C-H peroxidation of oxindole derivatives under batch. However, no example is demonstrated for the peroxidative dearomatization of naphthols and related results under catalyst-free conditions. Moreover, no model is shown for the C-H peroxidation of benzofuranone products under catalyst-free conditions. Furthermore, scalability and safety hazards under batch conditions have serious concerns. In addition, there is no example shown for the skeletal rearrangement of peroxides for the synthesis of dioxole-2-carboxamide derivatives under catalyst-free conditions. In this chapter, the research work is proposed to developed catalyst free peroxidation and skeletal rearrangement for the synthesis of dioxole-2-carboxamide derivatives under continuous-flow conditions.

1.8.C. Sequential Oxidative-Fragmentation and Skeletal Rearrangement of Peroxides for the Synthesis of Quinazolinone Derivatives

The quaternary peroxides are very reactive due to the weak O-O bond, which can be used to trigger unique rearrangement reactions. We anticipated the real possibility of rearrangement using base toward sequential oxidative-fragmentation and skeletal rearrangement of peroxyindoles with amines. Our expectations were pragmatic, and we observed two new reconstructions. In the first rearrangement, the reaction of sequential reaction of peroxyindole that includes base-mediated oxidative fragmentation to form isocyanate as a key intermediate further primary amine reacted with isocyanate resulted in skeletal rearrangement to synthesize exo-olefinic 3-substituted-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one good to excellent yield. However, the second innovative rearrangement, peroxyindole and amino alcohols accelerated skeletal rearrangement to synthesize

oxazoloquinazolinone. In this chapter, the research work is proposed to developed sequential oxidative-fragmentation and skeletal rearrangement of peroxides for the synthesis of quinazolinone derivatives.

1.8.D. Transition-Metal-Free Alkylative Aromatization of Tetralone Using Alcohol/Amino Alcohol towards the Synthesis of Bioactive Naphthols and Benzo[*e/g*]indole Derivatives

At the outset, most of the modern synthesis reactions are catalyzed by a specially designed metal catalyst and multidentate ligands, and some cases its requires stoichiometric bases. These transition-metal complexes are usually expensive, less abundant in nature, and much more sensitive to air/moisture. Besides, some of the transition-metal residues are difficult to separate from desired products that are not suitable for pharmaceuticals. Consequently, alternative efficient synthetic methods for the synthesis of naphthols and benzo[*e/g*]indoles, which avoid expensive transition-metal catalyst, is in high demand in contemporary research. In this context, this chapter involves multi-step reconstructions such as oxidation-condensation-isomerization-aromatization reactions in one step from tetralone and alcohols/amino alcohols in the presence of base *via* C−C/C−N bond formation for the synthesis of bioactive naphthols and benzo[*e/g*]indoles.

Overall, this thesis dealt with the peroxidation and rearrangement reactions toward synthesizing heterocyclic scaffolds under batch/continuous flow. All the chapters are interconnected with each other using peroxide as one of the essential compounds. Besides the general introduction, the introduction and literature background for each chapter are written separately to get a clear idea.

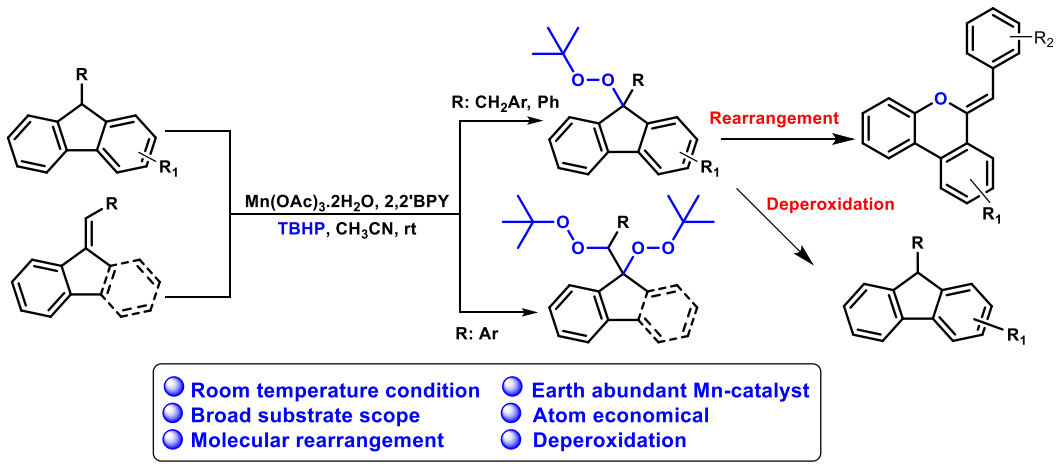
Chapter 2

Manganese-Catalyzed Synthesis of Quaternary Peroxides: Application in Catalytic Deperoxidation and Rearrangement Reactions

2. Manganese-Catalyzed Synthesis of Quaternary Peroxides: Application in Catalytic Deperoxidation and Rearrangement Reactions

2.1. Abstract

The present chapter describes a highly efficient, selective, and direct C-H peroxidation of 9-substituted fluorene achieved *via* radical-radical cross-coupling using Mn-2,2'-bipyridine-catalyst. Furthermore, this method effectively promotes the sterically hindered bis-peroxidation of various substituted arylidene-9*H*-fluorene/arylideneindolin-2-one derivatives to afford highly selective bisperoxides. This method has high selectivity over oxidative cleavage of the C=C bond that usually forms ketone and aldehyde. Moreover, a new approach for the synthesis of (*Z*)-6-benzylidene-6*H*-benzo[*c*]chromene has been achieved *via* an acid-catalyzed skeletal rearrangement of these peroxides. For the first time, unlike O-O bond cleavage, reductive C-O bond cleavage in peroxides using Pd-catalyst and H_2 is described, which enables the reversible reaction to afford exclusively deperoxidised products. A detailed mechanism for peroxidation, molecular rearrangement, and deperoxidation has been proposed with preliminary experimental studies.



Scheme 2.1.1. Present finding for the C-H peroxidation and bisperoxidation

2.2. Introduction and literature background on C-H peroxidation and bisperoxidation

Designing a new catalytic system for selective oxidative C-O bond formation is a difficult and long-standing goal in synthetic chemistry.[49] The organic peroxides are privileged scaffolds and the existence of reactive O-O bond makes them versatile intermediates in radical chemistry and many chemical syntheses. For instance, peroxides are used as precursors for radical polymerization initiation

in industrial production.[14] Moreover, the derivatives of heterocyclic peroxides function as an intriguing precursor for the skeletal rearrangement reactions.[46, 47a, 50] In contrast, several organic peroxides show promising medicinal properties by controlling the oxidative stress levels inside the cells and thus grabbed a significant attraction from across the scientific community. In the past decades, structurally discrete peroxides have been found to exhibit anticancer, antimalarial, anthelmintic, antiviral, and antifungal activities; these properties make them exciting pharmacophores in biology (Figure 2.2.1).[51, 44, 4a, 1a] Recently, Woerpel and co-workers discovered that the substituted 1,2-dioxlone derivatives show potent anticancer properties.[51c]

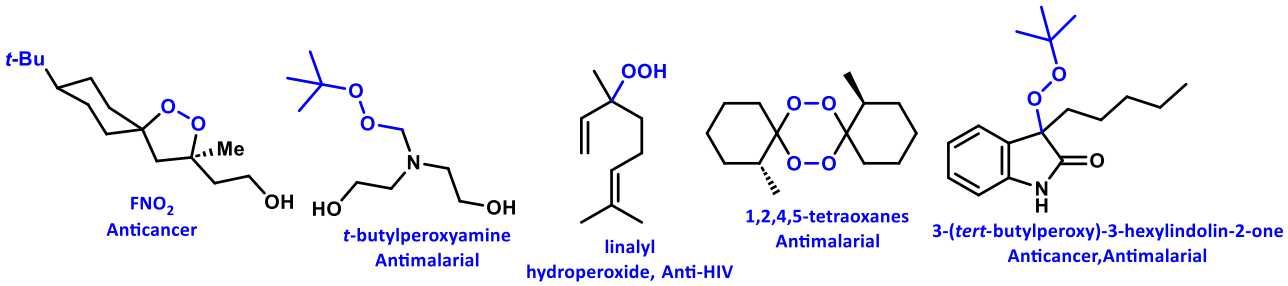
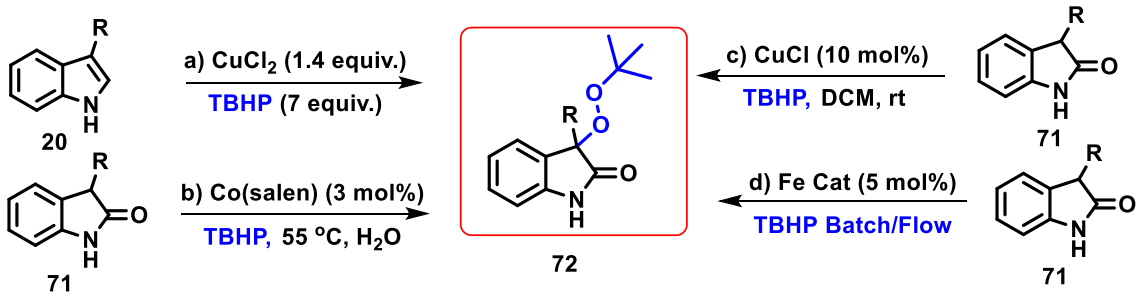


Figure 2.2.1. Representative bioactive compounds bearing peroxy functionality

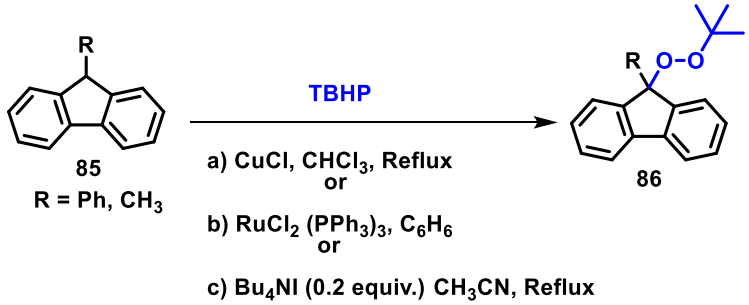
Metal-catalyzed peroxidation of organic moieties can be accomplished using peroxy donors such as hydrogen peroxide or alkyl hydroperoxides, and the overall reaction proceeds *via* "shunt" and "rebound" catalysis. The peroxidation of unactivated C-H bond and bisperoxidation of styrene derivatives are significant transformations in metal-catalyzed chemical reactions. The pioneering example of peroxidation of *α*-substituted carbonyl compounds using *tert*-butyl hydroperoxide (TBHP) and CuCl was demonstrated by Kharasch and Sosnovsky.[19] Interestingly, Murahashi and co-workers reported the peroxidation of amide and carbamate derivatives using TBHP and ruthenium catalysts.[20] An elegant method for peroxidation of dicarbonyl compounds was developed by Terent'ev and co-workers using $Cu(ClO_4)_2 \cdot 6H_2O$ and TBHP.[21] All of the above reports have been discussed in section 1.4. literature background on peroxidation Chapter 1.

Afterward, the direct C-H peroxidation of C3-substituted-2-oxindole derivatives were reported by Liu and Stoltz group independently using catalytic amounts of cobalt and copper catalyst, respectively.[52,46] Subsequently, Gnanaprakasam's group reported the C-H peroxidation of a carbonyl-containing class of compounds such as C3-substituted-2-oxindole derivatives using homogeneous and heterogeneous iron catalysts (Scheme 2.2.1.).[51b]



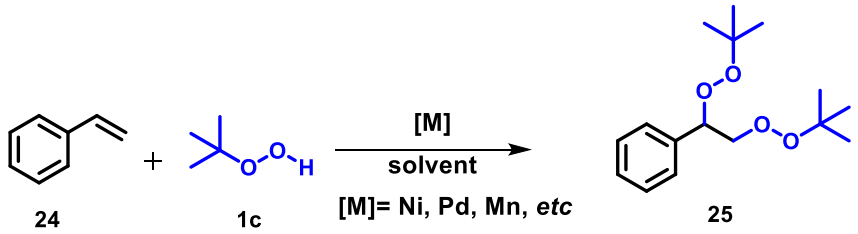
Scheme 2.2.1. Peroxidations of indole and C3-substituted-2-oxindole by using metal catalysts

Recently, the direct C-H peroxidation of barbituric acid derivatives using a copper catalyst or metal-free conditions was reported by Terent'ev and co-workers.[53a] Other groups reported the peroxidations of 9-substituted fluorene **85** using metals such as Cu,[53a] Ru,[53b] and metal-free approaches with *tert*-butyl hydroperoxide **1c** (Scheme 2.2.2).[53c]



Scheme 2.2.2. Peroxidation of 9-substituted fluorenes by metal and metal-free catalytic approach

Furthermore, the use of stoichiometric or catalytic reagents to obtain the organic peroxides has also been documented in the literature.[54] Besides, Feringa and co-workers found bisperoxidation using the dinuclear nickel complex while performing the peroxidation of styrene derivative.[25] Later, Corey and co-workers also observed the bisperoxidation of styrene in the presence of $Pd(OAc)_2$.[26] Recently, to overcome the limitations of previously reported bisperoxidtion, Terent'ev, and co-workers have reported the bisperoxidation of styrene using simple manganese catalyst with good yield (Scheme 2.2.3.).[27]



Scheme 2.2.3. Bisperoxidation of styrene **24** using a metal catalyst

2.3. The rationale of the present work

Fluorene derivatives have attracted by a chemist in the last few decades as they are helpful key chemical components for poly(alkylfluorene)s due to their chemical, physical, and photoelectric properties as the radical initiator and additives for the many chemical transformations.[55] Hence, the C-H peroxidation of substituted fluorenes generates quaternary peroxides, which may be helpful in chemical and therapeutic applications. However, to the best of our knowledge, there is no report for the peroxidation of a non-carbonyl class of compounds, such as 9-substituted fluorenes and vicinal bisperoxidation of arylidene-9*H*-fluorene derivatives using manganese catalyst. Furthermore, metal-catalyzed deperoxidation and molecular rearrangements using 9-substituted fluorene peroxides were not reported in the literature.

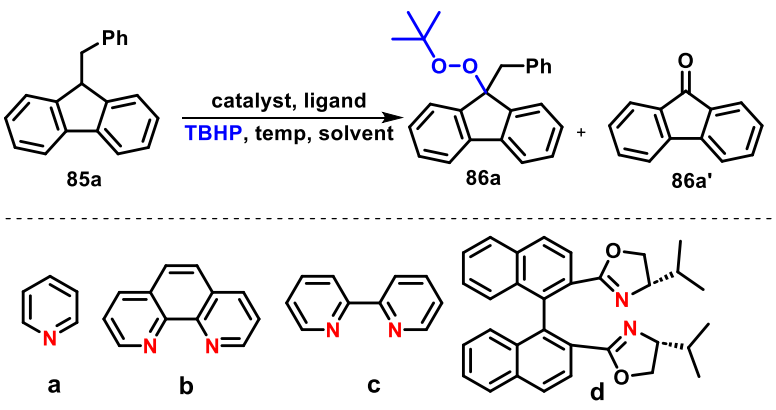
2.4. Results and discussion

In this chapter, we have developed the mild and efficient protocol for Mn-2,2'-bipyridine-catalyzed direct C-H peroxidation of 9-substituted fluorenes **85**, C3-substituted 2-oxindoles **71**, and vicinal bisperoxidation of olefin derivatives at room temperature.

2.4.1. Optimization studies

We began our study by investigating a variety of ligands and solvents (Table 2.4.1). Initially, the control reaction of compound **85a** and *tert*-butyl hydroperoxide (TBHP) **1c** without any catalyst was performed at room temperature, which showed no reaction (Table 2.4.1, entry 1). The critical role of 5 mol% of $Mn(OAc)_3.2H_2O$ on C-H peroxidation afforded product **86a** in 47% yield (Table 2.4.1, entry 2). Moreover, this transformation requires much more TBHP (4 equiv.), which may be due to the high reactivity of metal catalysts with peroxides, resulting in the decomposition of TBHP. While the use of 1, 2, and 3 equiv. of TBHP **1c** in this reaction led to 20%, 40%, and 70% yield of product **86a**. To improve the yield, we screened various ligands in this transformation and found that ligand **c** efficiently produced product **86a**. (Table 2.4.1, entries 3-6).

Table 2.4.1. Optimization of reaction conditions[a]



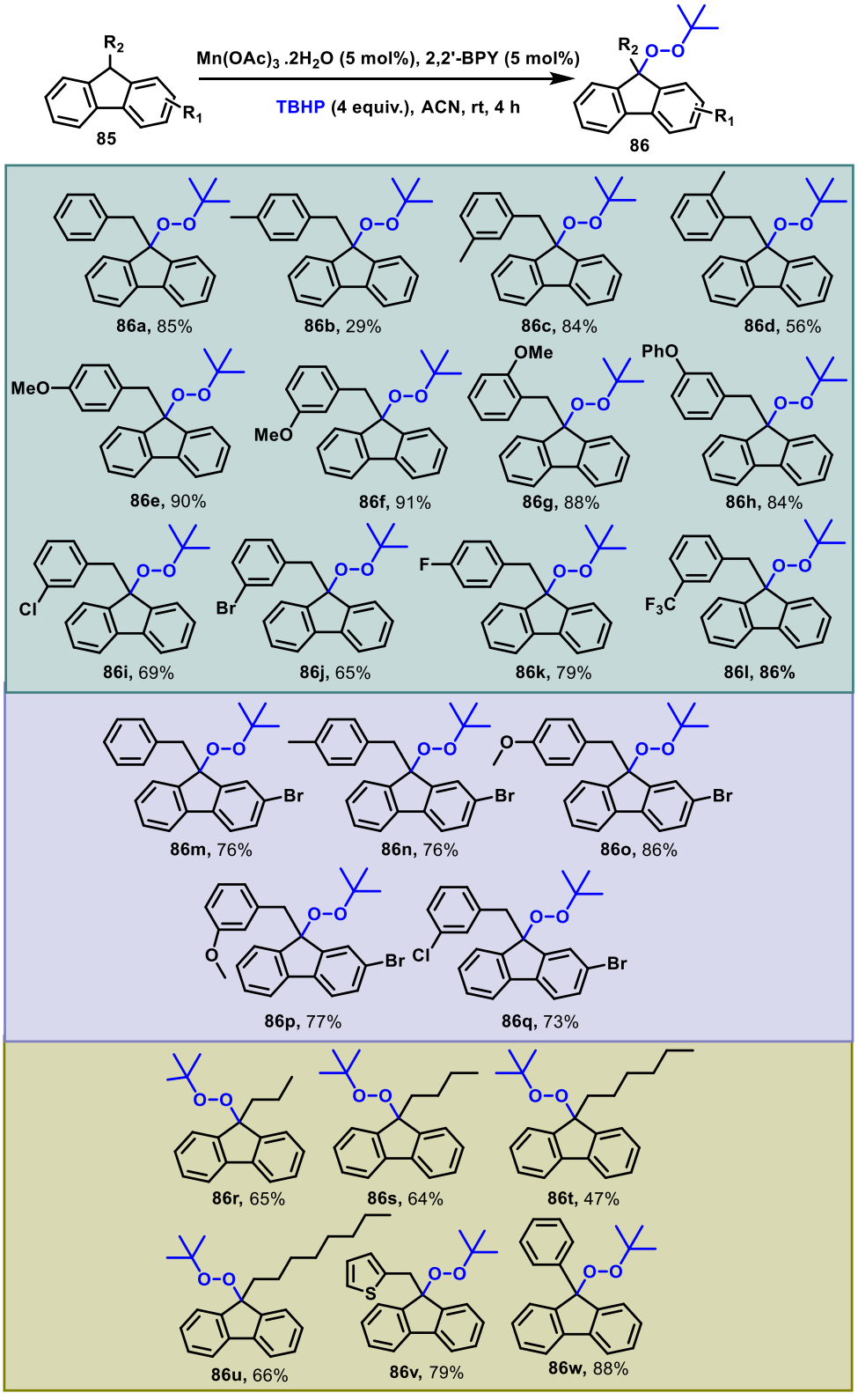
Entry	Catalyst	Ligand	Solvent	Yield of **86a/86a'** [%][c]
1	-	-	ACN	no reaction
2	$Mn(OAc)_3 \cdot 2H_2O$	-	ACN	47/trace
3	$Mn(OAc)_3 \cdot 2H_2O$	a	ACN	30/trace
4	$Mn(OAc)_3 \cdot 2H_2O$	b	ACN	81/5
5	$Mn(OAc)_3 \cdot 2H_2O$	c	ACN	85/7
6	$Mn(OAc)_3 \cdot 2H_2O$	d	ACN	19/trace
7	Jacobsen cat.	-	ACN	83/trace
8	$Mn(OAc)_3 \cdot 2H_2O$	c	DCM	62/trace
9	$Mn(OAc)_3 \cdot 2H_2O$	c	EtOH	57/trace
10	$Mn(OAc)_3 \cdot 2H_2O$	c	*t*-BuOH	64/trace
11	$Mn(OAc)_3 \cdot 2H_2O$	c	H_2O	no reaction
12	$Mn(OAc)_3 \cdot 2H_2O$	c	EtOAc	70/trace
13	$Mn(OAc)_3 \cdot 2H_2O$	c	THF	30/trace
14[b]	$Mn(OAc)_3 \cdot 2H_2O$	c	ACN	82/7
15	$Co(OAc)_2 \cdot 4H_2O$	c	ACN	83/-
16	$Cu(OAc)_2 \cdot H_2O$	c	ACN	20/30
17	$Ni(OAc)_2 \cdot 4H_2O$	c	ACN	-

[a]**Reaction conditions:** Catalyst (5 mol%, 0.0195 mmol), ligand (5 mol%, 0.0195 mmol), compound **85a** (0.39 mmol), TBHP in decane **1c** (4 equiv.) and solvent (2 mL) were stirred at room temperature for 4 h. [b]70% aqueous TBHP **1c'** (4 equiv.) is used. [c]Isolated yields.

The bipyridine ligand plays an important role in this transformation, probably due to the formation of an active and stable bipyridine-based Mn-complex, which can facilitate selective radical formation *via* association and dissociation pathways. Interestingly, the Jacobsen catalyst afforded the 83% desired product **86a** (Table 2.4.1, entry 7). Next, various solvents were investigated to improve the yield of the peroxidation reaction (Table 2.4.1, entries 8-13). From our studies, acetonitrile was found to be the

best solvent to provide **86a** in 85% yield after 4 h (Table 2.4.1, entry 5). To our delight, when the reaction was performed with a 70% aqueous solution of TBHP **1c'**, it provided a yield that was close to the yield for entry 5 (Table 2.4.1, entry 14). In most of the cases, a trace of fluoren-9-one **86a'** was observed.

2.4.2. Substrate scope for C-H peroxidation of 9-substituted fluorenes

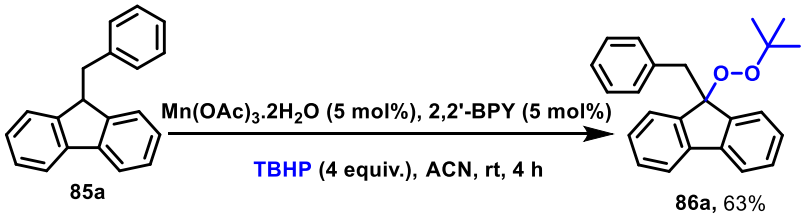


Scheme 2.4.1. Substrate scope for C-H peroxidation of 9-substituted fluorenes. The mentioned yields are isolated yields.

Interestingly, $Co(OAc)_2 \cdot 4H_2O$ also effectively catalyzes this reaction to afford product **86a** in 83% yield (Table 2.4.1, entry 15). Other metal salts $Cu(OAc)_2 \cdot H_2O$ and $Ni(OAc)_2 \cdot 4H_2O$, were not effective for this transformation (Table 2.4.1, entries 16, 17).

Next, this optimized condition was applied to generalize the substrate scope for the C-H peroxidation reaction. Initially, the C-H peroxidation of substrates having substituents on benzyl groups was tested, and the results are summarized in Scheme 2.4.1. The electron-donating group, such as 3-Me, 2-Me, 4-OMe, 3-OMe, 2-OMe, and 3-OPh, afforded low to excellent yields of the product **86b-h** (Scheme 2.4.1). Subsequently, the benzyl moiety bearing electron-withdrawing halogens functionalities such as 3-Cl, 3-Br, 4-F, and 3-CF_3 on fluorene provided moderate to a good yields of the corresponding products **86i-l** (Scheme 2.4.1). Next, the substrate scope is extended to C-H peroxidation of substrates having substituents on fluorene and the benzyl group. To our delight, the reaction of 9-benzyl-2-bromo-9*H*-fluorene under optimized conditions afforded the desired product **86m** in 76% yield. Accordingly, the other substrates bearing electronically active groups afforded expected products **86n-q** in good to excellent yields (Scheme 2.4.1). Next, the aliphatic moiety on the 9-position of fluorene also reacted well to afford product **86r-u** in moderate to good yields (Scheme 2.4.1). Moreover, the reaction of 2-((9*H*-fluoren-9-yl)methyl)thiophene and 9-phenyl-9*H*-fluorene with TBHP **1c** afforded **86v** and **86w** in 79% and 88% yields, respectively.

To our delight, the reaction preceded smoothly even at the gram scale to afford **86a** in 63% yield (Scheme 2.4.2).



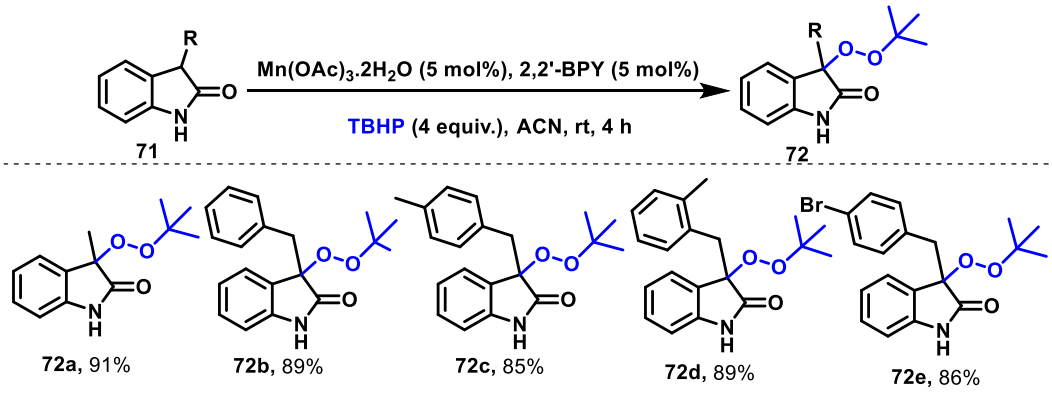
Scheme 2.4.2. Gram-scale reaction[a]

[a]**Reaction condition:** $Mn(OAc)_3.2H_2O$ (5 mol%, 0.30 mmol), 2,2'-bipyridine (**c**) (5 mol%, 0.30 mmol), compound **85a** (6.01 mmol, 1 equiv.), TBHP in decane **1c** (4 equiv.) and acetonitrile (10 mL) were stirred at room temperature for 4 h.

2.4.3. Substrate scope for C-H peroxidation of C3-substituted-2-oxindoles

To extend the substrate scope for the direct C-H peroxidation, C3-substituted 2-oxindole derivatives were treated with standard reaction conditions. For instance, the reaction of 3-methyl-2-

oxindole **71a** afforded a 91% yield of product 3-(*tert*-butylperoxy)-3-methylindolin-2-one **72a**. Next, the electron neutral, electron-donating, and electron-withdrawing substituents afforded good to excellent yields **72b-e** (Scheme 2.4.3).



Scheme 2.4.3. Substrate scope for C-H peroxidation of C3-substituted-2-oxindoles[a]

[a]**Reaction conditions:** $Mn(OAc)_3.2H_2O$ (5 mol%, 0.0125 mmol), 2,2'-bipyridine (**c**) (5 mol%, 0.0125 mmol), compound **71** (0.25 mmol), TBHP **1c** (4 equiv.), and acetonitrile (2 mL) were stirred at room temperature for 4 h. The mentioned yields are isolated yields.

2.4.4. Continuous-flow set up

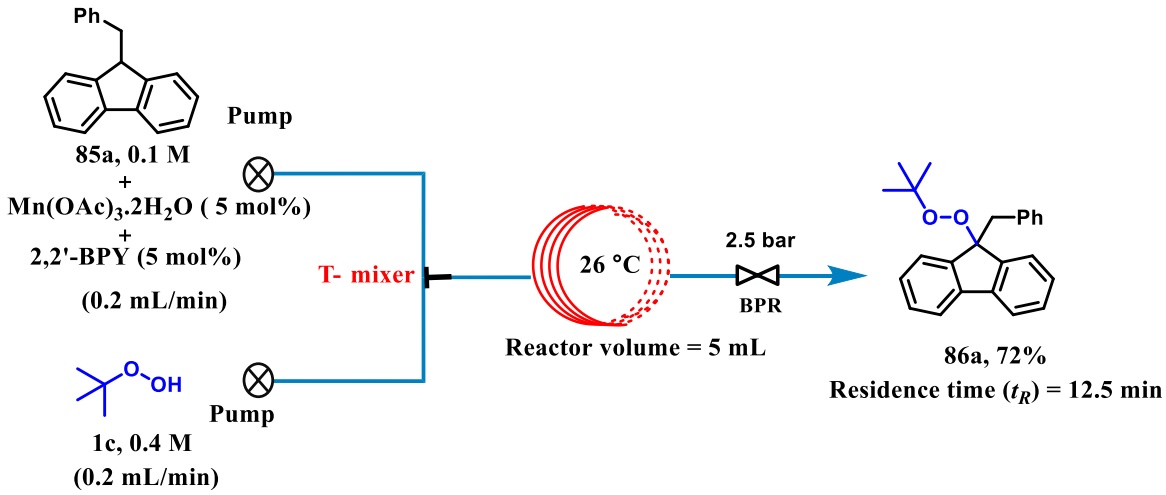


Figure 2.4.1. Continuous-flow set up for C-H peroxidation of 9-benzyl-9*H*-fluorene

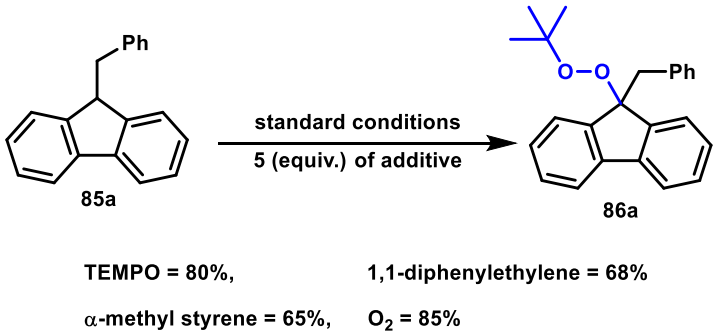
Metal salts react strongly with peroxides and give an exothermic reaction. Sometime, such exothermic reactions become runaway reactions on a large scale. Therefore, to minimize the explosive hazards of peroxides, the C-H peroxidation reaction was performed under continuous flow (Figure 2.4.1). Thus, in one pump, 5 mL of the mixture of 0.1 M solution of 9-benzyl-9*H*-fluorene **85a**, $Mn(OAc)_3.2H_2O$ (5 mol%) and 2,2'-bipyridine (5 mol%) in DCM and in another pump, 5 mL of 0.4

M solution of TBHP-decane **1c** in DCM was flown through the coil reactor with the flow rate of 0.2 mL/min to afford the peroxylated product **86a** in 72% yield with the residence time of 12.5 minutes (Figure 2.4.1). The compound **86a** was not completely soluble in acetonitrile; hence, we used dichloromethane as a solvent for a continuous flow experiment to get complete solubility.

2.5. Mechanistic investigations for the C-H peroxidation

2.5.1. Radical quenching experiment

The reaction was carried out by adding radical quenchers to prove the existence of a radical pathway in the peroxidation reaction. Accordingly, the reaction of 9-benzyl-9*H*-fluorene in the presence of (2,2,6,6-tetramethylpiperidine-1-oxyl) TEMPO or 1,1-diphenylethylene or α-methyl styrene or molecular oxygen was performed separately which produced 80%, 68%, 65%, and 85% yield of the product **86a** respectively (Scheme 2.5.1.). From these experiments, a decrease in the output of product **86a** indicates the radical nature of the reaction.



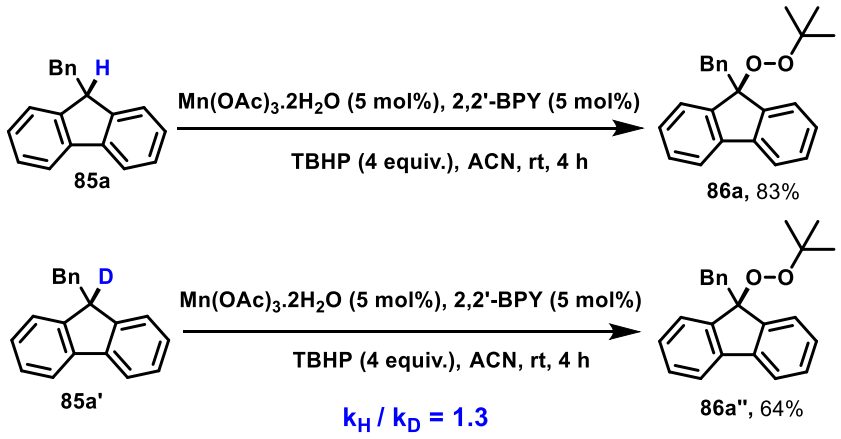
Scheme 2.5.1. Radical quenching experiments[a]

[a]**Reaction conditions**: 9-benzyl-9*H*-fluorene **85a** (0.25 mmol), 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) (1.25 mmol) or 1,1-diphenylethylene (1.25 mmol) or *α*-methylstyrene (1.25 mmol) or oxygen balloon in a 2 mL acetonitrile was stirred at room temperature for 4 h.

2.5.2. Deuteration and kinetic studies

In order to perform the kinetic isotope studies, we have prepared the starting material such as deuterated benzyl alcohol (Figure 2.5.1.). We observed 87.71% deuteration incorporation, and with the help of this deuterated benzyl alcohol, we prepared the deuterium-labeled compound **85a'**, where we observed 54.34% deuteration incorporation (Figure 2.5.3.).

Next, we have performed deuterium labeling experiments to elucidate the mechanistic aspects of the reaction. For instance, under standard reaction conditions, two parallel reactions were carried out with deuterium-labeled compound **85a'** and unlabeled compound **85a**. A primary kinetic isotope effect (KIE) $k_H/k_D = 1.3$ was observed, indicating that the breaking of the sp^3-C-H bond is involved in the rate-determining step (Scheme 2.5.2.).



Scheme 2.5.2. Deuterium labeling kinetic studies

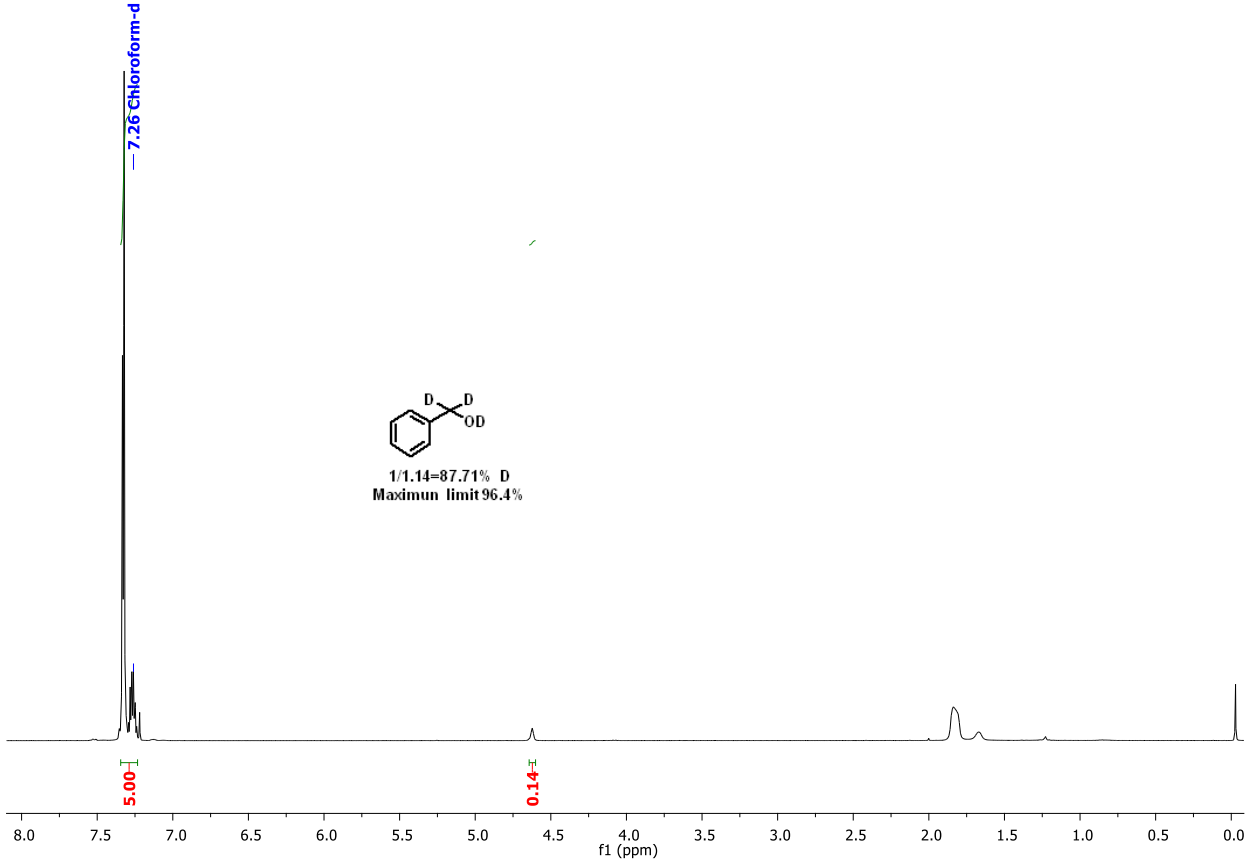


Figure 2.5.1. ^{1}H NMR of deuterated benzyl alcohol at 400 MHz in $CDCl_3$

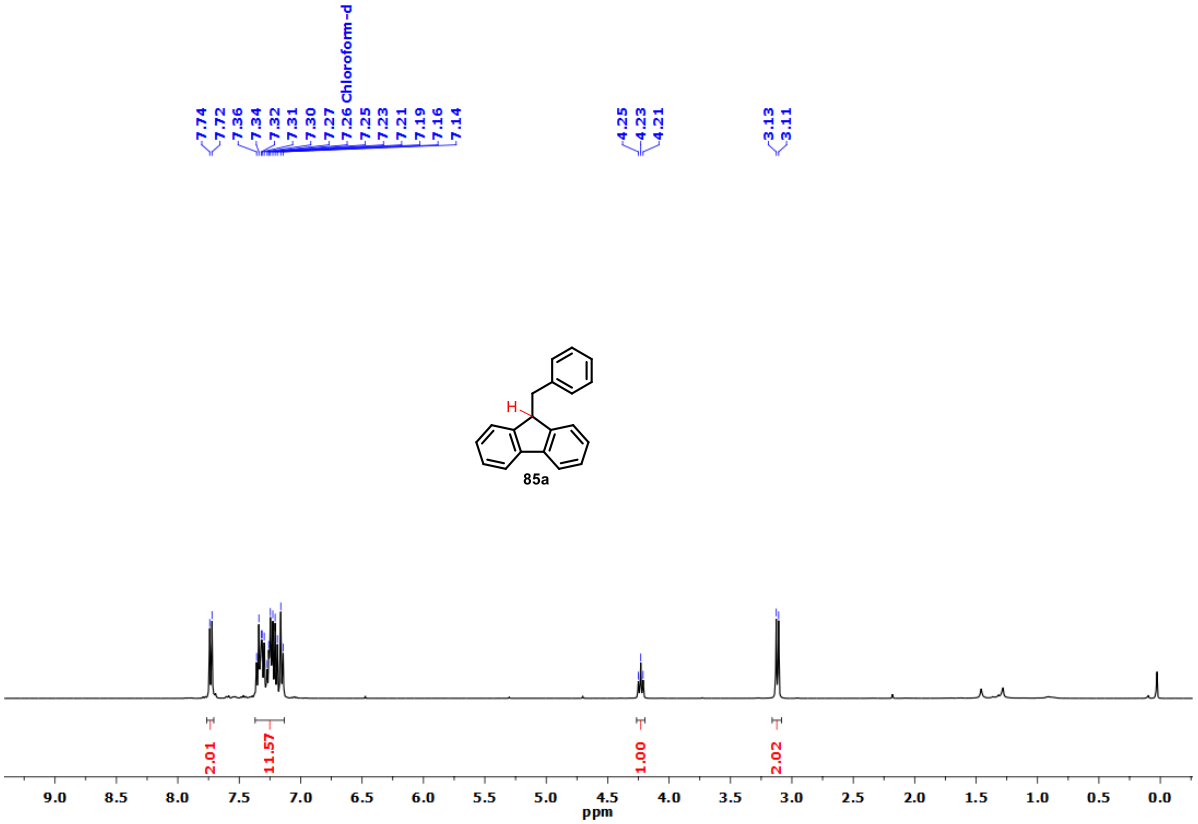


Figure 2.5.2. ^{1}H NMR of Compound **85a** at 400 MHz in $CDCl_3$

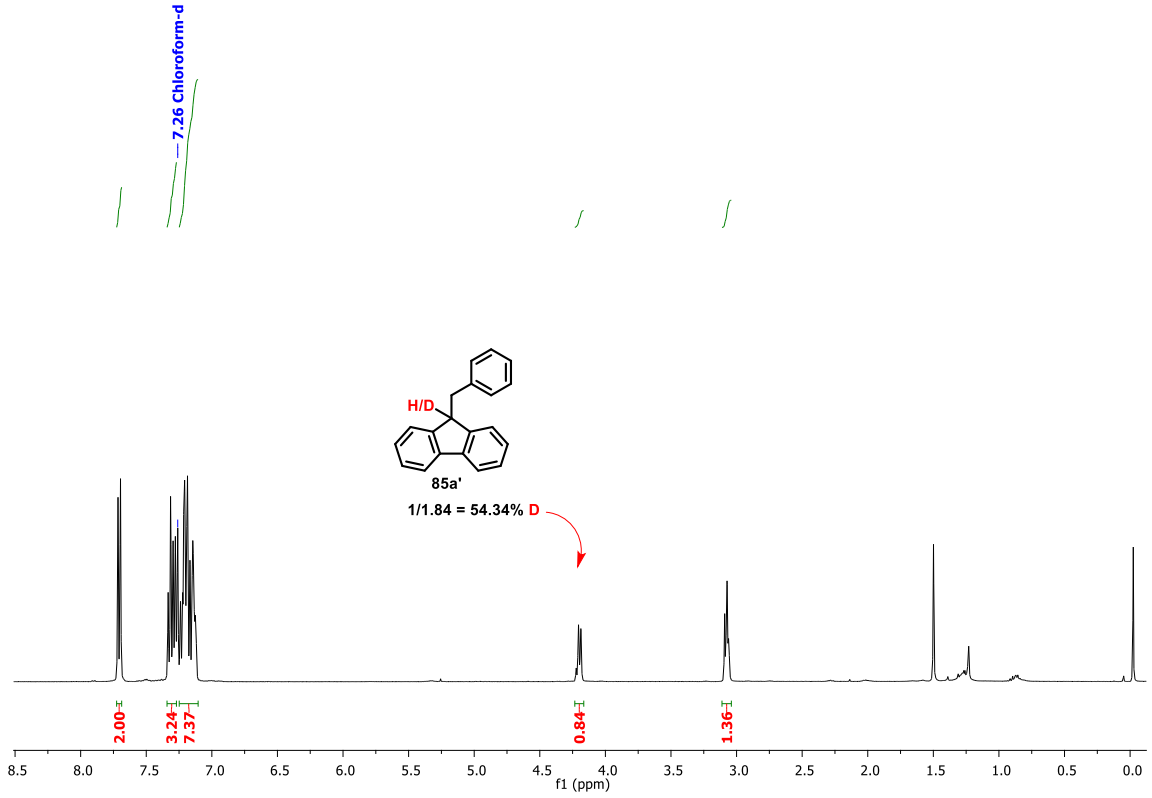
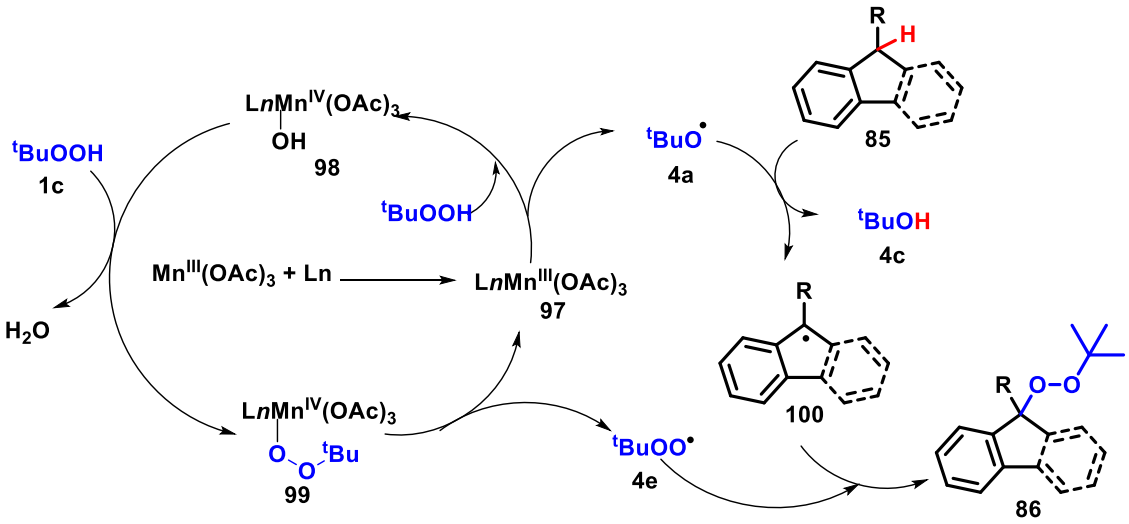


Figure 2.5.3. ^{1}H NMR of Compound **85a'** at 400 MHz in $CDCl_3$

2.6. Plausible mechanism for the Mn catalyzed C-H peroxidation

Based on preliminary experimental investigation and literature report,[27] a possible mechanism for Mn-catalyzed C-H peroxidation is proposed in Scheme 2.6.1. Initially, Manganese(III) acetate dihydrate reacts with 2,2'-bipyridine ligand to form complex **97**. Then, complex **97** will react with TBHP to give oxidized Mn(IV) intermediate **98** and *tert*-butoxy radical **4a**. Simultaneously, intermediate **98** reacts with another mole of TBHP to produce intermediate **99,** which undergoes homolytic cleavage to generate the *tert*-butylperoxy radical **4e**.



Scheme 2.6.1. Plausible mechanism for the Mn-catalyzed C-H peroxidation

On the other hand, the previously developed *tert*-butoxy radical **4a** abstracts a hydrogen atom from compound **85** to create the fluorene radical species **100**. The radical **4e** is associated with radical species **100** to give the desired peroxylated product **86** (Scheme 2.6.1.).

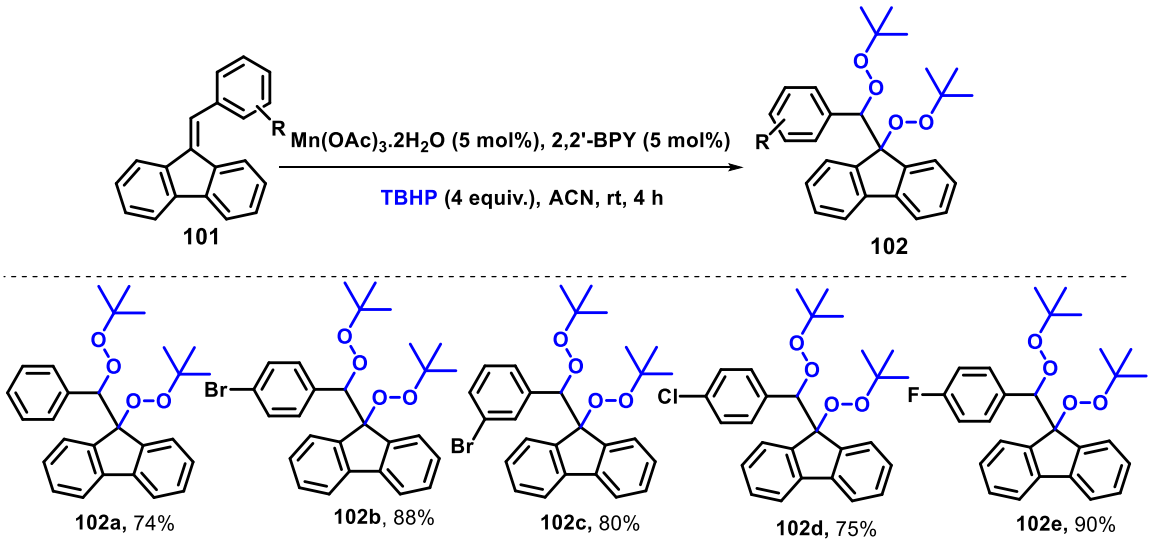
2.7. Synthesis of vicinal bis(*tert*-butyl)peroxides of arylidene-9*H*-fluorenes and 3-arylidene-indolin-2-ones

After obtaining fruitful results with 9-substituted fluorene **85**, we have focused on the vicinal bisperoxidation of arylidene-9*H*-fluorenes **101** and 3-arylidene-indolin-2-ones **103**.

2.7.1 Synthesis of vicinal bis(*tert*-butyl)peroxides of arylidene-9*H*-fluorenes

The reaction of 9-benzylidene-9*H*-fluorene **101a** with (4 equiv.) of TBHP and 5 mol% of $Mn(OAc)_3 \cdot 2H_2O$ at room temperature afforded bisperoxylated compound **102a** in 74% isolated yield. To spread the substrate scope, the reaction of other halogen-substituted arylidinefluorenes under standard reaction conditions afforded products **102b-e** in very good to excellent yields (Scheme 2.7.1.). Similarly, the bisperoxidation of arylidene-indolin-2-one derivatives **103a-e** also progressed smoothly in the presence of Mn-catalyst. The reaction of 3-arylidene-indolin-2-one with 4 equiv. of TBHP and 5 mol % of Mn-2,2'-bipyridine complex produced vicinal bisperoxylated compounds **104a-e** in good

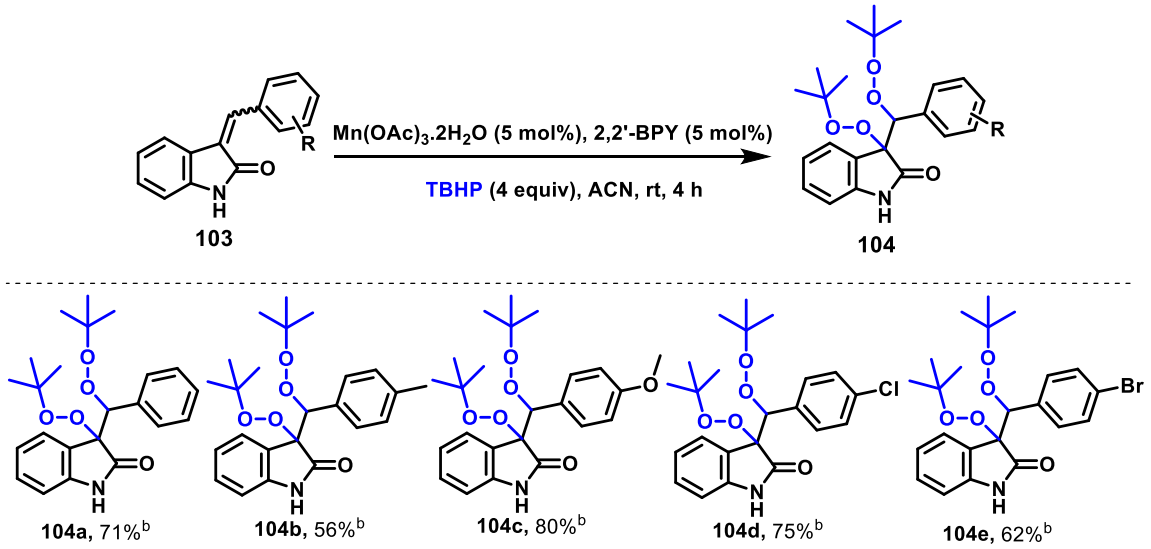
to excellent yields at room temperature (Scheme 2.7.2.). The structure and stereochemistry of compound **104e** were confirmed using single-crystal XRD (Figure 2.15B.19.).



Scheme 2.7.1. Synthesis of vicinal bis(*tert*-butyl)peroxides from arylidene-9*H*-fluorenes[a]

[a]**Reaction conditions:** $Mn(OAc)_3.2H_2O$ (5 mol%, 0.0125 mmol), 2,2'-bipyridine (**c**) (5 mol%, 0.0125 mmol), compound **101** (0.25 mmol, 1 equiv.), TBHP **1c** (4 equiv.), and acetonitrile (2 mL) were stirred at room temperature for 4 h. The mentioned yields are isolated yields.

2.7.2. Synthesis of vicinal bis(*tert*-butyl)peroxides of 3-arylidene-indolin-2-ones

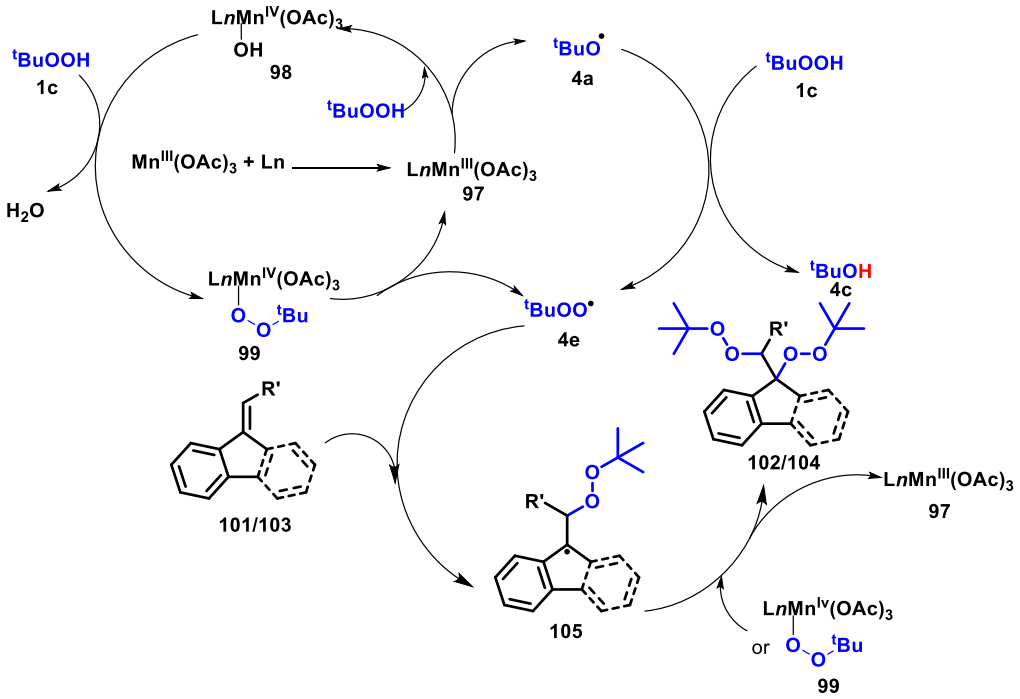


Scheme 2.7.2. Vicinal bisperoxidation of 3-arylidene-indolin-2-one **103**

[a]**Reaction conditions:** $Mn(OAc)_3.2H_2O$ (5 mol%, 0.0125 mmol), 2,2'-bipyridine (5 mol%, 0.0125 mmol), compound **103** (0.25 mmol, 1 equiv.), TBHP in decane **1c** (4 equiv.), and ACN (2 mL) were stirred at room temperature for 4 h. [b](dr = 1:3). The mentioned yields are isolated yields.

Moreover, the stereochemistry of all other bis peroxides **102a-e** and **104a-e** was comparatively assigned based on the crystal structure of **104e**.

2.8. Plausible mechanism for the Mn-catalyzed C=C bisperoxidation



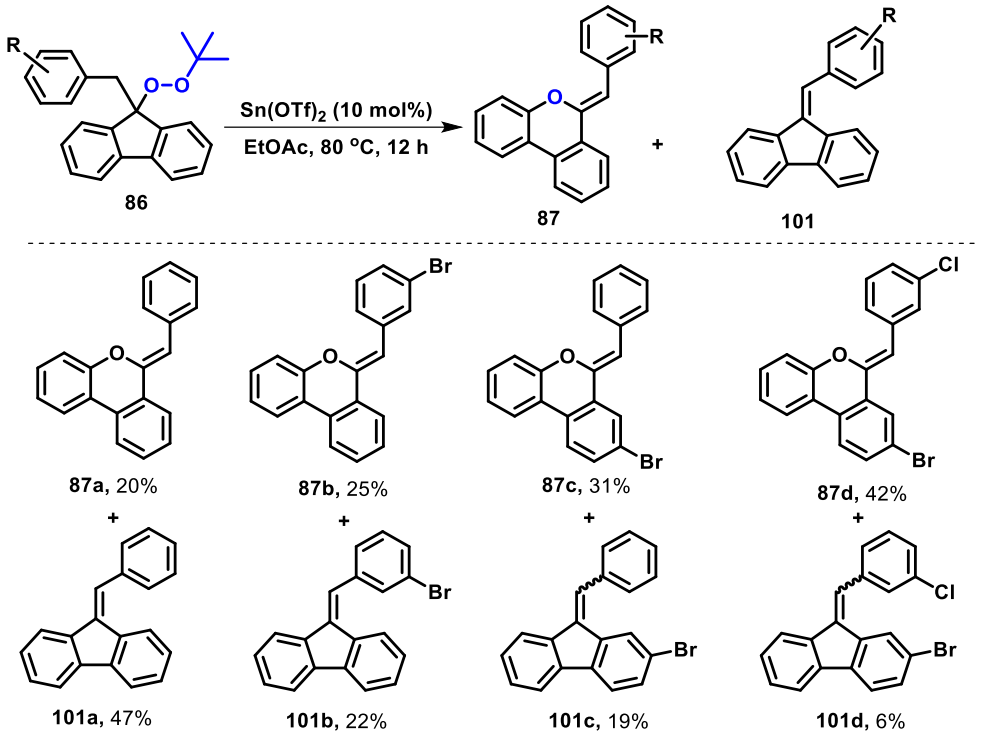
Scheme 2.8.1. Plausible mechanism for the Mn-catalyzed C=C bisperoxidation

The mechanism are similar to that of Scheme 2.6.1. However, in the case of bis-peroxidation, the *tert*-butyl peroxy radical **4e** combines with the olefin functionality of the reactant **101/103** to produce a mono-peroxide radical species **105** (Scheme 2.8.1.). Then, the intermediate **105** undergoes a recombination process with another in situ generated *tert*-butyl peroxy radical **4e** or from the Mn(IV) complex **99** to give the bis-peroxylated compound **102/104** (Scheme 2.8.1.).

2.9. Rearrangement of quaternary peroxides

The rearrangement reactions on electron-deficient oxygen have been extensively studied for peroxides.[14b] The representative example includes Baeyer-Villiger and Criegee rearrangement of peroxides. In this context, we envisioned a Lewis acid-catalyzed rearrangement of peroxides. Remarkably, the reaction of **86** with $Sn(OTf)_2$ afforded distinct rearrangement of peroxide. The use of Sn-catalyst afforded (*Z*)-6-benzylidene-6*H*-benzo[*c*]chromene **87a** in 20% yield along with 9-benzylidene-9*H*-fluorene **101a** in 47% yield respectively (Scheme 2.9.1.). Additional Lewis acids, such as 10 mol% of each $FeCl_3$, $Cu(OTf)_2$, $Sc(OTf)_3$, $In(OTf)_3$, and $AuCl_3$, were unsuccessful to afford the rearrangement product **87a**. The use of 10 mol% $BF_3.OEt_2$ afforded less conversion of peroxide with the rearrangement product **87a**. An electron-withdrawing group on the aryl ring increases the

yield of rearrangement products. Thus, bromo-substituted peroxides **85j**, **85m,** and **85q** were exposed to the rearrangement reaction using $Sn(OTf)_2$ as a catalyst which afforded **87b-d** in 25%, 31%, and 42% along with the 9-benzylidene-9*H*-fluorene **101b**, **101c**, and **101d** derivatives as a minor quantity (Scheme 2.9.1.). To our knowledge, there is no literature precedence for such rearrangements of 9-substituted-9-(*tert*-butylperoxy)-9*H*-fluorenes towards the synthesis of (*Z*)-6-benzylidene-6*H*-benzo[*c*]chromene **87a**.



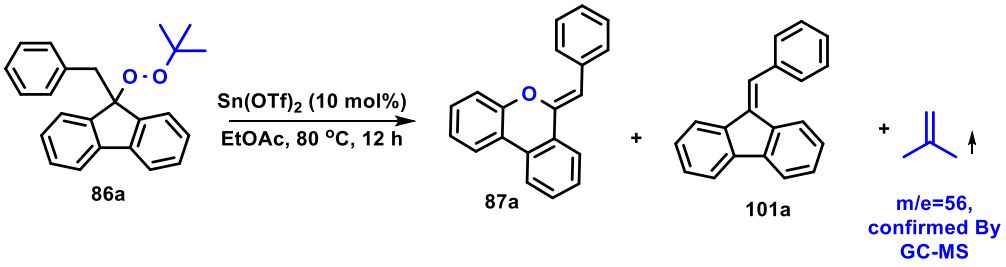
Scheme 2.9.1. Sn-catalyzed rearrangement of quaternary peroxides[a]

[a]**Reaction condition:** Compound **86** (0.25 mmol) and $Sn(OTf)_2$ (10 mol%) in 2 mL ethyl acetate was heated at 80 °C for 12 h in a sealed tube. The mentioned yields are isolated yield.

2.10. Mechanistic investigation

2.10.1. Detection of isobutylene gas using GC-MS

Interestingly, based on our experimental results and earlier literature reports, the possible reaction mechanism for the formation of rearranged product **87a** and elimination of product **101a** is shown in Scheme 2.10.1.[47a]



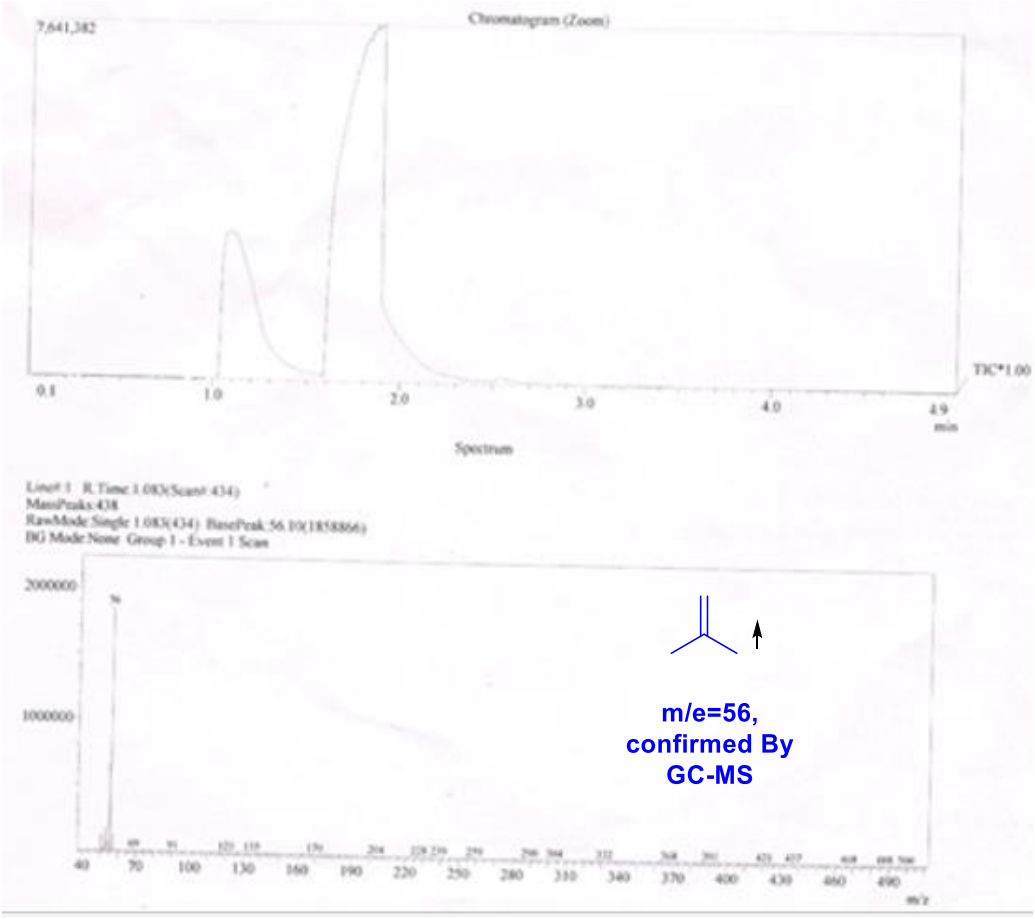


Figure 2.10.1. GC-MS spectra of gaseous phase of reaction mixture. After reaction completion, the gaseous component was taken using gas tight syringe and directly injected in the GC-MS instrument

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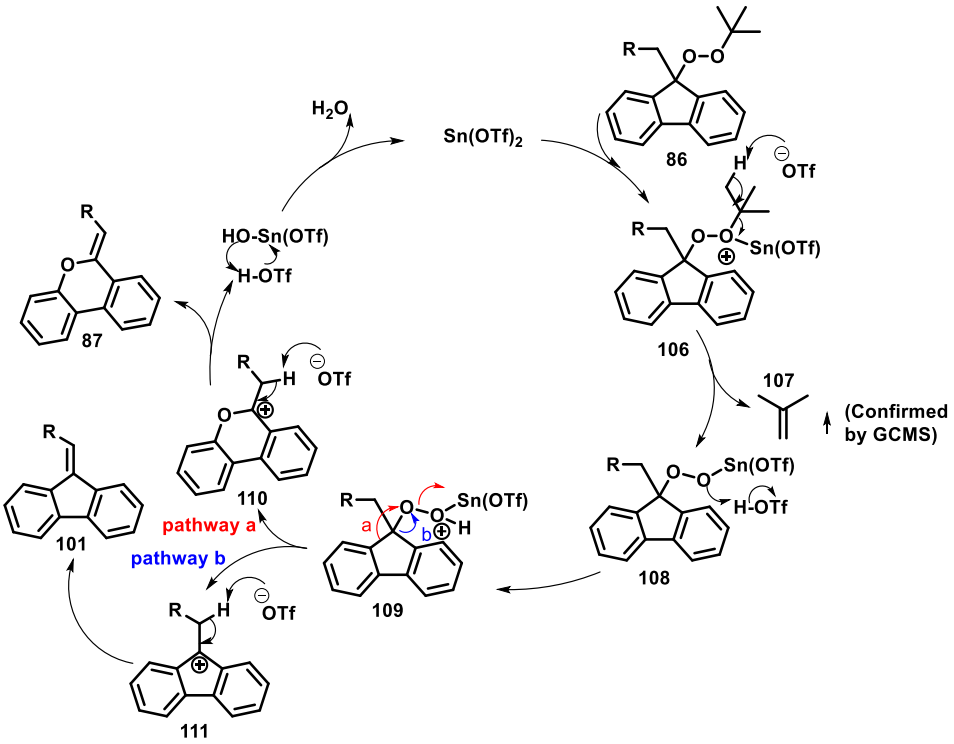
2.10.2. Plausible mechanism for rearrangement

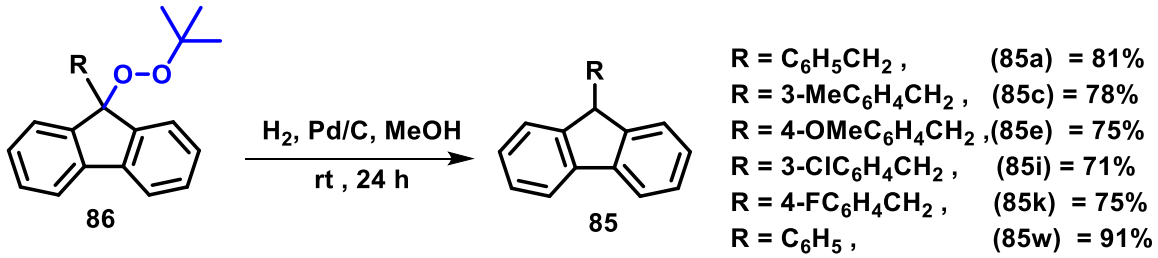
Initially, Tin(II)-trifluoromethanesulfonate ($Sn(OTf)_2$) coordinates with the peroxy (O-O) bond of **86** to produce complex **106**. In situ generation of triflate anion participates in the deprotonation of **106**, facilitating the generation of isobutylene gas **107** (confirmed by GC-MS, Figure 2.10.1.) to give Sn-chelated complex **108**. Further, the protonation of **108** by in situ generated TfOH produces SnOTf-chelated complex **109**. Then, **109** confers the synthesis of **87** and **101** *via* pathways 'a' and 'b'. In pathway 'a' ring expansion takes place with the removal of Sn(OH)OTf to afford carbocation **110**. The abstraction of a proton stabilizes this carbocation **110** by triflate anion to afford the desired product **87**. Whereas pathway 'b' to **101** may be obtained by removing Sn(OOH)OTf group.



Scheme 2.10.1. Plausible mechanistic pathway for the formation of **87** and **101** *via* rearrangement

2.11. Pd-C catalyzed deperoxidation

Moreover, the synthesized quaternary peroxides can be employed as valuable precursors for functional group transformations. In literature,[52] the reduction of the peroxide group using H_2, Pd/C was successfully employed for obtaining hydroxyl moiety.



Scheme 2.11.1. Pd-C catalyzed deperoxidation of peroxyfluorenes[a]

[a]**Reaction condition**: Peroxide **86** (0.15 mmol, 1 equiv.) and Pd/C (10 wt%, 10 mol%) in MeOH (2 mL) were stirred under a hydrogen balloon at room temperature for 8 h.

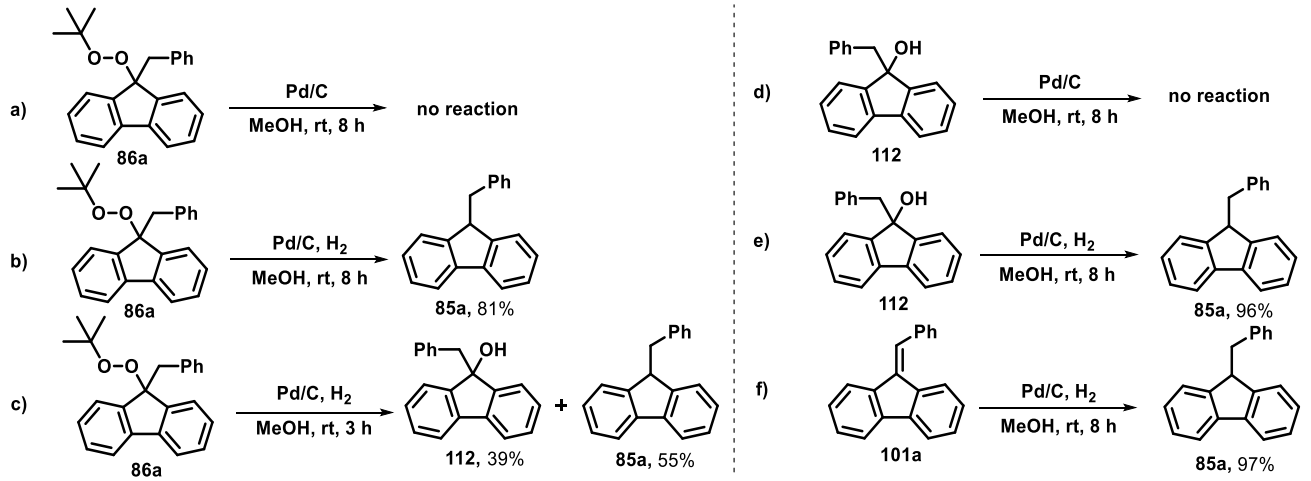
However, in divergence, we have observed the complete elimination of the peroxy group in high yield. To show the generalization, various substrates were successfully employed for the Pd/C mediated peroxide reduction to afford the reversible deperoxidation products **85a**, **85c**, **85e**, **85i**, **85k**, and **85w** in high yield (Scheme 2.11.1.).

2.12. Mechanistic investigation for the deperoxidation

To gain a mechanistic understanding, several control experiments were performed.

2.12.1. Control experiments for the deperoxidation

Initially, a control experiment was performed without molecular H_2 results with no reaction (Scheme 2.12.1.a). In the presence of molecular H_2, complete conversion was observed after 8 h (Scheme 2.12.1.b). However, the reaction was analyzed after 3 h, indicating the presence of the hydroxylated fluorene **112** (Scheme 2.12.1.c). Later, the hydroxyl compound **112** was prepared separately, and the reduction of **112** in the presence of Pd-C and molecular H_2 provided product **85a** in 96% yield (Scheme 2.12.1.e).

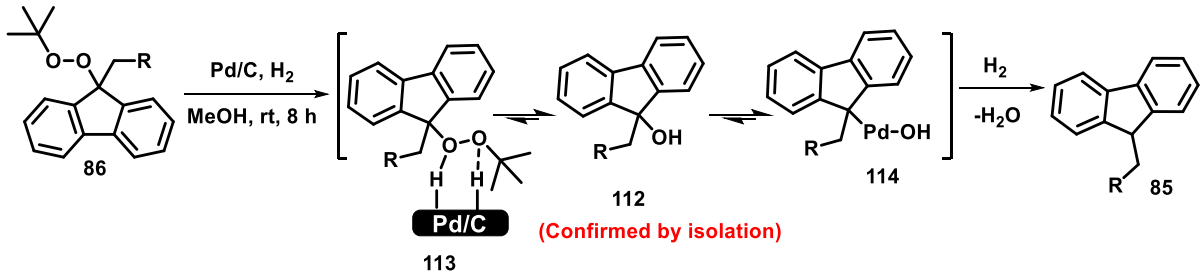


Scheme 2.12.1. Experimental investigation for deperoxidation pathway

However, there was no reaction without molecular H_2 (Scheme 2.12.1.d). This experiment proves that compound **112** serves intermediate in this reduction reaction. Finally, the hydrogenation of alkene **101a** was carried out in the presence of Pd-C and H_2, which afforded 97% of **85a** (Scheme 2.12.1.f). However, the possibility of alkene as an intermediate is ruled out since we observed the deperoxidation of 9-(*tert*-butylperoxy)-9-phenyl-9*H*-fluorene **85w** where the formation of alkene intermediate **101** is not possible (Scheme 2.11.1. compound **85w**).

2.12.2. Plausible mechanism for the deperoxidation of fluorene peroxides

Based on our experimental observations and the literature report,[56,57] we proposed a plausible mechanism for the deperoxidation (Scheme 2.12.2.). Initially, the peroxide will coordinate with H_2, Pd/C to form intermediate **113**. The elimination of *tert*-butanol will be commenced by hydrogenolysis to give intermediate **112**. The reduction of **112** to **85** proceeds through the insertion of Pd across the C-O bond of alcohol to form an intermediate **114**. Finally, in the presence of molecular hydrogen, intermediate **114** may undergo hydrogenation to give the desired product **85**.



Scheme 2.12.2. Reaction mechanism for the deperoxidation of fluorene peroxides

2.13. Conclusion

In summary, a novel class of quaternary peroxides has been synthesized using Mn-2,2'-bipyridine complex. The decrease in yield in the absence of ligand indicates the crucial role of ligand in this transformation. Among the series of nitrogen donor ligands, 2,2'-bipyridine was found to be the best ligand to afford the C-H peroxylated product in excellent yield. This catalytic method is applied to the vicinal bisperoxidation of arylidene-9*H*-fluorene/arylideneindolin-2-one derivatives under mild reactions condition. Advantageously, this C-H peroxidation reaction can be achieved on the gram scale without any difficulty. In contrast with the reduction of the -O-O- bond, for the first time, we reported (-C-O-) a bond reduction that led to the reversibility of the reaction. $Sn(OTf)_2$-catalyzed skeletal rearrangement of the quaternary peroxide provided the new type of ring-expansion route *via* intramolecular aryl migration on electron-deficient oxygen to form (*Z*)-6-benzylidene-6*H*-benzo[*c*]chromene derivatives. The mechanism has been studied in detail, and possible mechanisms for peroxidation, bisperoxidation, molecular rearrangement of peroxides, and deperoxidation reactions have been proposed.

2.14. Experimental section and characterization data

2.14.1. General information and data collection

The Manganese (III) acetate dihydrate 97% and *tert*-Butyl hydroperoxide (TBHP) 5.0-6.0 M in decane solution are purchased from Sigma-Aldrich. Starting materials **85, 71, 101a-e**, and **103a-e** were prepared by the reported method.[53-56] All the solvents used were dry grade. The column chromatographic separations were performed over 100-200 mesh size Silica-gel. Visualization was accomplished with UV light, PMA, and CAM stain, followed by heating. ^1H and $^{13}C\{^1H\}$ NMR spectra were recorded on 400 and 100 MHz, respectively, using Bruker or JEOL spectrometers. The values of the coupling constant (*J*) and chemical shift (δ) are expressed in hertz (Hz) and parts per million (ppm), respectively. Abbreviations used in the NMR follow-up experiments: b, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiple. High-Resolution Mass Spectra were recorded with waters-synapt G2 using electrospray ionization (ESI). Fourier-transform infrared (FT-IR) spectra were obtained with a

Bruker Alpha-E Fourier transform infrared spectrometer. Continuous-flow reactions were performed using Vapourtec R-series. “The reaction of a metal salt with organic peroxides may lead to an explosive reaction, and we have not faced any issue even at gram scale, be cautious while handling.”

2.14.2. Experimental procedure

A) General experimental procedure for C-H peroxidation of 9-substituted-9*H*-fluorene (85):

In a 20 mL re-sealable vial was added $Mn(OAc)_3.2H_2O$ (0.019 mmol, 5 mg, 5 mol%) and 2,2’-bipyridine (0.019 mmol, 3 mg, 5 mol%) in acetonitrile (2 mL). The solution was stirred at room temperature for 20-30 min to obtain deep-brown color, then 9-substituted-9*H*-fluorene **85** compound (0.39 mmol, 1 equiv.) was added. Finally, 5.0-6.0 M *tert*-butyl hydroperoxide (TBHP) **1c** in decane solution (1.56 mmol, 140 mg, 4 equiv.) was added without maintaining special conditions like an inert atmosphere, and the further tube was sealed with a rubber septum. The reaction mixture was kept at room temperature with stirring for 4 h. After completion of the reaction, a volatile component was evaporated using a vacuum. The residue was directly purified by silica gel column chromatography (EtOAc:*n*-hexane = 1:99).

Note: Although we have not encountered any difficulty or accident while handling the TBHP **1c**, for safety purposes after reaction completion, one can quench the unreacted peroxide with a suitable quencher.

B) General experimental procedure for C-H peroxidation of C3-substituted-2-oxindoles (71):

In a 20 mL re-sealable vial was added $Mn(OAc)_3.2H_2O$ (0.0125 mmol, 3 mg, 5 mol%) and 2,2’-bipyridine (0.0125 mmol, 2 mg, 5 mol%) in acetonitrile 2 mL. The solution was stirred at room temperature for 20-30 min to obtain deep-brown color, and then the C3-substituted-2-oxindoles compound **71** (0.25 mmol, 1 equiv.) was added. Finally, 5.0-6.0 M *tert*-butyl hydroperoxide (TBHP) in decane solution (1.0 mmol, 90 mg, 4 equiv.) **1c** was added without maintaining any special conditions like an inert atmosphere, and the further tube was sealed with a rubber septum. The reaction mixture was kept at room temperature with stirring for 4 h. After completion of the reaction, a volatile component was evaporated using a vacuum. The residue was directly purified by silica gel column chromatography (EtOAc:*n*-hexane = 20:80).

C) Experimental procedure for gram-scale C-H peroxidation of 9-benzyl-9*H*-fluorene (85a):

In a 50 mL round-bottom flask was added $Mn(OAc)_3.2H_2O$ (0.30 mmol, 81 mg, 5 mol%) and 2,2’-bipyridine (0.30 mmol, 47 mg, 5 mol%) in acetonitrile 20 mL. The solution was stirred at room temperature for 20-30 min to obtain deep-brown color, and then 9-benzyl-*9H*-fluorene compound **85a** (6 mmol, 1.536 g, 1 equiv.) was added. Finally, 5.0-6.0 M *tert*-butyl hydroperoxide (TBHP) **1c** in decane solution (24 mmol, 2.160 g, 4 equiv.) was added without maintaining any special conditions like an inert atmosphere, and the further tube was sealed with a rubber septum. The reaction mixture

was kept at room temperature for 4 h. After completion of the reaction, a volatile component was evaporated using a vacuum. The residue was directly purified by silica gel column chromatography (EtOAc:*n*-hexane = 1:99) afforded (1.300 g, 63%) of peroxide **85a** as a white semi-solid.

D) General experimental procedure for bis-peroxidation of 9-arylidene-9*H*-fluorene (101a-e) and arylideneindolin-2-one (103a-e):

In a 20 mL re-sealable vial was added $Mn(OAc)_3.2H_2O$ (0.0125 mmol, 3 mg, 5 mol%) and 2,2'-bipyridine (0.0125 mmol, 2 mg, 5 mol%) in acetonitrile 2 mL. The solution was stirred at room temperature for 20-30 min to obtain deep-brown color, and then added arylidene-9*H*-fluorene (**101a-e**) or arylideneindolin-2-one (**103a-e**) compounds (0.25 mmol, 1 equiv.). Finally, 5.0-6.0 M *tert*-butyl hydroperoxide (TBHP) **1c** in decane solution (1.0 mmol, 90 mg, 4 equiv.) was added without maintaining any special conditions like an inert atmosphere, and the further tube was sealed with a rubber septum. The reaction mixture was kept at room temperature with stirring for 4 h. After completion of the reaction, a volatile component was evaporated using a vacuum. The residue was directly purified by silica gel column chromatography for 9-arylidene-9*H*-fluorene **101** compound peroxidation (EtOAc:*n*-hexane = 1:99) and arylideneindolin-2-one **103** compound peroxidation (EtOAc:*n*-hexane = 10:90).

E) General experimental procedure for C-H peroxidation of 9-substituted-*9H*-fluorene (85a) under continuous flow:

The 0.1M of 9-benzyl-*9H*-fluorene **85a** (0.5 mmol, 128 mg, in 5 mL of DCM) was added $Mn(OAc)_3.2H_2O$ (0.0125 mmol, 3 mg, 5 mol%) and 2,2'-bipyridine (0.0125 mmol, 2 mg, 5 mol%) in 30 mL of the vial, parallelly the 0.4 M of TBHP **1c** (2 mmol, 180 mg in 5 mL of DCM) was taken another in 30 mL of vial. The both above-prepared solution were flown through the 5 mL SS coil reactor with a flow rate of 0.2 mL/min each at room temperature at 2.3 bar pressure. The reaction mixture was collected continuously after 12.5 min, the organic layer was concentrated under reduced pressure, and the residue was subjected to column chromatography purification using (EtOAc:*n*-hexane = 1:99) to afford corresponding peroxyfluorene **86a** in 72% yield**.**

F) Procedure for synthesis of deuterated benzyl alcohol:[58]

The deuterated benzyl alcohol was prepared by using the reported procedure by Gunanathan *et al*. In a typical procedure, benzyl alcohol (2 mmol), Ru-MACHO (0.004 mmol), and KO^{t}Bu (0.001 mmol) were charged in a 20 mL resealable vial which was equipped rubber septum and N_2 balloon. The D_2O (1.6 mL) was added using a syringe. The reaction mixture is purged with N_2, and the tube is sealed with a cap using a crimper. The reaction mixture was heated at 60 ^oC in an oil bath for 12 h. After completion of the reaction, the reaction mixture is extracted with dichloromethane. The combined organic layer is washed with a brine solution. Removing the solvent under reduced pressure provided

pure deuterated benzyl alcohol for further reaction. The ^{1}H-NMR data resembles the previous report, showing 87% deuterium incorporation (Figure 2.5.2.1.).

G) Procedure for the synthesis of deuterated 9-benzyl-9*H*-fluorene (85d-a):

In a 20 mL resealable tube, added [Ru(*p*-cymene)Cl_2] (3 mol%), KO^{t}Bu (1.5 equiv.), 9-benzyl-9*H*-fluorene **85a** (1 equiv.), and deuterated benzyl alcohol (1.5 equiv.), the vial was purged with N_2 and sealed with cap using a crimper. The reaction mixture was heated at 140 ^{o}C for 30 h. The reaction mixture was cooled, and the volatile component was evaporated using a vacuum and directly purified using column chromatography (EtOAc:*n*-hexane=1:99) to afford **85d-a** in 54.34% deuterium incorporation. This pure product is used for a further parallel reaction for kinetic study.

H) Procedure for the (parallel reaction) peroxidation of isotope-labeled 9-benzyl-9*H*-fluorene (85d-a) and without labeled 9-benzyl-9*H*-fluorene (85a):

In a 20 mL re-sealable vial was added $Mn(OAc)_3.2H_2O$ (0.0125 mmol, 3 mg, 5 mol%) and 2,2'-bipyridine (0.0125 mmol, 2 mg, 5 mol%) in acetonitrile 2 mL. The solution was stirred at room temperature for 20-30 min to obtain the deep-brown color. Later, compound (**85d-a**) or (**85a**) (0.19 mmol, 50 mg, 1 equiv.) was added, and finally, 5.0-6.0 M *tert*-butyl hydroperoxide (TBHP) in decane solution (0.78 mmol, 70 mg 4 equiv.) was added without maintaining any special conditions like inert atmosphere. The further tube was sealed with a rubber septum, and the reaction mixture was kept at room temperature for 4 hrs. Afterward, a volatile component was evaporated using a vacuum. The residue was directly purified by silica gel column chromatography (EtOAc:*n*-hexane = 1:99) to afford **86d-a** (41 mg, 64%) or **86a** (56 mg, 83%) as a white solid.

I) Radical quenching experiment: In a 20 mL re-sealable vial was added $Mn(OAc)_3.2H_2O$ (0.0125 mmol, 3 mg, 5 mol%) and 2,2'-bipyridine (0.0125 mmol, 2 mg, 5 mol%) in acetonitrile 2 mL was stirred at room temperature for 20−30 min. To the deep-brown solution was added 9-benzyl-9*H*-fluorene **85a** (64 mg, 0.25 mmol, 1 equiv.), 5.0-6.0 M *tert*-butyl hydroperoxide (TBHP) in decane solution (1.0 mmol, 90 mg, 4 equiv.) and finally 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) (5 equiv.) or 1,1-diphenylethylene (5 equiv.) or *α*-methylstyrene (5 equiv.) or molecular oxygen was added. The resulting solution was stirred at room temperature for 4 h. Volatile component was evaporated using a vacuum. The residue was directly purified by silica gel column chromatography (EtOAc:*n*-hexane = 1:99) to afford 80%, 68%, 65%, and 85% yield of product **86a,** respectively.

J) General experimental procedure for the rearrangement reaction of peroxides:[47a]

In a 20 mL re-sealable vial (equipped with a rubber septum and N_2 balloon) was added $Sn(OTf)_2$ (0.025 mmol, 10 mg, 10 mol%), and peroxy compound **86** (0.25 mmol, 1 equiv.) in the presence of ethyl acetate 2 mL. The tube was purged with N_2 and sealed with a cap using a crimper. The reaction mixture was heated at 80 ^{o}C in an oil bath for 12 h. After completion of the reaction, a volatile component was

evaporated under a vacuum. The residue was directly purified by silica gel chromatography (EtOAc:*n*-hexane = 1:99).

K) General experimental procedure for reductive deperoxidation of peroxyfluorenes:

A solution of peroxyfluorenes **86** (0.15 mmol, 1 equiv.) and Pd/C (10 wt%, 10 mol%, 16 mg) in MeOH (2 mL) was stirred under an atmosphere of hydrogen using a hydrogen balloon at room temperature for 8 h. After completion of the reaction, the mixture was filtered over celite and evaporated methanol using a vacuum. Finally, the resulting residue was purified using silica gel column chromatography (*n*-hexane) to afford the 9-substituted-*9H*-fluorene.

L) Experimental evidence for the formation of the hydroxy intermediate by isolation:

A solution of 9-benzyl-9-(*tert*-butylperoxy)-9*H*-fluorene **86a** (0.15 mmol, 1 equiv.) and Pd/C (10 wt%, 10 mol%, 16 mg) in MeOH (2 mL) was stirred under an atmosphere of hydrogen using hydrogen balloon at room temperature for 3 h. The mixture was filtered over celite, and evaporated methanol using a vacuum. Finally, the resulting residue was purified by using silica gel column chromatography (EtOAc:n-hexane = 5:95) to afford product 9-benzyl-9*H*-fluorene **85a** (21 mg, 55% isolated yield) as a white solid and intermediate 9-benzyl-9*H*-fluoren-9-ol **112** (15 mg, 39 % isolated yield) as a white solid.

M) Experimental procedure for the reduction of 9-benzyl-9*H*-fluoren-9-ol (112):

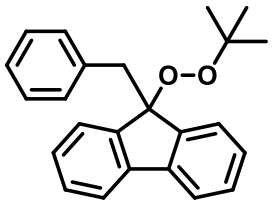
A solution of 9-benzyl-9*H*-fluoren-9-ol **(112)** (0.15 mmol, 1 equiv.) and Pd/C (10 wt%, 10 mol%, 16 mg) in MeOH (2 mL) was stirred under an atmosphere of hydrogen using hydrogen balloon at room temperature for 8 hrs. After completion of the reaction, the mixture was filtered over celite, and evaporated the methanol using a vacuum. Finally, the resulting residue was purified using silica gel column chromatography (*n*-hexane) to afford the 9-benzyl-9*H*-fluorene **85a** (37 mg, 96% isolated yield) as a white solid.

N) Experimental procedure for the reduction of 9-benzylidene-9*H*-fluorene:

A solution of 9-benzylidene-9*H*-fluorene **101a** (0.15 mmol, 1 equiv.) and Pd/C (10 wt%, 10 mol%, 16 mg) in MeOH (2 mL) was stirred under an atmosphere of hydrogen using hydrogen balloon at room temperature for 8 hrs. After completion of the reaction, the mixture was filtered over celite and evaporated methanol using a vacuum. Finally, the resulting residue was purified using silica gel column chromatography (*n*-hexane) to afford the 9-benzyl-9*H*-fluorene **85a** (37 mg, 97% isolated yield) as a white solid.

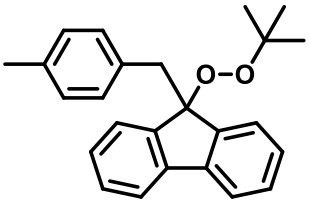
2.15A. Analytical data for the product:

*9-benzyl-9-(tert-butylperoxy)-9H-fluorene (**86a**):*



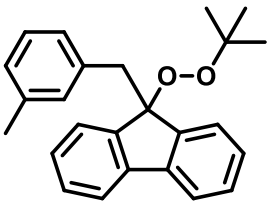
Prepared according to general procedure A, using 9-benzyl-9*H*-fluorene (100 mg, 0.39 mmol) to afford peroxyfluorene **86a** (114 mg, 0.33 mmol, 85 % yield) as a white semi-solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 1:99). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (m, 2H), 7.34-7.30 (m, 4H), 7.22-7.18 (m, 2H), 7.14-7.04 (m, 3H), 7.00-6.97 (m, 2H), 3.46 (s, 2H), 1.14 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 145.1, 140.4, 136.5, 131.1, 128.9, 127.5, 126.9, 126.3, 125.9, 119.7, 90.8, 79.7, 42.3, 26.7. FTIR (neat): 3438, 2929, 1194, 1017, cm^{-1}. HRMS (ESI-TOF) *m/z*: [M-OO^{t}Bu]$^{+}$ calcd for $C_{20}H_{15}$ 255.1168, Found: 255.1174.

*9-(tert-butylperoxy)-9-(4-methylbenzyl)-9H-fluorene (**86b**):*



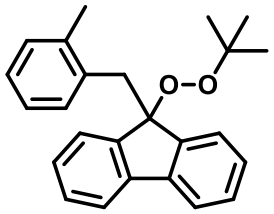
Prepared according to general procedure A, using 9-(4-methylbenzyl)-9*H*-fluorene (105 mg, 0.39 mmol) to afford peroxyfluorene **86b** (41 mg, 0.11 mmol 29 % yield) as a yellow semi-solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 1:99). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (m, 2H), 7.34-7.30 (m, 4H), 7.22 (td, *J* = 7.2, 1.1 Hz, 2H). 6.94-6.88 (m, 4H), 3.43 (s, 2H), 2.26 (s, 3H), 1.15 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 145.2, 140.4, 135.7, 133.3, 130.9, 128.8, 128.2, 126.9, 125.9, 119.7, 90.8, 79.6, 41.8, 26.7, 21.1. FTIR (neat): 2917, 1195, 830 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M-OO^{t}Bu]$^{+}$ calcd for $C_{21}H_{17}$ 269.1325, Found: 269.1334.

*9-(tert-butylperoxy)-9-(3-methylbenzyl)-9H-fluorene (**86c**):*



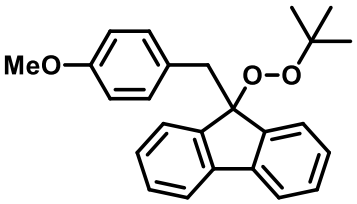
Prepared according to general procedure A, using 9-(3-methylbenzyl)-9*H*-fluorene (105 mg, 0.39 mmol) to afford peroxyfluorene **86c** (117 mg, 0.32 mmol, 84 % yield) as a yellow solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 1:99). Melting point: 72–74 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (m, 2H), 7.70 (m, 5H), 7.61-7.57 (m, 2H), 7.41-7.32 (m, 2H), 7.18 (d, *J* = 7.4 Hz, 1H), 3.80 (s, 2H) 2.60 (s, 3H), 1.54 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 145.3, 140.4, 136.8, 136.3, 132.1, 128.8, 128.1, 127.3, 127.0, 126.9, 125.9, 119.7, 90.8, 79.6, 42.2, 26.7, 21.4. FTIR (neat): 3462, 2913, 1199, 1060, 771 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M-OO^{t}Bu]$^{+}$ calcd for $C_{21}H_{17}$ 269.1325, Found: 269.1335

*9-(tert-butylperoxy)-9-(2-methylbenzyl)-9H-fluorene (**86d**):*



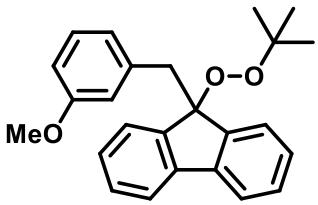
Prepared according to general procedure A, using 9-(2-methylbenzyl)-9*H*-fluorene (105 mg, 0.39 mmol) to afford peroxyfluorene **86d** (78 mg, 0.21 mmol, 56 % yield) as a yellow after purification by silica gel column chromatography (EtOAc:*n*-hexane = 1:99). Melting point: 69–71 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.5 Hz, 2H), 7.47-7.43 (m, 1H), 7.36 (td, *J* = 7.4, 1.2 Hz, 2H), 7.20-7.14 (m, 4H), 7.09-7.06 (m, 3H), 3.32 (s,2H), 1.79 (s, 3H), 1.12 (s, 9H).^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 145.9, 139.9, 137.9, 135.5, 132.2, 129.9, 128.8, 127.0, 126.7, 125.5, 125.3, 119.7, 90.5, 79.6, 38.8, 26.8, 19.9. FTIR (neat): 3446, 2972, 1188,1060 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M\text{-}OO^tBu]^+$ calcd for $C_{21}H_{17}$ 269.1325, found: 269.1335.

*9-(tert-butylperoxy)-9-(4-methoxybenzyl)-9H-fluorene (**86e**):*



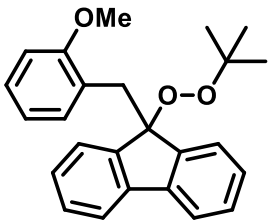
Prepared according to general procedure A, using 9-(4-methoxybenzyl)-9*H*-fluorene (112 mg, 0.39 mmol) to afford peroxyfluorene **86e** (131 mg, 0.35 mmol, 90 % yield) as a yellow semi-solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 1:99). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.51 (m, 2H), 7.31 (d, *J* = 7.2 Hz, 4H), 7.23-7.19 (m, 2H), 6.94-6.90 (m, 2H), 6.68-6.64 (m, 2H), 3.74 (s, 3H), 3.39 (s, 2H), 1.14 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.1, 145.2, 140.4, 132.0, 128.8, 128.6, 126.9, 125.9, 119.7, 112.9, 90.9, 79.6, 55.2, 41.4, 26.7. FTIR (neat): 2968, 1189, 1036 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M\text{-}OO^tBu]^+$ calcd for $C_{21}H_{17}$ 285.1274, Found: 285.1283.

*9-(tert-butylperoxy)-9-(3-methoxybenzyl)-9H-fluorene (**86f**):*



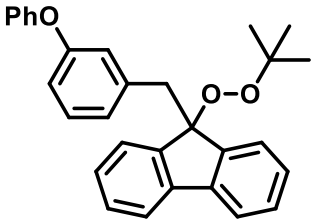
prepared according to general procedure A, using 9-(3-methoxybenzyl)-9*H*-fluorene (112 mg, 0.39 mmol) to afford peroxyfluorene **86f** (133 mg, 0.35 mmol, 91 % yield) as a yellow semi-solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 1:99). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.4 Hz, 2H), 7.40 (d, *J* = 7.4 Hz, 2H), 7.34 (td, *J* = 7.6, 1.2 Hz, 2H), 7.24 (td, *J* = 7.4,1.2 Hz, 2H), 7.08 (t, *J* = 7.8 Hz, 1H), 6.71-6.69 (m,1H), 6.61-6.58 (m, 2H), 3.64 (s, 3H), 3.50 (s, 2H), 1.19 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.8, 145.0, 140.4, 137.9, 128.9, 128.3, 126.9, 125.9, 123.6, 119.7, 115.8, 112.7, 90.8, 79.7, 55.1, 42.2, 26.7. FTIR (neat): 2927, 1190, 874 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{25}H_{26}O_3Na$ 397.1779, Found: 397.1777

*9-(tert-butylperoxy)-9-(2-methoxybenzyl)-9H-fluorene (**86g**):*



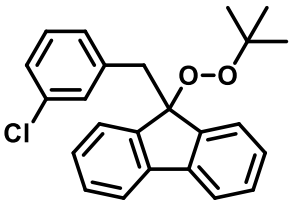
Prepared according to general procedure A, using 9-(2-methoxybenzyl)-9*H*-fluorene (112 mg, 0.39 mmol) to afford peroxyfluorene **86g** (129 mg, 0.34 mmol, 88 % yield) as a yellow semi-solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 1:99). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54-7.51 (m, 2H), 7.32-7.27 (m, 4H), 7.17 (td, *J* = 7.5, 1.1 Hz, 2H), 7.10 (dd, *J* = 11.9, 4.6 Hz, 2H), 6.73 (td, *J* = 7.5, 1.1 Hz, 1H), 6.65-6.63 (m, 1H), 3.54 (s, 2H), 3.42 (s, 3H), 1.13 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.9, 145.7, 140.3, 132.2, 128.6, 127.6, 126.6, 125.7, 125.0, 119.7, 119.4, 110.1, 90.9, 79.5, 54.7, 34.4, 26.7. FTIR (neat): 3340, 2916, 1174, 868 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M-OO^{t}Bu]$^{+}$ calcd for $C_{21}H_{17}$ 285.1274, Found: 285.1279.

*9-(tert-butylperoxy)-9-(3-phenoxybenzyl)-9H-fluorene (**86h**):*



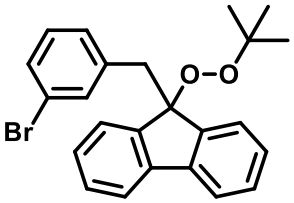
Prepared according to general procedure A, using 9-(3-phenoxybenzyl)-9*H*-fluorene (136 mg, 0.39 mmol) to afford peroxyfluorene **86h** (143 mg, 0.32 mmol, 84 % yield) as a yellow semi-solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 1:99). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.52 (m, 2H), 7.37-7.31 (m, 4H), 7.31-7.25 (m, 3H), 7.20 (td, *J* = 7.5, 1.1 Hz, 2H), 7.05 (m, 1H), 6.81-6.78 (m, 3H), 6.69-6.67 (m, 2H), 3.46 (s, 2H), 1.11 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.6, 156.2, 144.9, 140.4, 138.4, 129.7, 129.0, 128.7, 127.1, 126.2, 125.8, 122.8, 121.9, 119.8, 118.5, 117.6, 90.8, 79.8, 42.0, 26.7. FTIR (neat): 2977, 1249, 1186, 858 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M]$^{+}$ calcd for $C_{30}H_{28}O_3$ 436.2038, Found: 436.2029.

*9-(tert-butylperoxy)-9-(3-chlorobenzyl)-9H-fluorene (**86i**):*



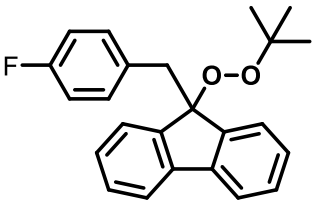
Prepared according to general procedure A, using 9-(3-chlorobenzyl)-9*H*-fluorene (113 mg, 0.39 mmol) to afford peroxyfluorene **86i** (102 mg, 0.26 mmol, 69% yield) as a yellow semi-solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 1:99). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 6.7, 0.8 Hz, 2H), 7.34 (td, *J* = 7.4, 1.3 Hz, 2H), 7.29-7.27 (m, 2H), 7.21 (td, *J* = 7.4, 1.1 Hz, 2H), 7.14-7.11 (m, 2H), 7.05-7.01 (m, 1H), 6.85-6.83 (m, 1H), 3.41 (s, 2H), 1.15 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 144.8, 140.4, 138.6, 133.3, 131.2, 129.2, 129.1, 128.6, 127.1, 126.5, 125.9, 119.8, 90.5, 80.0, 41.7, 26.7. FTIR (neat): 883, 1060, 1201, 2986, 3443 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M-OO^{t}Bu]$^{+}$ calcd for $C_{20}H_{14}Cl$ 289.0779, Found: 289.0783.

*9-(3-bromobenzyl)-9-(tert-butylperoxy)-9H-fluorene (**86j**):*



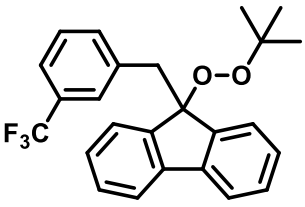
Prepared according to general procedure A, using 9-(3-bromobenzyl)-9*H*-fluorene (131 mg, 0.39 mmol) to afford peroxyfluorene **86j** (108 mg, 0.25 mmol, 65% yield) as a white solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 1:99). Melting point: 85–87 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.5 Hz, 2H), 7.34 (td, *J* = 7.4, 1.2 Hz, 2H), 7.28 (m, 4H), 7.22 (t, *J* = 7.4 Hz, 2H), 6.98 (t, *J* = 7.7 Hz, 1H), 6.89 (d, *J* = 7.6 Hz, 1H), 3.41 (s, 2H), 1.17 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 144.7, 140.3, 138.9, 134.2, 129.7, 129.4, 129.1, 129.0, 127.1, 125.9, 121.6, 119.8, 90.4, 80.0, 41.7, 26.7. FTIR (neat): 1056, 1209, 2983 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M-OO^{t}Bu]$^{+}$ calcd for $C_{20}H_{14}Br$ 333.0273, Found: 333.0273.

*9-(tert-butylperoxy)-9-(4-fluorobenzyl)-9H-fluorene (**86k**):*



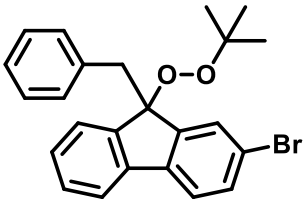
Prepared according to general procedure A, using 9-(4-fluorobenzyl)-9*H*-fluorene (107 mg, 0.39 mmol) to afford peroxyfluorene **86k** (112 mg, 0.30 mmol, 79 % yield) as a yellow solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 1:99). Melting point: 64-66 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.4 Hz, 2H), 7.35-7.30 (m, 4H), 7.23-7.19 (m, 2H), 6.93 (dd, *J* = 8.5, 5.7 Hz, 2H), 6.78 (t, *J* = 8.8 Hz, 2H), 3.43 (s, 2H), 1.14 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.7 (d, *J* = 242 Hz), 144.9, 140.4, 132.4 (d, *J* = 7.8 Hz), 132.1 (d, *J* = 3.2 Hz), 129.0, 127.0, 125.8, 119.8, 114.2 (d, *J* = 21.0 Hz), 90.7, 79.8, 41.4, 26.7. FTIR (neat): 2893, 1222, 877 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M-OO^{t}Bu]$^{+}$ calcd for $C_{20}H_{14}F$ 273.1074, Found: 273.1083.

*9-(tert-butylperoxy)-9-(3-(trifluoromethyl)benzyl)-9H-fluorene (**86l**):*



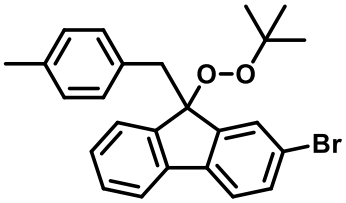
Prepared according to general procedure A, using 9-(3-(trifluoromethyl)benzyl)-9*H*-fluorene (126 mg, 0.39 mmol) to afford peroxyfluorene **86l** (139 mg,0.33 mmol, 86 % yield) as a yellow semi-solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 1:99). Melting point: 73–75 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.5 Hz, 2H), 7.36 (m, 2H), 7.30 (td, *J* = 7.4, 1.3 Hz, 2H), 7.23 (m, 2H), 7.17 (m, 3H), 7.07 (d, *J* = 7.7 Hz, 1H), 3.45 (s, 2H), 1.13 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 114.6, 140.3, 137.4, 134.4, 129.8 (q, *J* = 32.6 Hz), 129.2, 128.0 (q, *J* = 3.6), 127.8, 127.1, 125.8, 124.4 (q, *J* = 271.6 Hz), 123.2 (q, *J* = 3.2 Hz), 119.9, 90.4, 80.0, 42.0, 26.7. FTIR (neat): 3412, 2947, 1174, 885 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M-OO^{t}Bu]$^{+}$ calcd for $C_{21}H_{14}F_3$ 323.1042, Found: 323.1042.

*9-benzyl-2-bromo-9-(tert-butylperoxy)-9H-fluorene (**86m**):*



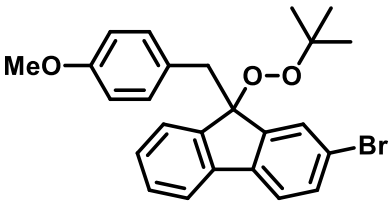
Prepared according to general procedure A, using 9-benzyl-2-bromo-9*H*-fluorene (130 mg, 0.39 mmol) to afford peroxyfluorene **86m** (125 mg, 0.29 mmol, 76% yield) as a yellow solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 1:99). Melting point: 65–67 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.5 Hz, 1H), 7.45-7.43 (m, 2H), 7.39-7.36 (m, 1H), 7.34-7.30 (m, 1H), 7.25-7.20 (m, 2H), 7.16-7.09 (m, 3H), 6.97 (m, 2H), δ 3.43 (d, *J* = 13.4 Hz, 1H), 3.36 (d, *J* = 13.6 Hz, 1H), 1.13 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 147.4, 144.8, 139.4, 139.3, 135.9, 131.9, 131.1, 129.2, 129.1, 127.6, 127.4, 126.6, 125.8, 121.0, 120.7, 119.8, 90.6, 80.0, 42.3, 26.8. FTIR (neat): 3425, 2979, 1263, 1188,1070 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M-OO^{t}Bu]$^{+}$ calcd for $C_{20}H_{14}Br$ 333.0273, Found: 333.0271.

2-bromo-9-(tert-butylperoxy)-9-(4-methylbenzyl)-9H-fluorene (***86n**):*



Prepared according to general procedure A, using 2-bromo-9-(4-methylbenzyl)-9*H*-fluorene (136 mg, 0.39 mmol) to afford peroxyfluorene **86n** (130 mg, 0.29 mmol, 76% yield) as a yellow solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 1:99). Melting point: 73–75 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51-7.49 (m, 1H), 7.47 (m, 1H), 7.45-7.43 (m, 1H), 7.39-7.37 (m, 1H), 7.34-6.30 (m, 2H), 7.24-7.22 (m, 2H), 6.94-6.84 (m, 4H), 3.41 (d, *J* = 13.6 Hz, 1H), 3.32 (d, *J* = 13.6 Hz, 1H), 2.26 (s, 3H), 1.13 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 147.5, 144.8, 139.4, 139.3, 136.0, 132.7, 131.8, 130.9, 129.1, 129.1, 128.3, 127.3, 125.8, 121.1, 120.7, 119.8, 90.6, 79.9, 41.9, 26.7, 21.2. FTIR (neat): 3425, 2979, 1263, 1188, 1070 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M-OO^{t}Bu]$^{+}$ calcd for $C_{21}H_{16}Br$ 347.0430, Found: 347.0441.

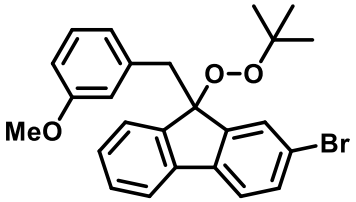
*2-bromo-9-(tert-butylperoxy)-9-(4-methoxybenzyl)-9H-fluorene (**86o**):*



Prepared according to general procedure A, using 2-bromo-9-(4-methoxybenzyl)-9*H*-fluorene (142 mg, 0.39 mmol) to afford peroxyfluorene **86o** (152 mg, 0.33 mmol, 86% yield) as a yellow solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 1:99). Melting point: 69–71 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.47 (m, 2H), 7.44 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.34-7.30 (m, 1H), 7.25-7.22 (m, 2H), 6.91-6.88 (m, 2H), 6.71-6.65 (m, 2H), 3.74 (s, 3H), 3.39 (d, *J* = 13.8 Hz, 1H), 3.30 (d, *J* = 13.8 Hz, 1H), 1.15 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.3, 147.5, 144.8, 139.4, 139.3, 132.0, 131.8, 129.1, 127.9, 127.3, 125.8, 121.1, 120.7, 119.8, 113.0, 90.7, 79.9, 55.2,

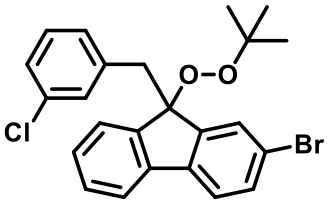
41.4, 26.7. FTIR (neat): 3471, 2968, 1245, 1184, 1045 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{25}H_{25}BrO_3Na$ 475.0884, Found: 475.0867

*2-bromo-9-(tert-butylperoxy)-9-(3-methoxybenzyl)-9H-fluorene (**86p**):*



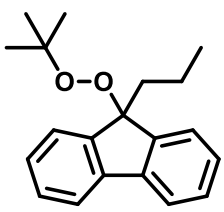
Prepared according to general procedure A, using 2-bromo-9-(3-methoxybenzyl)-9*H*-fluorene (142 mg, 0.39 mmol) to afford peroxyfluorene **86p** (137 mg, 0.30 mmol, 77% yield) as a yellow solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 1:99). Melting point: 74–75 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.52-7.48 (m, 2H), 7.44 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.39- 7.27 (m, 3H), 7.25-7.21 (m, 1H), 7.04-6.96 (m, 1H), 6.68 (ddd, *J* = 8.2, 2.6, 0.9 Hz, 1H), 6.56-6.50 (m, 2H), 3.65 (s, 3H), 3.43 (d, *J* = 14.0 Hz, 1H), 3.36 (d, *J* = 13.5 Hz, 1H), 1.15 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 158.9, 147.3, 144.5, 139.4, 139.3, 137.3, 131.9, 129.2, 128.5, 127.4, 125.8, 123.6, 121.1, 120.7, 119.9, 115.8, 113.0, 90.6, 80.0, 55.2, 42.3, 26.7. FTIR (neat): 3471, 2968, 1184, 1045 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{25}H_{25}BrO_3Na$ 475.0884, Found: 475.0872.

*2-bromo-9-(tert-butylperoxy)-9-(3-chlorobenzyl)-9H-fluorene (**86q**):*



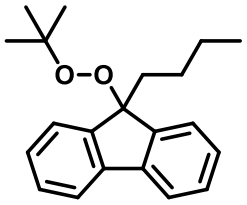
Prepared according to general procedure A, using 2-bromo-9-(3-chlorobenzyl)-9*H*-fluorene (144 mg, 0.39 mmol) to afford peroxyfluorene **86q** (130 mg, 0.28 mmol, 73% yield) as a yellow solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 1:99). Melting point: 85–87 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 7.52 Hz, 1H), 7.47-7.39 (m, 3H), 7.34 (td, *J* = 7.3, 1.3, 1H), 7.25-7.11 (m, 4H), 7.07 (t, *J* = 7.8 Hz, 1H), 6.84 (d, *J* = 7.5 Hz, 1H), 3.43 (d, *J* = 13.7 Hz, 1H), 3.30 (d, *J* = 13.7 Hz, 1H), 1.17 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 147.1, 144.3, 139.3, 139.2, 138.0, 133.4, 132.1, 131.2, 129.4, 129.2, 129.1, 128.8, 127.5, 126.8, 125.8, 121.2, 120.8, 120.0, 90.2, 80.2, 41.8, 26.7. FTIR (neat): 2961, 1197, 1067 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{24}H_{22}BrClO_2Na$ 479.0389, Found: 479.0375.

*9-(tert-butylperoxy)-9-propyl-9H-fluorene (**86r**):*



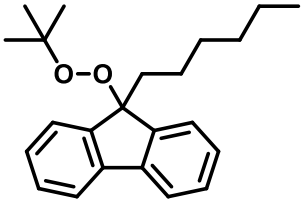
Prepared according to general procedure A, using 9-propyl-9*H*-fluorene (81 mg, 0.39 mmol) to afford peroxyfluorene **86r** (75 mg, 0.25 mmol, 65% yield) as a white semi-solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 1:99). ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (m, 2H), 7.54 (m, 2H), 7.37 (td, *J* = 7.5, 1.2 Hz, 2H), 7.29 (td, *J* = 7.4, 1.1 Hz, 2H), 2.31–2.27 (m, 2H), 1.12 (s, 9H), 0.92–0.86 (m, 2H), 0.78 (t, *J* = 7.2 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 145.8, 140.8, 128.8, 127.3, 125.0, 119.8, 91.2, 79.3, 38.1, 26.7, 17.3, 14.5. FTIR (neat): 3427, 1198, 884 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M\text{-}OO^tBu]^+$ calcd for $C_{16}H_{15}$ 207.1168, Found: 207.1170.

*9-butyl-9-(tert-butylperoxy)-9H-fluorene (**86s**):*



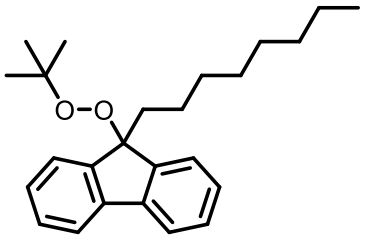
Prepared according to general procedure A, using 9-butyl-9*H*-fluorene (87 mg, 0.39 mmol) to afford peroxyfluorene **86s** (78 mg, 0.25 mmol, 64% yield) as a yellow semi-solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 1:99). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64-7.62 (m, 2H), 7.56-7.54 (m, 2H), 7.37 (td, *J* = 7.5, 1.2 Hz, 2H), 7.29 (td, *J* = 7.4, 1.1 Hz, 2H), 2.33- 2.29 (m, 2H), 1.23-1.16 (m, 2H), 1.11 (s, 9H), 0.87-0.79 (m, 2H), 0.76 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 145.7, 140.8, 128.8, 127.3, 125.0, 119.8, 91.2, 79.3, 35.5, 26.7, 25.9, 23.1, 14.0. FTIR (neat): 3487, 2858, 1197, 758 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M-OO^{t}Bu]$^{+}$ calcd for $C_{17}H_{17}$ 221.1325, Found: 221.1326.

*9-(tert-butylperoxy)-9-hexyl-9H-fluorene (**86t**):*



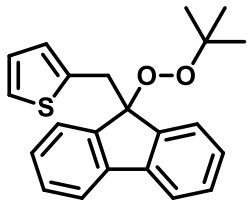
Prepared according to general procedure A, using 9-hexyl-9*H*-fluorene (98 mg, 0.39 mmol) to afford peroxyfluorene **86t** (62 mg, 0.18 mmol, 47% yield) as a white semi-solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 1:99). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.4 Hz, 2H), 7.56 (d, *J* = 7.3 Hz, 2H), 7.39 (td, *J* = 7.5, 1.2 Hz, 2H), 7.30 (td, *J* = 7.4, 1.2 Hz, 2H), 2.33-2.28 (m, 2H), 1.22-1.12 (m, 6H), 1.12 (s, 9H), 0.89 – 0.80 (m, 5H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 145.7, 140.8, 128.8, 127.3, 125.0, 119.8, 91.3, 79.3, 35.7, 31.6, 29.7, 26.7, 23.7, 22.7, 14.1. FTIR (neat): 757, 1196, 2958, 3464 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M-OO^{t}Bu]$^{+}$ calcd for $C_{19}H_{21}$ 249.1638, Found: 249.1639.

*9-(tert-butylperoxy)-9-octyl-9H-fluorene (**86u**):*



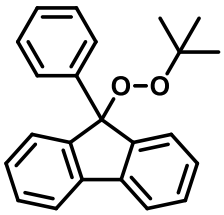
Prepared according to general procedure A, using 9-octyl-9*H*-fluorene (109 mg, 0.39 mmol) to afford peroxyfluorene **86u** (94 mg, 0.25 mmol, 66% yield) as a faint yellow semi-solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 1:99). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.5 Hz, 2H), 7.55 (dd, *J* = 7.4, 0.4 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 2H), 7.29 (t, *J* = 7.4 Hz, 2H), 2.32-2.28 (m, 2H), 1.39-1.15 (m, 10H), 1.15 (s, 9H), 0.87-0.81 (m, 5H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 145.7, 140.8, 128.8, 127.3, 125.0, 119.8, 91.3, 79.3, 35.7, 31.9, 30.0, 29.4, 29.3, 26.7, 23.7, 22.7, 14.2. FTIR (neat): 3473, 2924, 1196, 758 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M-OO^{t}Bu]$^{+}$ calcd for $C_{21}H_{25}$ 277.1951, Found: 277.1949.

*2-((9-(tert-butylperoxy)-9H-fluoren-9-yl)methyl)thiophene (**86v**):*



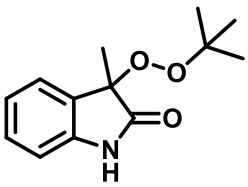
Prepared according to general procedure A, using 2-((9*H*-fluoren-9-yl)methyl)thiophene (102 mg, 0.39 mmol) to afford peroxyfluorene **86v** (108 mg, 0.30 mmol, 79% yield) as a greenish semi-solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 1:99). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 7.5 Hz, 2H), 7.39 (d, *J* = 7.5 Hz, 2H), 7.35 (td, *J* = 7.5, 1.2 Hz, 2H), 7.23 (td, *J* = 7.5, 1.1 Hz, 2H), 7.03 (dd, *J* = 5.1, 1.2 Hz, 1H), 6.76 (m, 1H), 6.55 (dd, *J* = 3.4, 0.9 Hz, 1H), 3.73 (s, 2H), 1.16 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 144.6, 140.7, 138.3, 129.2, 127.5, 127.2, 126.0, 125.7, 124.5, 119.8, 90.2, 79.9, 36.5, 26.7. FTIR (neat): 2962, 1655, 1200, 855 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M-OO^{t}Bu]$^{+}$ calcd for $C_{18}H_{13}S$ 261.0733, Found: 261.0740.

*9-(tert-butylperoxy)-9-phenyl-9H-fluorene (**86w**):*



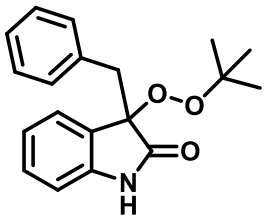
Prepared according to general procedure A, using 9-phenyl-9*H*-fluorene (95 mg, 0.39 mmol) to afford peroxyfluorene **86w** (114 mg, 0.34 mmol, 88% yield) as a white solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 1:99). Melting point: 91–93 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.5 Hz, 2H), 7.42-7.36 (m, 6H), 7.31-7.21 (m, 5H), 1.08 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 146.8, 141.6, 140.9, 129.1, 128.2, 127.6, 127.5, 126.8, 126.4, 119.9, 92.3, 79.9, 26.6. FTIR (neat): 3428, 2929, 1210, 883 cm^{-1}. HRMS (ESI-TOF) *m/z*: [M-OO^{t}Bu]$^{+}$ calcd for $C_{19}H_{13}$ 241.1012, Found: 241.1013.

*3-(tert-butylperoxy)-3-methylindolin-2-one (**72a**):*[51b]



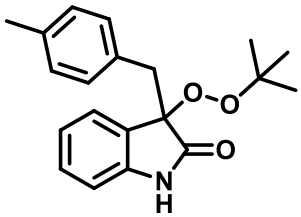
Prepared according to general procedure B, using 3-methylindolin-2-one (37 mg, 0.25 mmol) to afford peroxyoxindole **72a** (54 mg, 0.22 mmol, 91% isolated yield) as a white solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 20:80). The data for this compound is in agreement with reported compound.

*3-benzyl-3-(tert-butylperoxy)indolin-2-one (**72b**):* [51b]



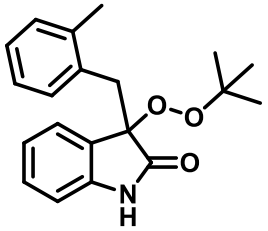
Prepared according to general procedure B, using 3-benzylindolin-2-one (56 mg, 0.25 mmol) to afford peroxyoxindole **72b** (69 mg, 0.22 mmol, 89% isolated yield) as a white solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 20:80). The data for this compound is in agreement with reported compound.

*3-(tert-butylperoxy)-3-(4-methylbenzyl)indolin-2-one (**72c**):*[51b]



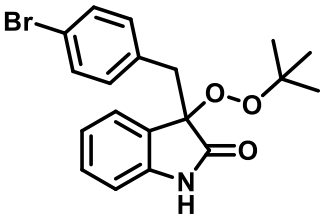
Prepared according to general procedure B, using 3-(4-methylbenzyl)indolin-2-one (59 mg, 0.25 mmol) to afford peroxyoxindole **62c** (69 mg, 0.21 mmol, 85% yield) as a yellow solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 20:80). The data for this compound is in agreement with reported compound.

*3-(tert-butylperoxy)-3-(2-methylbenzyl)indolin-2-one (**72d**):*[51b]



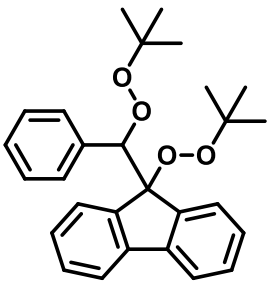
Prepared according to general procedure B, using 3-(2-methylbenzyl)indolin-2-one (59 mg, 0.25 mmol) to afford peroxyoxindole **72d** (72 mg, 0.22 mmol, 89% yield) as a yellow solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 20:80). The data for this compound is in agreement with reported compound.

*3-(4-bromobenzyl)-3-(tert-butylperoxy)indolin-2-one (**72e**):*[51b]



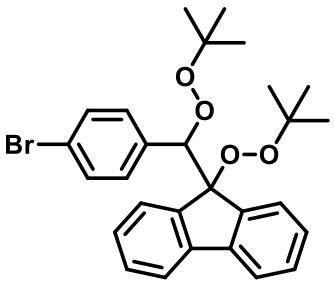
Prepared according to general procedure B, using 3-(4-bromobenzyl)indolin-2-one (75 mg, 0.25 mmol) to afford peroxyoxindole **62e** (78 mg, 0.20 mmol, 86% yield) as a light yellow solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 20:80). The data for this compound is in agreement with reported compound.

*9-(tert-butylperoxy)-9-((tert-butylperoxy)(phenyl)methyl)-9H-fluorene (**102a**):*



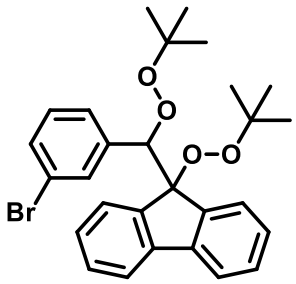
Prepared according to general procedure D, using 9-benzylidene-9*H*-fluorene (63.58 mg, 0.25 mmol) to afford bisperoxyfluorene & 9*H*-fluoren-9-one **102a** (80 mg, 74% yield) as a yellow solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 1:99). A minor quantity of **86a'** has been observed as inseparable mixture with **102a**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.3 Hz, 1H), 7.67 (d, *J* = 7.4 Hz, 1H), 7.52 (d, *J* = 7.3 Hz, 2H), 7.49 (td, *J* = 7.3, 1.1 Hz, 2H), 7.43 (t, *J* = 6.76 Hz, 2H), 7.36-7.25 (m, 6H), 7.22 (td, *J* = 7.4, 1.2 Hz, 1H), 7.15 (t, *J* = 7.4 Hz, 1H), 7.03-6.99 (m, 1H), 6.94 (t, *J* = 7.5 Hz, 2H), 6.87 (d, *J* = 7.9 Hz, 2H), 5.81 (s, 1H), 1.23 (s, 9H), 1.14 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 194.1, 144.6, 143.3, 142.3, 141.4, 140.9, 137.0, 134.8, 134.3, 129.2, 129.2, 129.0, 128.6, 127.6, 127.2, 126.9, 126.7, 126.7, 126.5, 124.5, 120.5, 119.5, 119.3, 92.8, 86.7, 80.7, 79.9, 26.7, 26.7. FTIR (neat): 1192, 1017, 732 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{28}H_{32}O_4Na$ 455.2198, Found: 455.2198.

*9-((4-bromophenyl)(tert-butylperoxy)methyl)-9-(tert-butylperoxy)-9H-fluorene (**102b**):*



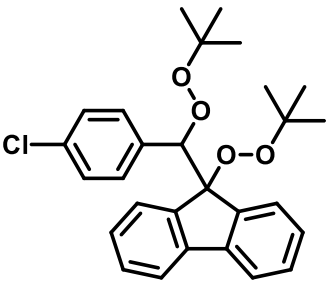
Prepared according to general procedure D, using 9-(4-bromobenzylidene)-9*H*-fluorene (83 mg, 0.25 mmol) to afford bisperoxyfluorene **102b** (112 mg, 0.21 mmol, 88% yield) as a yellow solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 1:99). Melting point: 116–118 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 7.4, 0.5 Hz, 1H), 7.34-7.28 (m, 2H), 7.23 (td, *J* = 7.5, 1.1 Hz, 1H), 7.19-7.11 (m, 3H),7.04 (t, *J* = 7.4 Hz, 1H), 6.96 (d, *J* = 8.2 Hz, 2H), 6.64 (d, *J* = 8.0 Hz, 2H), 5.68 (s, 1H), 1.10 (s, 9H), 1.02 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 142.8, 141.9, 141.4, 140.9, 136.3, 130.2, 129.9, 129.4, 129.2, 127.5, 127.0, 126.7, 126.6, 121.3, 119.7, 119.5, 92.4, 85.9, 80.8, 80.1, 26.7, 26.7. FTIR (neat): 1195, 1363, 1010, 737 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{28}H_{31}BrO_4Na$ 533.1303, Found: 533.1299.

*9-((3-bromophenyl)(tert-butylperoxy)methyl)-9-(tert-butylperoxy)-9H-fluorene (**102c**):*



Prepared according to general procedure D, using 9-(3-bromobenzylidene)-9*H*-fluorene (83 mg, 0.25 mmol) to afford bisperoxyfluorene **102c** (101 mg, 0.19 mmol, 80% yield) as a yellow semi-solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 1:99). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (m, 1H), 7.48-7.46 (m, 1H), 7.42-7.38 (m, 1H), 7.36 (td, *J* = 7.5, 1.2 Hz, 2H), 7.30 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.28-7.24 (m, 1H), 7.20-7.16 (m, 2H), 7.12 (m, 1H), 6.88-6.83 (m,2H), 5.81 (s, 1H), 1.22 (s, 9H), 1.18 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 142.6, 142.1, 141.3, 140.9, 139.6, 131.8, 130.2, 129.4, 129.3, 128.3, 127.4, 127.1, 127.0, 126.7, 120.9, 119.6, 119.5, 92.4, 85.8, 80.9, 80.2, 26.7, 26.6. FTIR (neat): 876, 1193, 2974 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{28}H_{31}BrO_4Na$ 533.1303, Found: 533.1295.

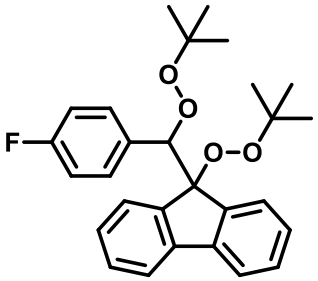
*9-(tert-butylperoxy)-9-((tert-butylperoxy)(4-chlorophenyl)methyl)-9H-fluorene (**102d**):*



Prepared according to general procedure D, using 9-(4-chlorobenzylidene)-9*H*-fluorene (77 mg, 0.26 mmol) to afford bisperoxyfluorene **102d** (92 mg, 0.19 mmol, 75% yield) as a yellow solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 1:99). Melting point: 105–107 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.4 Hz, 1H), 7.45 (m, 2H), 7.39 (m, 1H), 7.35 (m, 1H), 7.32 – 7.28 (m, 1H), 7.27-7.23 (m,1H), 7.17 (td, *J* = 7.5, 1.1 Hz, 1H), 6.98-6.92 (m, 2H), 6.83-6.80 (m, 2H), 5.82 (s, 1H), 1.24 (s, 9H), 1.16 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 142.9, 141.9, 141.4, 140.9, 135.7, 134.8, 132.9, 129.8, 129.4, 129.2, 127.5, 127.0, 126.7, 126.6, 119.7, 119.5, 92.5, 85.9, 80.8,

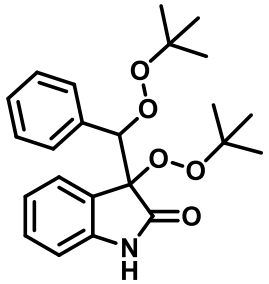
80.1, 26.7, 26.6. FTIR (neat): 3406, 1194, 1015, 873 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{28}H_{31}ClO_4Na$ 489.1809, Found: 489.1812.

*9-(tert-butylperoxy)-9-((tert-butylperoxy)(4-fluorophenyl)methyl)-9H-fluorene (**102e**):*



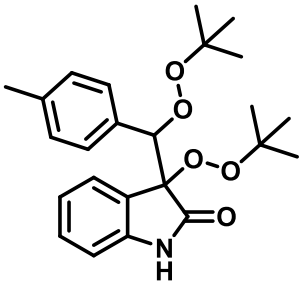
Prepared according to general procedure D, using 9-(4-fluorobenzylidene)-9*H*-fluorene (100 mg, 0.36 mmol) to afford bisperoxyfluorene **102e** (148 mg, 0.32 mmol, 90% yield) as a yellow solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 1:99). Melting point: 104–106 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.76-7.73 (m, 1H), 7.48-7.43 (m, 2H), 7.35 (dd, *J* = 15.2, 7.5 Hz, 2H), 7.29 (m, 1H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.16 (t, *J* = 7.4 Hz, 1H), 6.86-6.82 (m, 2H), 6.64 (td, *J* = 8.7, 1.3 Hz, 2H), 5.83 (d, *J* = 1.8 Hz, 1H), 1.25 (d, *J* = 1.5 Hz, 9H), 1.16 (d, *J* = 1.4 Hz, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.1 (d, *J* = 243.24 Hz), 143.1, 142.0, 141.0, 140.0, 134.8, 132.8 (d, *J* = 3.0 Hz), 130.0 (d, *J* = 8.1 Hz), 129.3, 129.1, 127.5, 127.0, 126.6, 126.5, 119.5 (d, *J* = 17.6 Hz), 113.6 (d, *J* = 21.09 Hz), 92.7, 86.0, 80.8, 80.0, 26.7, 26.7. FTIR (neat): 2973, 1195, 733 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{28}H_{31}FO_4Na$ 473.2103, found: 473.2112.

*3-(tert-butylperoxy)-3-((tert-butylperoxy)(phenyl)methyl)indolin-2-one (**104a** & **104a'**):*



Prepared according to general procedure D, using (*E/Z*)-3-benzylideneindolin-2-one (55.31 mg, 0.25 mmol) to afford bisperoxyoxindole diastereomers **104a** & **104a'** has a ratio (1:3) with overall yield was 71% (71 mg, 0.17 mmol) as a yellow solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 10:90). Selected signal for the major isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.69-7.66 (m, 1H), 7.36 (s, 1H), 7.23-7.19 (m, 1H), 7.09-7.05 (m, 4H), 6.98-6.96 (m, 2H), 6.53 (d, *J* = 7.7 Hz, 1H), 5.46 (s, 1H), 1.33 (s, 9H), 1.17 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.5, 141.5, 134.6, 129.9, 128.3, 128.1, 127.6, 127.4, 124.9, 122.3, 109.3, 88.5, 86.5, 81.5, 80.9, 26.7, 26.5. FTIR (neat): 3628, 2972, 1732, 1471, 1194, 1055 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{23}H_{30}NO_5$ 400.2124, Found: 400.2130.

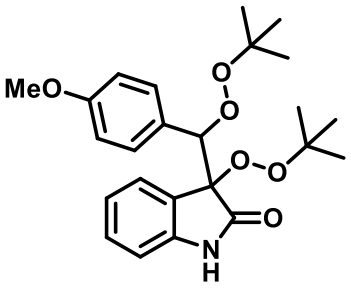
*3-(tert-butylperoxy)-3-((tert-butylperoxy)(p-tolyl)methyl)indolin-2-one (**104b** & **104b'**):*



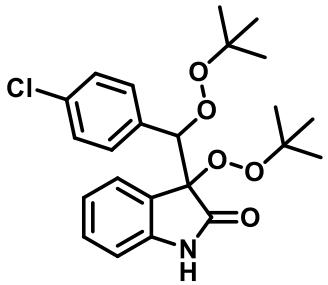
Prepared according to general procedure D, using (*E/Z*)-3-(4-methylbenzylidene)indolin-2-one (58.77 mg, 0.25 mmol) to afford bisperoxyoxindole diastereomers **104b** & **104b'** has a ratio (1:3) with overall yield was 56% (58 mg, 0.14 mmol) as a yellow solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 10:90). Selected signal for the major isomer: ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 6.9, 0.5 Hz, 1H), 7.56 (m, 1H), 7.22-7.18 (m, 2H), 7.07 (td, *J* = 7.6, 1.0 Hz, 1H), 6.85 (s, 3H), 6.55 (d, *J* =

7.6 Hz, 1H), 5.43 (s, 1H), 2.19 (s, 3H), 1.32 (s, 9H), 1.16 (s, 9H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 173.9, 141.7, 138.0, 132.8, 131.5, 129.8, 128.4, 128.2, 125.0, 122.2, 109.5, 88.6, 86.4, 81.4, 80.8, 26.6, 26.5, 21.3. FTIR (neat): 1733, 1472, 1121, 1020 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{24}H_{31}NO_5Na$ 436.2102, Found: 436.2103.

*3-(tert-butylperoxy)-3-((tert-butylperoxy)(4-methoxyphenyl)methyl)indolin-2-one (***104c** & **104c'***):* Prepared according to general procedure D, using (*E/Z*)-3-(4-methoxybenzylidene)indolin-2-one (62.77 mg, 0.25 mmol) to afford bisperoxyoxindole diastereomers has a ratio (1:3) **104c** & **104c'** with overall yield of 80% (85 mg, 0.19 mmol) as an orange solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 10:90). Selected signal for the major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (m, 1H), 7.68 (d, *J* = 7.2 Hz, 1H), 7.31-7.20 (m, 2H), 6.92-6.85 (m, 3H), 6.58 (d, *J* = 7.9 Hz, 2H), 5.43 (s, 1H), 3.65 (s, 3H), 1.34 (s, 9H), 1.17 (s, 9H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 174.2, 159.5, 141.8, 129.8, 129.5, 128.0, 126.6, 125.0, 122.1, 113.1, 109.6, 88.6, 86.1, 81.4, 80.8, 55.0, 26.6, 26.5. FTIR (neat): 1733, 1472, 1196, 1052, 874 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{24}H_{31}NO_6Na$ 452.2048, Found: 452.2052.

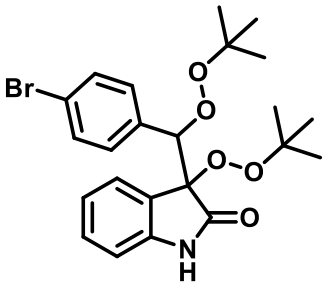


*3-(tert-butylperoxy)-3-((tert-butylperoxy)(4-chlorophenyl)methyl)indolin-2-one (***104d** & **104d'***):*
Prepared according to general procedure D, using (*E/Z*)-3-(4-chlorobenzylidene)indolin-2-one (63.92 mg, 0.25 mmol) to afford bisperoxyoxindole as a diastereomers **104d** & **104d'** in the ratio (1:3) with overall yield 75% (81 mg, 0.18 mmol) as a yellow solid. These diastereomers were separated by column purification afforded syn bisperoxyoxindole **104d'** (30 mg, 0.069 mmol, 28% yield), Melting point: 146–147 °C and anti bisperoxyoxindole **104d** (51 mg, 0.11 mmol, 47% yield) as a yellow solid (melting point: 132–134 °C) after purification by silica gel column chromatography (EtOAc:*n*-hexane = 10:90). Data for compound **104d**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (dt, *J* = 6.4, 3.2 Hz, 1H), 7.53 (s, 1H), 7.21 (td, *J* = 7.7, 1.3 Hz, 1H), 7.07 (td, 1H), 7.05-7.02 (m, 2H), 6.93-6.90 (m, 2H), 6.57 (d, *J* = 7.7 Hz, 1H), 5.43 (s, 1H), 1.31 (s, 9H), 1.15 (s, 9H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 173.6, 141.5, 134.2, 133.2, 130.1, 129.7, 127.9, 127.9, 124.5, 122.4, 109.7, 88.2, 85.7, 81.7, 81.0, 26.6, 26.5. FTIR (neat): 1733, 1472, 1196, 1020 cm^{-1}. HRMS (ESI) m/z **c**alcd for $C_{23}H_{28}ClNO_5Na$ 456.1553, Found: 456.1541. Data for compound **104d'**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 -7.30 (m, 4H), 7.23 (td, *J* = 7.7, 1.2 Hz, 1H), 6.82-6.82 (m, 2H), 6.43 (d, *J* = 7.4 Hz, 1H), 5.56 (s, 1H), 1.11 (s, 9H), 1.04 (s, 9H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 175.7, 142.4, 134.5, 134.1, 130.0, 129.7, 127.7, 127.0,



124.6, 121.6, 109.8, 84.7, 83.7, 81.6, 81.1, 26.6, 26.4. FTIR (neat): 1733, 1472, 1196, 1020 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{23}H_{28}ClNO_5Na$ 456.1553, Found: 456.1556.

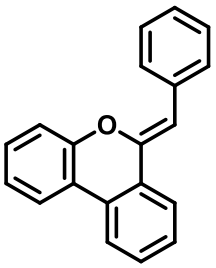
*3-((4-bromophenyl)(tert-butylperoxy)methyl)-3-(tert-butylperoxy)indolin-2-one (**104e & 104e'**)*:



Prepared according to general procedure D, using (*E/Z*)-3-(4-bromobenzylidene)indolin-2-one (75.03 mg, 0.25 mmol) to afford bisperoxyoxindole as a diastereomers **104e** & **104e'** in the ratio (1:3) with overall yield 62% (74 mg, 0.15 mmol) as a yellow solid. These diastereomers were separated by column purification afforded syn bisperoxyoxindole **104e'** (15 mg, 0.031 mmol, 13%), Melting point: 146–147 °C and anti bisperoxyoxindole **104e** (59 mg, 0.12 mmol, 49% yield) as a yellow solid (melting point: 138–139 °C) after purification by silica gel column chromatography (EtOAc:*n*-hexane = 10:90). Data for compound **104e**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 7.4, 0.5 Hz, 1H), 7.42 (s, 1H), 7.23-7.17 (m, 3H), 7.07 (td, *J* = 7.6, 0.9 Hz, 1H), 6.87-6.84 (m, 2H), 6.57 (d, *J* = 7.7 Hz, 1H), 5.41 (s, 1H), 1.31 (s, 9H), 1.15 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.5, 141.5, 133.8, 130.8, 130.1, 130.0, 127.9, 124.5, 122.6, 122.4, 109.7, 88.1, 85.8, 81.7, 81.0, 26.6, 26.5. FTIR (neat): 3566, 2914, 1753, 1622, 1473, 1194, 1121 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{23}H_{28}BrNO_5Na$ 500.1048, Found: 500.1050. Data for compound **104e'**: ^1H NMR (400 MHz, $CDCl_3$) δ 8.43 (m, 1H), 7.52-7.49 (m, 2H), 7.27-7.21 (m, 3H), 6.85 (m, 2H), 6.44 (d, *J* = 7.4 Hz, 1H), 5.54 (s, 1H), 1.11 (s, 9H), 1.04 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 175.7, 142.4, 135.0, 130.7, 130.0, 126.9, 124.6, 122.4, 121.6, 109.8, 84.6, 83.7, 81.6, 81.1, 26.6, 26.4. FTIR (neat): 3566, 2914, 1753, 1622, 1473, 1194, 1121 cm^{-1}. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{23}H_{28}BrNO_5Na$ 500.1048, Found: 500.1044.

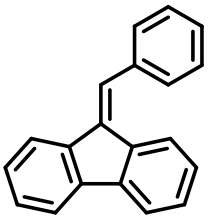
*(Z)-6-benzylidene-6H-benzo[c]chromene (**87a**)*:[59]

Prepared according to general procedure J, using 9-benzyl-9-(*tert*-butylperoxy)-9*H*-fluorene (86 mg, 0.25 mmol) to afford (*Z*)-6-benzylidene-6*H*-benzo[*c*]chromene **87a** (14 mg, 0.051 mmol, 20% yield) as a yellow solid and 9-benzylidene-9*H*-fluorene **101a** (30 mg, 0.118 mmol, 47% yield) as a white solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 1:99). Spectroscopic data matches with the previously reported compound.[59]



Data for the compound **87a**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.83 (m, 3H), 7.81 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.77 – 7.74 (m, 1H), 7.39– 7.27 (m, 5H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.18 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.12 – 7.07 (td, *J* = 7.4, 1.1 Hz, 1H), 6.27 (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.0, 147.8, 135.8, 129.8, 129.4, 128.8, 128.7, 128.5, 128.2, 127.9, 126.3, 124.0, 122.9, 122.6, 121.9, 119.6, 116.7, 103.6. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{15}O$ 271.1123, Found: 271.1120.

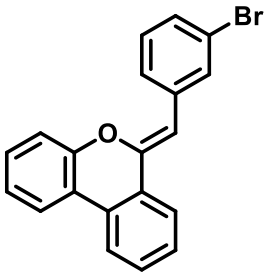
Data for 9-benzylidene-9*H*-fluorene (**101a**):[60] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.78 (m, 1H), 7.74 – 7.71 (m, 3H), 7.57 (dd, *J* = 14.7, 7.7 Hz, 3H), 7.49 – 7.45 (m, 2H), 7.42 – 7.29 (m, 4H), (td, *J* = 7.7, 1.0 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 141.5, 139.4, 137.2, 136.4, 135.9, 131.9, 131.1, 128.9, 128.6, 127.2, 126.9, 126.8, 125.8, 124.5, 120.4, 120.0, 120.0, 119.8. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{16}$ 255.1173, found: 255.1174.



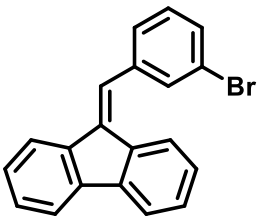
*(Z)-6-(3-bromobenzylidene)-6H-benzo[c]chromene (**87b**):*

Prepared according to general procedure J, using 9-(3-bromobenzyl)-9-(*tert*-butylperoxy)-9*H*-fluorene (106 mg, 0.25 mmol) to afford (*Z*)-6-(3-Bromobenzylidene)-6*H*-benzo[*c*]chromene **87b** (22 mg, 0.063 mmol, 25% yield) as a yellow solid. Melting point: 112–113 °C and 9-(3-bromobenzylidene)-9*H*-fluorene **101c** (18 mg, 0.054 mmol, 22% yield) as a yellow solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 1:99).

Data for the compound **87b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.86 (dd, *J* = 16.0, 7.8 Hz, 2H), 7.74 (dd, *J* = 12.2, 7.8 Hz, 2H), 7.45 (t, *J* = 7.5 Hz, 1H), 7.35– 7.30 (m, 3H), 7.23 (d, *J* = 7.9 Hz, 1H), 7.19 (d, *J* = 7.5 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 6.21 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 151.6, 148.9, 137.9, 131.4, 129.9, 129.9, 129.8, 128.9, 128.9, 128.3, 127.3, 124.0, 123.1, 122.6, 122.6, 122.0, 119.4, 116.7, 101.9. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{23}H_{29}BrNO_5$ 349.0228, Found: 349.0231.



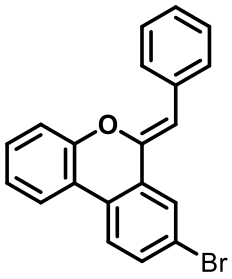
Data for 9-(3-bromobenzylidene)-9*H*-fluorene (**101c**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.5 Hz, 1H), 7.66 (d, *J* = 7.5 Hz, 2H), 7.51 (dd, *J* =13.9, 8.1 Hz, 4H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.36 - 7.43 (m, 1H), 7.20 - 7.26 (m, 2H), 7.06 – 7.02 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 141.5, 139.4, 139.3, 137.1, 136.4, 135.9, 131.8, 131.1, 128.9, 128.6, 127.2, 126.9, 125.8, 124.4, 122.2, 120.4, 120.0, 119.8. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{14}Br$ 333.0278, Found: 333.0289.



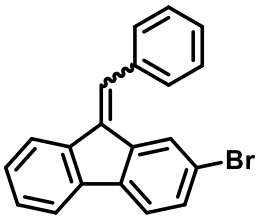
*(Z)-6-benzylidene-8-bromo-6H-benzo[c]chromene (**87c**):*

Prepared according to general procedure J, using 9-benzyl-2-bromo-9-(*tert*-butylperoxy)-9*H*-fluorene (106 mg, 0.25 mmol) to afford (*Z*)-6-benzylidene-8-bromo-6*H*-benzo[*c*]chromene **87c** (27 mg, 0.077 mmol, 31% yield) as a yellow solid and (*E/Z*)-9-benzylidene-2-bromo-9*H*-fluorene **101f** & **101f'** (16 mg, 0.048 mmol, 19% yield) as a yellow solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 1:99).

Data for the compound **71c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (m, 3H), 7.71 – 7.68 (m, 1H), 7.62 (d, *J* = 8.5 Hz, 1H), 7.45 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.30 – 7.23 (m, 2H), 7.13 (d, *J* = 7.7 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.17 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 151.8, 146.3, 135.3, 132.2, 130.2, 129.7, 129.0, 128.5, 127.2, 126.6, 126.6, 123.5, 123.0, 122.7, 122.4, 118.8, 116.8, 104.8. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{14}BrO$ 349.0228, Found: 349.0211.



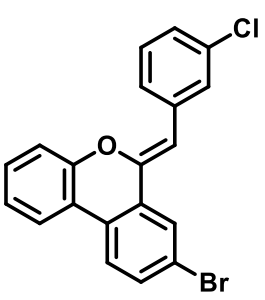
Data for (*E/Z*)-9-benzylidene-2-bromo-9*H*-fluorene (**101f** & **101f'**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 1.2 Hz, 1H), 7.71 – 7.69 (m, 1H), 7.65 – 7.64 (m, 2H), 7.60 (dd, *J* = 6.9, 2.4 Hz, 2H), 7.57 (s, 1H), 7.54 – 7.45 (m, 7H), 7.43 – 7.35 (m, 8H), 7.31 (td, *J* = 6.3, 1.0 Hz, 2H), 7.26 (t, *J* = 7.5 Hz, 1H), 7.04 (t, *J* = 7.6 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 141.5, 140.4, 140.1, 139.3, 138.4, 138.3, 138.0, 136.4, 136.4, 136.3, 135.6, 135.5, 131.3, 131.0, 129.3, 129.3, 128.8, 128.8, 128.8, 128.7, 128.6, 128.6, 128.5, 128.4, 127.5, 127.4, 127.1, 124.5, 123.7, 121.0, 121.0, 120.9, 120.5, 120.4, 119.9, 119.7. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{14}Br$ 333.0279, Found: 333.0244.



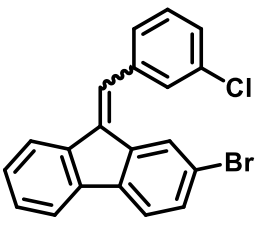
*(Z)-8-bromo-6-(3-chlorobenzylidene)-6H-benzo[c]chromene (**87d**):*

Prepared according to general procedure J, using 2-bromo-9-(*tert*-butylperoxy)-9-(3-chlorobenzyl)-9*H*-fluorene (114 mg, 0.25 mmol) to afford (*Z*)-8-bromo-6-(3-chlorobenzylidene)-6*H*-benzo[*c*]chromene **87d** (39 mg, 0.101 mmol, 42% yield) as a pale yellow solid, Melting point: 113–115 °C and (*E/Z*)-2-bromo-9-(3-chlorobenzylidene)-9*H*-fluorene **101g** & **101g'** (6 mg, 0.016 mmol, 6% yield) as a yellow solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 1:99).

Data for the compound **87d**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.77 (d, *J* = 1.4 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 1H), 7.58 (d, *J* = 7.7 Hz, 1H), 7.46 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.31 – 7.24 (m, 2H), 7.18 (d, *J* = 7.8 Hz, 1H), 7.12 – 7.05 (m, 2H), 6.08 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 151.4, 147.3, 137.1, 134.3, 132.6, 130.3, 129.6, 129.1, 128.6, 127.3, 127.0, 126.7, 126.4, 123.6, 123.3, 122.7, 122.5, 118.6, 116.8, 103.2. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{13}BrClO$ 382.9838, Found: 382.9841.

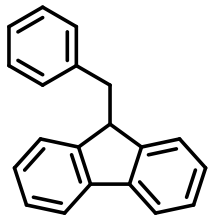


Data for (*E/Z*)-2-bromo-9-(3-chlorobenzylidene)-9*H*-fluorene (**101g** & **101g'**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 1.4 Hz, 1H), 7.72 (d, *J* = 7.1 Hz, 1H), 7.64 (d, *J* = 7.5 Hz, 2H), 7.60 (d, *J* = 1.4 Hz, 1H), 7.57 (s, 1H), 7.52-7.43 (m, 7H), 7.42-7.34 (m, 8H), 7.30 (t, *J* = 7.5 Hz, 2H), 7.09 (t, *J* = 7.6 Hz, 1H). ^{13}C{^{1}H}



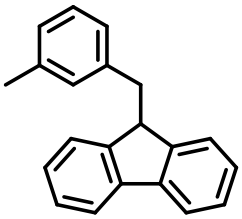
NMR (100 MHz, $CDCl_3$) δ 141.2, 140.6, 140.3, 139.0, 138.5, 138.3, 138.2, 138.1, 138.1, 136.6, 136.6, 136.1, 134.8, 134.7, 131.7, 131.4, 130.0, 129.2, 129.2, 128.9, 128.6, 128.5, 127.6, 127.5, 127.5, 127.3, 126.7, 126.6, 124.5, 123.8, 121.2, 121.1, 121.0, 120.6, 120.5, 120.0, 119.8. HRMS (ESI-TOF) *m/z*: $[M+H]^+$ calcd for $C_{20}H_{13}BrCl$ 366.9889, Found: 366.9896.

*9-benzyl-9H-fluorene (**85a**):*[61]



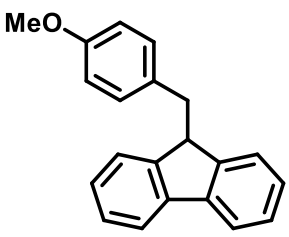
Prepared according to general procedure K, using 9-benzyl-9-(*tert*-butylperoxy)-9*H*-fluorene **86a** (51.6 mg, 0.15 mmol) to afford 9-benzyl-9*H*-fluorene **85a** (31 mg, 0.121 mmol, 81% yield) as a white solid after purification by silica gel column chromatography (*n*-hexane). The data for this compound is in agreement with the reported compound.

*9-(3-methylbenzyl)-9H-fluorene (**85c**):*



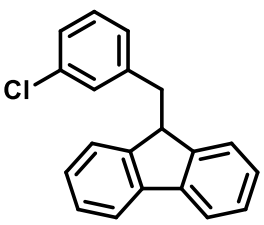
Prepared according to general procedure K, using 9-(*tert*-butylperoxy)-9-(3-methylbenzyl)-9*H*-fluorene **86c** (53.7 mg, 0.15 mmol) to afford 9-(3-methylbenzyl)-9*H*-fluorene **85c** (31 mg, 0.114 mmol, 78% yield) as a white solid after purification by silica gel column chromatography (*n*-hexane). The data for this compound is in agreement with the reported compound.[1-b] ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 7.4 Hz, 2H), 7.21 (td, *J* = 7.3, 0.9 Hz, 3H), 7.15 (d, *J* = 7.5 Hz, 2H), 7.06 (m, 3H), 4.22 (t, *J* = 7.7 Hz, 1H), 3.06 (d, *J* = 7.7 Hz, 2H), 2.37 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 147.0, 140.9, 139.9, 138.0, 130.4, 128.3, 127.3, 127.2, 126.7, 126.6, 119.9, 48.8, 40.2, 21.6. HRMS (ESI-TOF) *m/z*: $[M+Na]^+$ calcd for $C_{21}H_{18}Na$ 293.1306, Found: 293.1314.

*9-(4-methoxybenzyl)-9H-fluorene (**85e**):*[61]



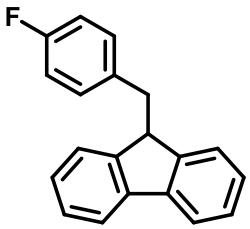
Prepared according to general procedure K, using 9-(*tert*-butylperoxy)-9-(4-methoxybenzyl)-9*H*-fluorene **86e** (56.1 mg, 0.15 mmol) to afford 9-(4-methoxybenzyl)-9*H*-fluorene **85e** (32 mg, 0.111 mmol, 75% yield) as a white solid after purification by silica gel column chromatography (*n*-hexane). The data for this compound is in agreement with the reported compound.

*9-(3-chlorobenzyl)-9H-fluorene (**85i**):* [61]



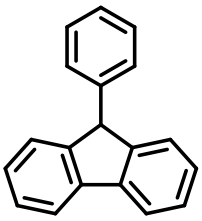
Prepared according to general procedure K, using 9-(*tert*-butylperoxy)-9-(3-chlorobenzyl)-9*H*-fluorene **86i** (56.2 mg, 0.15 mmol) to afford 9-(3-chlorobenzyl)-9*H*-fluorene **85i** (30 mg, 0.103 mmol, 71% yield) as a white solid after purification by silica gel column chromatography (*n*-hexane). The data for this compound is in agreement with the reported compound.

*9-(4-fluorobenzyl)-9H-fluorene (**85k**):* [61]



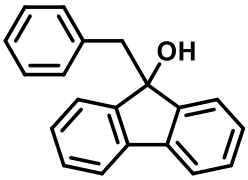
Prepared according to general procedure K, using 9-(*tert*-butylperoxy)-9-(4-fluorobenzyl)-9*H*-fluorene **86k** (54.3 mg, 0.15 mmol) to afford 9-(4-fluorobenzyl)-9*H*-fluorene **85k** (31 mg, 0.113 mmol, 75% yield) as a white solid after purification by silica gel column chromatography (*n*-hexane). The data for this compound is in agreement with the reported compound.

*9-phenyl-9H-fluorene (**85w**):*[62]



Prepared according to general procedure K, using 9-(*tert*-butylperoxy)-9-phenyl-9*H*-fluorene **86w** (49.5 mg, 0.15 mmol) to afford 9-phenyl-9*H*-fluorene **85w** (33 mg, 0.136 mmol, 91% yield) as a white solid after purification by silica gel column chromatography (*n*-hexane). The data for this compound is in agreement with the reported compound.

*9-benzyl-9H-fluoren-9-ol (**112**):*[61b]



Prepared according to general procedure L, using 9-benzyl-9-(*tert*-butylperoxy)-9*H*-fluorene **86a** (52 mg, 0.15 mmol) to afford 9-benzyl-9*H*-fluoren-9-ol **112** (15 mg, 0.055 mmol, 38% yield) as a white solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 5:95). Melting point: 138–140 °C. The data for this compound is in agreement with the reported compound. ^{1}H NMR (400 MHz, $CDCl_3$) 7.54 (d, J = 7.4 Hz, 2H), 7.35–7.22 (m, 6H), 7.18–7.10 (m, 3H), 6.98 (dd, J = 7.5, 2.0 2H), 3.30 (s, 2H), 2.17 (bs, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 148.3, 139.4, 136.4, 130.9, 129.0, 127.7, 127.6, 126.6, 124.4, 120.0, 82.4, 45.9. HRMS (ESI-TOF) *m/z*: $(M+H- H_2O)^+$ calcd for $C_{20}H_{15}$ 255.1168, Found: 255.1179.

2.15B. Appendix I: Copies of ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of representative compounds

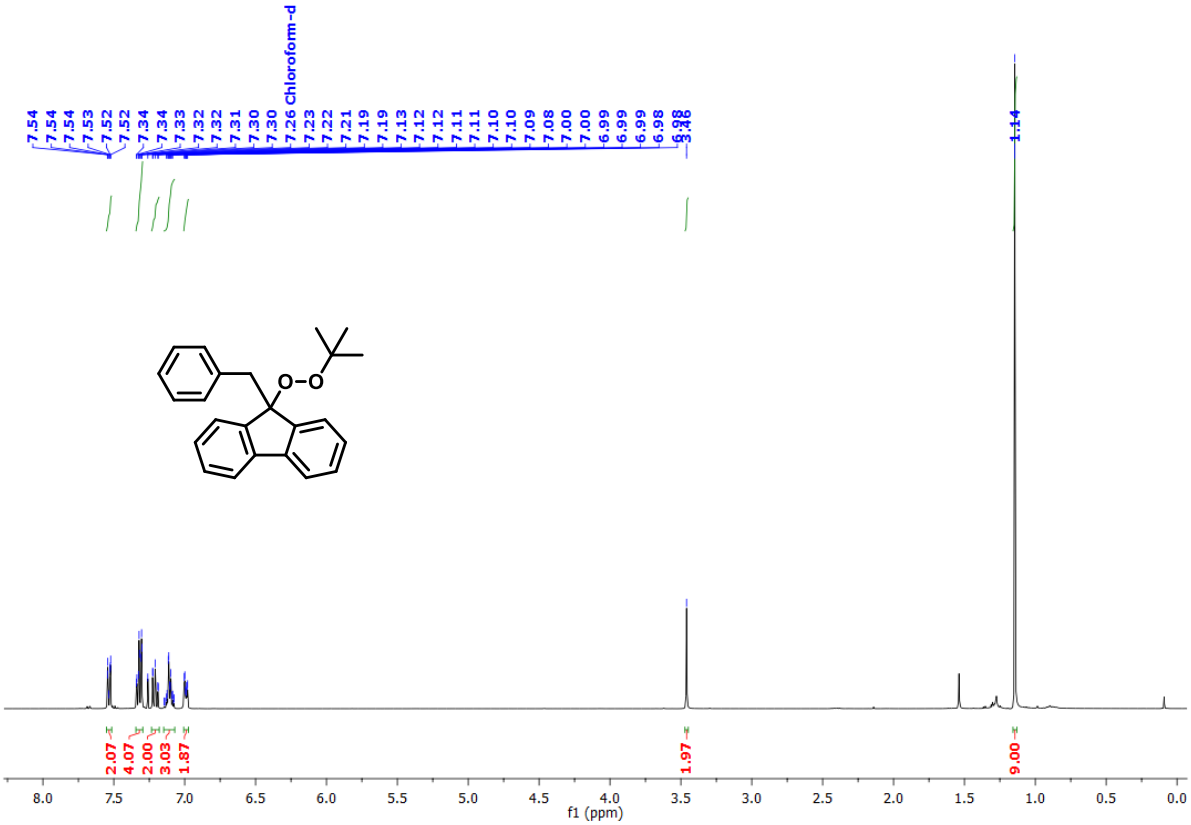


Figure 2.15B.1. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **86a**

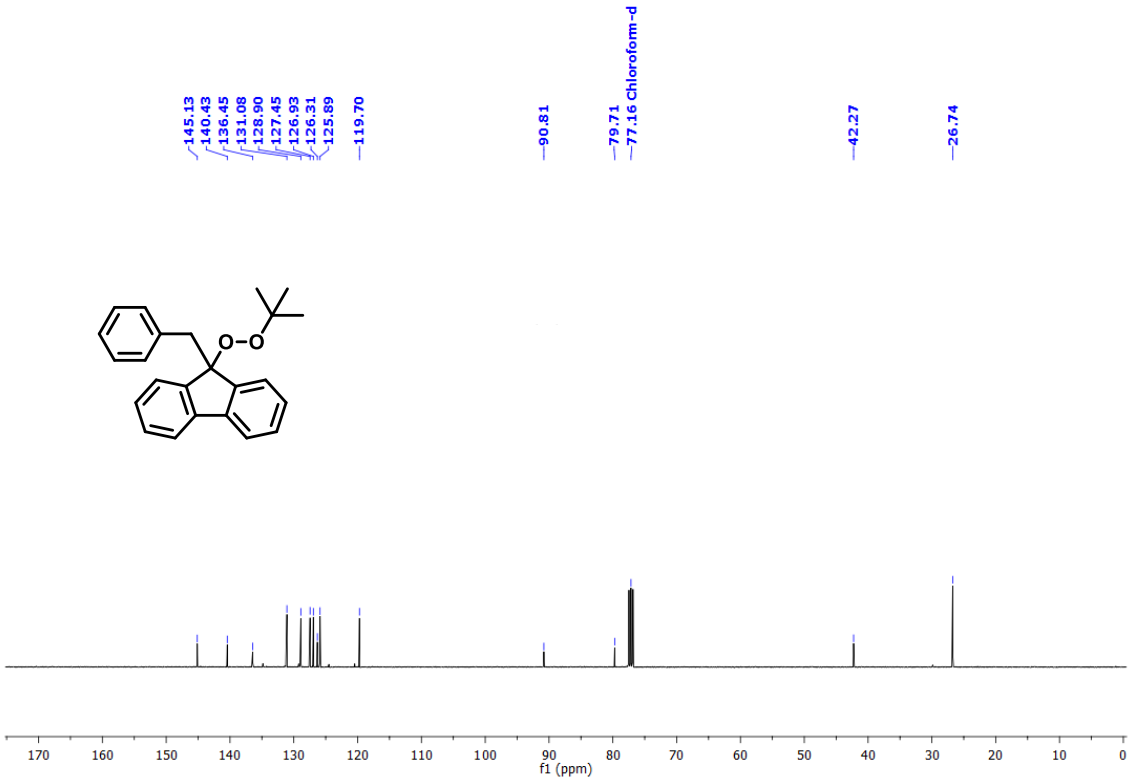


Figure 2.15B.2. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) of compound **86a**

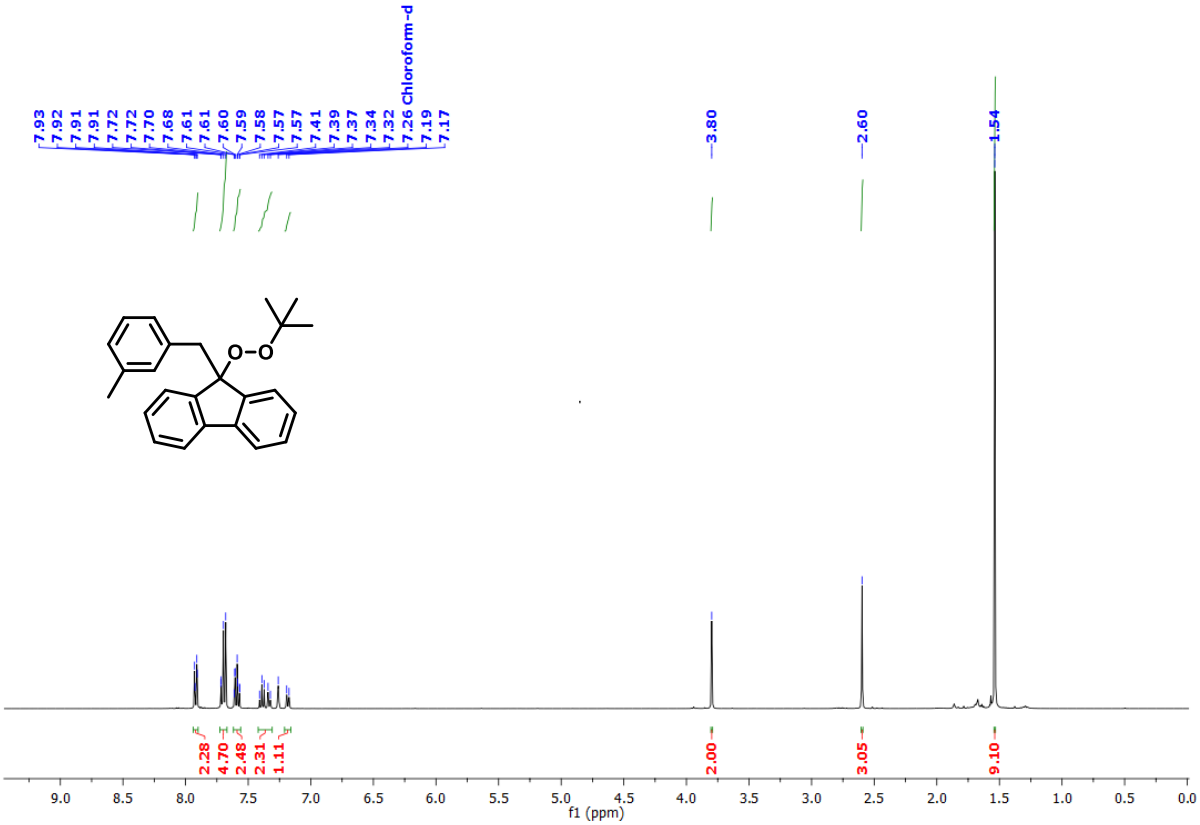


Figure 2.15B.3. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **86c**

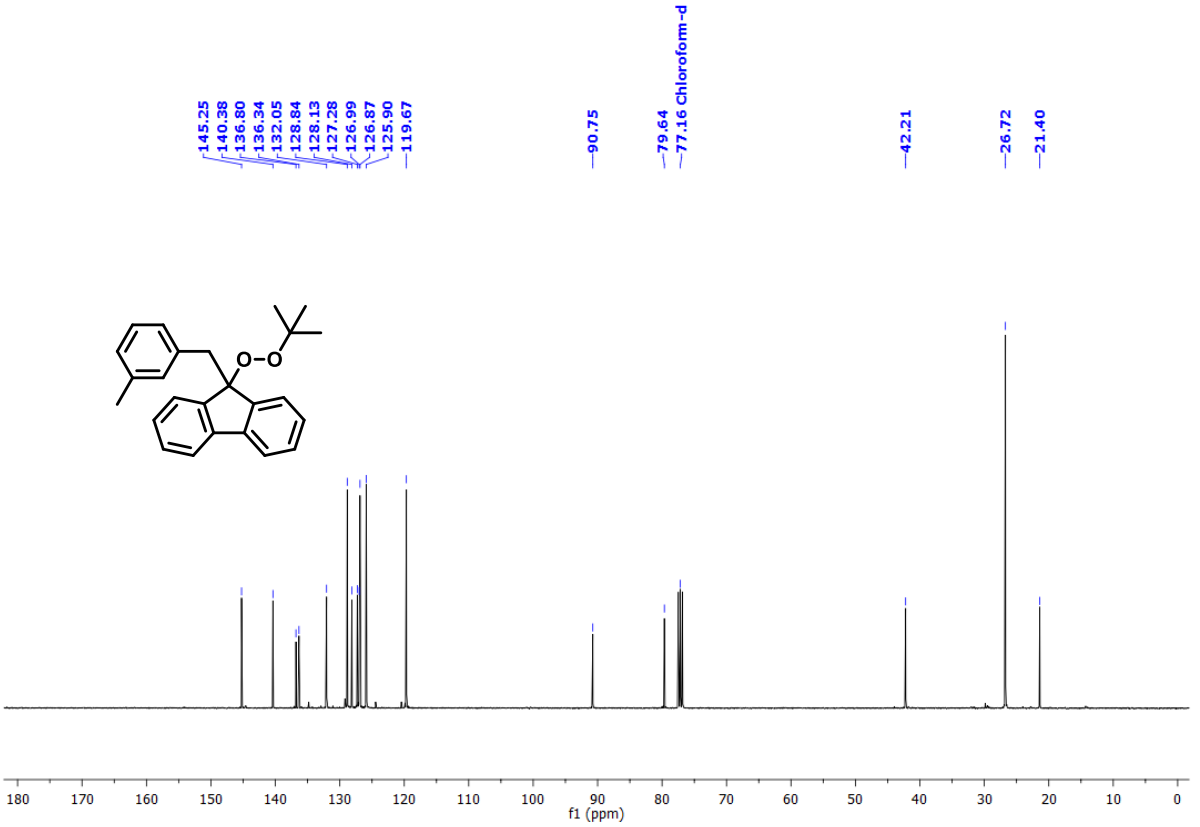


Figure 2.15B.4. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) of compound **86c**

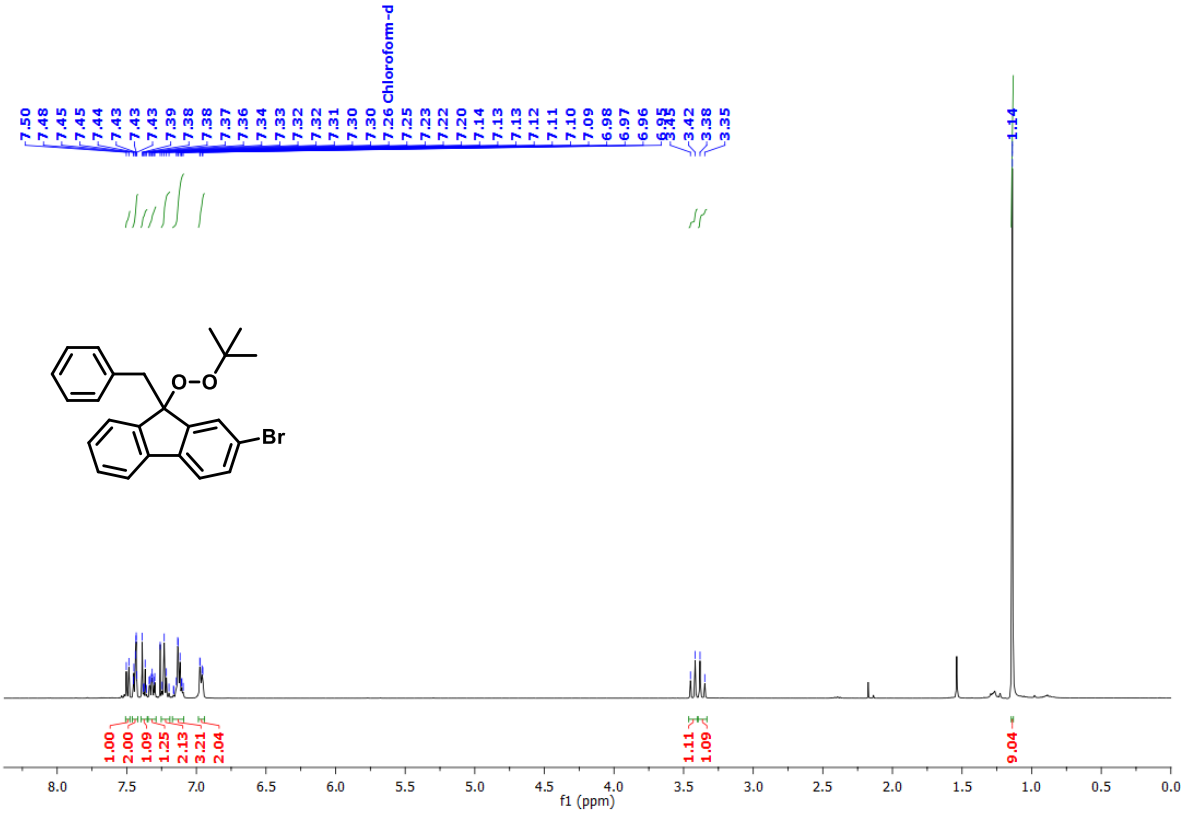


Figure 2.15B.5. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **86m**

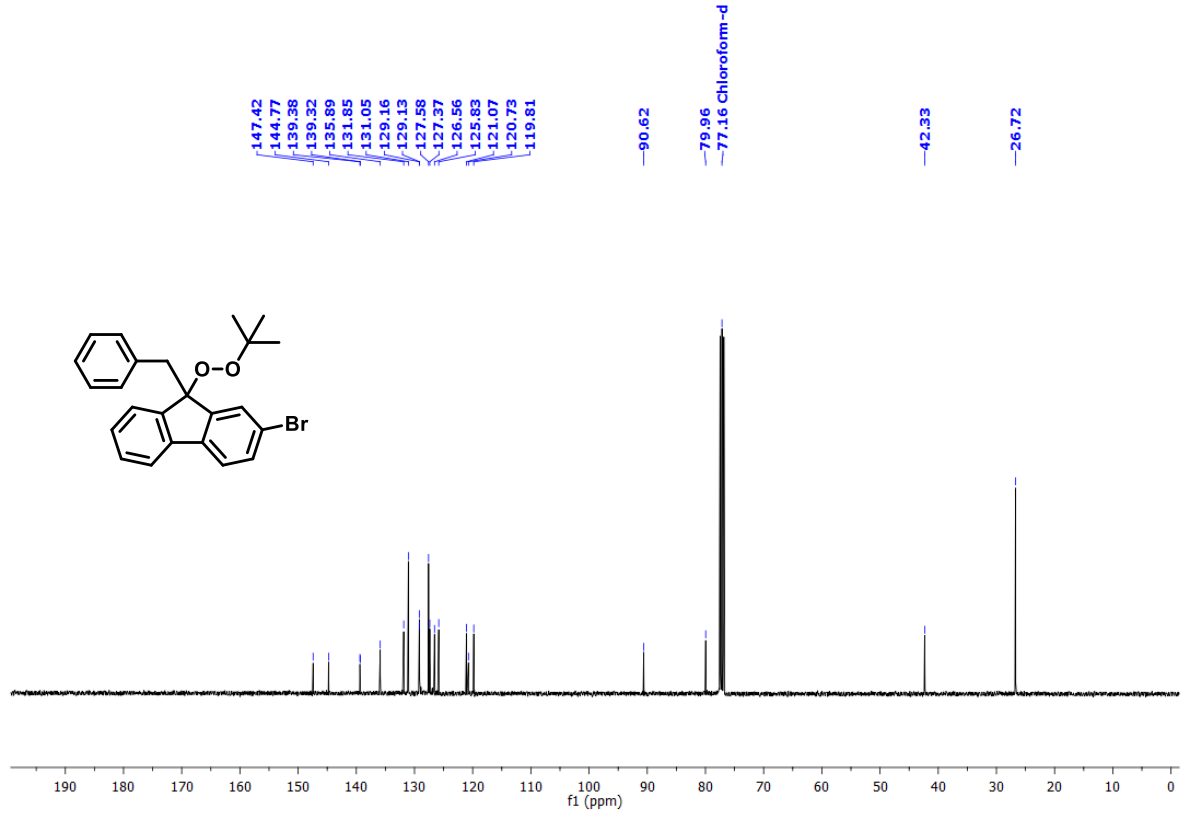


Figure 2.15B.6. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) of compound **86m**

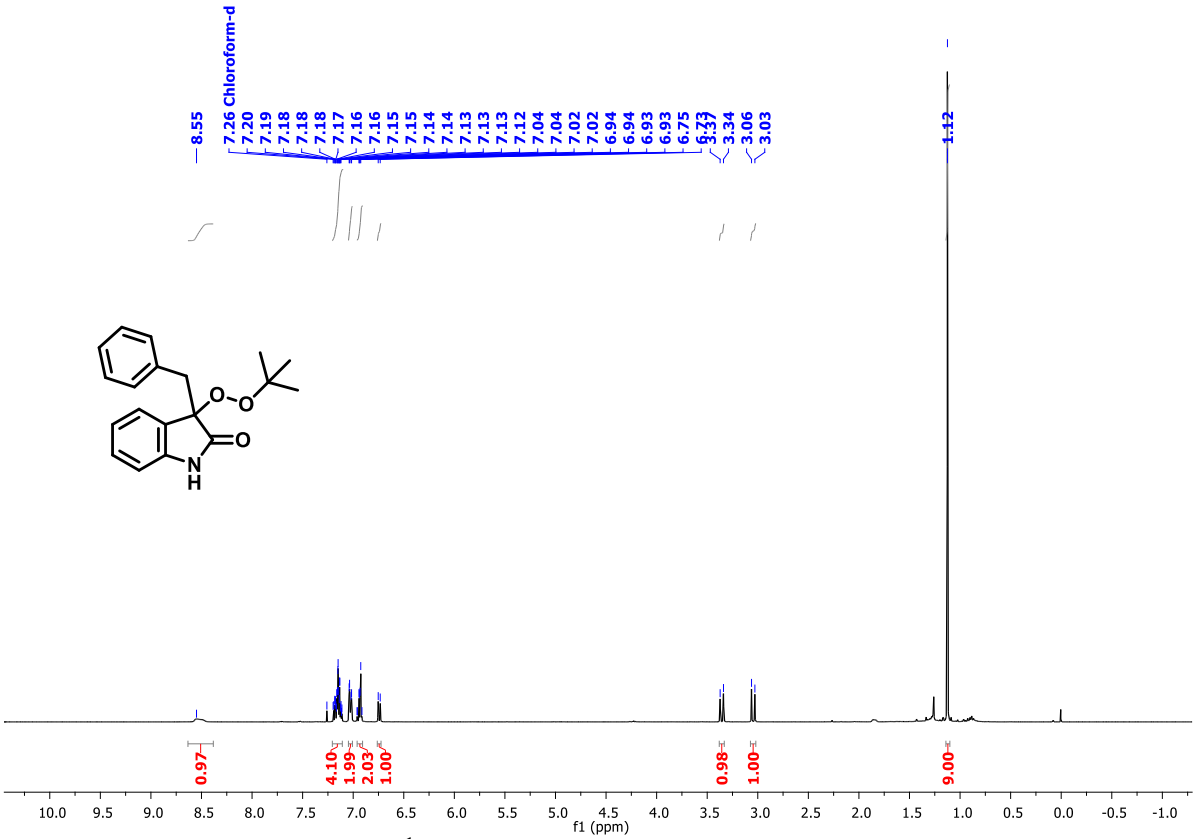


Figure 2.15B.7. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **72b**

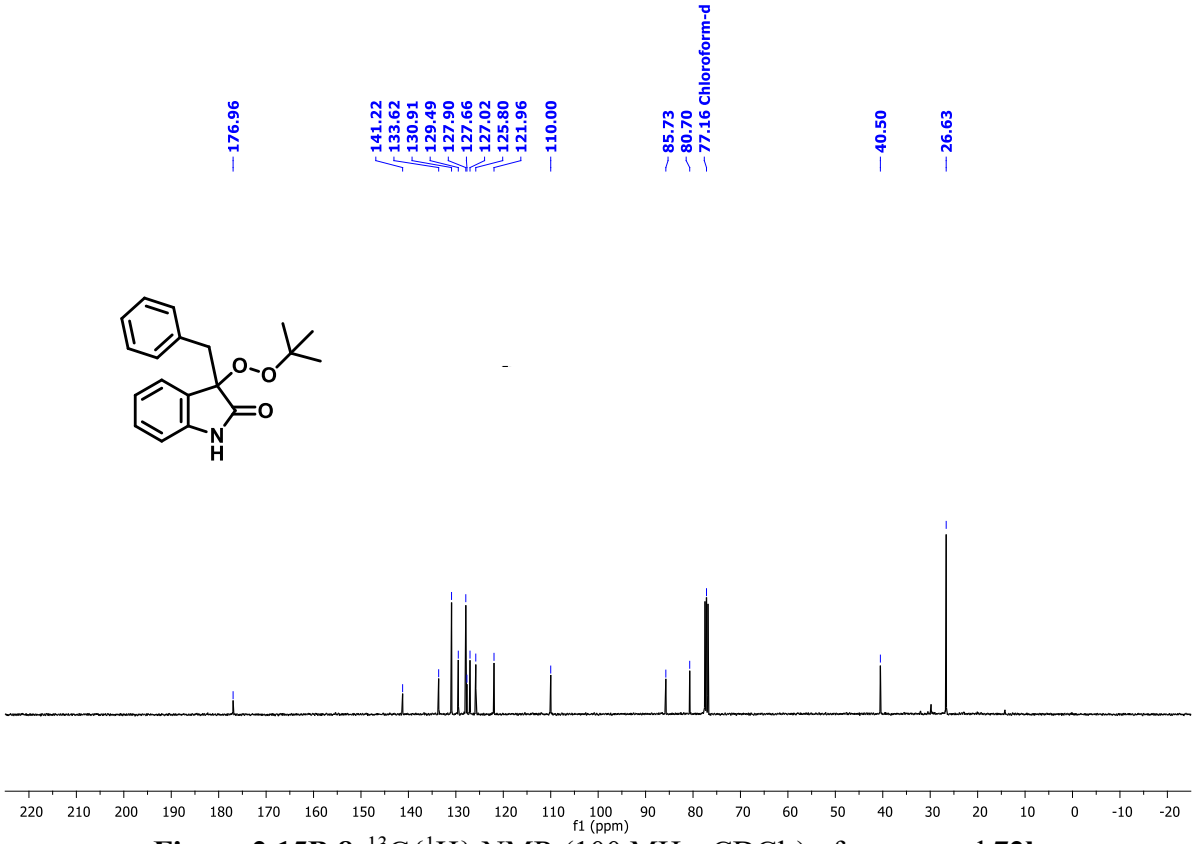


Figure 2.15B.8. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) of compound **72b**

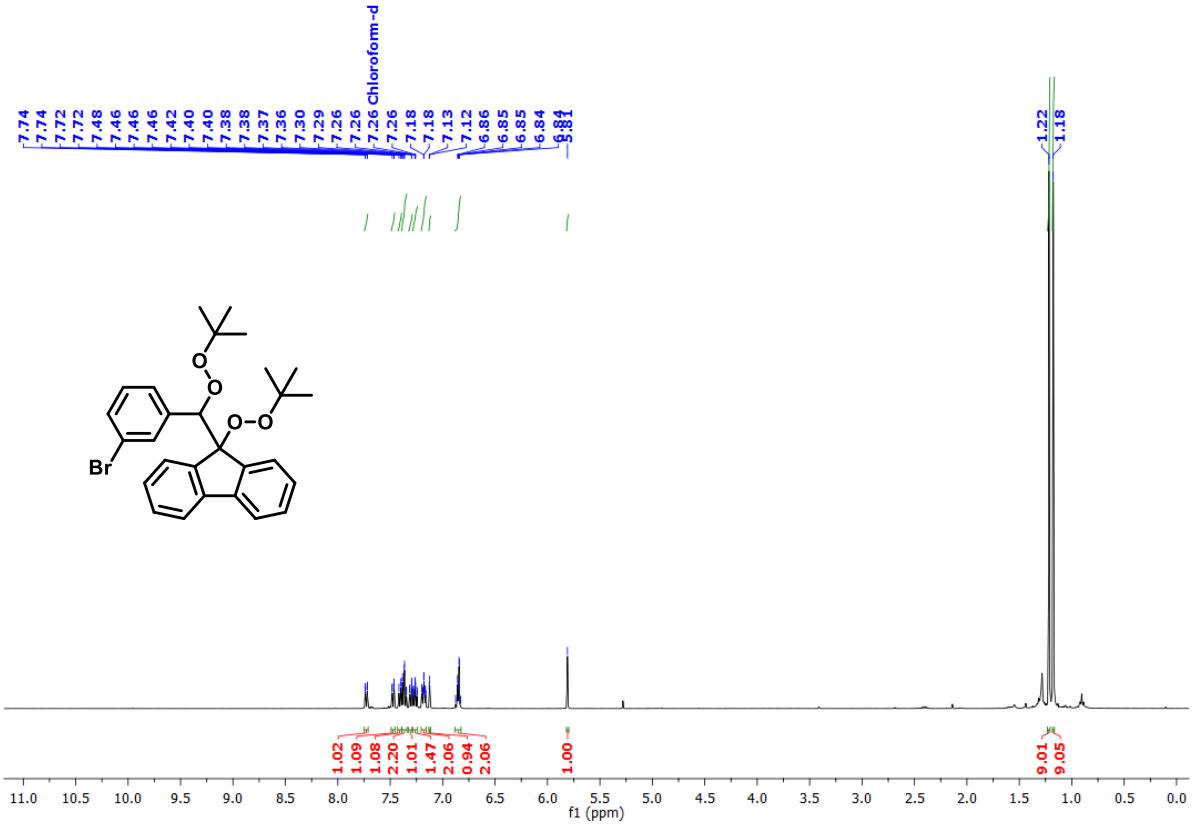


Figure 2.15B.9. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **102c**

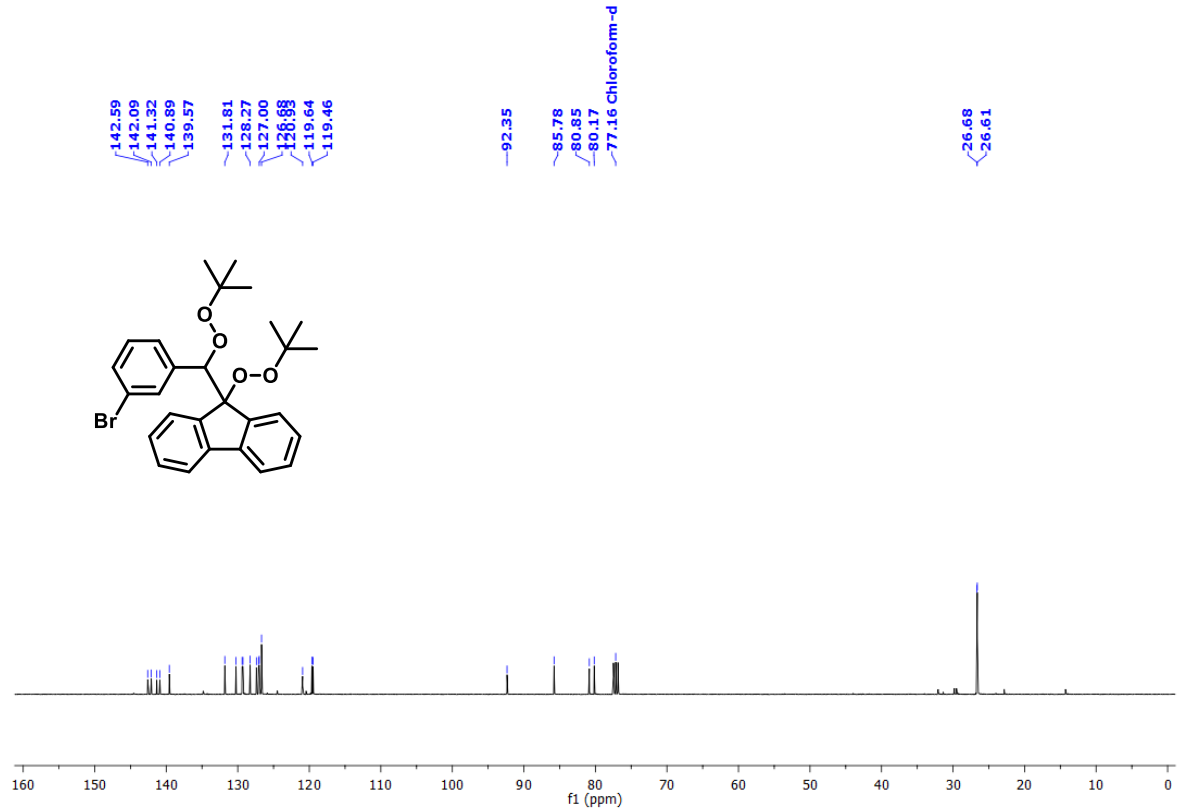


Figure 2.15B.10. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) of compound **102c**

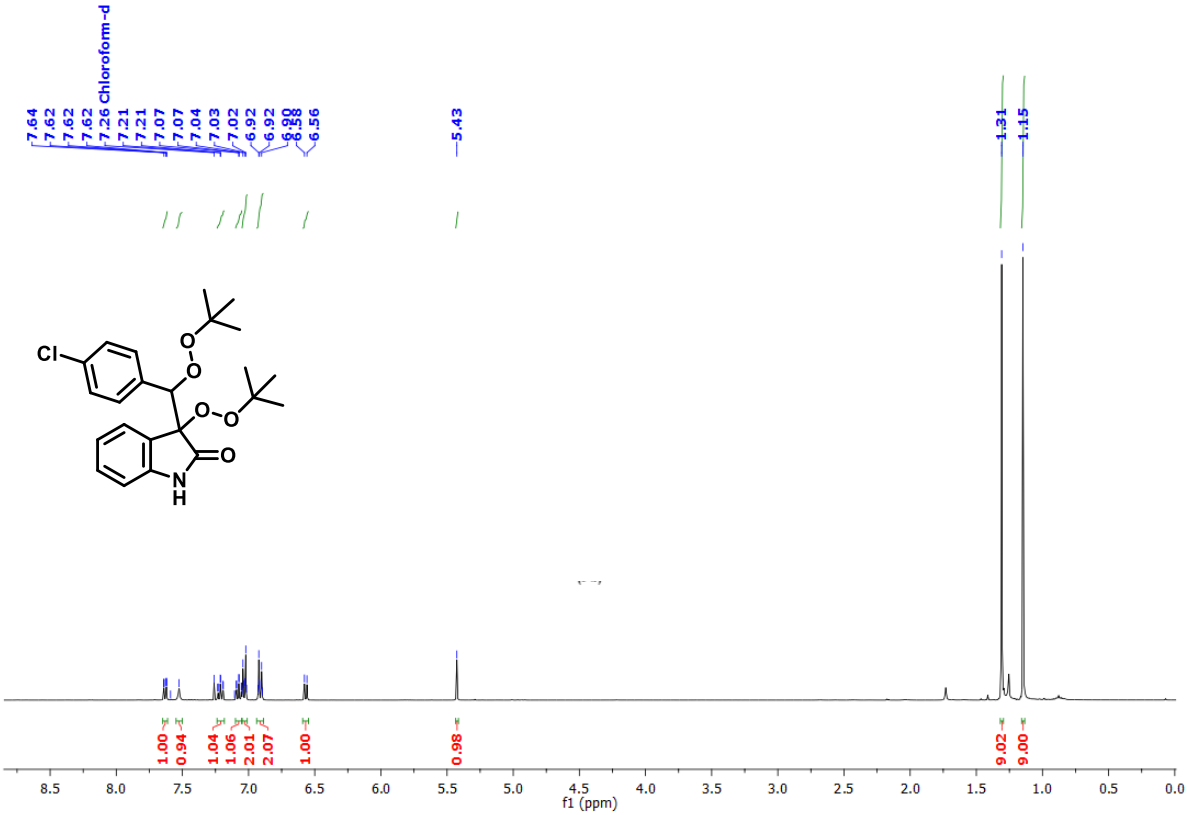


Figure 2.15B.11. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **104d**

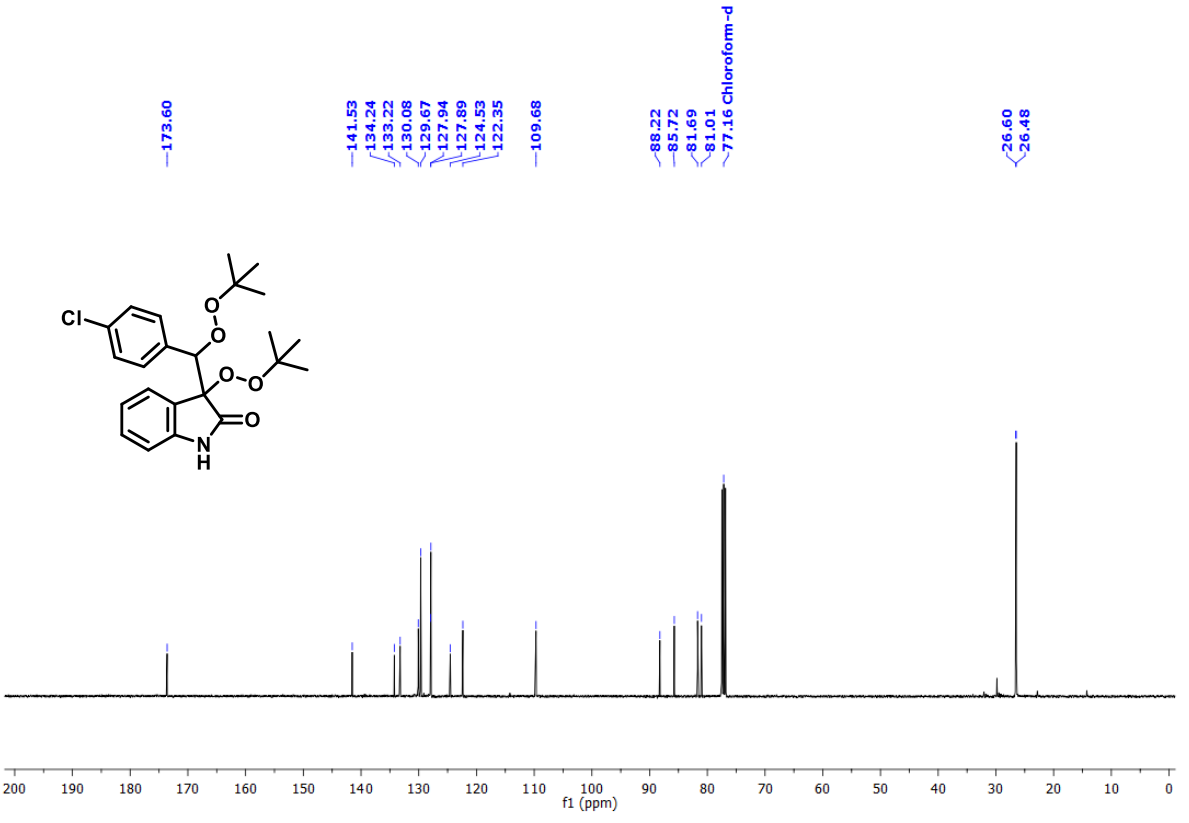


Figure 2.15B.12. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) of compound **104d**

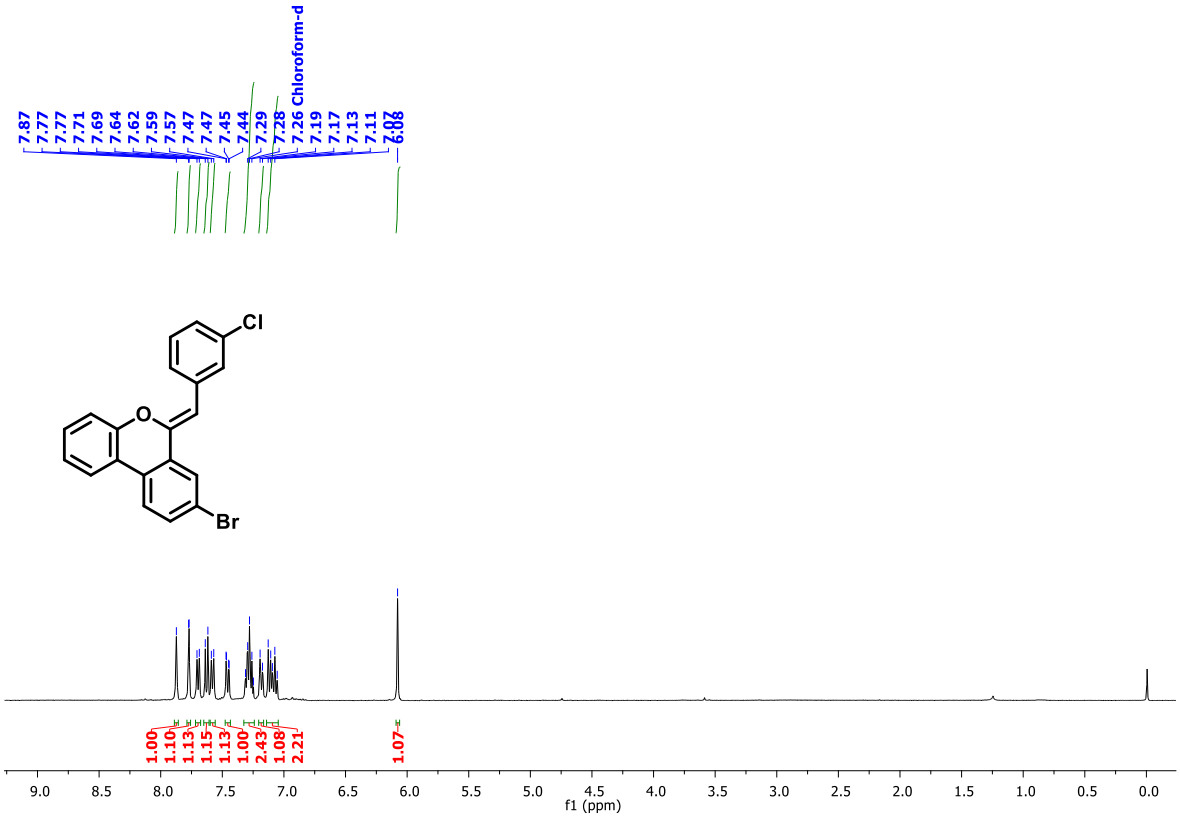


Figure 2.15B.13. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **87d**

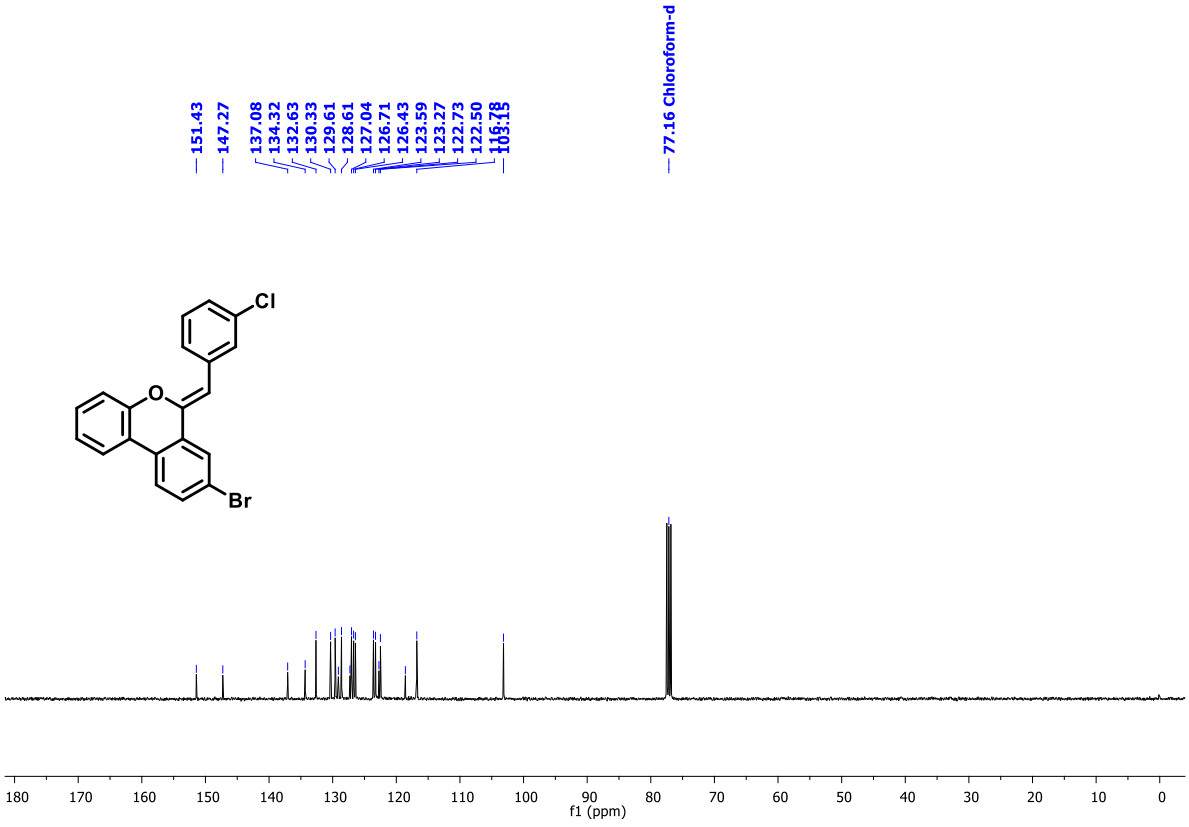


Figure 2.15B.14. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) of compound **87d**

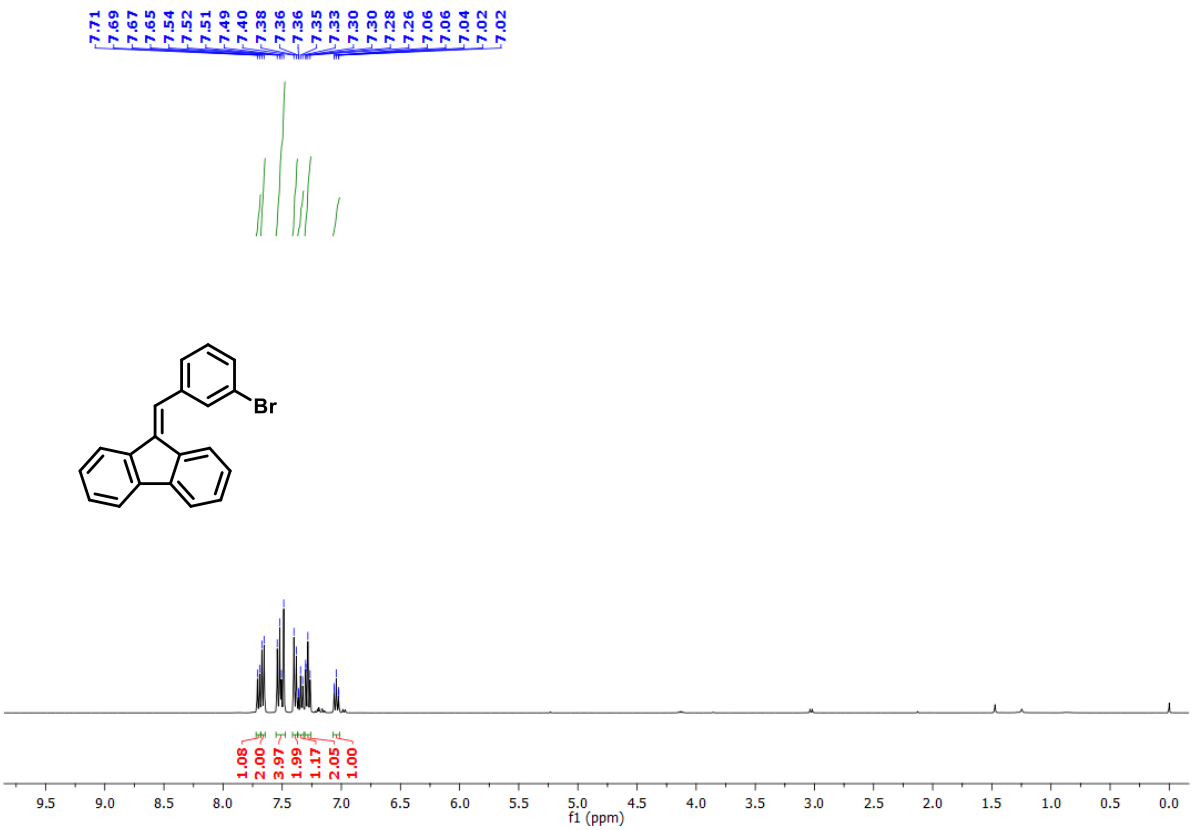


Figure 2.15B.15. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **101c**

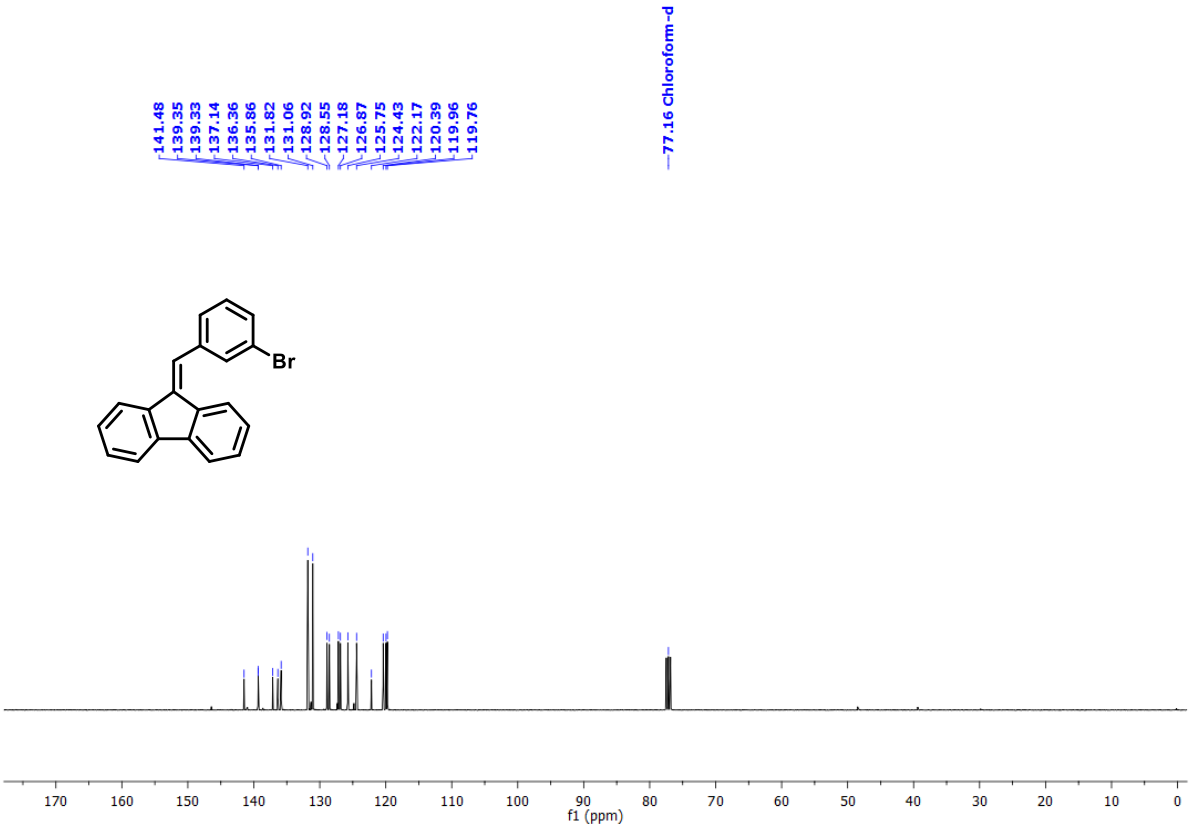


Figure 2.15B.16. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) of compound **101c**

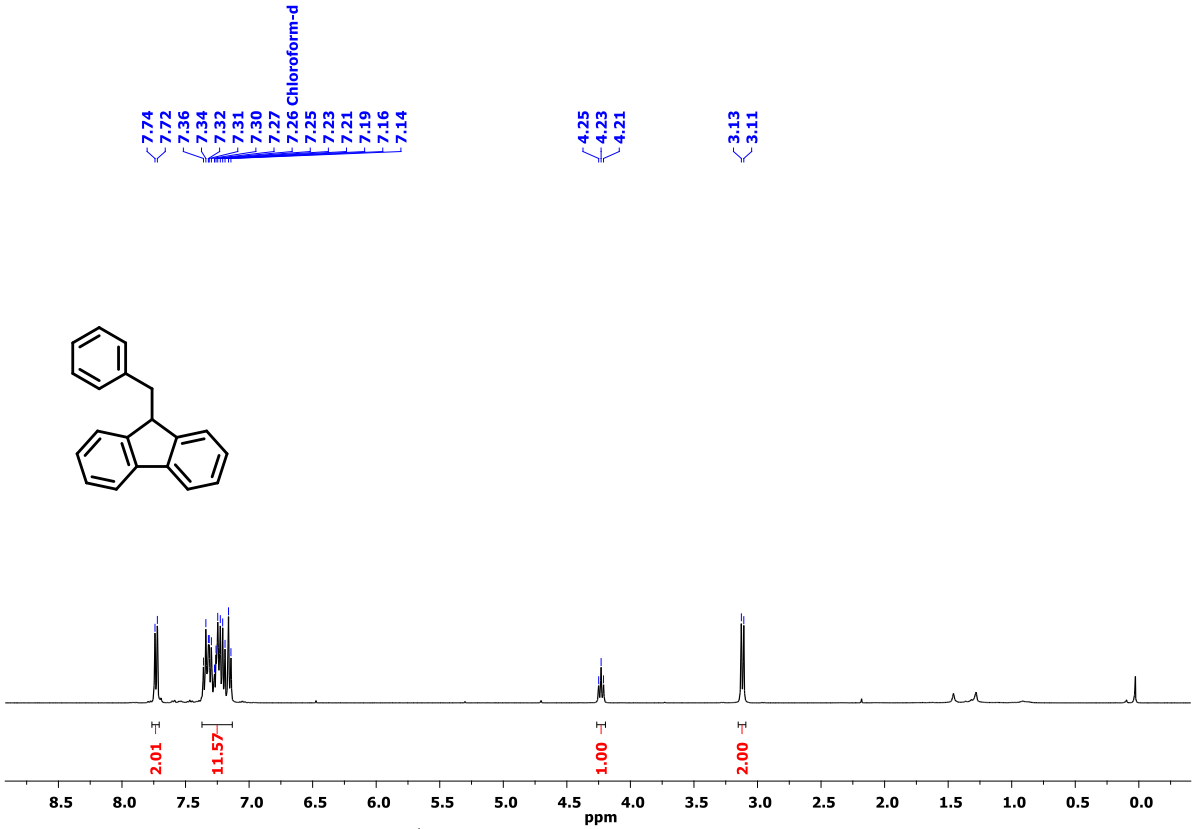


Figure 2.15B.17. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **85a**

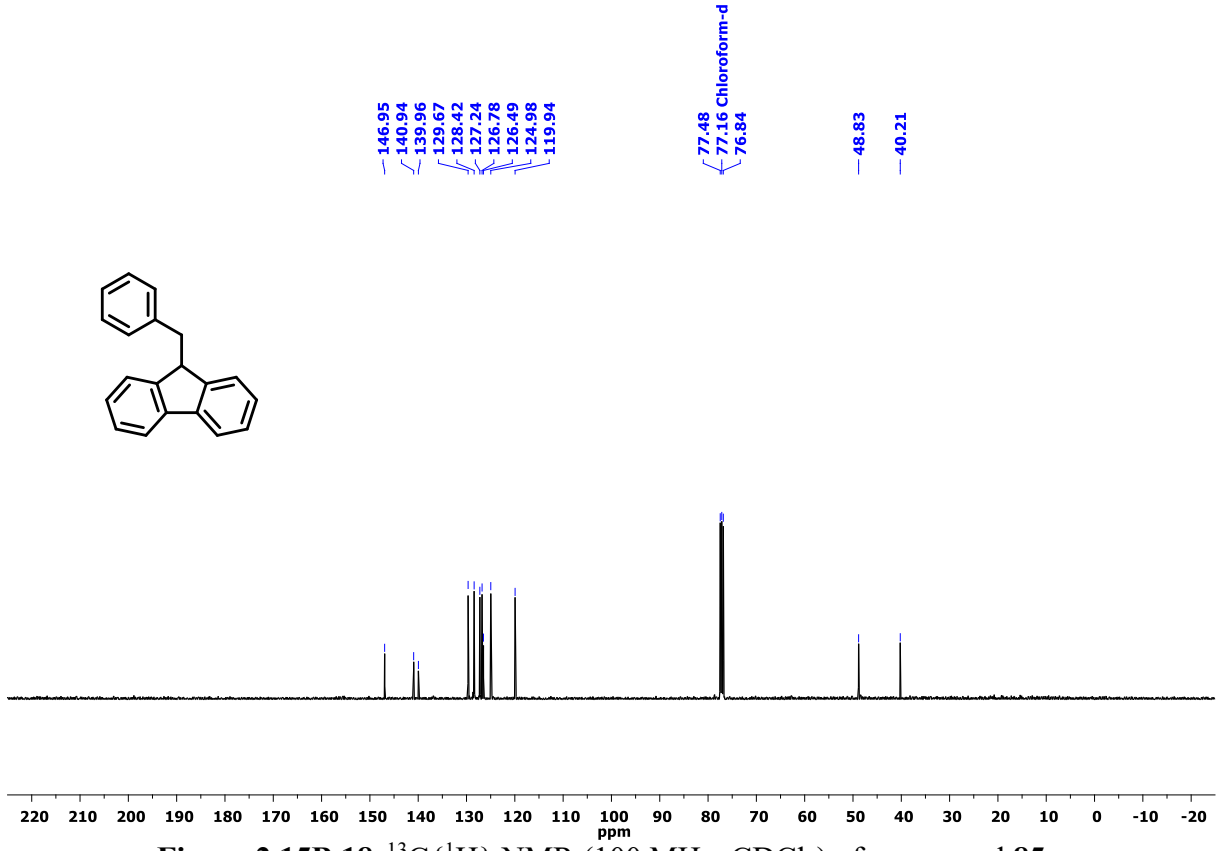


Figure 2.15B.18. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) of compound **85a**

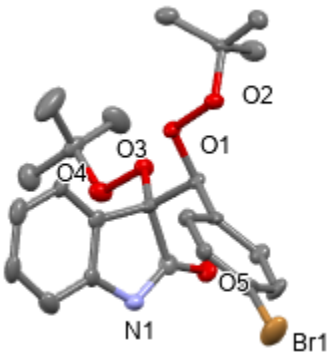


Figure 2.15B.19. Single crystal structure for compound **104e**

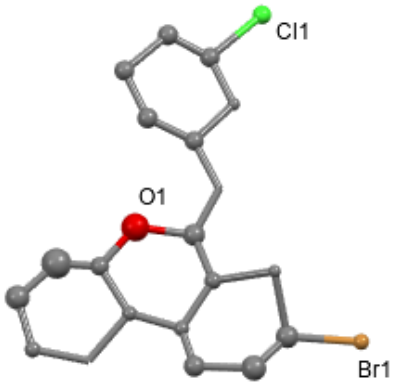


Figure 2.15B.20. Single crystal structure for compound **87d**

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Manganese-Catalyzed Synthesis of Quaternary Peroxides: Application in Catalytic Deperoxidation and Rearrangement Reactions

Author: Akash S. Ubale, Moreshwar B. Chaudhari, Moseen A. Shaikh, et al
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Date: Aug 1, 2020

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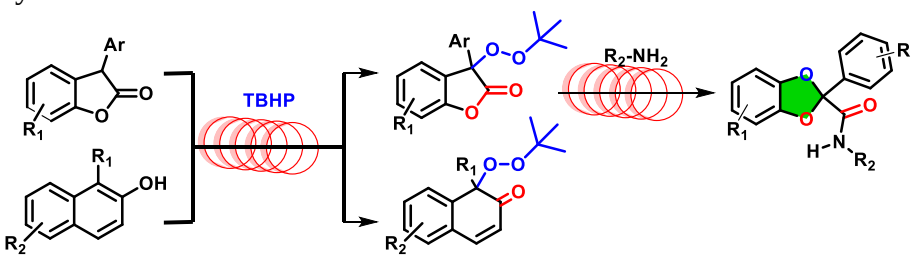
Chapter 3

Peroxidation and Skeletal Rearrangement for the Synthesis of Dioxole-2-carboxamide Derivatives under Continuous-Flow Conditions

3. Peroxidation and Skeletal Rearrangement for the Synthesis of Dioxole-2-carboxamide Derivatives under Continuous-Flow Conditions

3.1. Abstract

In this chapter, we have demonstrated the peroxidative dearomatisation of 2-naphthol and C-H peroxidation of 3-arylbenzofuran-2-ones under catalyst-free conditions using a continuous-flow module. Moreover, the novel approach for the synthesis of *N*-substituted-2-phenylbenzo[*d*][1,3]dioxole-2-carboxamide has been achieved *via* the skeletal rearrangement from peroxybenzofuranone and amines in the absence of catalyst under continuous flow. Mechanistic studies indicate that this peroxidation reaction proceeds *via* free radical generation under thermolytic conditions.



Scheme 3.1.1. Present finding peroxidation and skeletal rearrangement of peroxide

3.2. Introduction to the peroxides and rearrangements reactions

Peroxides (R-O-O-R) are the omnipresent functional group that acts as a source of hydroxyl functional groups due to the existence of reactive (O–O) bonds ($\Delta H°_{298}$ = 158−194 kJ mol^{-1}).[12] Organic peroxides represent key units in numerous natural products and bioactive compounds.[51a, 1a,3b,63] Moreover, the naphthalen-2(1*H*)-ones[64] and 3-hydroxy-3-substituted-benzofuran-2(3*H*)-one[65] are essential structural motifs in various natural products and biologically important

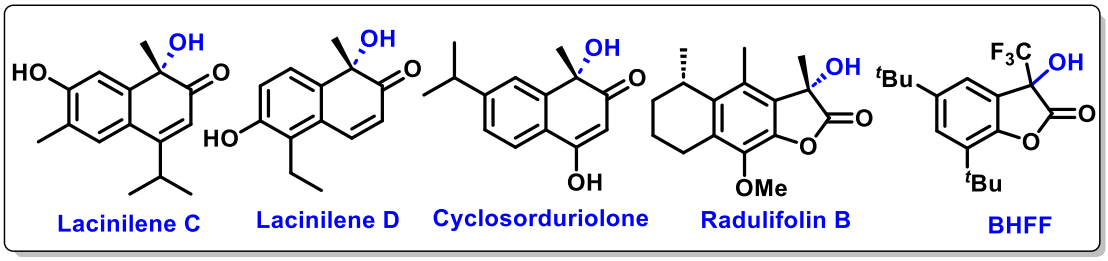
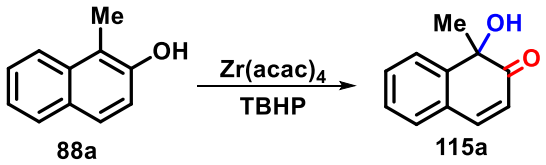


Figure 3.2.1. Selected biologically active *α*-ketol & benzofuranone natural products

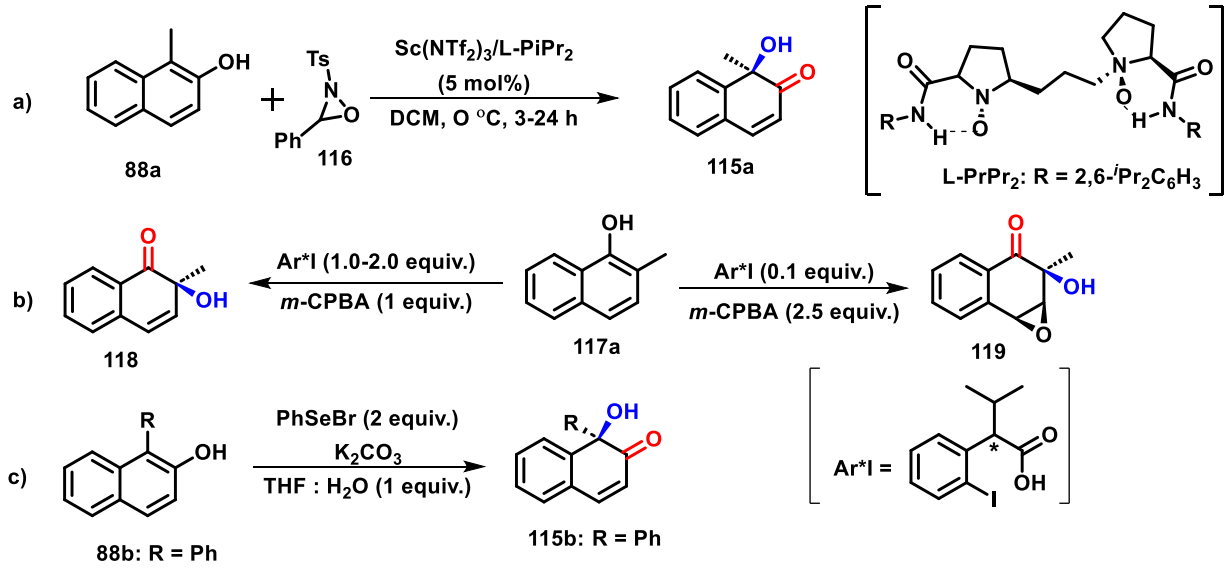
molecules, including anticancer compounds radulifolin B,[65a,b] BHFF act as the positive allosteric modulator of $GABA_B$ receptors and display potential therapeutic action against alcoholism[65b-e] (Figure 3.2.1.). Peroxidative dearomatization can be a reaction of enormous synthetic importance.[66]

In this regard, the peroxidative dearomatization of naphthols and reduction of peroxides normally give the quaternary hydroxyl motifs. Interestingly, an extensive literature survey has fetched us scanty reports focusing on oxidative and alkylative dearomatization *via* metal and metal-free approaches.[66,67] However, very limited significant reports on the dearomatization of naphthols are documented. For instance, the Krohn group reported the oxidation of naphthols **88a** to ketols **115a** catalyzed by zirconium as a catalyst and TBHP **1c** reagent (Scheme 3.2.1.).[68]



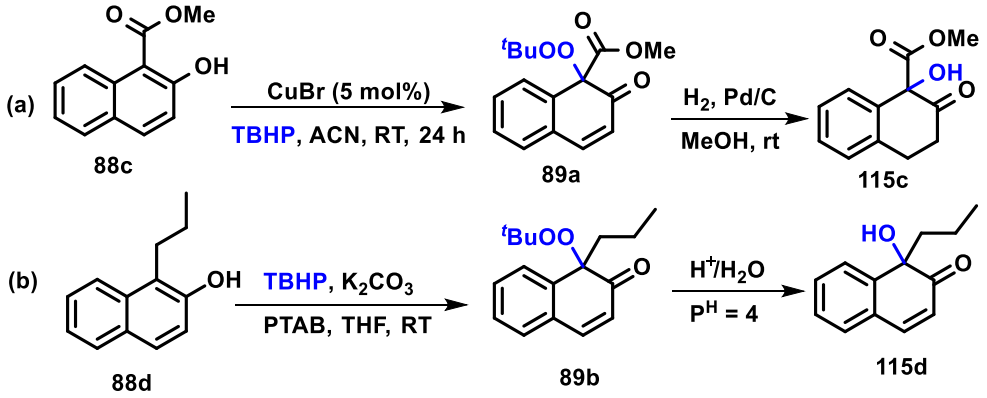
Scheme 3.2.1. Oxidation of naphthol by the Krohn group

Also, this can be achieved by using oxaziridines[69a] (Scheme 3.2.2. a) and chiral iodine complexes[69b] (Scheme 3.2.2. b). Furthermore, naphthols to α-ketols were reported by the Sarkar group using phenylselenyl bromide in open-air conditions (Scheme 3.2.2. c).[70]



Scheme 3.2.2. Various approaches for the synthesis of α-ketols

Later, Dhineshkumar *et al.* described the synthesis of quaternary peroxides from 2-naphthol **88c** derivative using a copper catalyst and then the reduction of peroxides with Pd/C (Scheme 3.2.3. (a)).[70] Subsequently, the Sarkar group reported metal-free conditions for oxidative amination, azidation, and peroxidation of 2-naphthol using the reagent system of TBHP, K_2CO_3, and phenyl trimethyl ammonium tribromide (PTAB). Further reduction of peroxides was achieved by using acidic conditions (Scheme 3.2.3. (b)).[72] However, there have been no reports on the peroxidation of 3-aryl-benzofuran-2(3*H*)-one.



Scheme 3.2.3. Oxidation of naphthol by the Dhineshkumar and Sarkar group

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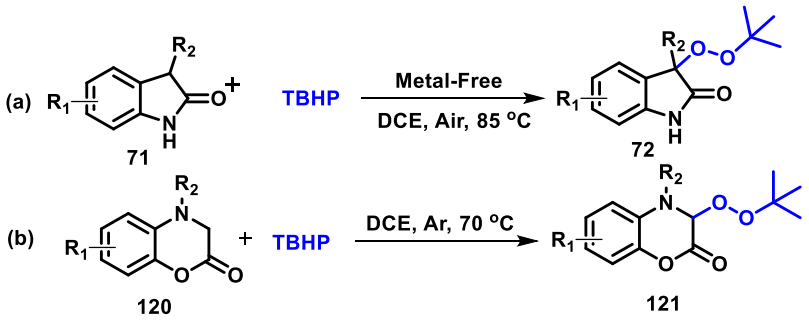
The rearrangement of organic peroxides is the critical step in many well-known processes such as the Baeyer–Villiger (BV),[15-a] the Criegee,[16-a] and Hock reactions,[39] the Kornblum–DeLaMare rearrangement,[40] and Dakin reaction[41] have been discussed in section 1.6. in Chapter 1. The skeletal rearrangement of the peroxides to access biologically significant intermediates is an attractive concept focused on these rearrangements for making heterocyclic scaffolds in organic synthesis. For instance, Stoltz and co-workers reported that 2-oxindole was subjected to C-H peroxidation by a Cu catalyst, followed by base-mediated fragmentation.[46] Literature background on the rearrangement of C3-substituted 2-oxindole peroxide using Brønsted and Lewis acid of peroxides was reported by the Gnanaprakasam group discussed in section 1.6 of Chapter 1.[73,47a-e]Other research groups have reported a few other rearrangements using different heterocyclic peroxides.[43,44,45] Recently, fewer metal-free conditions[74a-b,53a] have been accounted for the peroxidation of 3-substituted indolin-2-ones (Scheme 3.2.5. (a)),[74c] and 3,4-dihydro-1,4-benzoxazin-2-ones (Scheme 3.2.3. (b))[74d] despite the fact that several peroxidation reactions have been accomplished using metal[22,73,51b,52] toward the skeletal rearrangement reaction.



Scheme 3.2.4. Metal-free peroxidation of 3-substituted indolin-2-ones and 3,4-dihydro-1,4-benzoxazin-2-ones

---

In addition, the peroxidation of 2-naphthols has been carried out using a transition metal catalyst[71] and stoichiometric reagents.[72] Some of the transition-metal residues are undesirable to use in medicines and are difficult to remove from desired products.

Henceforth, developing a catalyst-free, operationally simple, and scalable route for the peroxidation of 2-naphthols and 3-arylbenzofuran-2-ones and further its rearrangements for the synthesis of heterocycles are fascinating in the chemical synthesis. In addition, batch conditions are explosive due to the high-energy molecules decomposing with heat, light, and shock during scale-up. Therefore, we chose to develop a continuous-flow protocol that enables green principles using controlled addition of reagents to enhance safety and scalability, increase heat transfer, and reduce reaction time.

3.2.1. Introduction about continuous flow chemistry

The continuous flow chemistry is a new instrumental technique for organic synthesis. Both homogeneous and heterogeneous catalysis are suitable for this new technique, in which the recycling of catalysts is authoritative. The continuous-flow reactor is a powerful synthetic device in the petrochemical, pharmaceutical industry, and it obeys several principles of green chemistry.[75] The continuous-flow reactor enables higher efficiency, safety, and mass transfer than conventional batch reactions.[76] Flow chemistry has proven to be a powerful synthesis tool that can handle unpleasant or hazardous substances and exothermic reactions with greater safety.

Typical parts of a continuous flow are as follows:

(a) **Pumps**: Pumps commonly used for continuous flow reactors are piston, peristaltic, or syringe pumps. The main function of a pump is to transfer the reagents, reactants, or solvents from a vessel or bottle to the reaction loops.

(a)  **(b)** 

Figure 3.2.1. (a) Set up of continuous flow; (b) Side view of coil reactor of the Vapourtec R-series from Dr. B. Gnanaprakasam's laboratory

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(b) **Reaction loops**: The loops introduce the reagents or solvent into a mixing junction (T-piece).

(c) **T-piece**: T-piece or mixing junction is essential, with the primary mixing point comprising two reagent streams mixed and fed into a reactor.

(d) **Coil reactor**: Many types of reactors run a continuous flow. Coiled reactors are mainly used for homogeneous reaction conditions, providing heating or cooling and retention time for a reaction.

(e) **Column reactor**: A column reactor is a hollow vertical glass or metal tube packed with a solid catalyst or reagents.

(f) **Back pressure regulator (BPR)**: A back pressure regulator used to superheat a solvent is possible. For instance, acetonitrile (ACN) has a boiling point of 82 ^{o}C, but we can heat the acetonitrile well beyond its boiling point. It will control the pressure in the system.

(g) **Downstream unit**: Various instruments such as IR, UV, and NMR, *etc.*, by integrating into the continuous flow system, the *in-line* analytics or reaction monitoring is possible.

3.3. The rationale of the present work

The synthesis of peroxide on a large scale is associated with safety hazards. This inspired us to develop an operationally simple and scalable route for their synthesis and further its rearrangements, which are in high demand in contemporary research. Further, functionalized

peroxynaphthols and peroxybenzofuranones are helpful precursors for synthesizing natural products containing α-ketol,[64] and 3-hydroxy-3-substituted-benzofuran-2(3*H*)-one.[65]

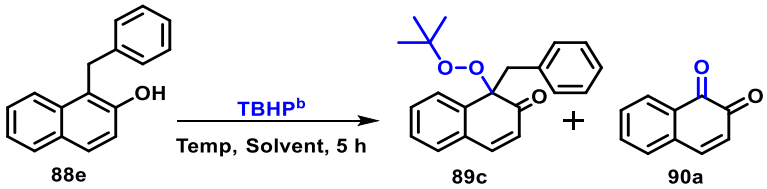
3.4. Results and discussion

In this chapter, we have discussed an efficient method for the peroxidation of naphthols and 3-arylbenzofuran-2(3*H*)-one under batch/continuous flow conditions. In addition, we have developed a new method for rearrangement towards dioxole-2-carboxamide derivatives by flow module.

3.4.1. Optimization studies in batch and continuous flow

To establish metal-free peroxidation of naphthols and 3-arylbenzofuran-2(3*H*)-one, optimization was first carried out with 1-benzylnaphthalen-2-ol **88e** and TBHP **1c** 5-6 M in decane.

Table 3.4.1. Optimization of reaction conditions for the peroxidation of 1-benzylnaphthalene-2-ol under batch conditions[a]



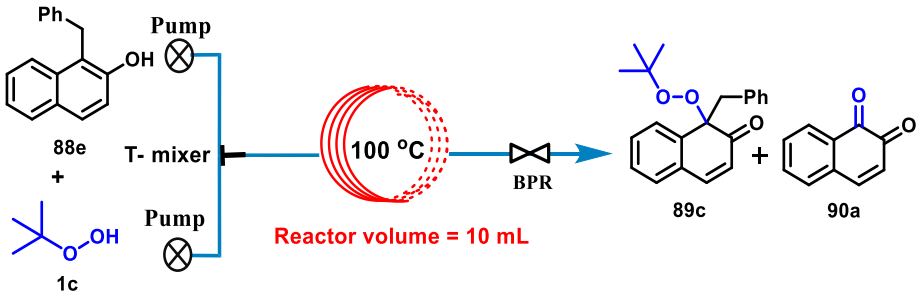
Entry	Solvent	Temp °C	Yield [%] **89c/90a**
1	ACN	rt	trace/ND
2	ACN	60	30/ND
3	ACN	80	48/ND
4[c]	ACN	80	45/ND
5	ACN	100	88/trace
6[d]	ACN	100	50/trace
7	DCE	80	85/trace
8	THF	80	10/ND
9	EtOAc	80	58/ND
10	EtOH	80	40/ND

[a]**Reaction conditions**: Compound **88e** (0.25 mmol), [b]TBHP **1c** (4 equiv.) 5-6 M in decane, [c]TBHP **1c'** 70% in water, and solvent (2 mL) was stirred in a preheated oil bath (see table) for 5 h. [d]Reaction performed for 2 h. ND = Not detected. The mentioned yields are isolated yields.

A control experiment **88e** and TBHP **1c** (4 equiv.) 5-6 M in decane at room temperature in acetonitrile (ACN) gave a trace amount of the desired product **89c** (Table 3.4.1., entry 1). Then, we carried out this reaction at 60 °C and obtained 30% of **89c** (Table 3.4.1., entry 2) and increased the temperature, which resulted in a slight increase in yield of 48% (Table 3.4.1., entry 3). TBHP **1c'** (4 equiv.) 70% in water at 80 °C also gave an almost similar yield to TBHP **1c** (4 equiv.) 5-6 M in decane (Table 3.4.1., entry 4). Notably, 88% of **89c** was obtained when the reaction was carried out at 100 °C (Table 3.4.1., entry 5). In addition, a decrease in yield was observed when the reaction time was reduced from 5 h to 2 h (Table 3.4.1, entry 6). Moreover, the yield in this reaction could not be improved with other solvents (Table 3.4.1., entries 7−10). These experimental solvent studies revealed that acetonitrile (ACN) is the best solvent for this reaction.

To extend the peroxidation reaction for scalability and avoid safety hazards, we optimized the reaction conditions in the continuous flow. Initially, solutions of **88e** (0.1 M) and (0.4 M) TBHP **1c** were passed through a coil reactor at 0.1 mL/min each at room temperature and 0.2 mL/min at 80 °C, resulting in a trace amount of the desired product **89c** (Table 3.4.2., entries 1, 2). When solutions of **88e** (0.1 M) and (0.4 M) TBHP **1c** were passed through a coil reactor at a flow rate of 0.1 mL/min each at 80 °C, **89c** was obtained in 41% yield (Table 3.4.2., entry 3) after two cycles with a residence time (t_R) of 50 min for each cycle. Slightly increasing yields of **89c** were observed with increasing reaction temperature, i.e., 47% and 75% yields of **89c** after 2 and 3 cycles, respectively (Table 3.4.2., entries 4 and 5). Subsequently, this reaction was studied at different concentrations of 0.05 M **88e** and 0.2 M TBHP **1c** and 0.2 M **88e** and 0.8 M TBHP **1c**, which gave 15% and 30% yields of **89c**, respectively (Table 3.4.2., entries 6 and 7). Finally, we kept the concentration of **88e** constant and varied the molar concentration of TBHP, and the results are shown in (Table 3.4.2., entries 8, 9, and 10). This optimization result showed that solutions of **88e** (0.1 M) and TBHP **1c** (0.6 M) passed through a coil reactor at 100 °C at 0.1 mL/min each gave product **89c** in 93% (Table 3.4.2., entry 10), where t_R = 50 min for each cycle.

Table 3.4.2. Optimization of reaction conditions for the peroxidation of 1-benzylnaphthalene-2-ol under continuous-flow[a]

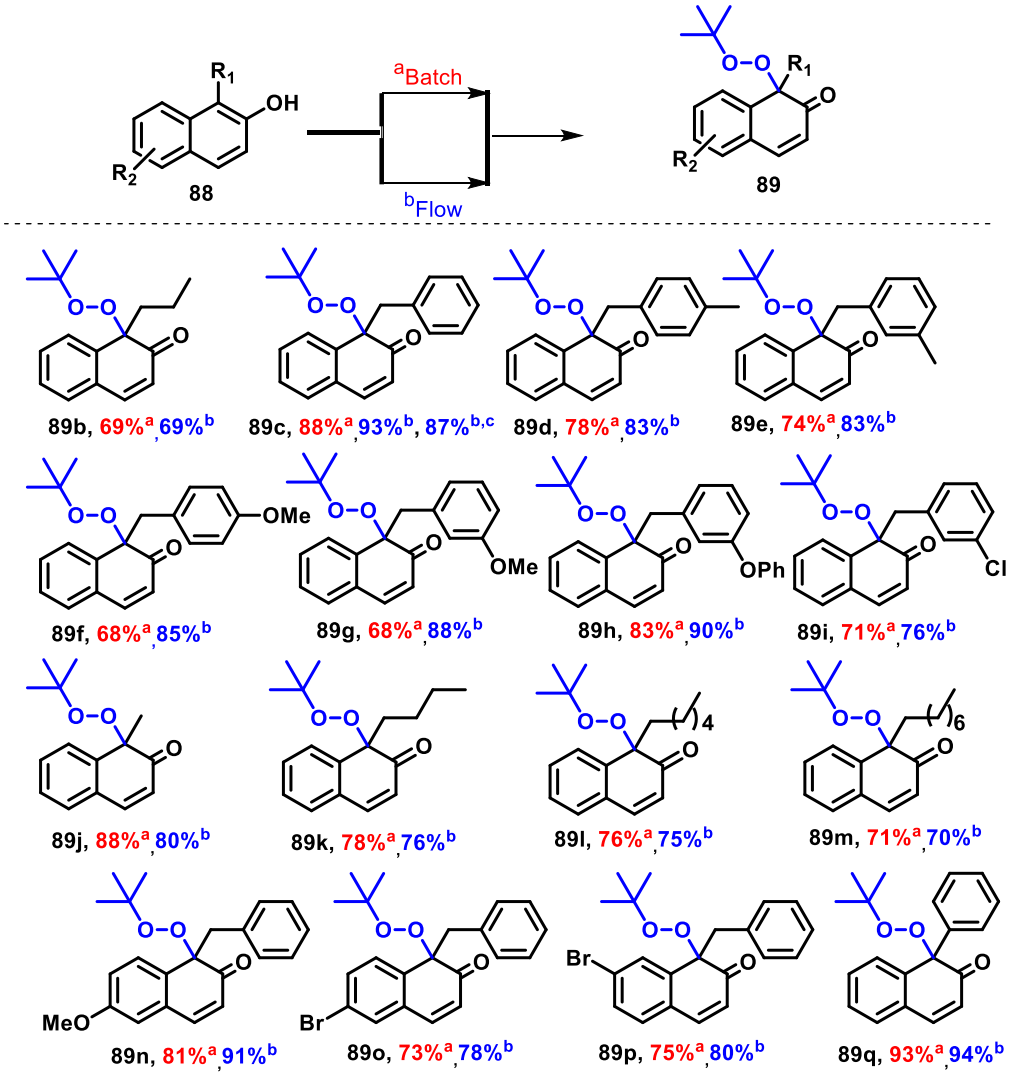


Entry	Conc. (M)		Flow rate in mL/min each	Temp ^{0}C	t_R (min)/ Number of runs	Yield **89c**/**90a** (%)
	88e	TBHP **1c**				
1	0.1	0.4	0.1	rt	50/1	trace/ND
2	0.1	0.4	0.2	80	50/1	trace/ND
3	0.1	0.4	0.1	80	100/2	41/ND
4	0.1	0.4	0.1	100	100/2	47/trace
5	0.1	0.4	0.1	100	150/3	75/trace
6	0.05	0.2	0.1	100	50/1	15/ND
7	0.2	0.8	0.1	100	50/1	30/ND
8	0.1	0.5	0.1	100	100/2	58/trace
9	0.1	0.6	0.1	100	100/2	70/trace
10	0.1	0.6	0.1	100	150/3	93/trace

[a]**Reaction conditions:** A 0.05-0.2 M (see table) solution of **72a** and 0.2-0.6 M (see table) TBHP **1c** were flown through the 10 mL SS tubular reactor (Vapourtec R-series) at a specified temperature. All solutions of **72a** and TBHP **1c** (5-6 M in decane) were prepared in 5 mL CH_3CN. t_R = residence time. ND = Not detected. The mentioned yields are isolated yields.

3.4.2. The substrate scope for the peroxidation 1-substituted-2-naphthols in batch and continuous flow

With the optimized conditions in hand, the scope of the substrate for batch/flow was applied to generalize the peroxidation of substituted naphthols.



Scheme 3.4.1. Substrate scope for substituted naphthols under batch/continuous flow.

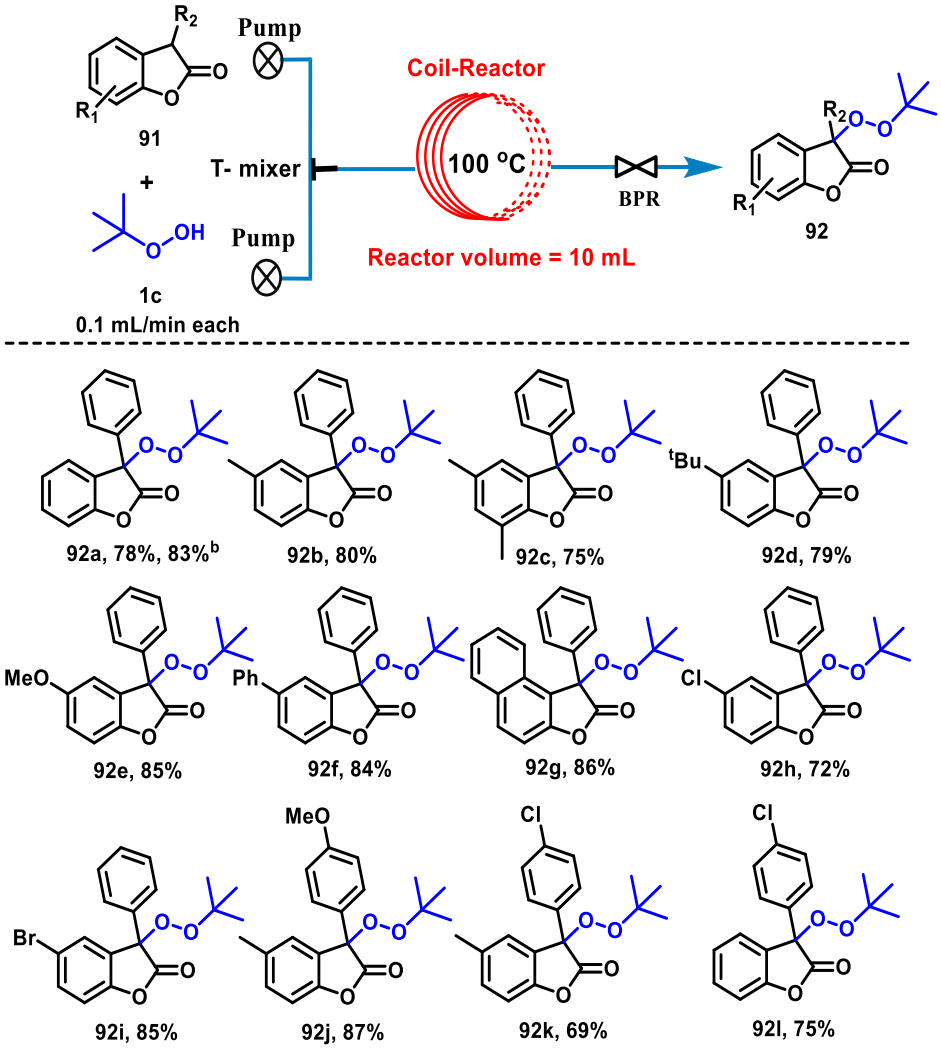
Reaction conditions. [a]Method A (Batch): Compound **88** (0.25 mmol), TBHP **1c** (4 equiv.) 5-6 M in decane and ACN (2 mL) were stirred in a preheated oil bath at 100 °C for 5 h. [b]Method B (Continuous-Flow): 0.1 M solution of **88** and 0.6 M TBHP **1c** were flown through the 10 mL SS tubular reactor (Vapourtec R-series) three times run at 100 °C. All solutions of **88** and TBHP **1c** (5-6 M in decane) were prepared from 5 mL CH_3CN. t_R = residence time. [c]Gram scale and isolated yields.

First, the peroxidation of substrates with substituents on benzyl groups were tested, and the results are summarized in Scheme 3.4.1. The electron-neutral 1-benzylnaphthalen-2-ol **88e** afforded **89c** in 88% and 93% yields under standard batch and continuous flow conditions,

respectively (Scheme 3.4.1.). Next, benzyl groups with electron-donating groups such as 4-Me, 3-Me, 4-OMe, 3-OMe, 2-OMe, and 3-OPh gave good to excellent yields of products **89d-89h** (Scheme 3.4.1.). In addition, electron-withdrawing substituents such as 3-Cl on the benzyl group gave a moderate yield of the corresponding product **89i** (Scheme 3.4.1.). To our delight, the aliphatic moiety on the 1-position of the naphthol also reacted well and gave the products **89b** and **89j**–**89m** in moderate to good yield (Scheme 3.4.1.). The substrate such as 1-benzyl-6-methoxynaphthalen-2-ol, 1-benzyl-6-bromonaphthalen-2-ol, 1-benzyl-7-bromonaphthalen-2-ol with batch and flow led to the products **89n**–**89p** in good to excellent yield (Scheme 3.4.1.). Encouragingly, the reaction of 1-phenylnaphthalen-2-ol gave product **89q** in yields of 93% and 94% in batch and continuous flow, respectively. The structure of product **89q** was confirmed by single-crystal XRD (Figure 3.8.17.).

3.4.3. The substrate scope for the peroxidation of 3-substituted benzofuran-2(3*H*)-ones in continuous flow

Next, the peroxidation of 3-substituted benzofuran-2(3*H*)-ones **91** in continuous flow were studied (Scheme 3.4.2.). The reaction of 0.1 M solution of **91a** and 0.6 M TBHP **1c** flowing through the 10 mL SS tubular reactor under standard conditions gave the product **92a** in 78% yield. The electron-rich group of 5-substituted-3-phenylbenzofuran-2(3*H*)-one afforded **92b**-**92e** in 75% to 85% yields (Scheme 3.4.2.). Further, 3,5-diphenylbenzofuran-2(3*H*)-one and 1-phenylnaphtho[2,1-*b*]furan-2(1*H*)-one afforded product **92f** in 84% and **92g** in 86% yield, respectively (Scheme 3.4.2.). The electron-withdrawing group of 5-substituted-3-phenylbenzofuran-2(3*H*)-one afforded **92h** and **92i** in 72% to 85% yield. The 3-(4-methoxy-phenyl)-5-methylbenzofuran-2(3*H*)-one and the 3-(4-chlorophenyl)benzofuran-2(3*H*)-one afforded **92j**, **92k**, and **92l** in 87%, 69% and 75% yields, respectively. To our delight, a gram-scale reaction was also performed, producing 87% and 83% of products **89c** and **92a** through the flow method.



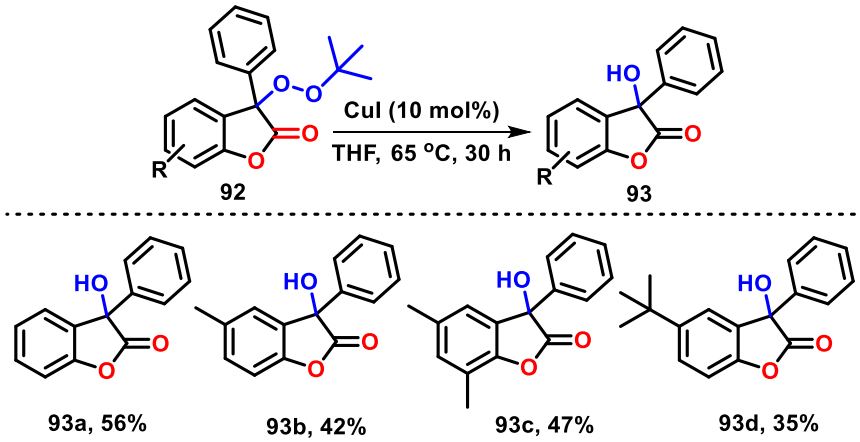
Scheme 3.4.2. Substrate scope for peroxidation of 3-aryl benzofuran-2(3*H*)-ones under continuous flow[a]

[a]**Reaction conditions**: Method B Continuous flow: 0.1 M solution of **91** and 0.6 M TBHP **1c** were flown through the 10 mL SS tubular reactor (Vapourtec R-series) thrice at 100 °C. All solutions of **91** and TBHP **1c** (5-6 M in decane) were prepared in 5 mL CH_3CN. [b]Gram scale and isolated yields.

3.4.4. The substrate scope of 3-hydroxy-5-substituted-3-phenylbenzofuran-2(3*H*)-one and 1,2-naphthoquinone

Next, the application of peroxybenzofuranone derivatives was investigated to synthesize bioactive 3-hydroxy-5-substituted-3-phenylbenzofuran-2(3*H*)-one by a reduction reaction. For example, the reduction of peroxybenzofuranone was carried out using **92a** in the presence of 10

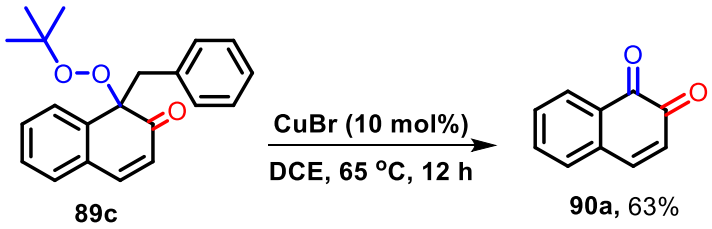
mol% CuI, afforded **93a** in 56% yield (Scheme 3.4.3.). Next, the reduction of substituted peroxybenzofuranone **92** has been performed using CuI afforded **93b-93d** in moderate yields (Scheme 3.4.3.). The starting material was recovered in all these reactions, and a trace amount of uncharacterized product was observed on the TLC.



Scheme 3.4.3. Synthesis of 3-hydroxy-5-substituted-3-phenylbenzofuran-2(3*H*)-one[a]

[a]**Reaction condition:** CuI (10 mol%), THF, 65 °C, 30 h. The mentioned yields are isolated yields.

Moreover, oxidative cleavage has been performed using **89c** in the presence of catalytic CuBr to afford 1,2-naphthoquinone **90a** in 63% yield (Scheme 3.4.4). The synthesized 1,2-naphthoquinone **90a** and 3-hydroxy-3-phenylbenzofuran-2(3*H*)-one **93** can be used as valuable precursors for the synthesis of various bioactive molecules.[64,65]



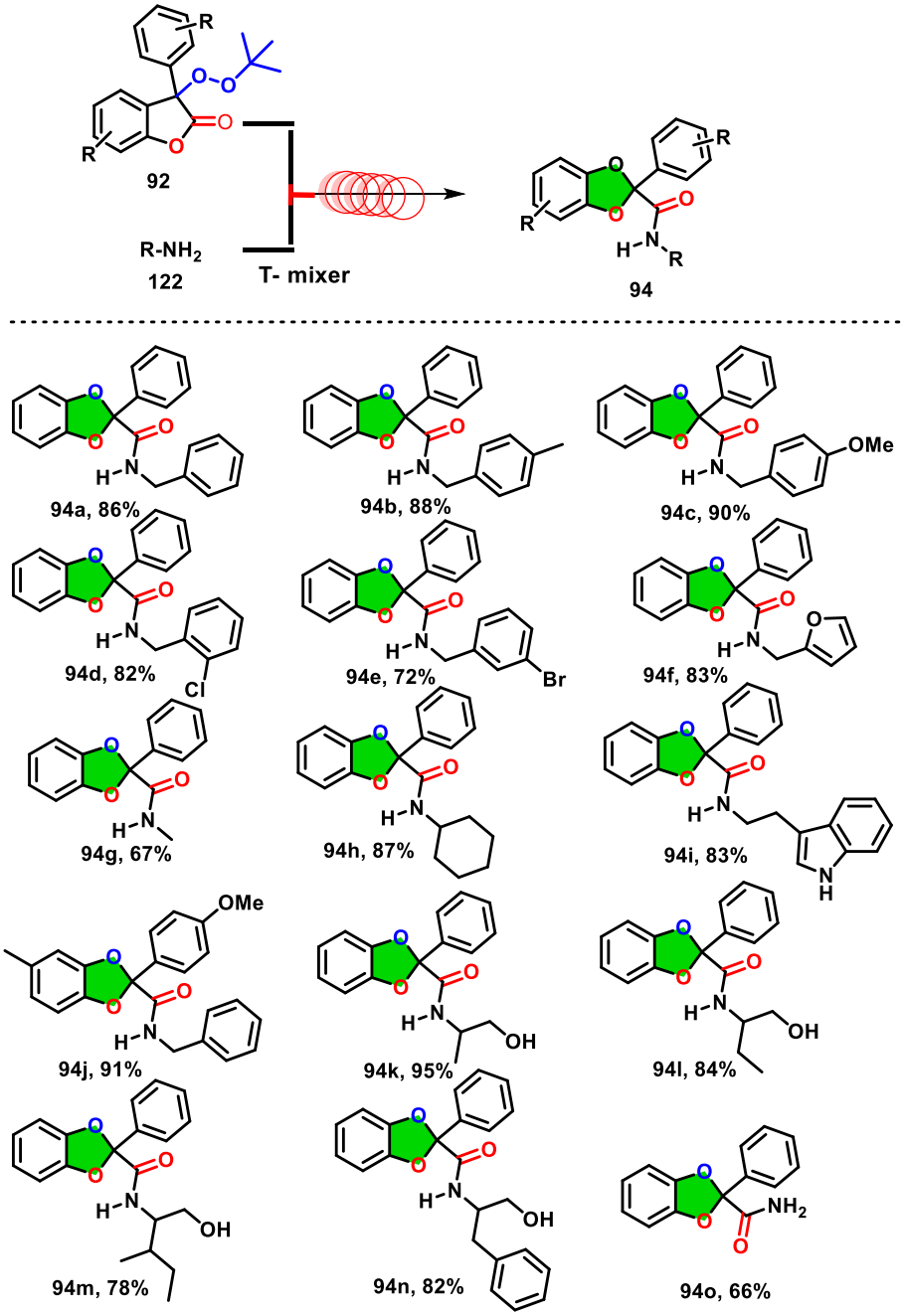
Scheme 3.4.4. Synthesis of 1,2-naphthoquinone *via* Hock cleavage[a]

[a]**Reaction condition:** CuBr (10 mol%), DCE, 65 °C, 12 h. The mentioned yield are isolated yields.

3.4.5. Substrate scope of *N*-substituted-2-phenylbenzo[*d*][1,3]dioxole-2-carboxamide in flow

In addition, we have envisioned the molecular reconstruction of peroxides **92** to *N*-substituted-2-phenylbenzo[*d*][1,3]dioxole-2-carboxamide **94** derivatives in a continuous flow

approach. For instance, compound **92** (0.1 M, 5 mL ACN) in a 30-mL vial was combined in a T-piece with a stream of amines **122** (0.2 M, 5 mL of ACN) in another 30-mL vial.



Scheme 3.4.5. Substrate scope of *N*-substituted-2-phenylbenzo[*d*][1,3]dioxole-2-carboxamide[a]

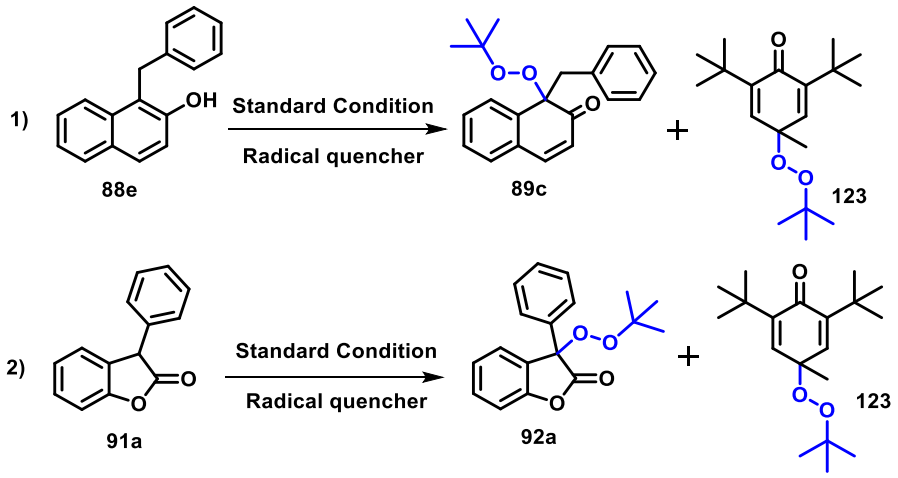
[a]**Reaction condition:** Continuous-flow: The compound **92** (0.1 M, 5 mL of ACN) in a 30 mL vial was combined in a T-piece with a stream of amines **122** (0.2 M, 5 mL of ACN) in another 30 mL vial. All solutions of peroxybenzofuranone **92** and amine **122** were prepared in 5 mL CH_3CN.

Furthermore, the prepared solutions were flown through a 10 mL SS coil reactor at a flow rate of 0.1 mL/min and run three times at 100 °C at 3-4 bar pressure, furnished *N*-benzyl-2-phenylbenzo[*d*][1,3]dioxole-2-carboxamide **94a** in 86% isolated yield. Other amines also reacted well in this reaction, giving **94b**-**94j** in good to excellent yields (Scheme 3.4.5.). Similarly, the formation of the *N*-(1-hydroxy-substituted)-2-phenylbenzo[*d*][1,3]dioxole-2-carboxamide derivative afforded **94k**-**94n** in good to excellent yields. The 2-phenylbenzo[*d*][1,3]dioxole-2-carboxamide **94o** was also synthesized effectively by this method afford in 66% isolated yield (Scheme 3.4.5.).

3.5. Mechanistic investigations

To understand the reaction pathway, a series of control experiments were performed on this peroxidation of naphthol and benzofuran.

3.5.1. Radical quenching experiment for peroxidation



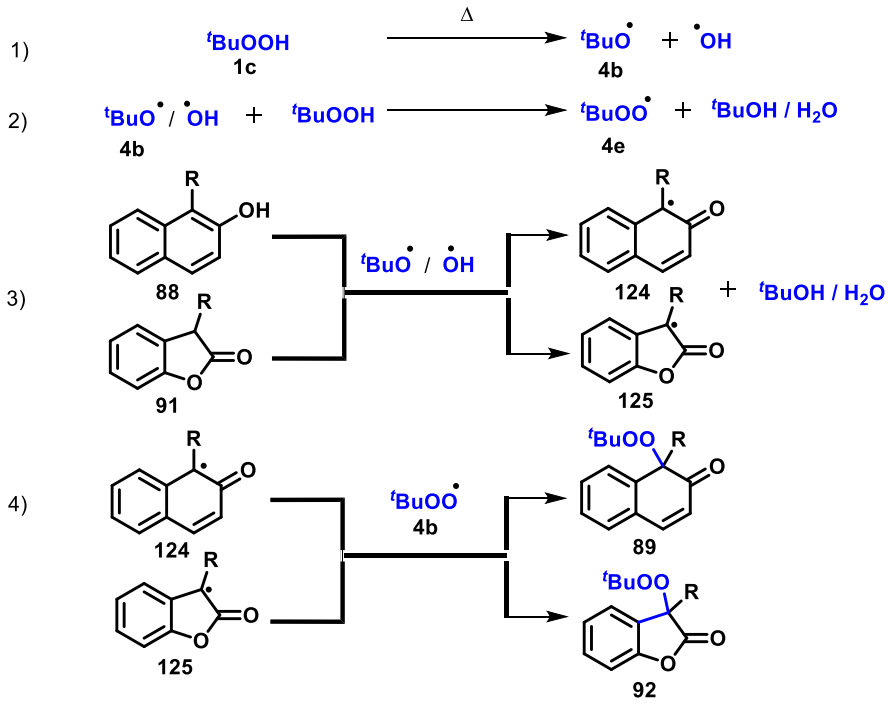
Entry	Radical quencher (2 equiv.)	Yield	Yield
1	None	**89c,** (88%)	**92a,** (78%)
2	TEMPO	**89c,** (74%)	**92a,** (11%)
3	BHT	**89c,** (6%), **123** (55%)	**92a** (33%), **123** (49%)

Scheme 3.5.1. Radical quenching experiment

When 2.0 equiv. of radical scavengers such as TEMPO or BHT were added to the reaction, the yield of **89c** and **92a** decreased significantly, indicating the radical pathway of this reaction. This reaction is a radical process, and BHT can scavenge the radical intermediate and provide the desired product **123** in 55% and 49% yields with 1-benzylnaphthalen-2-ol **88e** and 3-phenylbenzofuran-2(3*H*)-one **91a** respectively (Scheme 3.5.1.).

3.5.2. Plausible mechanism for peroxidation

Based on previous literature precedent[74c,74d] and control experiments, we proposed a plausible mechanism for the peroxidation of 2-naphthols and benzofuranones (Scheme 3.5.2.).



Scheme 3.5.2. Plausible mechanism for the for the peroxidations of 1-substituted-2-naphthols and 3-aryl benzofuran-2(3*H*)-ones

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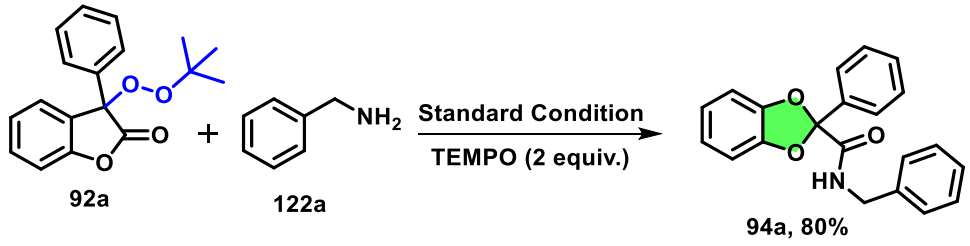
Initially, upon heating TBHP, the (O–O) bond cleaved to form a *tert*-butoxyl radical and a hydroxyl radical in the system (Scheme 3.5.2.). Subsequently, *tert*-butoxyl **4b** or hydroxyl radicals react with TBHP **1c** under hydrogen abstraction to form *tert*-butylperoxy radicals **4e** (Scheme 3.5.2.). At the same time, the hydrogen atom from the 2-naphthols, mainly from the hydroxy group **88** or adjacent to the carbonyl group of the benzofuranones **91**, is abstracted by the *tert*-butoxyl **4b** or hydroxyl radical to form the radical intermediate **124** or **125** (Scheme 3.5.2.). Finally, radical

124 or **125** is captured by the *tert*-butylperoxy radical **4e** to give the desired products **89** and **92** (Scheme 3.5.2.).

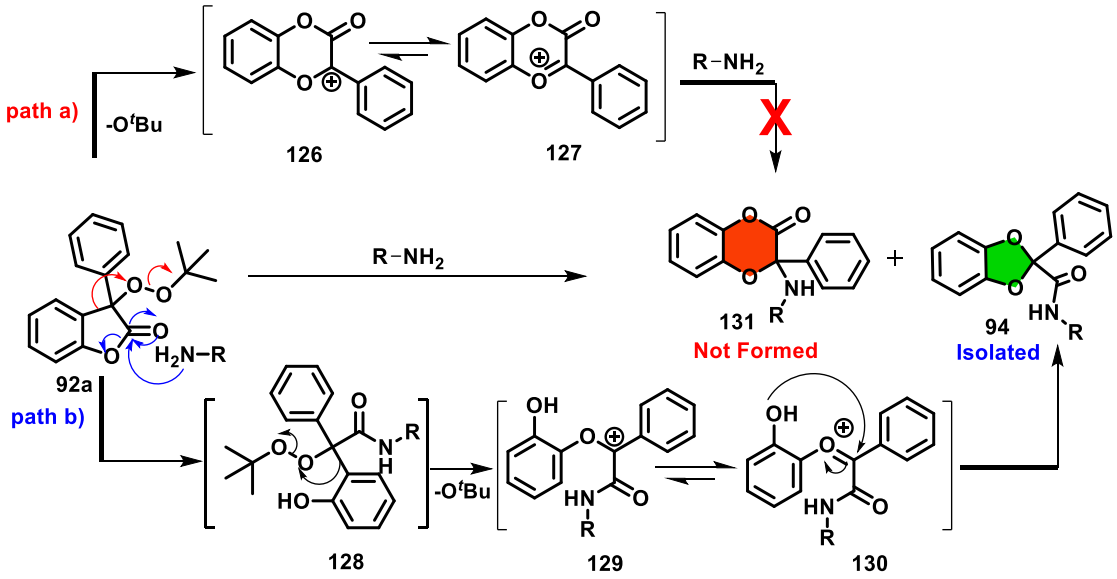
3.5.3. Radical quenching experiment for rearrangement

Similarly, to gain additional insight into the reaction pathway and to clarify the mechanism for rearrangement reactions of **92a** to **94a**, a control experiment was carried out. If the reaction had taken the radical path, radical adducts could have formed when the radical quencher TEMPO, was used in the reaction. However, we were unable to detect any adducts in the reaction. There was no change in the yields of **94a** when the reaction was performed in the presence of TEMPO as a radical scavenger (Scheme 3.5.3.), and it demonstrated the reaction did not follow a radical path.



Scheme 3.5.3. Radical quenching experiment for the rearrangement

3.5.4. Plausible mechanism for rearrangement



Scheme 3.5.4. A plausible mechanism for the *N*-substituted-2-phenylbenzo[*d*][*1,3*]dioxole-2-carboxamide

For the rearrangement leading to **94a**, we have proposed the two possible pathways as shown in Scheme 3.5.4. In pathway (a), we envision the migration of the aryl group to oxygen, which would lead to the 3-(substituted-amino)-3-phenylbenzo[*b*][1,4]dioxin-2(3*H*)-one product **131** *via* the intermediate **126**/**127** (Scheme 3.5.4., path a). However, in path (a) product **131** was not observed in the reaction. In pathway (b), peroxybenzofuranone **92a** was followed by a reaction similar to that in 4-oxa-Grob fragmentation,[77] Path b allowed fragmentation of the C2−C3 bond by amine **122** attack and formation of the intermediate **128** (Scheme 3.5.4.). The intermediate **128** formed in situ was very unstable and could not be isolated. Moreover, the hydroxy-aryl group of intermediate **128** migrates to oxygen to give the desired product **94a** *via* intermediate **129**/**130** (Scheme 3.5.4., path b).

3.6. Conclusion

In summary, we have developed an approach for the metal-free C–H peroxidation of bioactive 2-naphthols and benzofuranone derivatives by batch and continuous flow. The innovation in this work was the utilization of a continuous flow setup for the peroxidation process, which offers advantages in terms of scalability and safety compared to traditional batch methods. Further, we have successfully carried out the peroxidation of benzofuranone derivatives and converted the resulting peroxides into *N*-substituted-2-phenylbenzo[*d*][1,3]dioxole-2-carboxamide derivatives. This transformation exhibited high efficiency, with yields reaching up to 95%. These final derivatives are potentially bioactive, implying their potential use in various biological applications. Moreover, the synthesized peroxide has been successfully converted into the bioactive 3-hydroxy-3-phenylbenzofuran-2(3*H*)-one and 1,2-naphthoquinone. To explain the observed reactions, we have proposed a plausible mechanism based on both experimental findings and information available in the existing scientific literature.

3.7. Experimental section and characterization data

3.7.1. General information and data collection:

The naphthols, phenols, mandelic acid, and *tert*-butyl hydroperoxide (TBHP) 5.0–6.0 M in decane solution (CAS No–416665) were used as a starting material purchased from Sigma-Aldrich. All the solvents used in the reactions for optimization and substrate were dry grade. The chromatographic column separations were achieved over 100–200 mesh size silica-gel. Visualization completed with UV light, PMA, and CAM stain accompanies heating. Using a Bruker or JEOL spectrometer, the ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded at 400 and 100

MHz, respectively. The values of the coupling constant (*J*) and chemical shift (δ) are expressed in hertz (Hz) and parts per million (ppm), respectively. Brief information used in NMR follow-up experiments: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad; dt, doublet of triplet; ddd, doublet of doublets of doublets. High-Resolution Mass Spectra were recorded by waters-synapt G2 using electrospray ionization (ESI–TOF). Infrared (ATIR) spectra were obtained with a Bruker Alpha-E infrared spectrometer. The melting point was measured using the BUCHI M–560 melting-point instrument. All melting points of the substrates were measured in an open glass capillary tube. The flow chemistry experiments were conducted on a Vapourtec R–series instrument with an SS coil reactor (10 mL). The 1-substituted-2-naphthols were prepared according to the literature,[78a-e] **88e**, **88f**, **88h**, (**88l**-**88p)**, **88r**, and **88t**[78e] were known compounds. The compounds **88g**, **88i**, **88j**, **88k**, **88q,**[78d] and **88s**[78d] were new. The derivative of 3-aryl benzofuran-2(3*H*)-ones (**91a-91l)** were prepared according to the literature,[79] All of the substrates **91** were known compounds.[79] Single-crystal diffraction analysis data were collected at 100 K with a BRUKER KAPPA APEX III CCD Duo diffractometer (operated at 1500 W power; 50 kV, 30 mA) using graphite monochromatic Mo Kα radiation and Cu Kα radiation. More information on the crystal structures **89q**, **92g**, **94a**, and **94d** can be obtained from the Cambridge Crystallographic Data Centre (CCDC) via deposition numbers **89q** (2252438), **92g** (2203780), **94a** (2252449), and **94d** (2252424).

"***Although the reaction of organic peroxides is explosive, we have not faced any issues, even at the gram scale.***"

3.7.2. Experimental procedure

A. 1. Preparation of the starting material: Derivatives of 1-substituted-2-naphthols were prepared according to the literature.[78-80,65b]

Step-I: General procedure for the synthesis of 2-naphthol Mannich bases.[78a]

To a solution of β-naphthols (1 g, 6.93 mmol, 1.0 equiv.) in 5 mL of 95% ethanol, aldehyde (10.39 mmol, 1.5 equiv.), and pyrrolidine (739.29 mg, 10.39 mmol, 1.5 equiv.) were added. The reaction mixture was refluxed for 12 h and brought to room temperature. The precipitate was filtered and washed with 40% ethanol in hexane.

Step-II: General procedure for the synthesis of 1-substituted-2-naphthols (88).[78b]

A mixture of the appropriate 2-naphthol Mannich base (0.7 mmol, 1 equiv.), ammonium formate (7 mmol, 10 equiv.), and Pd/C (33 mg, 10 wt %, 10 mol %) in methanol (15 ml) was refluxed for

2 h. The reaction mixture was filtered on a celite bed, the methanol was concentrated, and the product was extracted with ethyl acetate and water. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated in a vacuum to yield a solid product, which was washed with ice-cold dichloromethane (3 ml).

A. 2. Preparation of the starting material: Derivative of 1-substituted-2-naphthols (88) was prepared according to the modified literature procedure.[78c]

β-naphthols (300 mg, 2 mmol, 1 equiv.), alcohols (2 mmol, 2 equiv.), Pd/C (221 mg, 10 wt %, 10 mol %), lithium *tert*-butoxide (16 mg, 0.2 mmol, 0.1 equiv.), and finally, toluene (4.0 mL) were added to an oven-dried 20 mL resealable pressure tube, which is equipped with a rubber septum. The tube was purged with nitrogen and sealed with a cap using a crimper. Further, the tube was placed in a preheated oil bath at 160 ºC, and the mixture was stirred vigorously for 24 h. The reaction mixture was cooled to room temperature and filtered through a plug of celite. The filtrate was concentrated under vacuum, and the resulting residue was purified by 100−200 mesh silica-gel column chromatography using ethyl acetate/petroleum ether (10:90) to afford the pure product of 1-substituted-2-naphthols **88**.

A. 3. Preparation of the starting material: Derivative of 1-substituted-2-naphthols (88) was prepared according to the modified literature procedure.[78d]

Substituted naphthols (1.3 mmol, 1 equiv.) and LiOH (62 mg, 2.6 mmol, 2 equiv.) were finely crushed, mixed, and stirred for 15 minutes. $PhCH_2Br$ (445 mg, 2.6 mmol, 2 equiv.) was added, and the mixture was heated at 85°C for 2 h. 50 ml of diethyl ether was added. After filtration on Florisil, the filtrate was evaporated, and the residue was purified using silica gel column chromatography on ethyl acetate/petroleum ether (10:90) to afford the pure product 1-substituted-2-naphthols **88q**, and **88s**.

A. 4. Starting materials preparation: derivative of 3-aryl benzofuran-2(3*H*)-ones (91) were prepared according to the literature.[79]

Mandelic acid (2.7 mmol, 2.0 equiv.), phenol (1.3 mmol, 1.0 equiv.), and $Ni(OTf)_2$ (98 mg, 0.27 mmol, 10 mol%) were added to an oven-dried Schlenk tube of 20 mL, which was equipped with a magnetic stirring bar. The mixture was vigorously stirred at 160 °C for 12 h under vacuum conditions before being cooled to room temperature. Then 15 mL of water was added, and the resulting mixture was subject to extraction with EtOAc (15 mL×3). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and concentrated in a vacuum. Further purification

by flash column chromatography on the silica gel and eluted with ethyl acetate/petroleum ether (10:90) to afford the pure product of 3-aryl benzofuran-2(3H)-ones **91**.

B. General experimental procedure for dearomative peroxidation of 1-substituted-2-naphthols (89) under batch conditions.

In a 20 mL re-sealable vial was added 1-substituted-2-naphthols compound **88** (0.25 mmol, 1 equiv.) and 5.0-6.0 M *tert*-butyl hydroperoxide (TBHP) **1c** in decane solution (1.00 mmol, 181 µL, 4 equiv.) without maintaining any special conditions like inert atmosphere. Further, the tube was sealed with a cap using a crimper. The reaction mixture was stirred at 100 °C for 5 h in a preheated oil bath. After completion of the reaction, a volatile component was evaporated using a vacuum. The residue was directly purified by silica gel column chromatography (EtOAc:*n*-hexane = 5:95).

C. General experimental procedure for dearomative peroxidation of 1-substituted-2-naphthols (89) under continuous-flow.

The 1-substituted-2-naphthols compound **88** (0.50 mmol, 1 equiv.) in a 30 mL vial, and simultaneously 5.0-6.0 M *tert*-butyl hydroperoxide (TBHP) in decane solution (3.00 mmol, 545 µL, 6 equiv.) was taken in another 30 mL vial. All solutions of **88** and TBHP **1c** (5-6 M in decane) were prepared from 5 mL CH_3CN. Next, the prepared solutions were flown through a 10 mL SS coil reactor with a flow rate of 0.1 mL/min each at 100 ^oC temperature with 3-4 bar pressure. The reaction mixture was continuously collected after 50 min; later, on the first run, the same reaction mixture was subjected to the next run with a residence time of 50 min for each cycle. After running three cycles, the volatile component was evaporated using a vacuum, and the residue was directly purified by silica gel column chromatography (EtOAc:*n*-hexane = 5:95).

D. General experimental procedure for C-H peroxidation of 3-aryl benzofuran-2(3*H*)-ones (91) under continuous flow.

The 3-aryl benzofuran-2(3*H*)-ones compound **91** (0.50 mmol, 1 equiv.) in a 30 mL vial, and simultaneously 5.0 - 6.0 M *tert*-butyl hydroperoxide (TBHP) in decane solution (3.00 mmol, 545 µL, 6 equiv.) was taken in another 30 mL vial. All solutions of **91** and TBHP **1c** (5-6 M in decane) were prepared from 5 mL CH_3CN. Next, the prepared solutions were flown through a 10 mL SS coil reactor with a flow rate of 0.1 mL/min each at 100 ^oC temperature with 3-4 bar pressure. The reaction mixture was continuously collected after 50 min; later, on the first run, the same reaction mixture was subjected to the next run with a residence time of 50 min for each cycle. After running

three cycles, the volatile component was evaporated using a vacuum, and the residue was directly purified by silica gel column chromatography (EtOAc:*n*-hexane = 5:95).

E. Experimental procedure for gram-scale dearomative peroxidation of 1-benzylnaphthalen-2-ol (88e) and 3-phenylbenzofuran-2(3*H*)-one (91a) under continuous flow.

The compound 1-benzylnaphthalen-2-ol **88e** (1.171g in 50 mL ACN) / compound 3-phenylbenzofuran-2(3*H*)-one **91** (1.051 g in 50 mL ACN) and 0.6 M of 5.0-6.0 M *tert*-butyl hydroperoxide (TBHP) in decane solution (5.45 mL in 50 mL ACN) was prepared, and the prepared solutions were flown through a 10 mL SS coil reactor with a flow rate of 0.1 mL/min each at 100 ºC temperature with 3-4 bar pressure, after running 3 cycles with the residence time of 50 min for each cycle, a volatile component was evaporated using a vacuum, and the residue was directly purified by silica gel column chromatography (EtOAc:*n*-hexane = 5:95), afforded **89c** in 1.405 g, 87%) as a yellow semisolid and **92a** in (1.240 g, 83%) as a white solid.

F. Experimental procedure for the synthesis of 3-hydroxy-5-substituted-3-phenylbenzofuran-2(3*H*)-one (93).

In a 20 mL re-sealable vial was added CuI (4.7 mg, 0.025 mmol, 10 mol%) and peroxybenzofuranone **92** (0.25 mmol, 1 equiv.). in THF (2 mL). The tube was sealed with a cap using a crimper. The reaction mixture was heated at 65 ºC in an oil bath for 30 h. After completion of the reaction, a volatile component was evaporated using a vacuum. The residue was directly purified by silica gel column chromatography (EtOAc: *n*-hexane = 20:80).

G. General experimental procedure for the synthesis of *N*-substituted-2-phenylbenzo[*d*][1,3]dioxole-2-carboxamide (94) from 3-(*tert*-butylperoxy)-3-arylbenzofuran-2(3*H*)-one (92).

The compound 3-(*tert*-butylperoxy)-3-arylbenzofuran-2(3*H*)-one **92** (0.1 M, 5 mL of ACN) in a 30 mL vial was combined in a T-piece with a stream of amines **122** (0.2 M, 5 mL of ACN) in a 30 mL another vial. All solutions of peroxybenzofuranone and amine were prepared in (5 mL) CH_3CN. Next, the prepared solutions were flown through a 10 mL SS coil reactor with a flow rate of 0.1 mL/min each at 100 °C at 3-4 bar pressure. The reaction mixture was continuously collected after 50 min; later, on the first run, the same reaction mixture was subjected to the next run with a residence time of 50 min for each cycle. After running three cycles, the volatile component was evaporated using a vacuum, and the residue was directly purified by silica gel column chromatography (EtOAc:*n*-hexane = 30:70-50:50).

H. Experimental procedure for the synthesis of naphthalene-1,2-dione (90a).

In a 20 mL re-sealable vial was added CuBr (3.5 mg, 0.025 mmol, 10 mol%), DCE (2 mL), and finally 1-benzyl-1-(*tert*-butylperoxy)naphthalen-2(1*H*)-one **89c** (81 mg, 0.25 mmol, 1 equiv.). The tube was sealed with a cap using a crimper. The reaction mixture was heated at 65 ^{o}C in an oil bath for 12 h. After completion of the reaction, a volatile component was evaporated using a vacuum. The residue was directly purified by silica gel column chromatography (EtOAc: *n*-hexane = 15:85).

I. Mechanistic studies radical quenching experiment

I.1. Radical quenching experimental procedure for peroxidation.

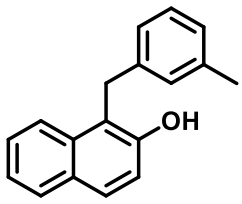
In a 20 mL resealable vial were added 1-benzylnaphthalen-2-ol **88e/**3-aryl benzofuran-2(3*H*)-ones compound **91a** (0.25 mmol, 1 equiv.), 5.0−6.0 M TBHP **1c** in decane solution (1.00 mmol, 181 μL, 4 equiv.) and finally TEMPO (2 equiv.) or BHT (2 equiv.) without maintaining any special conditions like inert atmosphere. Further, the tube was sealed with a cap using a crimper. The reaction mixture was stirred at 100 °C for 5 h. in a preheated oil bath. After completion of the reaction, a volatile component was evaporated using a vacuum. The residue was directly purified by silica gel column chromatography (EtOAc:*n*-hexane = 5:95) to afford 74% and 11% yields of products **89c** and **92a** with TEMPO and 06% and 33% yields of products **89c** and **92a** with BHT. Interestingly the radical quenching experiments were performed with BHT by using 1-benzylnaphthalen-2-ol **88e** and 3-aryl benzofuran-2(3*H*)-ones compound **91a** afforded 55% and 49% yields of product **123**, respectively.

I.2. Radical quenching experimental procedure for rearrangement.

In a 20 mL resealable vial were added 3-(*tert*-butylperoxy)-3-arylbenzofuran-2(3*H*)-one **91a** (75 mg, 0.25 mmol, 1 equiv.), benzylamine **122a** (54 mg, 0.50 mmol, 2 equiv.) and finally, TEMPO (78 mg, 0.50 mmol, 2 equiv.) was added to the resulting reaction mixture. Further, the tube was sealed with a cap using a crimper. The reaction mixture was stirred at 100 °C for 24 h in a preheated oil bath. After completion of the reaction, a volatile component was evaporated using a vacuum. The residue was directly purified by silica gel column chromatography (EtOAc: *n*-hexane = 50:50) to afford (67 mg, 80%) yields of products **94a.**

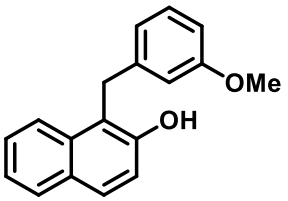
3.7.3. Analytical data for the product.

1-(3-methylbenzyl)naphthalen-2-ol **(88g):**



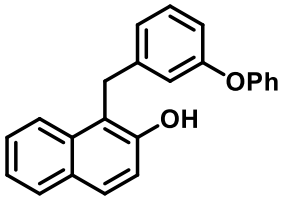
Prepared according to general procedure A.2, using naphthalen-2-ol (300 mg, 2 mmol) and 3-methylbenzyl alcohol (508 mg, 4 mmol) to afford 1-(3-methylbenzyl)naphthalen-2-ol **88g** (300 mg, 58% yield) as a yellow semisolid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 10:90). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.4 Hz, 1H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.40 – 7.36 (m, 1H), 7.29 – 7.25 (m, 1H), 7.10 –7.7.06 (m, 1H), 7.01 – 6.92 (m, 4H), 5.37 (s, 1H), 4.36 (s, 2H), 2.20 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 151.4, 140.1, 138.3, 133.8, 129.5, 129.0, 128.60, 128.56, 128.50, 127.0, 126.7, 125.3, 123.5, 123.3, 118.4, 118.0, 30.7, 21.5. IR (neat): 3374, 2923, 1618, 1495, 1248 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{18}H_{17}O$ $(M+H)^+$ 249.1279, found: 249.1279.

1-(3-methoxybenzyl)naphthalen-2-ol **(88i):**



Prepared according to general procedure A.2, using naphthalen-2-ol (300 mg, 2 mmol) and (3-methoxyphenyl)methanol (575 mg, 4 mmol) to afford 1-(3-methoxybenzyl)naphthalen-2-ol **88i** (260 mg, 47% yield) as a yellow semisolid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 10:90). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.5 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.69 (d, *J* = 8.8 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.35 (m, 1H), 7.19 (t, *J* = 7.9 Hz, 1H), 7.09 (d, *J* = 8.8 Hz, 1H), 6.88 – 6.79 (m, 2H), 6.76 – 6.71 (m, 1H), 5.36 (s, 1H), 4.45 (s, 2H), 3.74 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 159.9, 151.4, 142.0, 133.8, 129.63, 129.55, 128.6, 126.8, 123.4, 123.3, 120.8, 118.2, 118.0, 114.5, 111.2, 55.2, 30.8. IR (neat): 3399, 2922, 1595, 1446, 1261 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{18}H_{16}O_2$ $(M)^+$ 264.1150, found: 264.1152.

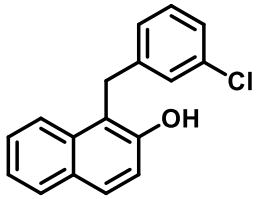
1-(3-phenoxybenzyl)naphthalen-2-ol **(88j):**



Prepared according to general procedure A.2, using naphthalen-2-ol (250 mg, 1.7 mmol) and (3-phenoxyphenyl)methanol (694 mg, 3.4 mmol) to afford 1-(3-phenoxybenzyl)naphthalen-2-ol **88j** (250 mg, 44% yield) as a yellow semisolid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 10:90). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.5 Hz, 1H), 8.01 (d, *J* =

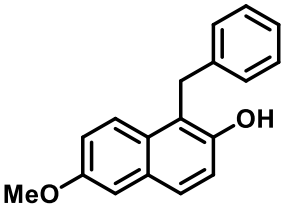
8.1 Hz, 1H), 7.88 (d, *J* = 8.8 Hz, 1H), 7.67 (t, *J* = 7.7 Hz, 1H), 7.58 – 7.50 (m, 3H), 7.36 – 7.28 (m, 2H), 7.24 – 7.14 (m, 5H), 7.02 (d, *J* = 7.8 Hz, 1H), 5.55 (s, 1H), 4.67 (s, 2H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 157.4, 157.2, 151.2, 142.6, 133.7, 129.8, 129.5, 128.7, 126.8, 123.4, 123.31, 123.27, 123.2, 119.2, 118.9, 118.1, 117.9, 116.5, 30.3. IR (neat): 3432, 3063, 1566, 1482, 1246 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{23}H_{19}O_2$ $(M+H)^+$ 327.1385, found: 327.1385.

1-(3-chlorobenzyl)naphthalen-2-ol **(88k):**



Prepared according to general procedure A.2, using naphthalen-2-ol (250 mg, 1.7 mmol) and (3-chlorophenyl)methanol (494 mg, 3.4 mmol) to afford 1-(3-chlorobenzyl)naphthalen-2-ol **88k** (200 mg, 43% yield) as a yellow solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 10:90). Melting point: 98−100 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.80 (m, 1H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.60 (d, *J* = 8.8 Hz, 1H), 7.36 – 7.31 (m, 1H), 7.25-7.21 (m, 1H), 7.14 – 7.06 (m, 4H), 7.01 – 6.98 (m, 1H), 4.97 (s, 1H), 4.36 (s, 2H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 151.3, 140.1, 133.8, 129.8, 129.6, 128.71, 128.68, 128.65, 128.3, 127.0, 126.8, 126.3, 123.5, 123.4, 118.3, 118.0, 30.8. IR (neat): 3527, 2925, 1616, 1263 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{17}H_{13}ClO$ $(M)^+$ 268.0655, found: 268.0655.

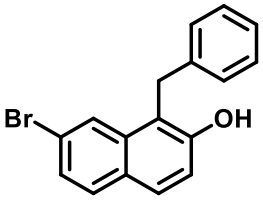
1-benzyl-6-methoxynaphthalen-2-ol **(88q):**



Prepared according to general procedure A.3, using 6-methoxynaphthalen-2-ol (226 mg, 1.3 mmol) to afford 1-benzyl-6-methoxynaphthalen-2-ol **88q** (228 mg, 66% yield) as a yellow solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 10:90). Melting point: 107−109 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 9.9 Hz, 1H), 7.48 (d, *J* = 8.8 Hz, 1H), 7.14 – 7.01 (m, 7H), 6.98 (d, *J* = 8.8 Hz, 1H), 4.97 (s, 1H), 4.33 (s, 2H), 3.79 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 155.8, 149.8, 140.2, 130.5, 129.1, 128.7, 128.3, 127.2, 126.2, 125.1, 119.2, 118.8, 118.5, 107.0, 55.43, 30.93. IR (neat): 3402, 2924, 1590, 1496, 1263 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{18}H_{16}O_2$ $(M+H)^+$ 264.1150, found: 264.1150.

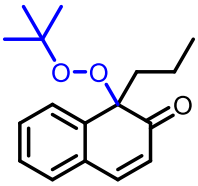
1-benzyl-7-bromonaphthalen-2-ol **(88s):**

Prepared according to general procedure A.3, using 7-bromonaphthalen-2-ol (300 mg, 1.3 mmol) to afford 1-benzyl-7-bromonaphthalen-2-ol **88s** (240 mg, 57% yield) as a yellow solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 10:90). Melting point: 90−92 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 6.5 Hz, 1H), 7.67 (d, *J* = 5.0 Hz, 2H), 7.43 (d, *J* = 7.7 Hz, 1H), 7.35 – 7.09 (m, 6H), 5.17 (s, 1H), 4.40 (s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 152.2, 139.5, 135.2, 130.3, 128.9, 128.6, 128.3, 128.0, 126.8, 126.5, 125.8, 121.5, 118.4, 117.8, 30.77. IR (neat): 3406, 2928, 1603, 1454, 1240 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{17}H_{13}BrO$ $(M)^+$ 312.0150, found: 312.0150.



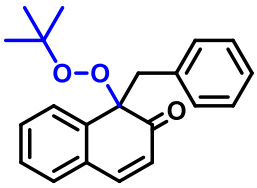
1-(tert-butylperoxy)-1-propylnaphthalen-2(1H)-one **(89b):**

Prepared according to general procedure B (batch) and C (continuous-flow), using 1-propylnaphthalen-2-ol (47 mg, 0.25 mmol)/(93 mg, 0.50 mmol) to afford 1-(*tert*-butylperoxy)-1-propylnaphthalen-2(1*H*)-one **89b** (48 mg, 69% yield) using batch and (95 mg, 69%) using continuous-flow as a yellow semisolid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 5:95). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.8 Hz, 1H), 7.42 (td, *J* = 7.5, 1.6 Hz, 1H), 7.35 (d, *J* = 10.1 Hz, 1H), 7.32 – 7.27 (m, 2H), 6.16 (d, *J* = 9.9 Hz, 1H), 1.93 (td, *J* = 12.3, 4.8 Hz, 1H), 1.68 (td, *J* = 12.5, 4.6 Hz, 1H), 1.30 – 1.24 (m, 2H), 1.14 (s, 9H), 0.73 (t, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 200.0, 144.8, 143.7, 131.1, 129.8, 129.0, 127.9, 127.4, 126.0, 85.5, 80.0, 43.1, 26.7, 16.1, 14.3. IR (neat): 2919, 2850, 1735, 1683, 1198 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{17}H_{22}O_3Na$ $(M+Na)^+$ 297.1467, found: 297.1474.



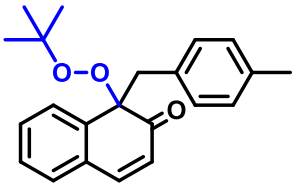
1-benzyl-1-(tert-butylperoxy)naphthalen-2(1H)-one **(89c):**

Prepared according to general procedure B (batch) and C (continuous-flow), using 1-benzylnaphthalen-2-ol (59 mg, 0.25 mmol)/(117 mg, 0.50 mmol) to afford 1-benzyl-1-(*tert*-butylperoxy)naphthalen-2(1*H*)-one **89c** (71 mg, 88% yield) using batch and (150 mg, 93%) using continuous-flow as a yellow semisolid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 5:95). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.42 (m, 1H), 7.37 (td, *J* = 7.6, 1.3 Hz, 1H), 7.29 (td, *J* = 7.4, 1.4 Hz, 1H), 7.17 – 7.00 (m, 5H), 6.65 – 6.63 (m, 2H), 5.96 (d, *J* = 9.9 Hz, 1H), 3.17 (d, *J* = 12.5 Hz, 1H), 3.05 (d, *J* = 12.5 Hz, 1H), 1.20 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 199.4, 144.6, 142.2, 133.0, 131.3, 130.7, 129.3, 128.9, 128.1, 128.0, 127.7, 127.0, 125.7, 85.9, 80.3, 47.1, 26.8.



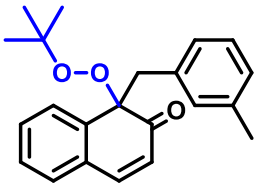
IR (neat): 2980, 1677, 1253, 1192, 743 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{21}H_{22}O_3Na$ $(M+Na)^+$ 345.1467, found: 345.1463.

1-(tert-butylperoxy)-1-(4-methylbenzyl)naphthalen-2(1H)-one **(89d):**



Prepared according to general procedure B (batch) and C (continuous-flow), using 1-(4-methylbenzyl)naphthalen-2-ol (62 mg, 0.25 mmol)/(124 mg, 0.50 mmol) to afford 1-(*tert*-butylperoxy)-1-(4-methylbenzyl)naphthalen-2(1*H*)-one **89d** (66 mg, 78% yield) using batch and (140 mg, 83%) using continuous-flow as a yellow semisolid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 5:95). ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.6 Hz, 1H), 7.36 (t, *J* = 7.4 Hz, 1H), 7.28 (t, *J* = 7.3 Hz, 1H), 7.14 (d, *J* = 7.3 Hz, 1H), 7.07 (d, *J* = 9.8 Hz, 1H), 6.83 (d, *J* = 7.1 Hz, 2H), 6.51 (d, *J* = 7.1 Hz, 2H), 5.95 (d, *J* = 9.8 Hz, 1H), 3.12 (d, *J* = 12.5 Hz, 1H), 2.99 (d, *J* = 12.6 Hz, 1H), 2.21 (s, 3H), 1.18 (s, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 199.5, 144.7, 142.4, 136.5, 131.3, 130.5, 129.8, 129.3, 128.8, 128.4, 128.1, 127.9, 125.7, 85.9, 80.3, 46.8, 26.8, 21.2. IR (neat): 2922, 1732, 1677, 1258, 1192, 738 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{22}H_{24}O_3Na$ $(M+Na)^+$ 359.1623, found: 359.1618.

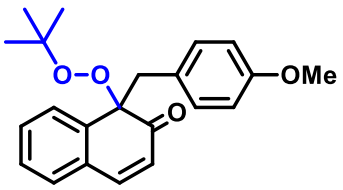
1-(tert-butylperoxy)-1-(3-methylbenzyl)naphthalen-2(1H)-one (**89e**):



Prepared according to general procedure B (batch) and C (continuous-flow), using 1-(3-methylbenzyl)naphthalen-2-ol (62 mg, 0.25 mmol)/(124 mg, 0.50 mmol) to afford 1-(*tert*-butylperoxy)-1-(3-methylbenzyl)naphthalen-2(1*H*)-one **89e** (62 mg, 74% yield) using batch and (140 mg, 83%) using continuous-flow as a yellow semisolid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 5:95). ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (dd, *J* = 7.7, 0.7 Hz, 1H), 7.37 (td, *J* = 7.6, 1.3 Hz, 1H), 7.29 (td, *J* = 7.4, 1.4 Hz, 1H), 7.15 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.08 (d, *J* = 9.9 Hz, 1H), 6.93 – 6.91 (m, 2H), 6.45 – 6.43 (m, 2H), 5.96 (d, *J* = 9.9 Hz, 1H), 3.12 (d, *J* = 12.4 Hz, 1H), 3.00 (d, *J* = 12.4 Hz, 1H), 2.13 (s, 3H), 1.20 (s, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 199.5, 144.6, 142.4, 137.1, 132.9, 131.6, 131.4, 129.3, 128.8, 128.1, 127.9, 127.7, 127.6, 127.5, 125.7, 86.0, 80.3, 47.2, 26.8, 21.3. IR (neat): 2690, 1734, 1679, 1245, 1198, 845, 767 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{22}H_{24}O_3Na$ $(M+Na)^+$ 359.1623, found: 359.1615.

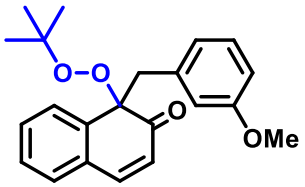
1-(tert-butylperoxy)-1-(4-methoxybenzyl)naphthalen-2(1H)-one (**89f**):

Prepared according to general procedure B (batch) and C (continuous-flow), using 1-(4-methoxybenzyl)naphthalen-2-ol (66 mg, 0.25 mmol)/(132 mg, 0.50 mmol) to afford 1-(*tert*-butylperoxy)-1-(4-methoxybenzyl)naphthalen-2(1*H*)-one **89f** (60 mg, 68% yield) using batch and (150 mg, 85%) using continuous-flow as a yellow solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 5:95). Melting point: 98−100 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.43 (m, 1H), 7.37 (td, *J* = 7.6, 1.3 Hz, 1H), 7.29 (td, *J* = 7.4, 1.3 Hz, 1H), 7.15 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.09 (d, *J* = 9.9 Hz, 1H), 6.59 – 6.53 (m, 4H), 5.96 (d, *J* = 9.9 Hz, 1H), 3.72 (d, *J* = 3.7 Hz, 3H), 3.11 (d, *J* = 12.7 Hz, 1H), 2.99 (d, *J* = 12.7 Hz, 1H), 1.19 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 199.65, 158.59, 144.69, 142.39, 131.64, 131.34, 129.32, 128.85, 128.06, 127.92, 125.69, 124.97, 113.09, 85.97, 80.25, 55.19, 46.40, 26.77. IR (neat): 2921, 1730, 1675, 1251, 738 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{22}H_{24}O_4Na$ $(M+Na)^+$ 375.1572, found: 375.1570.



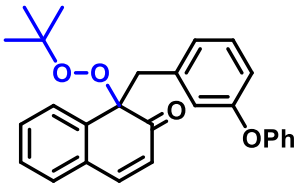
1-(tert-butylperoxy)-1-(3-methoxybenzyl)naphthalen-2(1H)-one (**89g**):

Prepared according to general procedure B (batch) and C (continuous-flow), using 1-(3-methoxybenzyl)naphthalen-2-ol (82 mg, 0.25 mmol)/(132 mg, 0.50 mmol) to afford 1-(*tert*-butylperoxy)-1-(3-methoxybenzyl)naphthalen-2(1*H*)-one **89g** (71 mg, 68% yield) using batch and (155 mg, 88%) using continuous-flow as a yellow semisolid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 5:95). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.46 (m, 1H), 7.38 (td, *J* = 7.6, 1.3 Hz, 1H), 7.29 (td, *J* = 7.4, 1.3 Hz, 1H), 7.15 (dd, *J* = 7.5, 0.9 Hz, 1H), 7.08 (d, *J* = 9.9 Hz, 1H), 6.98 – 6.92 (m, 1H), 6.65 (ddd, *J* = 8.3, 2.6, 0.8 Hz, 1H), 6.27 (d, *J* = 7.6 Hz, 1H), 6.14 – 6.13 (m, 1H), 5.96 (d, *J* = 9.9 Hz, 1H), 3.57 (s, 3H), 3.15 (d, *J* = 12.4 Hz, 1H), 3.02 (d, *J* = 12.4 Hz, 1H), 1.19 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 199.4, 158.9, 144.6, 142.3, 134.5, 131.4, 129.4, 128.9, 128.6, 128.1, 128.0, 125.8, 123.2, 115.5, 113.3, 85.8, 80.3, 55.1, 47.2, 26.8. IR (neat): 2922, 1732, 1677, 1259, 1193, 743 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{22}H_{24}O_4Na$ $(M+Na)^+$ 375.1572, found: 375.1581.



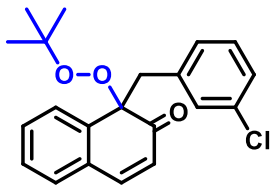
1-(tert-butylperoxy)-1-(3-phenoxybenzyl)naphthalen-2(1H)-one (**89h**):

Prepared according to general procedure B (batch) and C (continuous-flow), using 1-(3-phenoxybenzyl)naphthalen-2-ol (53 mg, 0.35 mmol)/(163 mg, 0.50 mmol) to afford 1-(*tert*-butylperoxy)-1-(3-phenoxybenzyl)naphthalen-2(1*H*)-one **89h** (81 mg, 83% yield) using batch and (187 mg, 90%) using continuous-flow as a yellow semisolid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 5:95). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.41 (m, 1H), 7.33 (td, *J* = 7.5, 1.4 Hz, 1H), 7.30 – 7.25 (m, 3H), 7.1 – 7.12 (m, 2H), 7.08 – 7.01 (m, 2H), 6.82 – 6.78 (m, 3H), 6.47 (d, *J* = 7.7 Hz, 1H), 6.27 – 6.26 (m, 1H), 5.99 (d, *J* = 9.9 Hz, 1H), 3.13 (d, *J* = 12.6 Hz, 1H), 3.00 (d, *J* = 12.6 Hz, 1H), 1.17 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 199.2, 157.3, 156.5, 144.7, 142.0, 135.1, 131.2, 129.7, 129.4, 129.00, 128.95, 128.1, 128.0, 125.9, 125.7, 123.2, 121.2, 118.8, 118.0, 85.7, 80.4, 46.8, 26.8. IR (neat): 2921, 1734, 1678, 1251, 877, 841 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{27}H_{26}O_4Na$ $(M+Na)^+$ 437.1729, found: 437.1725.



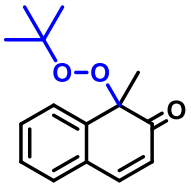
1-(tert-butylperoxy)-1-(3-chlorobenzyl)naphthalen-2(1H)-one (**89i**):

Prepared according to general procedure B (batch) and C (continuous-flow), using 1-(3-chlorobenzyl)naphthalen-2-ol (67 mg, 0.25 mmol)/(134 mg, 0.50 mmol) to afford 1-(*tert*-butylperoxy)-1-(3-chlorobenzyl)naphthalen-2(1*H*)-one **89i** (63 mg, 71% yield) using batch and (135 mg, 76%) using continuous-flow as a yellow semisolid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 5:95). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.44 (m, 1H), 7.37 (td, *J* = 7.5, 1.3 Hz, 1H), 7.29 (td, *J* = 7.4, 1.4 Hz, 1H), 7.16 – 7.14 (m, 1H), 7.09 – 7.01 (m, 3H), 6.66 – 6.63 (m, 2H), 5.96 (d, *J* = 9.9 Hz, 1H), 3.16 (d, *J* = 12.5 Hz, 1H), 3.05 (d, *J* = 12.5 Hz, 1H), 1.20 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): 199.4, 144.7, 142.3, 133.1, 131.3, 130.7, 129.4, 128.9, 128.1, 128.0, 127.7, 127.0, 125.7, 85.9, 80.3, 47.2, 26.8. IR (neat): 2920, 1733, 1677, 1261, 1189, 740 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{21}H_{22}O_3Cl$ $(M+H)^+$ 357.1257, found: 357.1266.



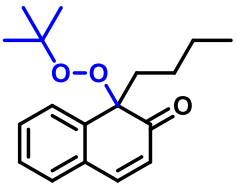
1-(tert-butylperoxy)-1-methylnaphthalen-2(1H)-one (**89j**):

Prepared according to general procedure B (batch) and C (continuous-flow), using 1-methylnaphthalen-2-ol (40 mg, 0.25 mmol)/(79 mg, 0.50 mmol) to afford 1-(*tert*-butylperoxy)-1-methylnaphthalen-2(1*H*)-one **89j** (55 mg, 88% yield) using batch and (98 mg, 80%) using continuous-flow as a yellow semisolid after



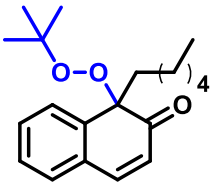
purification by silica gel column chromatography (EtOAc:*n*-hexane = 5:95). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.8 Hz, 1H), 7.45 – 7.40 (m, 1H), 7.38 (d, *J* = 9.9 Hz, 1H), 7.34 – 7.27 (m, 2H), 6.16 (d, *J* = 9.9 Hz, 1H), 1.43 (s, 3H), 1.15 (s, 9H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 199.6, 144.8, 144.6, 130.1, 130.0, 129.1, 127.9, 127.1, 125.1, 82.6, 80.1, 26.8, 26.7. IR (neat): 2922, 1726, 1681, 1248, 1198, 759 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{15}H_{18}O_3Na$ $(M+Na)^+$ 269.1154, found: 269.1147.

1-butyl-1-(tert-butylperoxy)naphthalen-2(1H)-one (**89k**):



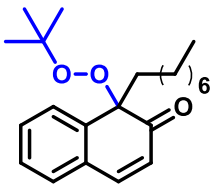
Prepared according to general procedure B (batch) and C (continuous-flow), using 1-butylnaphthalen-2-ol (50 mg, 0.25 mmol)/(104 mg, 0.50 mmol) to afford 1-butyl-1-(*tert*-butylperoxy)naphthalen-2(1*H*)-one **89k** (56 mg, 78% yield) using batch and (109 mg, 76%) using continuous-flow as a yellow semisolid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 5:95). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.58 (m, 1H), 7.42 (td, *J* = 7.5, 1.6 Hz, 1H), 7.36– 7.26 (m, 3H), 6.16 (d, *J* = 9.9 Hz, 1H), 2.00 – 1.91 (m, 1H), 1.70 (td, *J* = 12.3, 4.7 Hz, 1H), 1.28 – 1.16 (m, 2H), 1.13 (s, 9H), 0.89 – 0.80 (m, 2H), 0.73 (t, *J* = 7.2 Hz, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 200.0, 144.9, 143.7, 131.2, 129.8, 129.0, 127.9, 127.4, 126.1, 85.4, 80.0, 40.8, 26.7, 24.6, 22.9, 13.8. IR (neat): 2925, 1727, 1680, 1246, 1197, 757 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{18}H_{24}O_3Na$ $(M+Na)^+$ 311.1623, found: 311.1631.

1-(tert-butylperoxy)-1-hexylnaphthalen-2(1H)-one (**89l**):



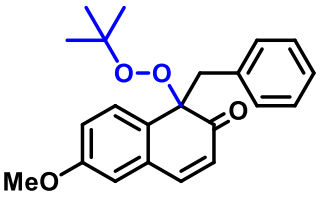
Prepared according to general procedure B (batch) and C (continuous-flow), using 1-hexylnaphthalen-2-ol (57 mg, 0.25 mmol)/(144 mg, 0.50 mmol) to afford 1-(*tert*-butylperoxy)-1-hexylnaphthalen-2(1*H*)-one **89l** (60 mg, 76% yield) using batch and (118 mg, 75%) using continuous-flow as a yellow semisolid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 5:95). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.8 Hz, 1H), 7.42 (td, *J* = 7.5, 1.6 Hz, 1H), 7.35 (d, *J* = 10.0 Hz, 1H), 7.32 – 7.28 (m, 2H), 6.18 – 6.14 (m, 1H), 1.95 (td, *J* = 12.8, 4.1 Hz, 1H), 1.69 (td, *J* = 12.0, 4.5 Hz, 1H), 1.30 – 1.21 (m, 1H), 1.14 (s, 9H), 1.09 – 1.03 (m, 5H), 0.93 – 0.84 (m, 2H), 0.78 (t, *J* = 7.0 Hz, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz): δ 200.0, 144.9, 143.7, 131.2, 129.8, 129.0, 127.8, 127.4, 126.1, 85.4, 80.0, 41.0, 31.5, 29.5, 26.7, 22.6, 22.4, 14.1. IR (neat): 2923, 1727, 1683, 1196, 741 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{20}H_{28}O_3Na$ $(M+Na)^+$ 339.1936, found: 339.1934.

1-(tert-butylperoxy)-1-octylnaphthalen-2(1H)-one (**89m**):



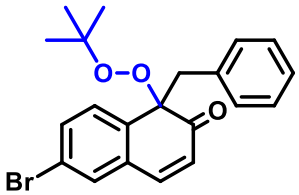
Prepared according to general procedure B (batch) and C (continuous-flow), using 1-octylnaphthalen-2-ol (64 mg, 0.25 mmol)/(128 mg, 0.50 mmol) to afford 1-(*tert*-butylperoxy)-1-octylnaphthalen-2(1*H*)-one **89m** (61 mg, 71% yield) using batch and (120 mg, 70%) using continuous-flow as a yellow semisolid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 5:95). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.8 Hz, 1H), 7.41 (td, *J* = 7.5, 1.6 Hz, 1H), 7.34 (d, *J* = 10.1 Hz, 1H), 7.31 – 7.27 (m, 2H), 6.16 (d, *J* = 9.9 Hz, 1H), 1.95 (td, *J* = 12.9, 4.0 Hz, 1H), 1.69 (td, *J* = 11.9, 4.4 Hz, 1H), 1.30 – 1.19 (m, 5H), 1.13 (s, 9H), 1.12 – 1.04 (t, *J* = 15.1 Hz, 7H), 0.82 (t, *J* = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 200.0, 144.8, 143.7, 131.2, 129.8, 129.0, 127.8, 127.4, 126.1, 85.4, 80.0, 41.0, 31.9, 29.8, 29.2, 26.7, 22.7, 22.4, 14.2. IR (neat): 2926, 1826, 1234, 1191, 749 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{22}H_{32}O_3Na$ $(M+Na)^+$ 367.2249, found: 367.2250.

1-benzyl-1-(tert-butylperoxy)-6-methoxynaphthalen-2(1H)-one (**89n**):



Prepared according to general procedure B (batch) and C (continuous-flow), using 1-benzyl-6-methoxynaphthalen-2-ol (66 mg, 0.25 mmol)/(132 mg, 0.50 mmol) to afford 1-benzyl-1-(*tert*-butylperoxy)-6-methoxynaphthalen-2(1*H*)-one **89n** (71 mg, 81% yield) using batch and (160 mg, 91%) using continuous-flow as a yellow semisolid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 5:95). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.6 Hz, 1H), 7.13 – 7.00 (m, 4H), 6.92 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.67 – 6.65 (m, 3H), 5.95 (d, *J* = 9.9 Hz, 1H), 3.84 (s, 3H), 3.15 (d, *J* = 12.4 Hz, 1H), 3.03 (d, *J* = 12.4 Hz, 1H), 1.18 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 199.7, 159.3, 144.5, 134.1, 133.3, 132.4, 130.7, 129.4, 127.7, 126.9, 126.3, 115.1, 113.6, 85.5, 80.2, 55.5, 47.0, 26.8. IR (neat): 2921, 1732, 1674, 1270, 1187, 739 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{22}H_{24}O_4Na$ $(M+Na)^+$ 375.1572, found 375.1574.

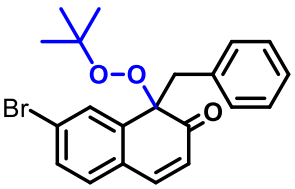
1-benzyl-6-bromo-1-(tert-butylperoxy)naphthalen-2(1H)-one (**89o**):



Prepared according to general procedure B (batch) and C (continuous-flow), using 1-benzyl-6-bromonaphthalen-2-ol (78 mg, 0.25 mmol)/(157 mg, 0.50 mmol) to afford 1-benzyl-6-bromo-1-(*tert*-butylperoxy)naphthalen-2(1*H*)-one **89o** (73 mg, 73% yield) using batch and (157mg, 78%) using continuous-flow as a yellow semisolid after purification by silica gel

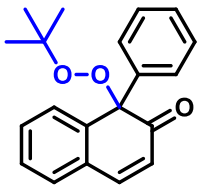
column chromatography (EtOAc:*n*-hexane = 5:95). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.30 (d, *J* = 2.0 Hz, 1H), 7.26 (m, 1H), 7.16 – 7.05 (m, 3H), 7.00 (d, *J* = 10.0 Hz, 1H), 6.68 – 6.66 (m, 2H), 6.00 (d, *J* = 10.0 Hz, 1H), 3.13 (d, *J* = 12.6 Hz, 1H), 3.02 (d, *J* = 12.6 Hz, 1H), 1.18 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 198.7, 143.0, 141.0, 133.1, 132.7, 132.1, 131.3, 130.7, 129.8, 127.9, 127.2, 126.8, 121.8, 85.7, 80.6, 46.8, 26.7. IR (neat): 2973, 1680, 1243, 1193, 879 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{21}H_{21}O_3BrNa$ $(M+Na)^+$ 423.0572, found: 423.0570.

1-benzyl-7-bromo-1-(tert-butylperoxy)naphthalen-2(1H)-one (**89p**):



Prepared according to general procedure B (batch) and C (continuous-flow), using 1-benzyl-7-bromonaphthalen-2-ol (78 mg, 0.25 mmol)/(157 mg, 0.50 mmol) to afford 1-benzyl-7-bromo-1-(*tert*-butylperoxy)naphthalen-2(1*H*)-one **89p** (75 mg, 75% yield) using batch and (160 mg, 80%) using continuous-flow as a yellow semisolid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 5:95). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 2.0 Hz, 1H), 7.43 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.16 – 7.01 (m, 5H), 6.67 – 6.65 (m, 2H), 5.99 (d, *J* = 10.0 Hz, 1H), 3.13 (d, *J* = 12.6 Hz, 1H), 3.03 (d, *J* = 12.6 Hz, 1H), 1.20 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 198.4, 144.2, 143.4, 132.6, 131.4, 131.2, 130.7, 130.2, 130.0, 127.9, 127.3, 126.0, 124.3, 85.6, 80.7, 47.1, 26.8. IR (neat): 2922, 1732, 1679, 1247, 1192, 746 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{21}H_{21}O_3BrNa$ $(M+Na)^+$ 423.0572, found: 423.0565.

1-(tert-butylperoxy)-1-phenylnaphthalen-2(1H)-one (**89q**):



Prepared according to general procedure B (batch) and C (continuous-flow), using 1-phenylnaphthalen-2-ol (55 mg, 0.25 mmol)/(110 mg, 0.50 mmol) to afford 1-(*tert*-butylperoxy)-1-phenylnaphthalen-2(1*H*)-one **89q** (72 mg, 93% yield) using batch and (145 mg, 94%) using continuous-flow as a white solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 5:95). Melting point: 112−114 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.50 (m, 1H), 7.44 – 7.36 (m, 4H), 7.25 – 7.16 (m, 5H), 6.07 (d, *J* = 10.0 Hz, 1H), 1.27 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 197.5, 144.6, 143.2, 138.8, 131.5, 130.1, 129.4, 129.0, 128.7, 128.5, 128.4, 126.9, 125.1, 87.0, 80.7, 26.8. IR (neat): 2980,1682, 1233, 1193, 756 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{20}H_{20}O_3Na$ $(M+Na)^+$ 331.1310, found: 331.1312.

Naphthalene-1,2-dione (**90a**):[81,70]

Prepared according to general procedure H, using 1-benzyl-1-(*tert*-butylperoxy)naphthalen-2(1*H*)-one **89c** (81 mg, 0.25 mmol) to afford Naphthalene-1,2-dione **90a** (25 mg, 63% yield) as a brown solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 20:80). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 – 8.10 (m, 1H), 7.65 (td, *J* = 7.6, 1.4 Hz, 1H), 7.51 (td, *J* = 7.6, 1.1 Hz, 1H), 7.45 (d, *J* = 10.1 Hz, 1H), 7.37 (d, *J* = 7.5 Hz, 1H), 6.44 (d, *J* = 10.1 Hz, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 181.02, 179.05, 145.50, 135.98, 134.93, 131.77, 131.02, 130.38, 129.99, 128.09. IR (neat): 2922, 1651, 1456, 1281, 741 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{10}H_7O_2$ $(M+H)^+$ 159.0446, found 159.0440. The spectral data were identical to the reported compound.[81,70]

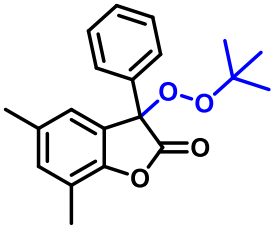
3-(tert-butylperoxy)-3-phenylbenzofuran-2(3H)-one (**92a**):

Prepared according to general procedure D, using 3-phenylbenzofuran-2(3*H*)-one (105 mg, 0.50 mmol) to afford 3-(*tert*-butylperoxy)-3-phenylbenzofuran-2(3*H*)-one **92a** (117 mg, 78% yield) as a white solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 5:95). Melting point: 72−74 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.36 (m, 7H), 7.26 (ddd, *J* = 7.5, 6.9, 0.9 Hz, 1H), 7.16 (d, *J* = 8.1 Hz, 1H), 1.20 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 173.3, 154.4, 134.7, 131.1, 129., 128.8, 127.4, 126.6, 126.5, 124.5, 111.2, 85.5, 81.8, 26.6. IR (neat): 2922, 1820, 1621, 1230, 1059, 757 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{18}H_{18}O_4Na$ $(M+Na)^+$ 321.1103, found: 321.1098.

3-(tert-butylperoxy)-5-methyl-3-phenylbenzofuran-2(3H)-one (**92b**):

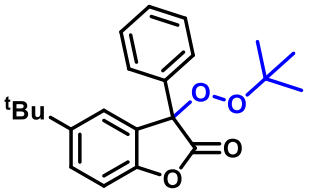
Prepared according to general procedure D, using 5-methyl-3-phenylbenzofuran-2(3*H*)-one (112 mg, 0.50 mmol) to afford 3-(*tert*-butylperoxy)-5-methyl-3-phenylbenzofuran-2(3*H*)-one **92b** (125 mg, 80% yield) as a white solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 5:95). Melting point: 96−98 °C. ^{1}H NMR (400 MHz, $CDCl_3$) 7.47 – 7.44 (m, 2H), 7.39 – 7.36 (m, 3H), 7.23 (m, 2H), 7.04 (d, *J* = 8.2 Hz, 1H), 2.40 (s, 3H), 1.22 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 173.7, 152.3, 134.9, 134.2, 131.5, 129.6, 128.8, 127.4, 126.8, 126.3, 110.8, 85.7, 81.8, 26.6, 21.3. IR (neat): 2981, 1818, 1227, 1191,1074, 740 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{19}H_{20}O_4Na$ $(M+Na)^+$ 335.1259, found: 335.1266.

3-(tert-butylperoxy)-5,7-dimethyl-3-phenylbenzofuran-2(3H)-one (**92c**):



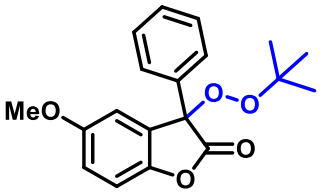
Prepared according to general procedure D, using 5,7-dimethyl-3-phenylbenzofuran-2(3*H*)-one (119 mg, 0.50 mmol) to afford 3-(*tert*-butylperoxy)-5,7-dimethyl-3-phenylbenzofuran-2(3*H*)-one **92c** (122 mg, 75% yield) as a white solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 5:95). Melting point: 109−111°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.44 (m, 2H), 7.39 – 7.35 (m, 3H), 7.05 (d, *J* = 0.6 Hz, 1H), 7.01 (s, 1H), 2.36 (s, 3H), 2.32 (s, 3H), 1.22 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 173.9, 150.8, 135.1, 133.8, 133.1, 129.6, 128.7, 127.4, 125.8, 124.0, 120.8, 86.1, 81.7, 26.6, 21.3, 15.0. IR (neat): 2981, 1816, 1196, 1074, 742 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{20}H_{22}O_4Na$ $(M+Na)^+$ 349.1416, found: 349.1406.

5-(tert-butyl)-3-(tert-butylperoxy)-3-phenylbenzofuran-2(3H)-one (**92d**):



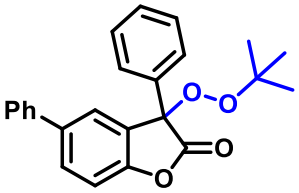
Prepared according to general procedure D, using 5-(*tert*-butyl)-3-phenylbenzofuran-2(3*H*)-one (134 mg, 0.50 mmol) to afford 5-(*tert*-butyl)-3-(*tert*-butylperoxy)-3-phenylbenzofuran-2(3*H*)-one **92d** (140 mg, 79% yield) as a yellow solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 5:95). Melting point: 74−76°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.42 (m, 4H), 7.40 – 7.36 (m, 3H), 7.08 (d, *J* = 8.5 Hz, 1H), 1.34 (s, 9H), 1.17 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 173.4, 152.3, 147.6, 134.7, 129.6, 128.7, 127.7, 127.4, 125.7, 123.6, 110.3, 85.7, 81.5, 34.9, 31.5, 26.4. IR (neat): 2922, 1820, 1188, 1070, 739 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{22}H_{26}O_4Na$ $(M+Na)^+$ 377.1729, found: 377.1721.

3-(tert-butylperoxy)-5-methoxy-3-phenylbenzofuran-2(3H)-one (**92e**):



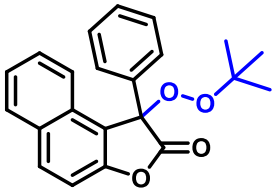
Prepared according to general procedure D, using 5-methoxy-3-phenylbenzofuran-2(3*H*)-one (120 mg, 0.50 mmol) to afford 3-(*tert*-butylperoxy)-5-methoxy-3-phenylbenzofuran-2(3*H*)-one **92e** (140 mg, 85% yield) as a yellow semisolid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 5:95). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 – 7.43 (m, 2H), 7.39 – 7.34 (m, 3H), 7.08 (d, *J* = 8.7 Hz, 1H), 6.98 – 6.94 (m, 2H), 3.82 (s, 3H), 1.22 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 173.7, 156.8, 148.2, 134.8, 129.7, 128.8, 127.33, 127.25, 116.5, 111.8, 111.7, 86.0, 81.8, 56.0, 26.6. IR (neat): 2922, 1815, 1204, 1059, 755 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{19}H_{20}O_5Na$ $(M+Na)^+$ 351.1208, found: 351.1201.

3-(tert-butylperoxy)-3,5-diphenylbenzofuran-2(3H)-one (**92f**):



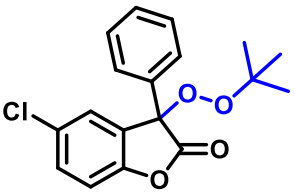
Prepared according to general procedure D, using 3,5-diphenylbenzofuran-2(3*H*)-one (144 mg, 0.50 mmol) to afford 3-(*tert*-butylperoxy)-3,5-diphenylbenzofuran-2(3*H*)-one **92f** (157 mg, 84% yield) as a white solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 5:95). Melting point: 125−127 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.63 (d, *J* = 2.0 Hz, 1H), 7.60 – 7.57 (m, 2H), 7.52 – 7.44 (m, 4H), 7.41 – 7.35 (m, 4H), 7.24 (d, *J* = 8.4 Hz, 1H), 1.23 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 173.4, 153.9, 140.3, 138.0, 134.6, 129.9, 129.8, 129.1, 128.9, 127.6, 127.4, 127.1, 127.0, 125.1, 111.5, 85.7, 81.9, 26.61. IR (neat): 2979, 1819, 1185, 1064, 733 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{24}H_{22}O_4Na$ $(M+Na)^+$ 397.1416, found: 397.1407.

1-(tert-butylperoxy)-1-phenylnaphtho[2,1-b]furan-2(1H)-one (**92g**):



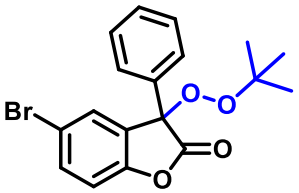
Prepared according to general procedure D, using 1-phenylnaphtho[2,1-*b*]furan-2(1*H*)-one (130 mg, 0.50 mmol) to afford 1-(*tert*-butylperoxy)-1-phenylnaphtho[2,1-*b*]furan-2(1*H*)-one **92g** (150 mg, 86% yield) as a white solid after purification by silica gel column chromatography (EtOAc: *n*-hexane = 5:95). Melting point: 150−152 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.8 Hz, 1H), 7.94 – 7.88 (m, 1H), 7.72 – 7.70 (m, 1H), 7.45 – 7.39 (m, 5H), 7.37 – 7.31 (m, 3H), 1.18 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 173.9, 152.6, 134.5, 132.4, 131.3, 130.1, 129.7, 129.3, 128.9, 127.7, 127.3, 125.1, 123.9, 118.2, 111.7, 86.6, 81.7, 26.6. IR (neat): 2925, 1820, 1255, 974, 738 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{22}H_{20}O_4Na$ $(M+Na)^+$ 371.1259, found: 371.1252.

3-(tert-butylperoxy)-5-chloro-3-phenylbenzofuran-2(3H)-one (**92h**):



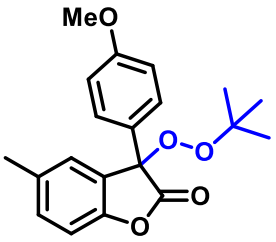
Prepared according to general procedure D, using 5-chloro-3-phenylbenzofuran-2(3*H*)-one (122 mg, 0.50 mmol) to afford 3-(*tert*-butylperoxy)-5-chloro-3-phenylbenzofuran-2(3*H*)-one **92h** (120 mg, 72% yield) as a yellow semisolid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 5:95). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.38 (m, 7H), 7.11 (d, *J* = 8.5 Hz, 1H), 1.23 (s, 9H). 13C{1H} NMR ($CDCl_3$, 100 MHz): δ 172.7, 152.7, 134.1, 131.2, 130.0, 129.9, 129.0, 128.2, 127.2, 126.5, 112.5, 85.5, 82.1, 26.5. IR (neat): 2922, 1824, 1186, 1066, 734 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{18}H_{17}ClNaO_4$$(M+Na)^+$ 355.0713, found: 355.0718.

5-bromo-3-(tert-butylperoxy)-3-phenylbenzofuran-2(3H)-one (**92i**):



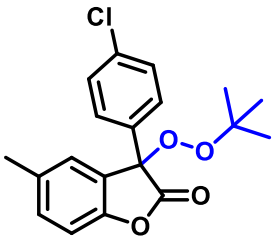
Prepared according to general procedure D, using 5-bromo-3-phenylbenzofuran-2(3*H*)-one (145 mg, 0.50 mmol) to afford 5-bromo-3-(*tert*-butylperoxy)-3-phenylbenzofuran-2(3*H*)-one **92i** (160 mg, 85% yield) as a yellow semisolid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 5:95). ^{1}H NMR (400 MHz, $CDCl_3$) 7.57 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.52 (d, *J* = 2.1 Hz, 1H), 7.41 (m, 5H), 7.06 (d, *J* = 8.5 Hz, 1H), 1.23 (s, 9H). 13C{1H} NMR ($CDCl_3$, 100 MHz): δ 172.6, 153.3, 134.0, 130.0, 129.4, 129.0, 128.7, 127.2, 117.2, 113.0, 85.4, 82.2, 26.5. IR (neat): 2979 1824, 1186, 1065, 735 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{18}H_{17}O_4BrNa$ $(M+Na)^+$ 399.0208, found: 399.0206.

3-(tert-butylperoxy)-3-(4-methoxyphenyl)-5-methylbenzofuran-2(3H)-one (**92j**):



Prepared according to general procedure D, using 3-(4-methoxyphenyl)-5-methylbenzofuran-2(3*H*)-one (127 mg, 0.50 mmol) to afford 3-(*tert*-butylperoxy)-3-(4-methoxyphenyl)-5-methylbenzofuran-2(3*H*)-one **92j** (149 mg, 87% yield) as a white solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 5:95). Melting point: 119−121°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.39 (m, 2H), 7.24 – 7.21 (m, 2H), 7.03 (d, *J* = 8.1 Hz, 1H), 6.91 – 6.87 (m, 2H), 3.80 (s, 3H), 2.41 (s, 3H), 1.20 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 174.0, 160.7, 152.3, 134.0, 131.4, 129.1, 126.8, 126.6, 126.2, 114.2, 110.8, 85.2, 81.6, 55.5, 26.6, 21.4. IR (neat): 2976, 1814, 1250, 1066, 820 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{20}H_{22}O_5Na$ $(M+Na)^+$ 365.1365, found: 365.1358.

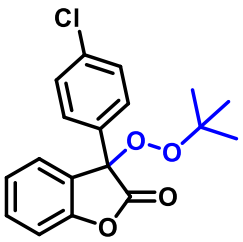
3-(tert-butylperoxy)-3-(4-chlorophenyl)-5-methylbenzofuran-2(3H)-one (**92k**):



Prepared according to general procedure D, using 3-(4-chlorophenyl)-5-methylbenzofuran-2(3*H*)-one (130 mg, 0.50 mmol) to afford 3-(*tert*-butylperoxy)-3-(4-chlorophenyl)-5-methylbenzofuran-2(3*H*)-one **92k** (120 mg, 69% yield) as a white solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 5:95). Melting point: 90−92°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.38 (m, 4H), 7.25 (m, 1H), 7.17 (s, 1H), 7.05 (d, *J* = 8.2 Hz, 1H), 2.40 (s, 3H), 1.20 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 173.2, 152.3, 135.9, 134.4, 133.3, 131.8, 129.0, 128.9, 126.7, 125.7, 111.0, 85.1, 81.9, 26.5, 21.3. IR (neat): 2980, 1818, 1190,

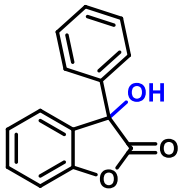
1077, 737 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{19}H_{19}O_4ClNa$ $(M+Na)^+$ 369.0870, found: 369.0865.

3-(tert-butylperoxy)-3-(4-chlorophenyl)benzofuran-2(3H)-one (**92l**):



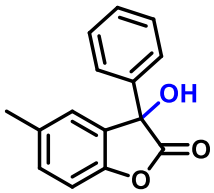
Prepared according to general procedure D, using 3-(4-chlorophenyl)benzofuran-2(3*H*)-one (122 mg, 0.50 mmol) to afford 3-(*tert*-butylperoxy)-3-(4-chlorophenyl)benzofuran-2(3*H*)-one **92l** (125 mg, 75% yield) as a white solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 5:95). Melting point: 94−96 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (td, *J* = 8.0, 1.5 Hz, 1H), 7.420– 7.38 (m, 5H), 7.27 (td, *J* = 7.5, 0.9 Hz, 1H), 7.17 (d, *J* = 8.1 Hz, 1H), 1.18 (s, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 172.9, 154.4, 136.0, 133.1, 131.4, 129.0, 128.9, 126.5, 125.9, 124.7, 111.4, 84.9, 82.0, 26.5. IR (neat): 2982, 1819, 1187, 1063, 741 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{18}H_{17}O_4ClNa$ $(M+Na)^+$ 355.0713, found: 355.0721.

3-hydroxy-3-phenylbenzofuran-2(3H)-one (**93a**):[65b]



Prepared according to procedure F, using 3-(*tert*-butylperoxy)-3-phenylbenzofuran-2(3*H*)-one **92a** (75 mg, 0.25 mmol) to afford 3-hydroxy-3-phenylbenzofuran-2(3*H*)-one **93a** (32 mg, 56% yield) as a yellow solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 20:80). The data for this compound are in agreement with the reported compound.[65b] ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.32 (m, 7H), 7.21 (m, 2H), 2.84 (s, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 176.4, 153.4, 138.9, 131.2, 129.5, 129.2, 129.0, 125.52, 125.51, 125.3, 111.6. 77.3. IR (neat): 3448, 2961, 1814, 1619, 1487, 1246, 1072, 1049 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{14}H_{11}O_3$ $(M+H)^+$ 227.0708, found: 227.0700.

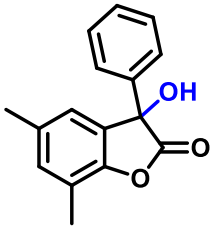
3-hydroxy-5-methyl-3-phenylbenzofuran-2(3H)-one (**93b**):[65b]



Prepared according to procedure F, 3-(*tert*-butylperoxy)-5-methyl-3-phenylbenzofuran-2(3H)-one 92b (78 mg, 0.25 mmol) to afford 3-hydroxy-5-methyl-3-phenylbenzofuran-2(3*H*)-one **93b** (25 mg, 42% yield) as a yellow oil after purification by silica gel column chromatography (EtOAc:*n*-hexane = 20:80). The data for this compound are in agreement with the reported compound.[65b] ^1H NMR (400 MHz, CDCl3) δ 7.44 – 7.35 (m, 5H), 7.22 – 7.19 (m, 1H), 7.13 (m, 1H), 7.08 (d, *J* = 8.2 Hz, 1H), 3.35 (s, 1H), 2.33 (s, 3H); $^{13}C\{^1H\}$ NMR (CDCl3, 100 MHz) δ 176.7, 151.4, 139.2, 135.1,

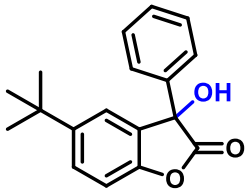
131.6, 129.3, 129.1, 129.0, 125.8, 125.5, 111.2, 21.2; IR (neat): 3670, 2924, 1815, 1621, 1488, 1073 cm^{-1}; HRMS (ESI-TOF): m/z calculated for $C_{15}H_{13}O_3$ (M+H)+ 241.0865, found:241.0866.

3-hydroxy-5,7-dimethyl-3-phenylbenzofuran-2(3H)-one (**93c**):



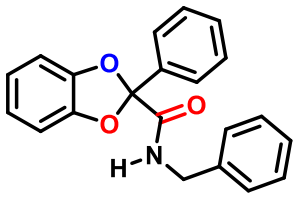
Prepared according to procedure F, using 3-(*tert*-butylperoxy)-5,7-dimethyl-3-phenylbenzofuran-2(3*H*)-one **92c** (82 mg, 0.25 mmol) to afford 3-hydroxy-5,7-dimethyl-3-phenylbenzofuran-2(3*H*)-one **93c** (30 mg, 47% yield) as a yellow semisolid after purification by silica gel column chromatography (EtOAc: n-hexane = 20:80). ^{1}H NMR (400 MHz, CDCl3) δ 7.44 – 7.32 (m, 5H), 7.02 (s, 1H), 6.94 (s, 1H), 3.45 (s, 1H), 2.33 (s, 3H), 2.29 (s, 3H); ^{13}C{^{1}H} NMR (CDCl3, 100 MHz) δ 176.9, 149.8, 139.2, 134.8, 133.1, 129.0, 128.9, 125.5, 122.9, 121.4, 77.8, 21.1, 15.0; IR (neat): 3450, 2925, 1808, 1630, 1481, 1165, 1019 cm^{-1}; HRMS (ESI-TOF): m/z calculated for $C_{16}H_{14}NaO_3$ (M+Na)+ 277.0841, found: 277.0842.

5-(tert-butyl)-3-hydroxy-3-phenylbenzofuran-2(3H)-one (**93d**):



Prepared according to procedure F, using 5-(*tert*-butyl)-3-(*tert*-butylperoxy)-3-phenylbenzofuran-2(3*H*)-one **92d** (89 mg, 0.25 mmol) to afford 5-(*tert*-butyl)-3-hydroxy-3-phenylbenzofuran-2(3*H*)-one **93d** (25 mg, 35% yield) as a yellow semisolid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 20:80). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.35 (m, 7H), 7.12 (d, *J* = 8.5 Hz, 1H), 3.41 (s, 1H), 1.30 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 176.8, 151.3, 148.8, 139.1, 129.4, 129.1, 129.0, 128.8, 128.2, 125.6, 122.2, 110.9, 35.0, 31.6; IR (neat): 3453, 2962, 1815, 1712, 1622, 1487, 1366, 1067 cm^{-1}; HRMS (ESI-TOF): m/z calculated for $C_{18}H_{18}NaO_3$ $(M+Na)^+$ 305.1154, found: 305.1159.

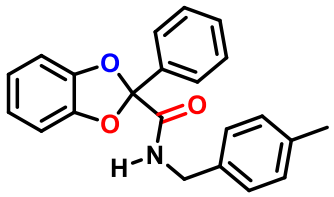
N-benzyl-2-phenylbenzo[d][1,3]dioxole-2-carboxamide (**94a**):



Prepared according to general procedure G, using 3-(*tert*-butylperoxy)-3-phenylbenzofuran-2(3*H*)-one **92a** (150 mg, 0.50 mmol) and benzylamine (107 mg, 1 mmol) to afford *N*-benzyl-2-phenylbenzo[*d*][1,3]dioxole-2-carboxamide **94a** (143 mg, 86% yield) as a white solid after purification by silica gel column chromatography (EtOAc: *n*-hexane = 30:70). Melting point: 93−95 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (m, 2H), 7.44 – 7.41 (m, 3H), 7.34 – 7.28 (m, 3H), 7.22 – 7.19 (m, 2H), 7.07 (s, 1H), 6.95 – 6.87 (m, 4H), 4.50 (d, *J* = 5.8 Hz, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 167.2, 146.2, 137.3, 136.1, 130.1, 128.9, 128.6, 127.9,

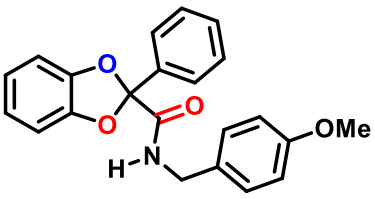
127.89, 125.87, 122.6, 111.5, 109.5, 77.4, 43.7. IR (neat): 3300, 3051, 1669, 1480, 1231 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{21}H_{18}NO_3$ $(M+H)^+$ 332.1287, found: 332.1287.

N-(4-methylbenzyl)-2-phenylbenzo[d][1,3]dioxole-2-carboxamide (**94b**):



Prepared according to general procedure G, using 3-(*tert*-butylperoxy)-3-phenylbenzofuran-2(3*H*)-one **92a** (150 mg, 0.50 mmol) and 4-methylbenzylamine (121 mg, 1 mmol) to afford *N*-(4-methylbenzyl)-2-phenylbenzo[*d*][1,3]dioxole-2-carboxamide 94**b** (153 mg, 88% yield) as a white solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 30:70). Melting point: 105−107 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.70 (m, 2H), 7.44 – 7.40 (m, 3H), 7.13 – 7.08 (m, 4H), 7.0 (s, 1H), 6.93 – 6.87 (m, 4H), 4.45 (d, *J* = 5.7 Hz, 2H), 2.33 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$,100 MHz) δ 167.1, 146.2, 137.7, 136.2, 134.3, 130.1, 129.6, 128.6, 127.9, 125.9, 122.5, 111.5, 109.5, 43.5, 21.2. IR (neat): 3311, 3059, 1677, 1479, 1230 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{22}H_{20}NO_3$ $(M+H)^+$ 346.1443, found: 346.1436.

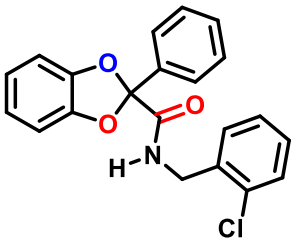
N-(4-methoxybenzyl)-2-phenylbenzo[d][1,3]dioxole-2-carboxamide (**94c**):



Prepared according to general procedure G, using 3-(*tert*-butylperoxy)-3-phenylbenzofuran-2(3*H*)-one **92a** (150 mg, 0.50 mmol) and 4-methoxybenzylamine (137 mg, 1 mmol) to afford N-(4-methoxybenzyl)-2-phenylbenzo[*d*][1,3]dioxole-2-carboxamide **94c** (164 mg, 90% yield) as a white solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 30:70). Melting point: 108−110 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.70 (m, 2H), 7.43 – 7.40 (m, 3H), 7.16 – 7.12 (m, 2H), 6.99 (s, 1H), 6.94 – 6.82 (m, 6H), 4.42 (d, *J* = 5.7 Hz, 2H), 3.79 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 167.0, 159.3, 146.2, 136.2, 130.1, 129.4, 129.3, 128.6, 125.9, 122.5, 114.3, 111.5, 109.4, 55.4, 43.3. IR (neat): 3334, 2922, 1603, 1478, 1235 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{22}H_{20}NO_4$ $(M+H)^+$ 362.1392, found: 362.1388.

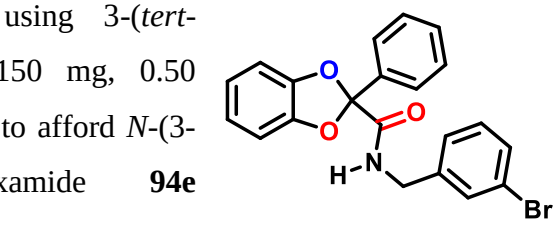
N-(2-chlorobenzyl)-2-phenylbenzo[d][1,3]dioxole-2-carboxamide (**94d**):

Prepared according to general procedure G, using 3-(*tert*-butylperoxy)-3-phenylbenzofuran-2(3*H*)-one **92a** (150 mg, 0.50 mmol) and 2-chlorobenzylamine (142 mg, 1 mmol) to afford *N*-(2-chlorobenzyl)-2-phenylbenzo[*d*][1,3]dioxole-2-carboxamide **94d** (150 mg, 82% yield) as a white solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 30:70). Melting point: 136−138 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.70 (m, 2H), 7.42 – 7.39 (m, 3H), 7.35 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.26 – 7.15 (m, 4H), 6.96 – 6.86 (m, 4H), 4.58 (d, *J* = 6.1 Hz, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 167.2, 146.2, 136.0, 134.8, 133.8, 130.2, 130.1, 129.7, 129.3, 128.6, 127.3, 125.9, 122.6, 111.5, 109.5. 41.71. IR (neat): 3325, 1680, 1481, 1233 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{21}H_{17}ClNO_3$ $(M+H)^+$ 366.0897, found: 366.0894.



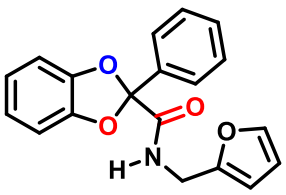
N-(3-bromobenzyl)-2-phenylbenzo[d][1,3]dioxole-2-carboxamide (**94e**):

Prepared according to general procedure G, using 3-(*tert*-butylperoxy)-3-phenylbenzofuran-2(3*H*)-one **92a** (150 mg, 0.50 mmol) and 3-bromobenzylamine (186 mg, 1 mmol) to afford *N*-(3-bromobenzyl)-2-phenylbenzo[*d*][1,3]dioxole-2-carboxamide **94e** (148 mg, 72% yield) as a white solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 30:70). Melting point: 135−137 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.71 (m, 2H), 7.44 – 7.38 (m, 4H), 7.31 (s, 1H), 7.17 – 7.10 (m, 3H), 6.96 – 6.88 (m, 4H), 4.46 (d, *J* = 6.0 Hz, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 167.4, 146.1, 139.7, 135.9, 131.0, 130.8, 130.5, 130.2, 128.7, 126.3, 125.9, 122.9, 122.7, 111.4, 109.5, 42.9. IR (neat): 3314, 1678, 1479, 1231 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{21}H_{17}BrNO_3$ $(M+H)^+$ 410.0392, found: 410.0393.



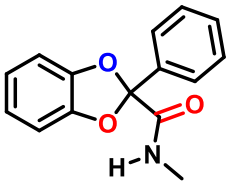
N-(furan-2-ylmethyl)-2-phenylbenzo[d][1,3]dioxole-2-carboxamide (**94f**):

Prepared according to general procedure G, using 3-(*tert*-butylperoxy)-3-phenylbenzofuran-2(3*H*)-one **92a** (150 mg, 0.50 mmol) and furfurylamine (97 mg, 1 mmol) to afford *N*-(furan-2-ylmethyl)-2-phenylbenzo[*d*][1,3]dioxole-2-carboxamide **94f** (130 mg, 80% yield) as a white solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 30:70). Melting point: 76−78 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.70 (m, 2H), 7.43 – 7.39 (m, 3H), 7.35 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.09 (s, 1H), 6.96 – 6.86 (m, 4H), 6.31 (dd, *J* = 3.2, 1.9 Hz, 1H),



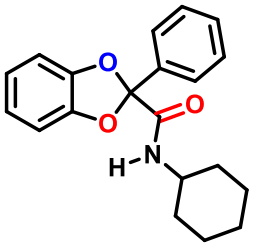
6.19 (dd, *J* = 3.2, 0.7 Hz, 1H), 4.49 (d, *J* = 5.6 Hz, 2H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 167.0, 150.3, 146.2, 142.6, 136.0, 130.1, 128.6, 125.9, 122.5, 111.4, 110.6, 109.4, 108.0, 36.8. IR (neat): 2920, 1603, 1481, 1234 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{19}H_{16}NO_4$ $(M+H)^+$ 322.1079, found: 322.1069.

N-methyl-2-phenylbenzo[d][1,3]dioxole-2-carboxamide (**94g**):



Prepared according to general procedure G, using 3-(*tert*-butylperoxy)-3-phenylbenzofuran-2(3*H*)-one **92a** (150 mg, 0.50 mmol) and methylamine (31 mg, 1 mmol) to afford *N*-methyl-2-phenylbenzo[*d*][1,3]dioxole-2-carboxamide **94g** (86 mg, 67% yield) as a white solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 30:70). Melting point: 116−118 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.70 (m, 2H), 7.43– 7.39 (m, 3H), 6.95 – 6.86 (m, 4H), 6.80 (s, 1H), 2.88 (d, *J* = 5.0 Hz, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 167.8, 146.2, 136.2, 130.1, 128.6, 125.9, 122.5, 111.5, 109.4, 26.4. IR (neat): 3320, 1677, 1480, 1232 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{15}H_{14}NO_3$ $(M+H)^+$ 256.0973, found: 256.0963.

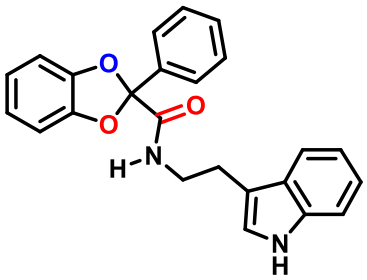
N-cyclohexyl-2-phenylbenzo[d][1,3]dioxole-2-carboxamide (**94h**):



Prepared according to general procedure G, using 3-(*tert*-butylperoxy)-3-phenylbenzofuran-2(3*H*)-one **92a** (150 mg, 0.50 mmol) and cyclohexylamine (99 mg, 1 mmol) to afford *N*-cyclohexyl-2-phenylbenzo[*d*][1,3]dioxole-2-carboxamide **94h** (142 mg, 87% yield) as a white solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 30:70). Melting point: 128−130 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.68 (m, 2H), 7.43 – 7.38 (m, 3H), 6.95 – 6.86 (m, 4H), 6.63 (d, *J* = 7.8 Hz, 1H), 3.84 – 3.74 (m, 1H), 1.92 – 1.88 (m, 2H), 1.71 – 1.58 (m, 3H), 1.40 – 1.11 (m, 5H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 166.0, 146.3, 136.4, 130.0, 128.5, 125.9, 122.4, 111.4, 109.4, 48.6, 32.9, 25.5, 24.8. IR (neat): 2918, 2851, 1682, 1482, 1235 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{20}H_{22}NO_3$ $(M+H)^+$ 324.1599, found: 324.1592.

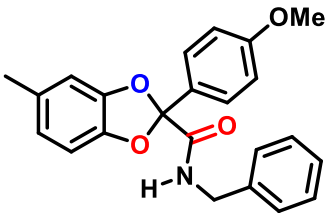
N-(2-(1H-indol-3-yl)ethyl)-2-phenylbenzo[d][1,3]dioxole-2-carboxamide (**94i**):

Prepared according to general procedure G, using 3-(*tert*-butylperoxy)-3-phenylbenzofuran-2(3*H*)-one **92a** (150 mg, 0.50 mmol) and tryptamine (160 mg, 1 mmol) to afford *N*-(2-(1*H*-indol-3-yl)ethyl)-2-phenylbenzo[*d*][1,3]dioxole-2-carboxamide **94i** (160 mg, 83% yield) as a yellow solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 30:70). Melting point: 85−87 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.69 (m, 2H), 7.58 (d, *J* = 7.9 Hz, 1H), 7.41 - 7.36 (m, 4H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 6.94 (s, 1H), 6.89 (s, 4H), 6.74 (d, *J* = 1.5 Hz, 1H), 3.65 (q, *J* = 6.4 Hz, 2H), 2.99 (t, *J* = 6.6 Hz, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 167.3, 167.2, 146.2, 136.5, 136.1, 130.0, 128.5, 127.2, 125.9, 122.5, 122.4, 122.2, 119.5, 118.6, 112.2, 111.5, 109.3, 40.0, 25.1. IR (neat): 3316, 1679, 1480, 1232 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{24}H_{21}N_2O_3$ $(M+H)^+$ 385.1552, found: 385.1551.



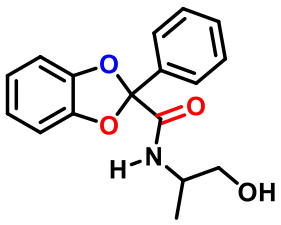
N-benzyl-2-(4-methoxyphenyl)-5-methylbenzo[d][1,3]dioxole-2-carboxamide (**94j**):

Prepared according to general procedure G, using 3-(*tert*-butylperoxy)-3-(4-methoxyphenyl)-5-methylbenzofuran-2(3*H*)-one **92j** (171 mg, 0.50 mmol) and benzylamine (107 mg, 1 mmol) to afford *N*-benzyl-2-(4-methoxyphenyl)-5-methylbenzo[*d*][1,3]dioxole-2-carboxamide **94j** (150 mg, 91% yield) as a yellow semi-solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 30:70). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.62 (m, 2H), 7.34 – 7.28 (m, 3H), 7.22 – 7.20 (m, 2H), 7.05 (t, *J* = 5.0 Hz, 1H), 6.94 – 6.90 (m, 2H), 6.79 – 6.74 (m, 2H), 6.69 – 6.64 (m, 1H), 4.49 (d, *J* = 5.8 Hz, 2H), 3.81 (s, 3H), 2.28 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 167.5, 161.0, 146.3, 144.1, 137.4, 132.4, 128.9, 128.3, 127.9, 127.8, 127.5, 122.4, 114.0, 111.7, 110.2, 108.8, 55.5, 43.7, 21.3. IR (neat): 3315, 2921, 1679, 1493, 1245 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{23}H_{22}NO_4$ $(M+H)^+$ 376.1549, found: 376.1545.



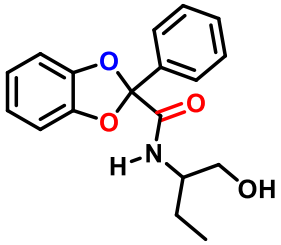
N-(1-hydroxypropan-2-yl)-2-phenylbenzo[d][1,3]dioxole-2-carboxamide (**94k**):

Prepared according to general procedure G, using 3-(*tert*-butylperoxy)-3-phenylbenzofuran-2(3*H*)-one **92a** (150 mg, 0.50 mmol) and 2-aminopropan-1-ol (75 mg, 1 mmol) to afford *N*-(1-hydroxy-3-phenylpropan-2-yl)-2-phenylbenzo[*d*][1,3]dioxole-2-carboxamide **94k** (143 mg, 95% yield) as a white solid after purification by silica gel column



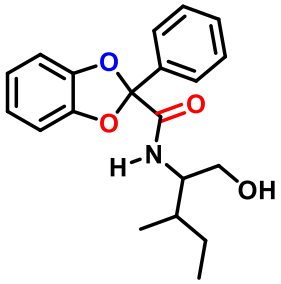
chromatography (EtOAc:*n*-hexane = 50:50). Melting point: 115−117 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.69 (m, 2H), 7.41 – 7.39 (m, 3H), 6.96 – 6.86 (m, 5H), 4.11 – 4.00 (m, 1H), 3.67 – 3.53 (m, 2H), 2.32 (s, 1H), 1.20 (d, *J* = 6.8 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 167.4, 146.2, 146.1, 136.2, 130.1, 128.6, 125.9, 122.6, 111.4, 109.4, 66.4, 66.3, 48.0, 17.0. IR (neat): 3406 2922, 1673, 1481, 1232 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{17}H_{18}NO_4$ $(M+H)^+$ 300.1236, found: 300.1232.

N-(1-hydroxybutan-2-yl)-2-phenylbenzo[d][1,3]dioxole-2-carboxamide (**94l**):



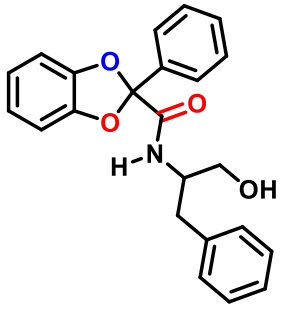
Prepared according to general procedure G, using 3-(*tert*-butylperoxy)-3-phenylbenzofuran-2(3*H*)-one **92a** (150 mg, 0.50 mmol) and 2-amino-1-butanol (89 mg, 1 mmol) to afford *N*-(1-hydroxy-3-phenylpropan-2-yl)-2-phenylbenzo[*d*][1,3]dioxole-2-carboxamide **94l** (132 mg, 84% yield) as a yellow solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 50:50). Melting point: 96−98 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.69 (m, 2H), 7.41 – 7.39 (m, 3H), 6.95 – 6.86 (m, 5H), 3.91 – 3.81 (m, 1H), 3.68 – 3.55 (m, 2H), 1.68 – 1.45 (m, 2H), 0.85 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 167.7, 146.2, 136.2, 130.1, 128.6, 125.9, 122.6, 111.5, 109.44, 109.38, 64.4, 53.5, 24.1, 10.5. IR (neat): 3406, 2965, 1674, 1480, 1233 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{18}H_{20}NO_4$ $(M+H)^+$ 314.1392, found: 314.1390.

N-(1-hydroxy-3-methylpentan-2-yl)-2-phenylbenzo[d][1,3]dioxole-2-carboxamide (**94m**):



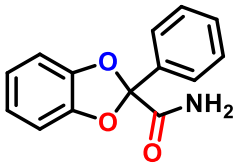
Prepared according to general procedure G, using 3-(*tert*-butylperoxy)-3-phenylbenzofuran-2(3*H*)-one **92a** (150 mg, 0.50 mmol) and 2-amino-3-methylpentan-1-ol (117 mg, 1 mmol) to afford *N*-(1-hydroxy-3-phenylpropan-2-yl)-2-phenylbenzo[*d*][1,3]dioxole-2-carboxamide **94m** (134 mg, 78% yield) as a yellow solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 50:50). Melting point: 156−158 °C. ^{1}H NMR (400 MHz, $CDCl_3$) 7.76 – 7.68 (m, 2H), 7.41 (m, 3H), 6.98 – 6.86 (m, 5H), 3.82 – 3.75 (m, 1H), 3.70 (d, *J* = 4.0 Hz, 2H), 2.15 (s, 1H), 1.72 – 1.63 (m, 1H), 1.45 – 1.33 (m, 1H), 1.11 – 1.00 (m, 1H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.81 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 167.9, 146.2, 136.1, 130.2, 128.6, 125.9, 122.6, 111.6, 109.5, 109.4, 63.3, 56.3, 35.5, 25.5, 15.7, 11.2. IR (neat): 3377, 3262, 2964, 1651, 1481, 1232 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{20}H_{24}NO_4$ $(M+H)^+$ 342.1705, found: 342.1700.

N-(1-hydroxy-3-phenylpropan-2-yl)-2-phenylbenzo[d][1,3]dioxole-2-carboxamide (**94n**):



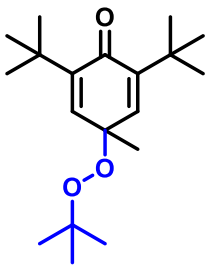
Prepared according to general procedure G, using 3-(*tert*-butylperoxy)-3-phenylbenzofuran-2(3*H*)-one **92a** (150 mg, 0.50 mmol) and (S)-(−)-2-amino-3-phenyl-1-propanol (151 mg, 1 mmol) to afford *N*-(1-hydroxy-3-phenylpropan-2-yl)-2-phenylbenzo[*d*][1,3]dioxole-2-carboxamide **94n** (154 mg, 82% yield) as a white solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 50:50). Melting point: 90−92 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 –7.56 (m, 2H), 7.41 – 7.33 (m, 3H), 7.20 – 7.18 (m, 3H), 7.11 – 7.05 (m, 3H), 6.92 – 6.88 (m, 3H), 4.22 – 4.10 (m, 1H), 3.64 – 3.68 (m, 2H), 2.88 (ddd, *J* = 21.4, 13.8, 7.1 Hz, 2H) 2.06 (s, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 167.6, 146.12, 146.06, 137.2, 135.9, 130.1, 129.3, 128.7, 128.6, 126.8, 125.8, 122.53, 122.51, 111.4, 109.4, 109.3, 63.7, 53.1, 36.8. IR (neat): 3407, 2920, 2851, 1482, 1265 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{23}H_{22}NO_4$ $(M+H)^+$ 376.1549, found: 376.1549.

2-phenylbenzo[d][1,3]dioxole-2-carboxamide (**94o**):



Prepared according to general procedure G, using 3-(*tert*-butylperoxy)-3-phenylbenzofuran-2(3*H*)-one **92a** (150 mg, 0.50 mmol) and ammonia solution (17 mg, 1 mmol) to afford 2-phenylbenzo[*d*][1,3]dioxole-2-carboxamide **94o** (80 mg, 66% yield) as a white solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 50:50). Melting point: 185−187 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.31 (m, 2H), 7.43 – 7.39 (m, 3H), 6.96 – 6.81 (m, 4H), 6.66 (s, 1H), 6.17 (s, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 169.8, 146.2, 135.8, 130.2, 128.7, 125.9, 122.6, 111.2, 109.4. IR (neat): 2919, 2851, 1694, 1482, 1234 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{14}H_{11}NNaO_3$ $(M+Na)^+$ 264.0637, found: 264.0625.

2,6-di-tert-butyl-4-(tert-butylperoxy)-4-methylcyclohexa-2,5-dien-1-one (**123**):[82]



Prepared according to general procedure I, using 1-benzylnaphthalen-2-ol **88e** and BHT (110 mg, 0.50 mmol) to afford 2,6-di-*tert*-butyl-4-(*tert*-butylperoxy)-4-methylcyclohexa-2,5-dien-1-one **123** (55 mg, 55% yield) as a yellow solid. Using 3-aryl benzofuran-2(3*H*)-ones compound **91a** (0.25 mmol, 1 equiv.) and BHT (110 mg, 0.50 mmol) to afford 2,6-di-*tert*-butyl-4-(*tert*-butylperoxy)-4-methylcyclohexa-2,5-dien-1-one **123** (75 mg, 49% yield) as a yellow solid after purification by silica gel column chromatography (EtOAc:*n*-hexane = 10:90). ^{1}H NMR (400 MHz,

$CDCl_3$) δ 6.56 (s, 2H), 1.33 (s, 3H), 1.22 (s, 18H), 1.18 (s, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 186.8, 146.8, 142.0, 79.5, 76.4, 34.9, 29.6, 26.6, 24.4. The spectral data were identical to the reported compound.

3.8. Appendix II: Copies of ^1H and $^{13}C\{^1H\}$ NMR spectra of representative compounds

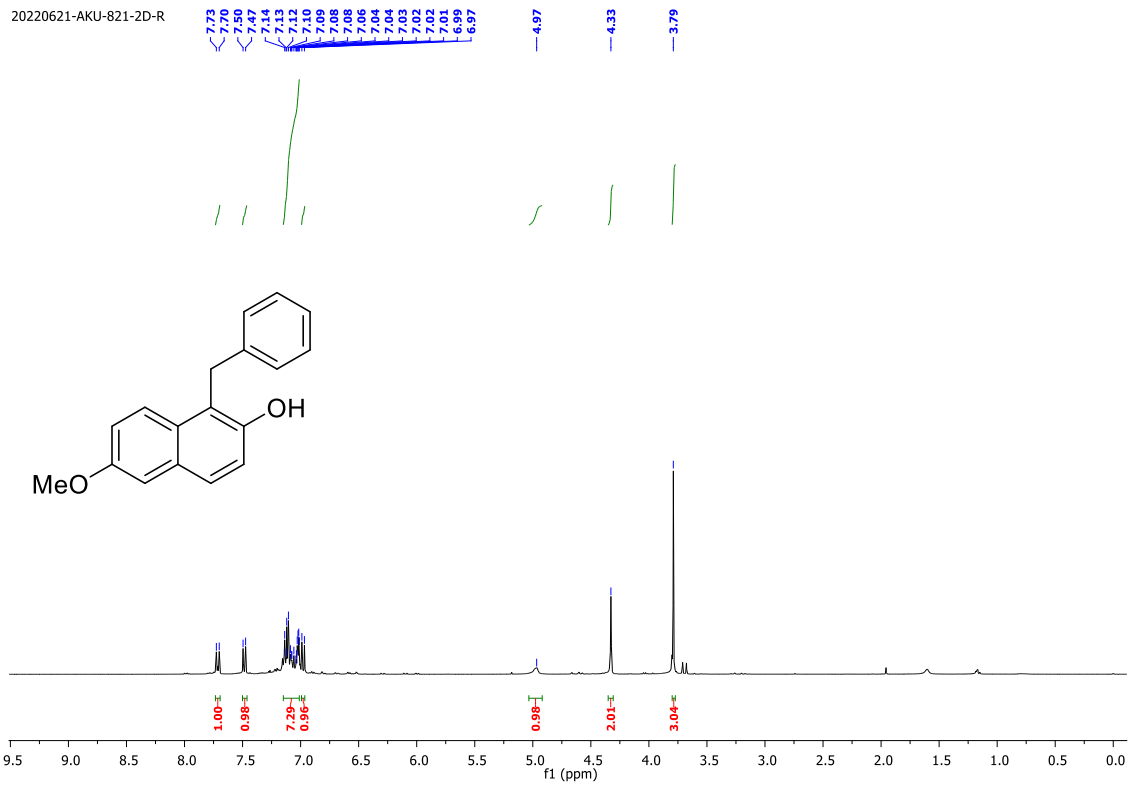


Figure 3.8.1. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **88q**

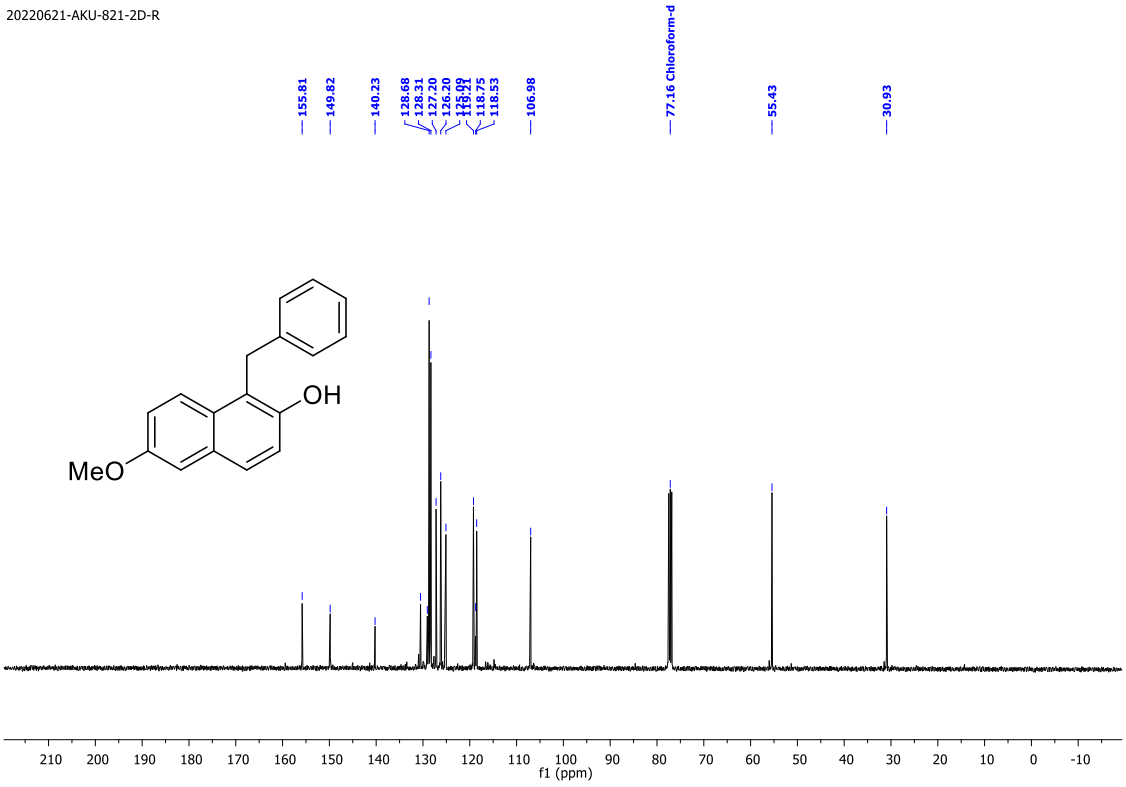


Figure 3.8.2. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) of compound **88q**

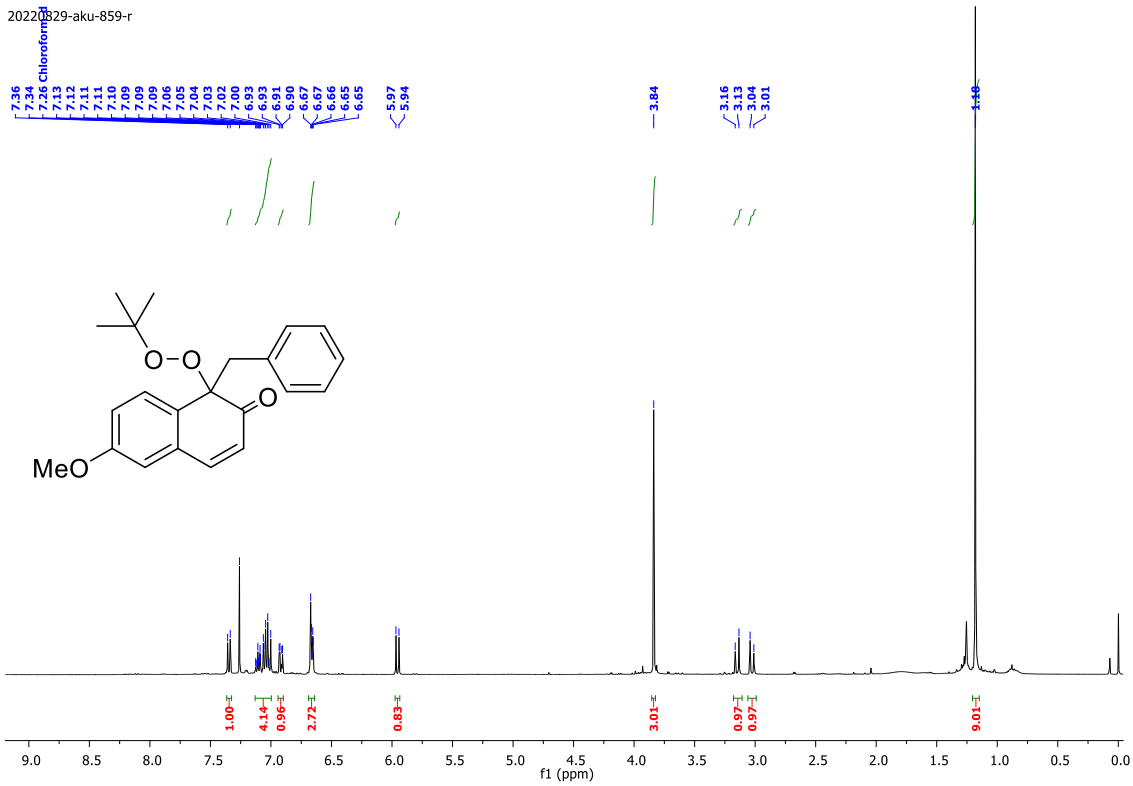


Figure 3.8.3. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **89n**

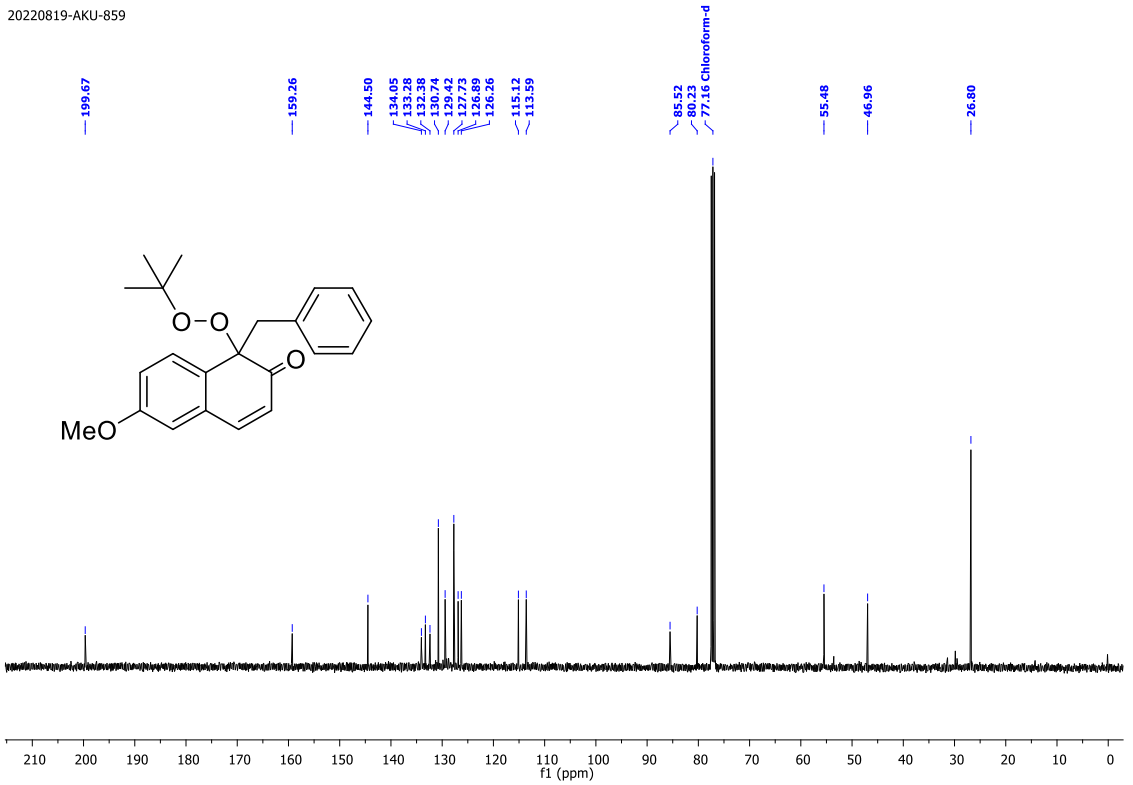


Figure 3.8.4. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) of compound **89n**

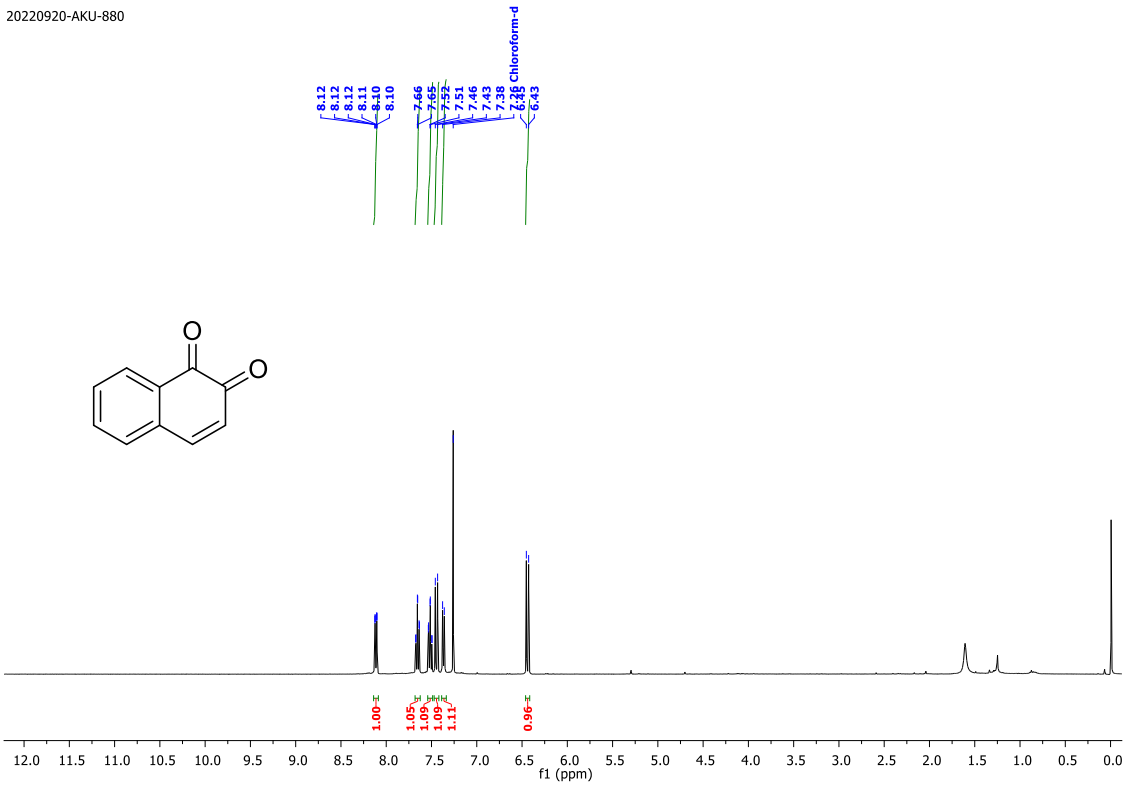


Figure 3.8.5. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **90a**

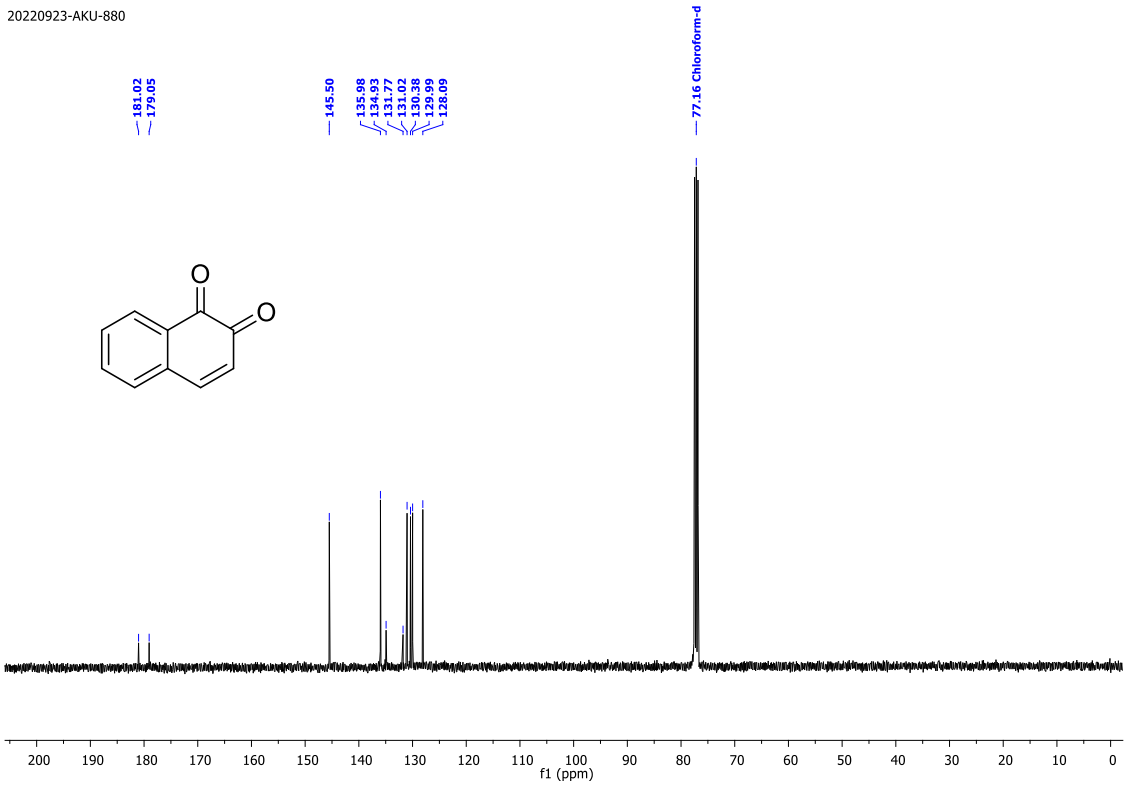


Figure 3.8.6. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) of compound **90a**

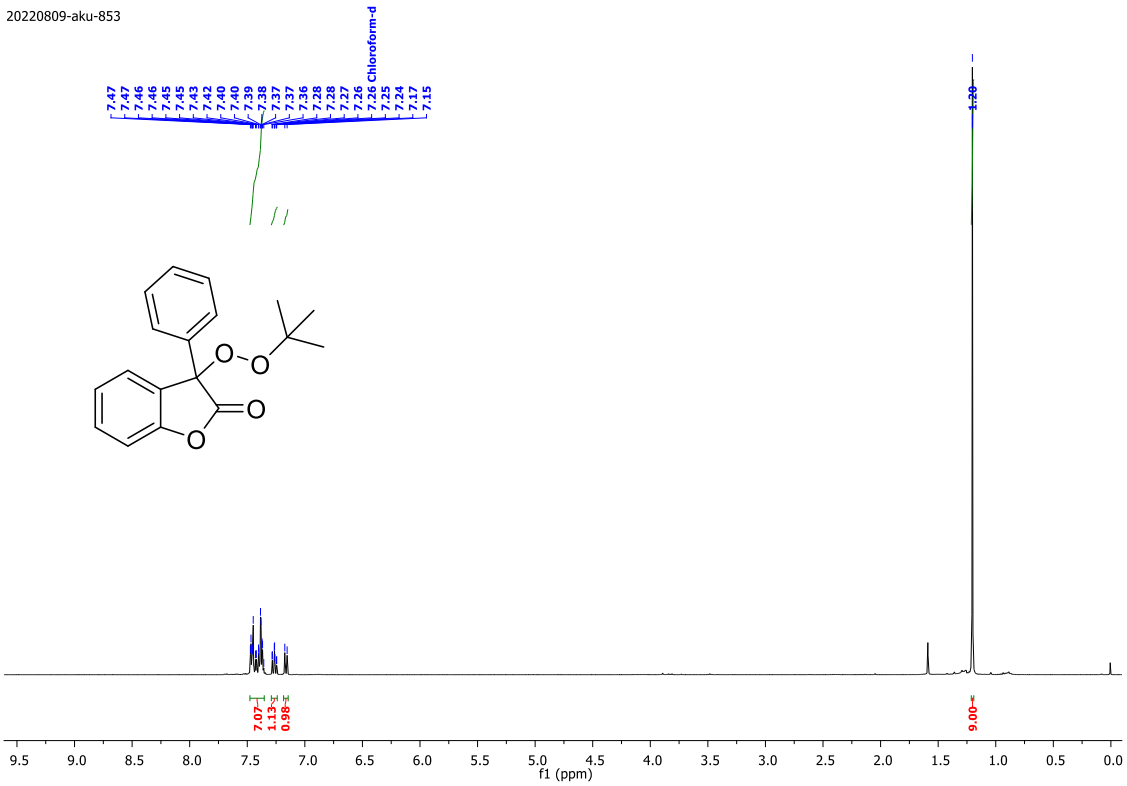


Figure 3.8.7. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **92a**

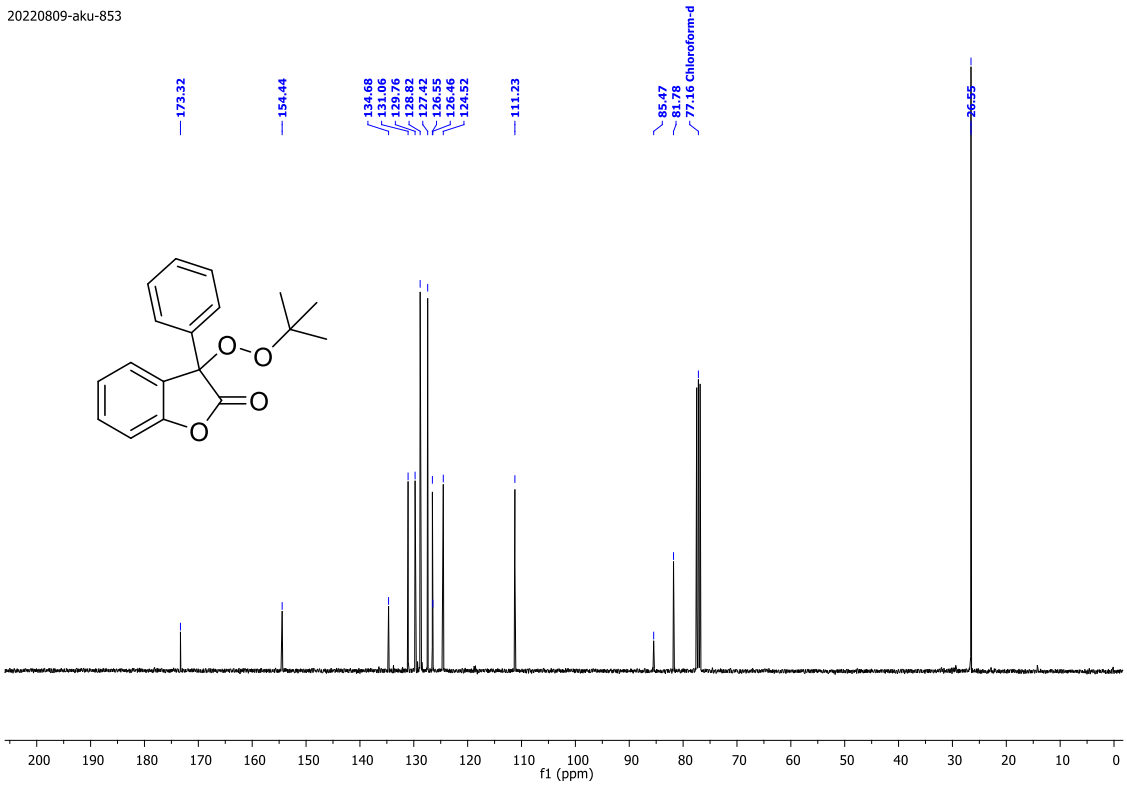


Figure 3.8.8. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) of compound **92a**

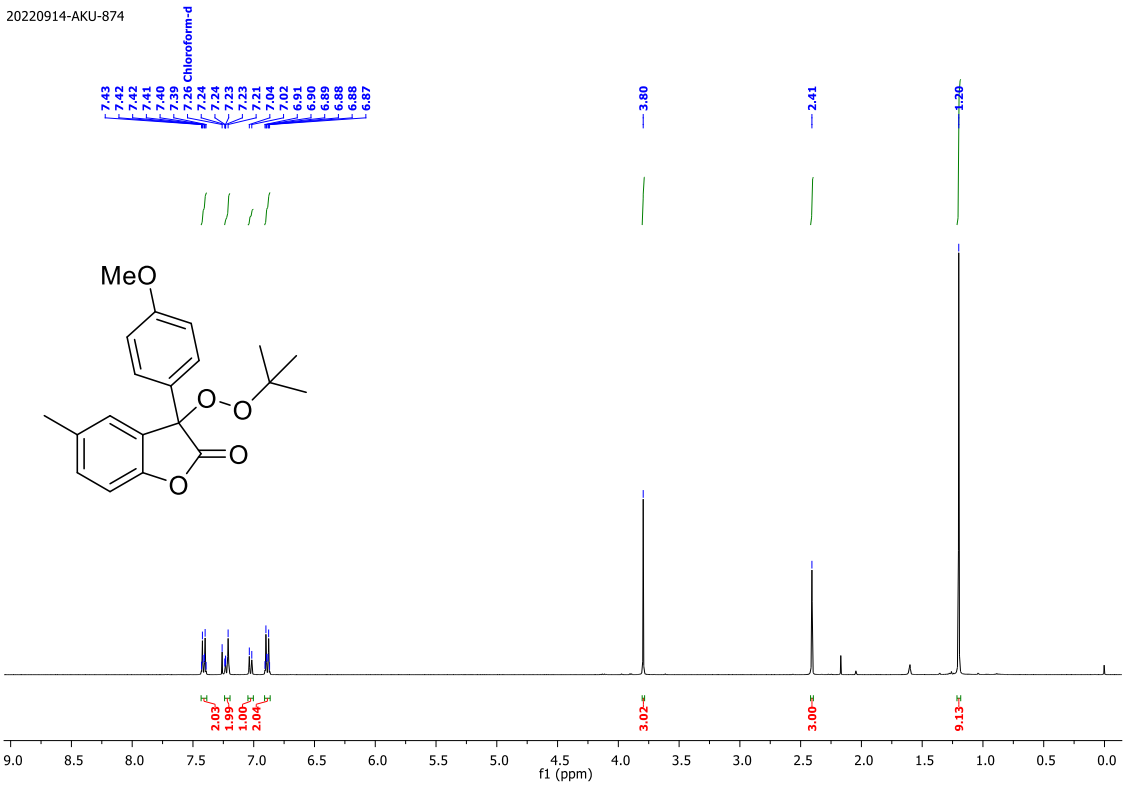


Figure 3.8.9. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **92j**

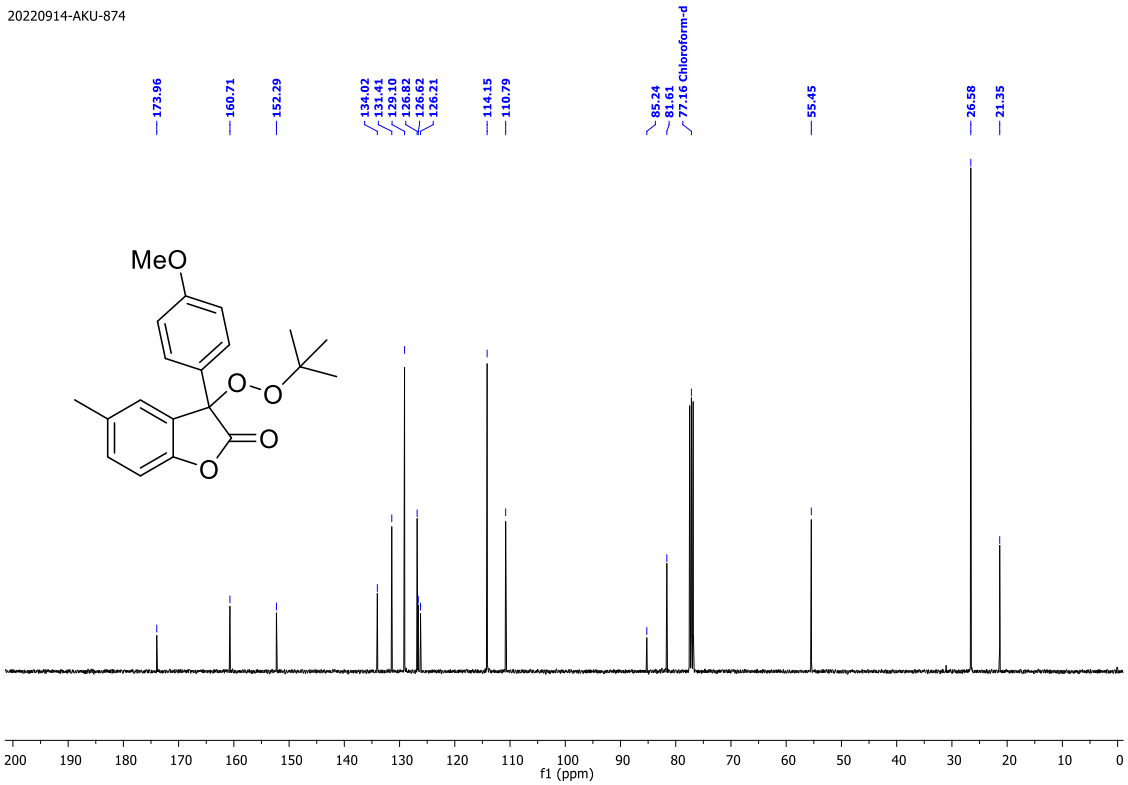


Figure 3.8.10. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) of compound **92j**

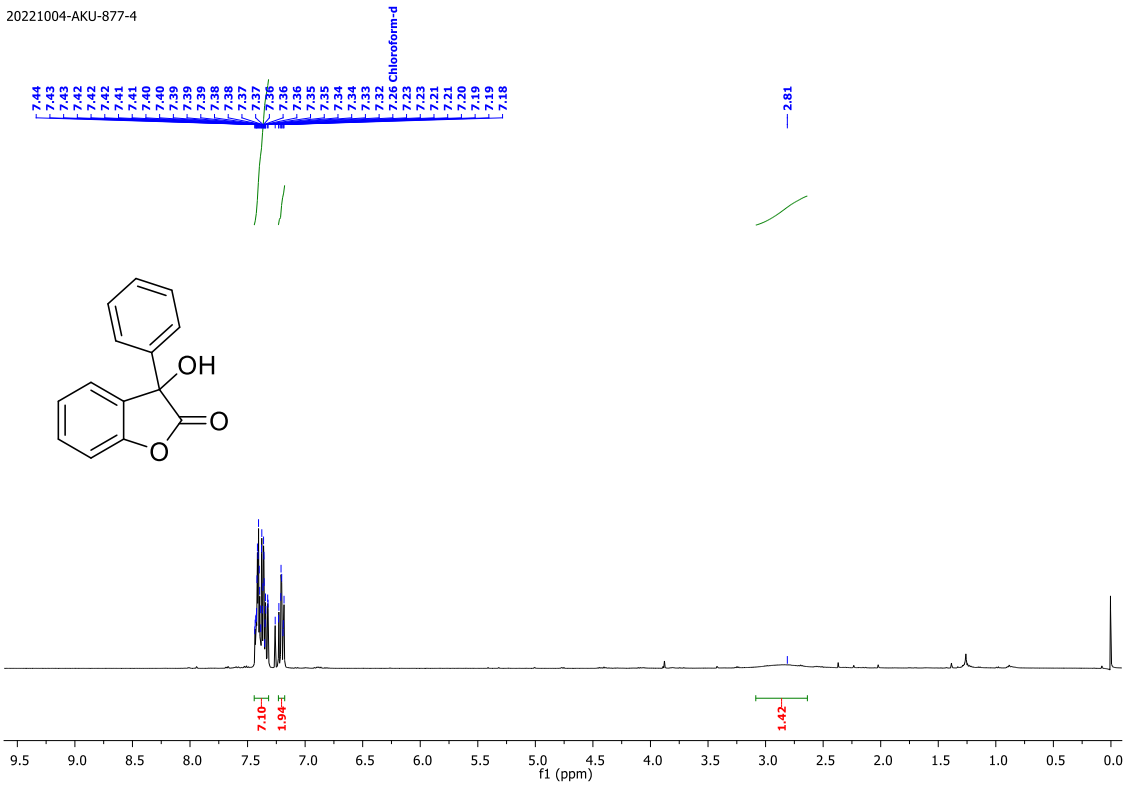


Figure 3.8.11. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **93a**

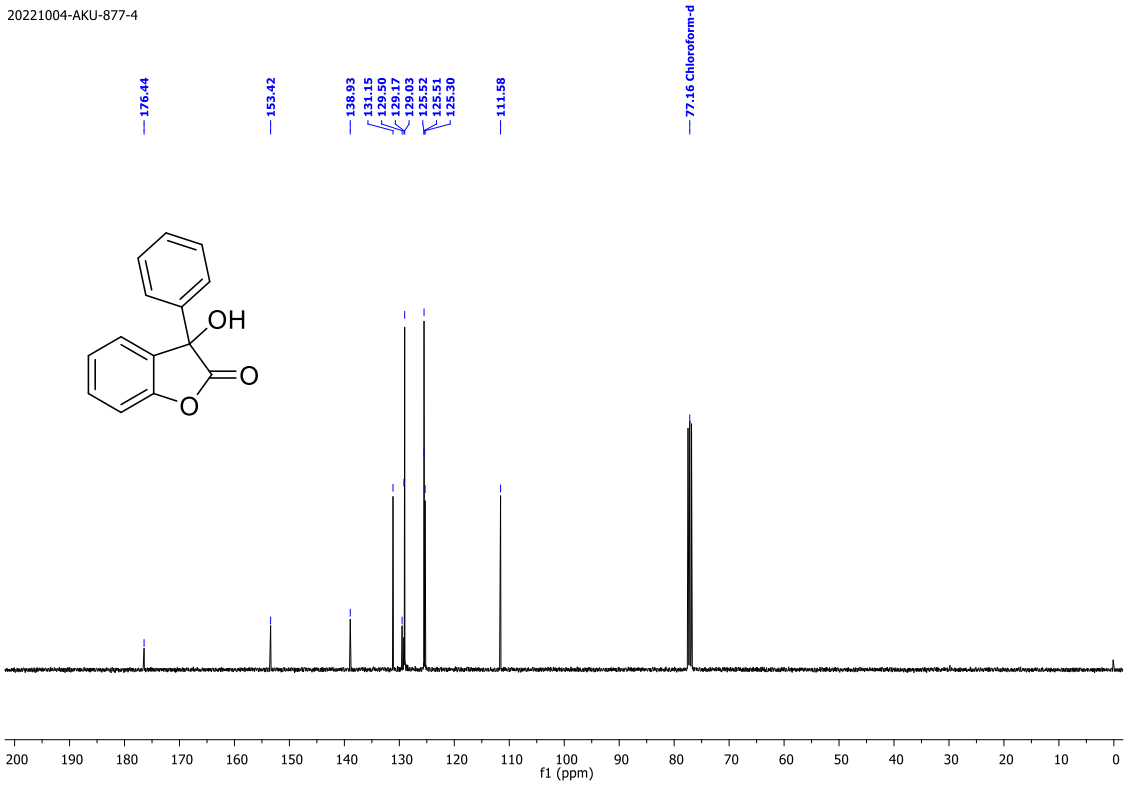


Figure 3.8.12. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) of compound **93a**

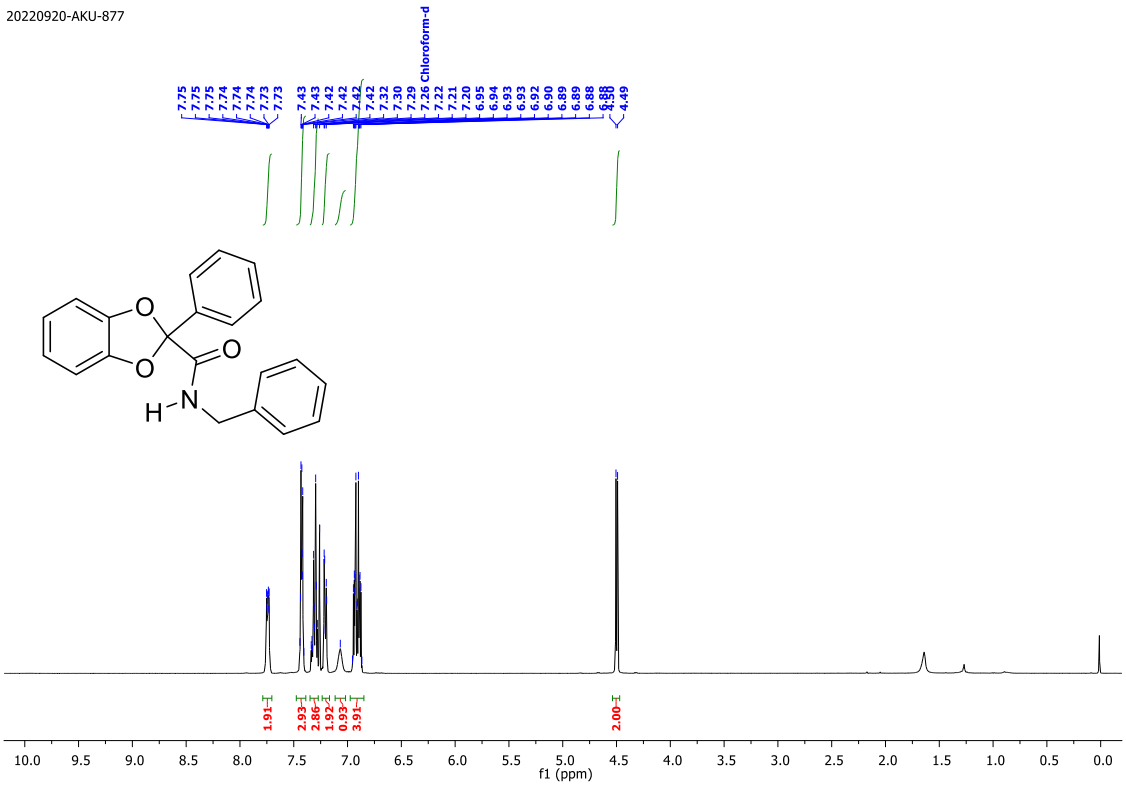


Figure 3.8.13. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **94a**

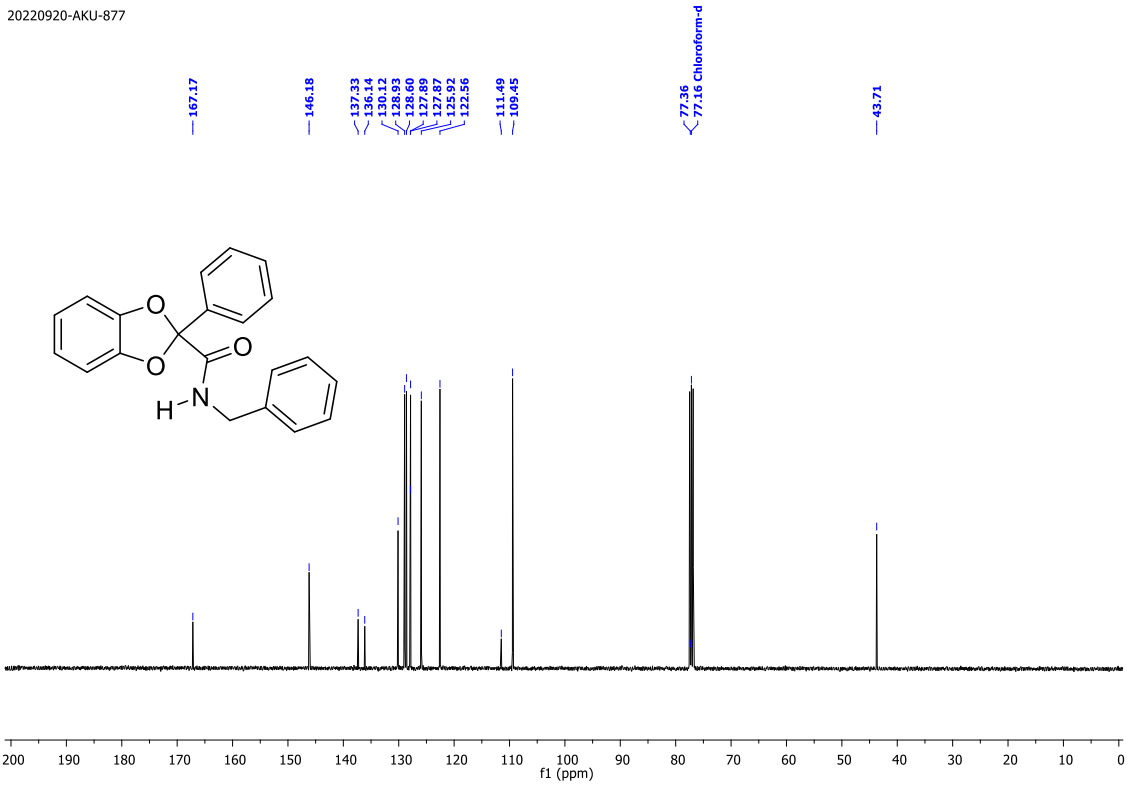


Figure 3.8.14. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) of compound **94a**

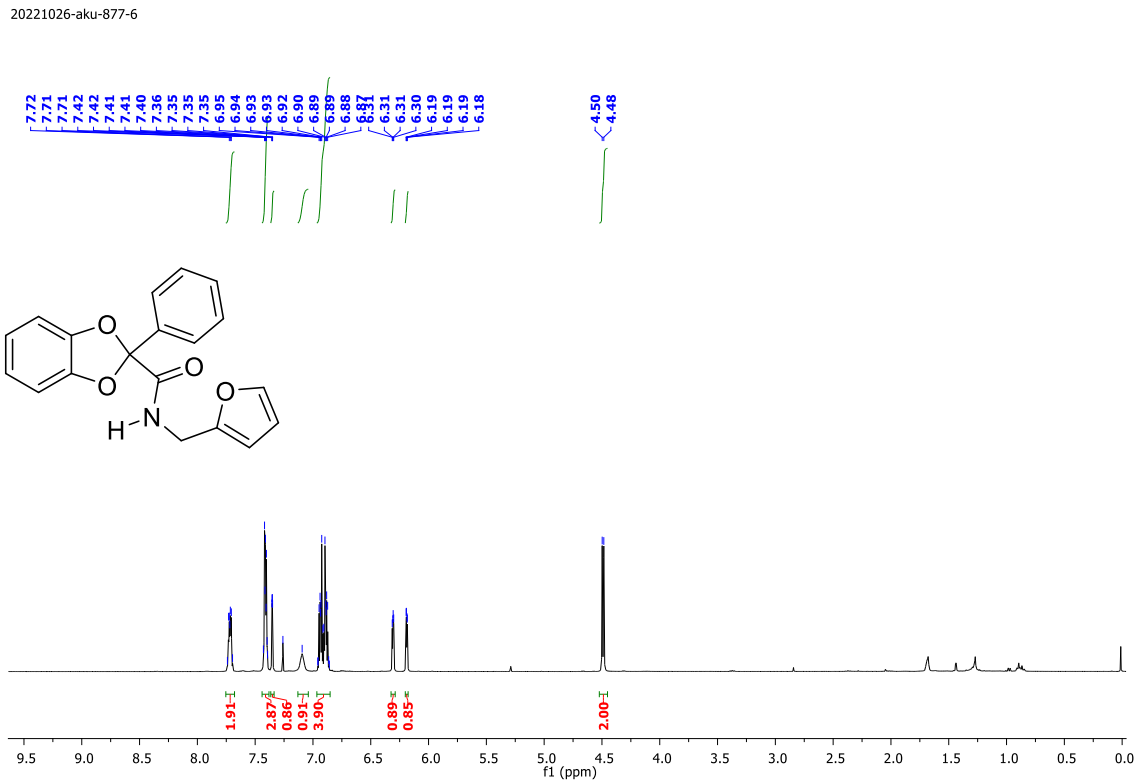


Figure 3.8.15. ^{1}H NMR (400 MHz, $CDCl_3$) of compound **94f**

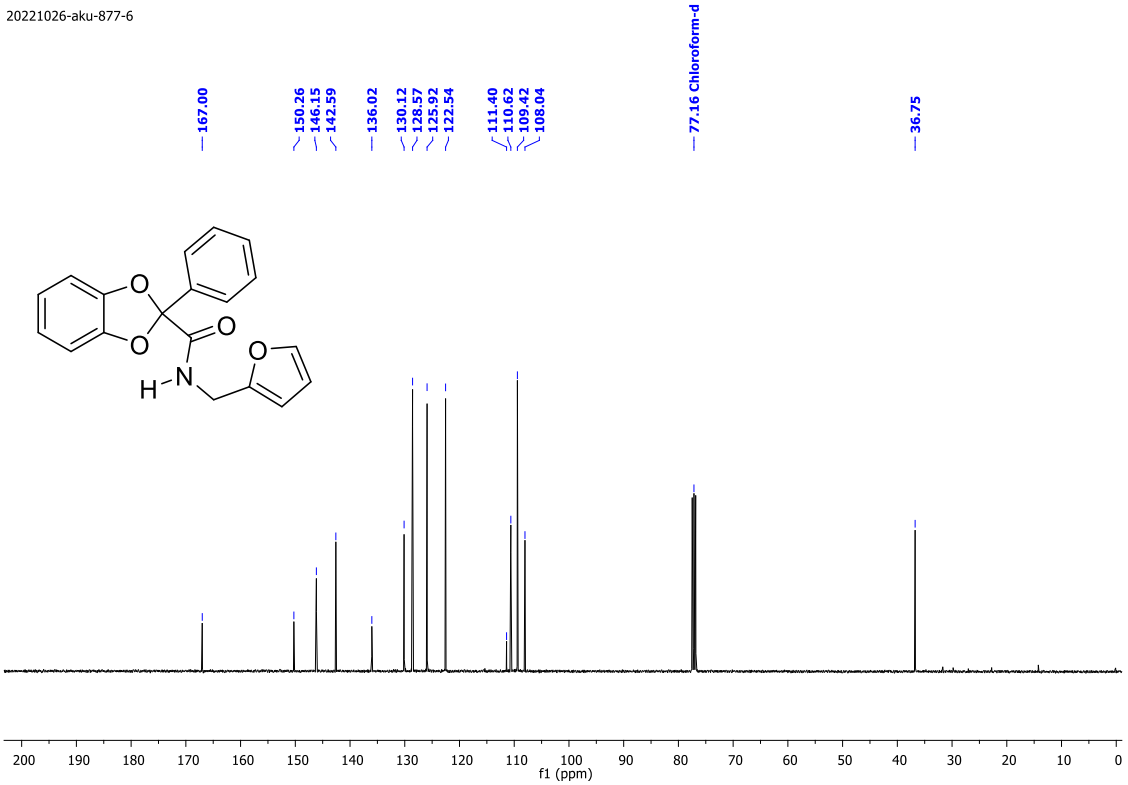


Figure 3.8.16. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) of compound **94f**

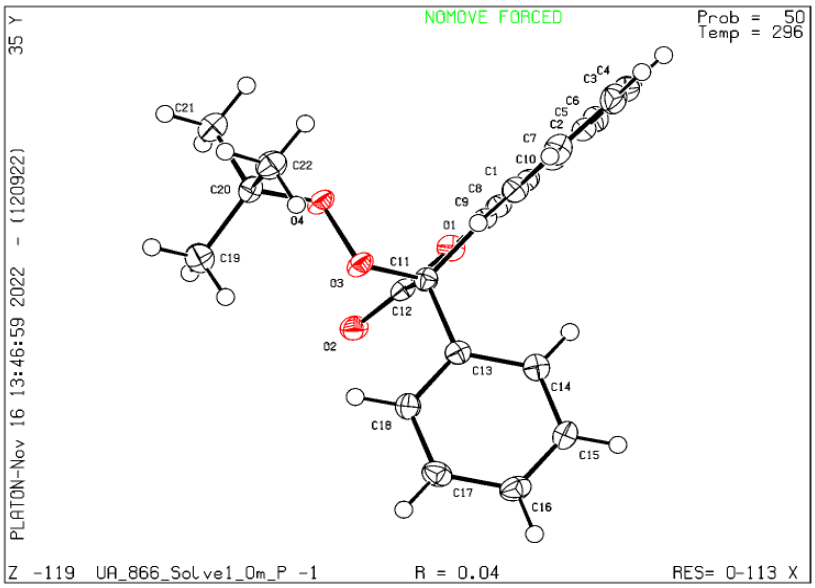


Figure 3.8.17. ORTEP crystal structure of **89q** showing thermal ellipsoids at the 50% probability level**.**

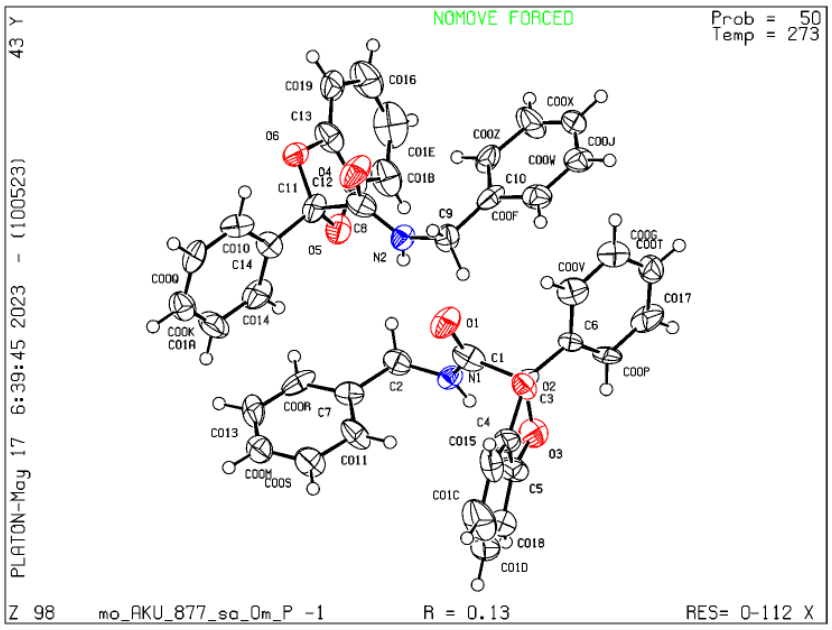


Figure 3.8.18. ORTEP crystal structure of **94a** showing thermal ellipsoids at the 50% probability level.

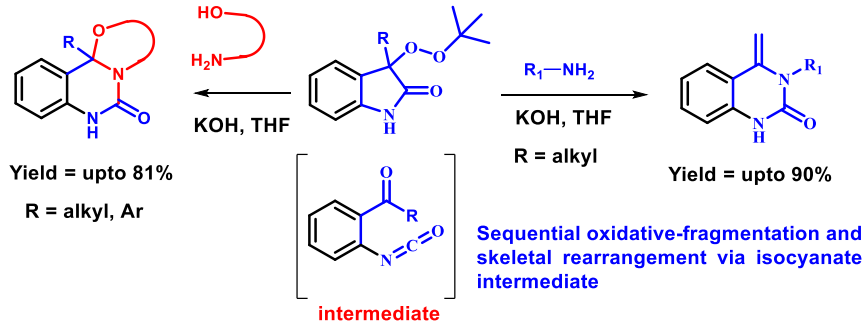
Chapter 4

Sequential Oxidative-Fragmentation and Skeletal Rearrangement of Peroxides for the Synthesis of Quinazolinone Derivatives

4. Sequential Oxidative-Fragmentation and Skeletal Rearrangement of Peroxides for the Synthesis of Quinazolinone Derivatives

4.1. Abstract

In this chapter, we have demonstrated for the first time a sequential reaction of peroxyoxindole involving base-promoted oxidative fragmentation to isocyanate formation and skeletal rearrangement accelerated by primary amines or amino alcohols to synthesize exo-olefinically substituted quinazolinones or oxazoloquinazolinones. The advantages of this new reaction include the wide substrate scope, absence of transition metals, and room temperature reaction conditions. The formation of the isocyanate as a key intermediate that accelerates oxidative skeletal rearrangement was confirmed by trapping experiments and spectroscopic evidence.



Scheme 4.1.1 Present finding oxidative-fragmentation and skeletal rearrangement of peroxide

4.2. Introduction to the rearrangement of peroxides

Heterocycles are the most important and significant chemical entities in pharmaceuticals and agricultural applications.[83] There are several alkaloids contain various heterocycles in the backbone. Peroxide-functionalized heterocycles are an important intermediate in various oxidative transformations.[50a-c] Moreover, the peroxide functionality of oxindole or 3-substituted-2-oxindole derivatives makes them intriguing starting materials for structurally diverse rearrangement reactions.[84a,b] In general, peroxides are known to undergo Baeyer–Villiger oxidation[15a,15c,15f] and the Hock process[39] for the preparation of phenol from cumene hydroperoxide, in which an aryl/alkyl group migrates to an electron-deficient oxygen atom, has been extensively studied under an acidic source. Synthetically, the Kornblum-DeLaMare rearrangement is one of the most important rearrangements in organic peroxides for the production of ketones and alcohols under

basic conditions.[40] Based on these rearrangements, the skeletal rearrangement of peroxides to access biologically important intermediates is an attractive paradigm in organic synthesis. Recently, Stoltz and co-workers reported a seminal work on the direct C-H peroxidation of 2-oxindole with a Cu-catalyst followed by base-mediated fragmentation.[46] Subsequently, Gnanaprakasam and co-workers reported the rearrangement of C3-substituted 2-oxindole peroxide using Lewis and Brønsted acids.[47a,47b,73] Some other rearrangements were also described by other research groups using various heterocyclic peroxides.[43,44,45] All these reactions with Scheme were discussed in section 1.6 of Chapter 1.

The heterocyclic compounds with nitrogen, like C4-substituted quinazolinones[85] and quinazolinediones[86] display a variety of biological characteristics, including Na^+/Ca^{2+} exchanger inhibitor,[87] anti-inflammatory,[88] anticancer,[89] antimalarials,[90] antidiabetic[91] and antihypertensive[92] activities (Figure 4.2.1.). Therefore, they play the discovery of drugs and have a key role in medicinal chemistry, and the correlations between drugs and their targets are crucial for the specific biological activity and effects of the drug's action.

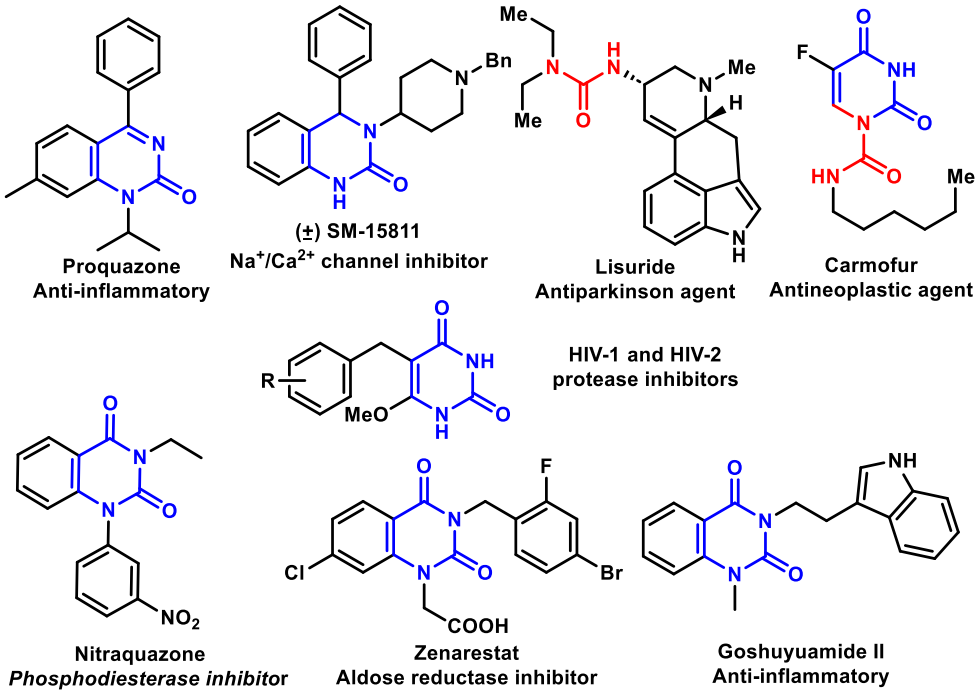
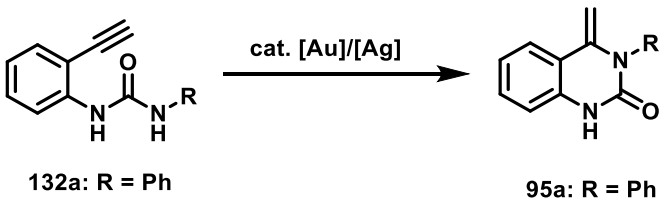


Figure 4.2.1. Pharmacologically active quinazolinone framework**.**

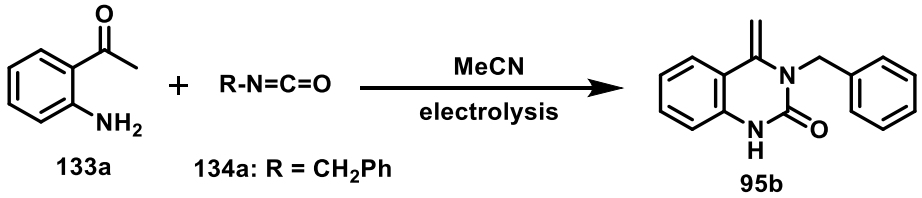
Few pioneering methods for the synthesis of 4-methylene-3,4-dihydroquinazolin-2-ones have been described in the literature.[93a,b] Gimeno et al. reported the Au(I)-complex catalyzed

synthesis of 4-methylen-3,4-dihydroquinazolin-2-ones **95a** from 1-(o-alkynylaryl)urea **132a** (Scheme 4.2.1.).[93c-e]



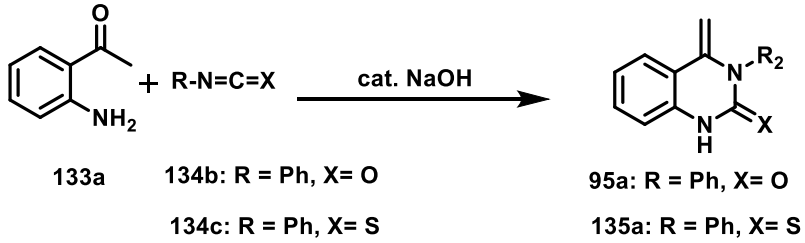
Scheme 4.2.1. Synthesis of 4-methylen-3,4-dihydroquinazolin-2-ones by Gimeno group

Subsequently, the synthesis of 3-substituted 2-quinazolinones **95b** from the reaction of 2-aminoacetophenone **133a** was described by Isidoro Barba and co-workers *via* the cyanomethyl anion electrically generated upon reduction of acetonitrile at a graphite electrode (Scheme 4.2.2).[93f]



Scheme 4.2.2. Synthesis of 3-substituted 2-quinazolinones by Isidoro group

To avoid the use of expensive ligands or catalysts, Yongmin Ma and co-workers have recently described deviant methods for the synthesis of 4-alkenylquinazolinones **95a** and 4-alkenylquinazolinethiones **135a** using catalytic amounts of NaOH under reflux conditions (Scheme 4.2.3.).[94]



Scheme 4.2.3. Synthesis of 4-alkenylquinazolinones and 4-alkenylquinazolinethiones by Yongmin group

4.3. The rationale of the present work

Despite the advantages and disadvantages of the described protocol for quinazolinone derivatives, the development of an attractive and innovative approach to these heterocycles is an

ever-growing paradigm in chemical synthesis. From the literature, it appears that quinazolinone derivatives have not been made using peroxide rearrangements. As part of our investigation on the modification of peroxides to produce heterocycles (Scheme 4.2.1. C),[47a,47b,73] we envisioned to study the rearrangement of peroxide for the synthesis of 4-methylene-3-substituted quinazolinone.

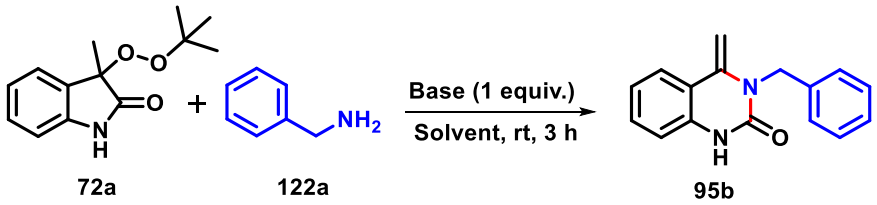
4.4. Results and discussion

In this chapter, we have developed the transition metal-free oxidative fragmentation of peroxyoxindole derivatives for the synthesis of bioactive quinazolinone derivatives in the presence of various amine nucleophiles using base.

4.4.1. Optimization studies

To demonstrate base-mediated oxidative fragmentation and skeletal rearrangement to 4-methylene-3-substituted quinazolinone, initial optimization was conducted with peroxide **72a** and **122a**. Control experiments with 3-(*tert*-butylperoxy)-3-methylindolin-2-one **72a** and benzylamine **122a** in the absence of a base at room temperature or 60 °C in THF were not afforded the product 3-benzyl-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one **95b** (Table 4.4.1., entries 1, 2). Further, product **95b** was characterized by spectroscopic techniques and single-crystal XRD (Figure 4.9.23.). The base plays a crucial role in the oxidative fragmentation of the peroxide. When this reaction was carried out in the presence of Na_2CO_3, product **95b** was obtained in 25% yield (Table 4.4.1., entry 3). In the next reaction with K_2CO_3, **95b** was not obtained (Table 4.4.1., entry 4). Interestingly, the reaction works well in the presence of Cs_2CO_3 and gives the product **95b** in 74% yield. In addition, we have investigated a variability of bases for this reaction. It is noteworthy that the addition of NaOH leads to a slight improvement in the yield of product **95b** to 77% yield (Table 4.4.1, entry 6). An excellent yield was obtained for **95b** in the case of KOH as a base (Table 4.4.1, entry 7). Other bases such as KO*t*Bu and LiO*t*Bu also formed product **95b** in 75% and 82% yields, respectively (Table 4.4.1., entries 8 and 9). From our review of bases, KOH is the best base for this transformation. In addition, a decrease in yield was observed when the amount of KOH was decreased (Table 4.4.1, entries 10 and 11). Next, different solvents were tried to increase the yield of product **95b**, but no progress was observed (Table 4.4.1., entries 12−17). In the case of water used as a solvent, the desired product **95b** was not detected. From this experimental study, THF is the best solvent in this transformation and gives **95b** in 87% yield after 3 hours (Table 4.4.1., entry 7).

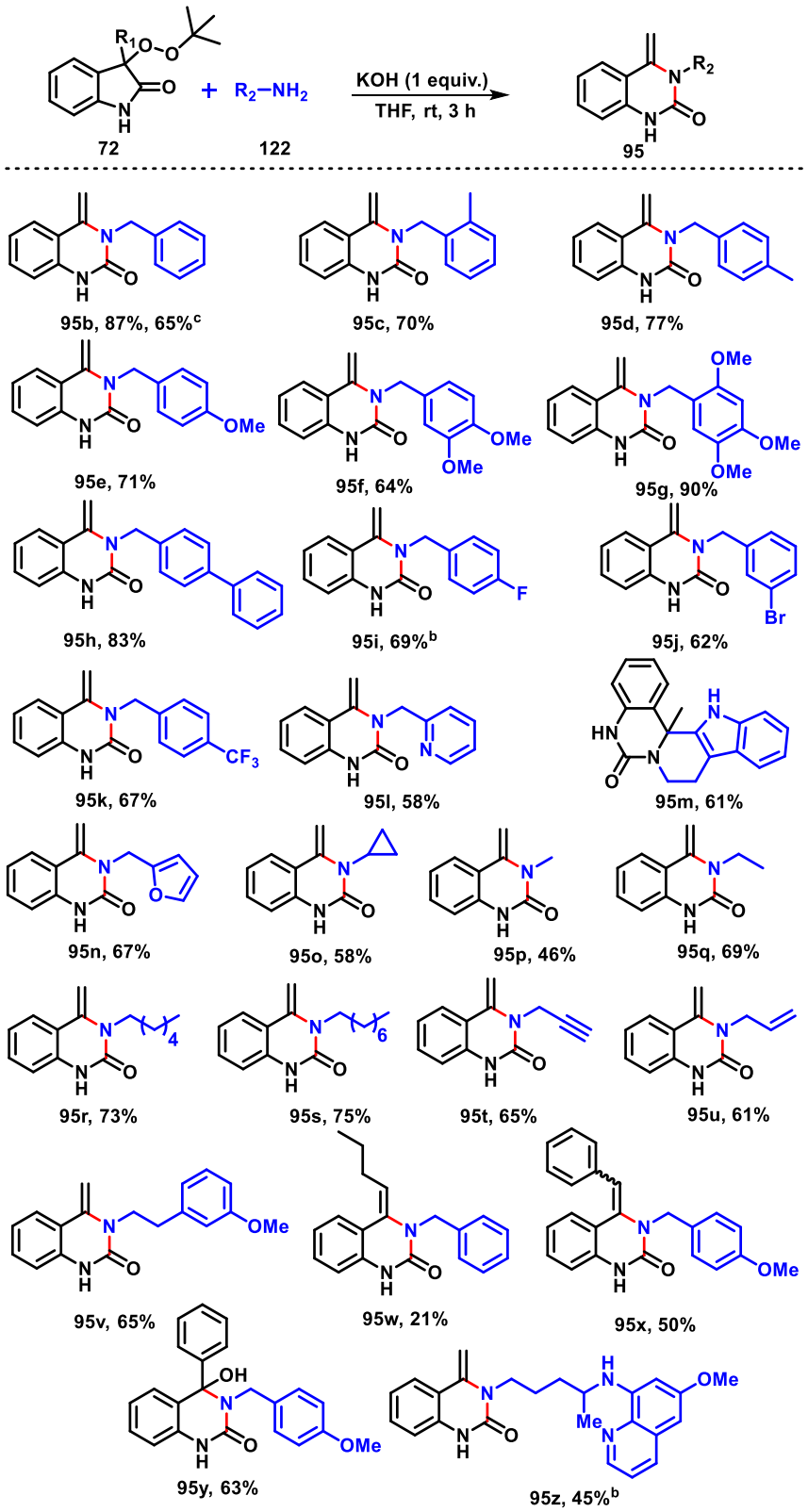
Table 4.4.1. Optimization of reaction conditions[a]



Entry	Base	Solvent	Yield [%] of **95b**
1	-	THF	no reaction
[b]2	-	THF	no reaction
3	Na_2CO_3	THF	25
4	K_2CO_3	THF	no reaction
5	Cs_2CO_3	THF	74
6	NaOH	THF	77
7	KOH	THF	87
8	*t*-BuOK	THF	75
9	*t*-BuOLi	THF	82
[c]10	KOH	THF	27
[d]11	KOH	THF	55
12	KOH	DCM	67
13	KOH	EtOH	78
14	KOH	*t*-BuOH	55
15	KOH	H_2O	no reaction
16	KOH	EtOAc	76
17	KOH	ACN	80

[a]**Reaction condition:** Base (0.35 mmol), 3-(*tert*-butylperoxy)-3-methylindolin-2-one **72a** (0.35 mmol), benzylamine **122a** (0.42 mmol), and solvent (2 mL) were stirred at room temperature for 3 h. [b]At 60 °C. [c]0.2 equiv. base used, [d]0.5 equiv. base used. The mentioned yields are isolated yields.

4.4.2. Substrate scope for quinazolinone derivatives

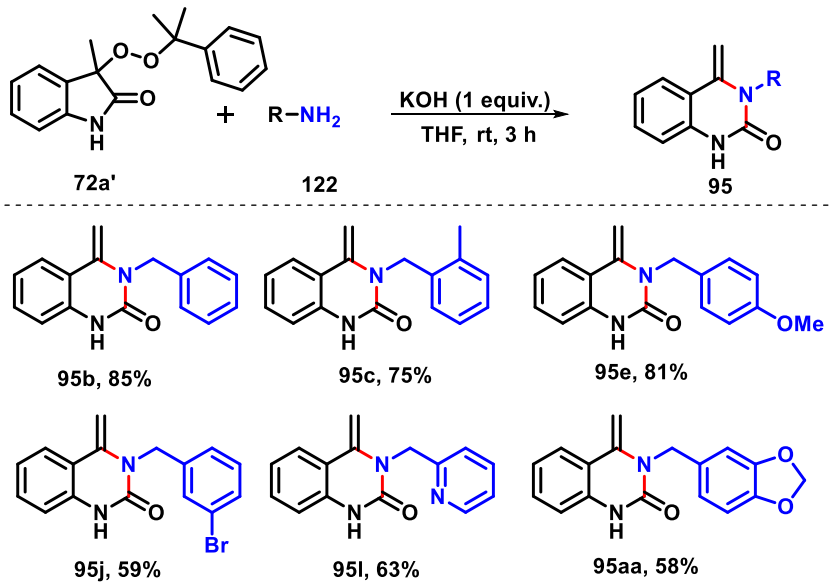


Scheme 4.4.1. Substrate scope for quinazolinone derivatives [a]

[a]**Reaction conditions:** KOH (19 mg, 0.35 mmol, 1 equiv.), peroxy compound **72** (0.35 mmol, 1 equiv.), amines **122** (0.42 mmol, 1.2 equiv.) in THF (2 mL) were stirred at room temperature for 3 h. [b]2 equiv. base used. The mentioned yields are isolated yields. For product **95w**, 3-butyl-3-(*tert*-butylperoxy)indolin-2-one **72g** has been used. For product **95x**, 3-benzyl-3-(*tert*-butylperoxy)indolin-2-one **72b** has been used. For **95y**, 3-phenyl-3-(*tert*-butylperoxy)indolin-2-one **72f** has been used. [c]Gram scale.

Next, we started our research with the objective of expanding the range of substrates for quinazolinone derivatives. First, the electron-rich benzylamines such as 2-Me, 4-Me, 4-OMe, 3,4-OMe 2,3,4-OMe, and 4-Ph gave 64%-90% yields of product **95c-95h** (Scheme 4.4.1.). Subsequently, moderate to good yields of the corresponding products **95i-95k** were obtained in the presence of electron-withdrawing substituents such as 4-F, 3-Br, and 4-CF_3 on benzylamines (Scheme 4.4.1.). Fortunately, the heteroarylamines were well tolerated under optimized experimental conditions. 2-Picolylamine, tryptamine, and furfurylamine were successfully converted in **95l**, **95m,** and **95n** in 58%, 61%, and 67% yields, respectively (Scheme 4.4.1.). In addition, the scope of the reaction with primary aliphatic amines were analyzed. When cyclopropyl, methyl, ethyl, hexyl, and octyl amines were subjected to the optimized standard conditions, the products **95o**−**95s** were isolated in moderate to good yields (Scheme 4.4.1.). In addition, propargylamine and allylamine afforded the corresponding products **95t** and **95u** in 65% and 61% yields, respectively. In particular, 3-methoxyphenethylamine afforded the quinazolinone product **95v** in 65% yield. Similarly, the reaction of 3-butyl-3-(*tert*-butylperoxy)indolin-2-one **72g** with **122a** gave the product **95w** as an exclusive *E*-isomer in 21% yield. Moreover, the reaction of peroxide **72b** with 4-methoxybenzylamine **122d** gave the product **95x** as an *E/Z* mixture in 50% yield (Scheme 4.4.1.). A reaction of peroxide **72f** with **122d** gave the product **95y** in 63% yield. In addition, this reaction with primaquine bisphosphate amine afforded the corresponding product **95z** in 45% yield. However, the reaction of **72a** with aniline or 4-methoxy aniline or tryptophan resulted in a complicated reaction mixture that was difficult to separate by column chromatography. Next, a gram-scale reaction with **72a** (1.0 g, 4.25 mmol) and **122a** was also successfully carried out under optimized conditions to give a 65% yield of product **95b**.

Remarkably, the reaction of **72a'** with amines instinctively led to the desired derivatives of 4-methylene-3-substituted quinazolinone in 58%-85% yield (Scheme 4.4.2.).

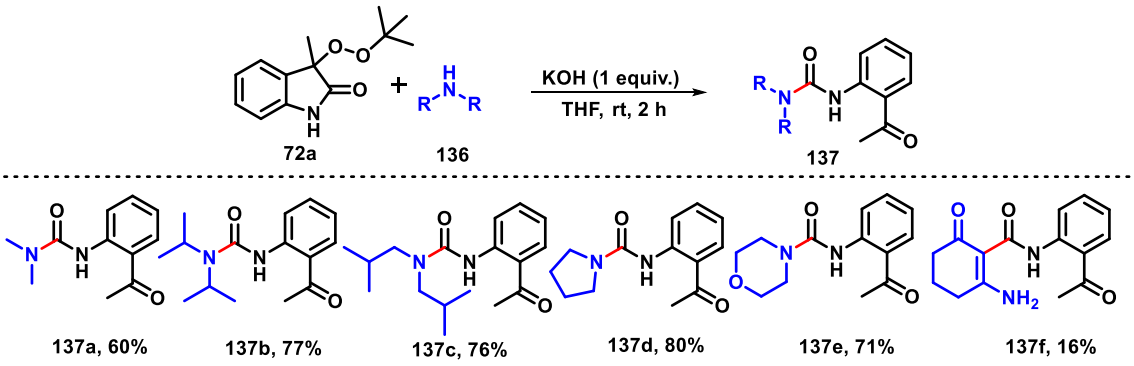


Scheme 4.4.2. Substrate scope for quinazolinone derivatives

[a]**Reaction conditions**: KOH (19 mg, 0.35 mmol, 1 equiv.), peroxy compound **72a'** (0.35 mmol, 1 equiv.), and amines **122a** (0.42 mmol, 1.2 equiv.) in THF (2 mL) were stirred at room temperature for 3 h. The mentioned yields are isolated yields.

4.4.3. Substrate scope for urea derivatives

Peroxyoxindole reacts with secondary amine-based nucleophiles, as compared to primary amines, to produce a variation of urea derivatives. (Scheme 4.4.3.).

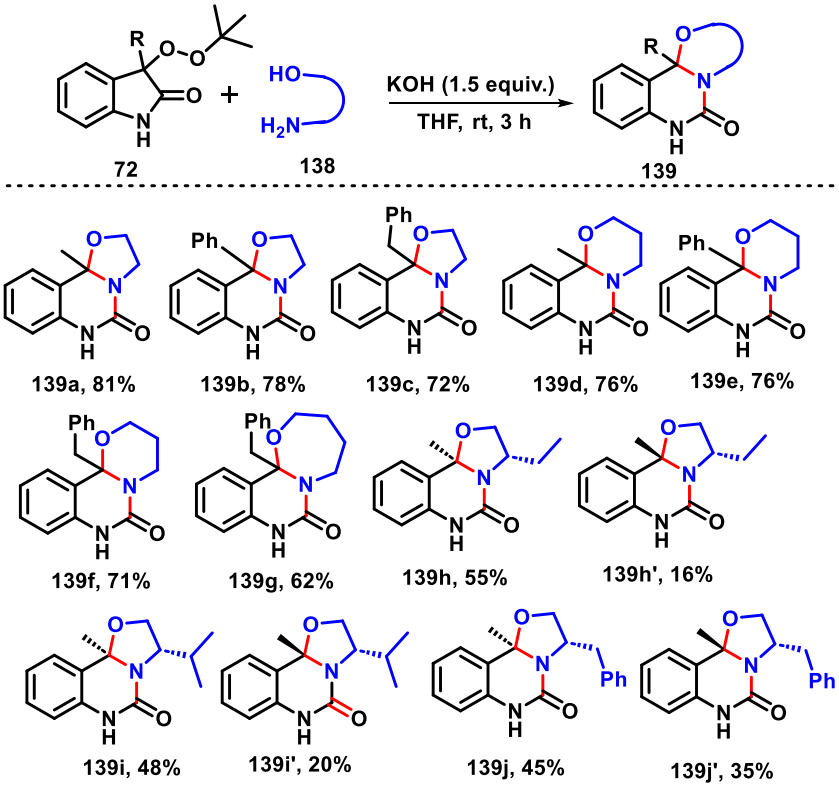


Scheme 4.4.3. Synthesis of urea derivatives[a]

[a]**Reaction conditions**: KOH (0.35 mmol), compound **72a** (0.35 mmol), compound **136** (0.42 mmol), and THF (2 mL) were stirred at room temperature for 2 h. The mentioned yields are isolated yields.

For example, the reaction of **72a** and secondary amine **136** with various substitutions such as -$N(Me)_2$, -$N(iPr)_2$, -$N(iBu)_2$ using KOH (1 equiv.) for 2 h gave the urea derivative **137a-137c** in moderate to good yields (Scheme 4.4.3.). In addition, pyrrolidine, morpholine, and 3-aminocyclohex-2-en-1-one gave 80%, 71%, and 16% yields of products **137d**, **137e**, and **137f** respectively.

4.4.4. Substrate scope for polyheterocycle scaffolds



Scheme 4.4.4. Synthesis of polyheterocycle scaffolds **139** from peroxides **72**

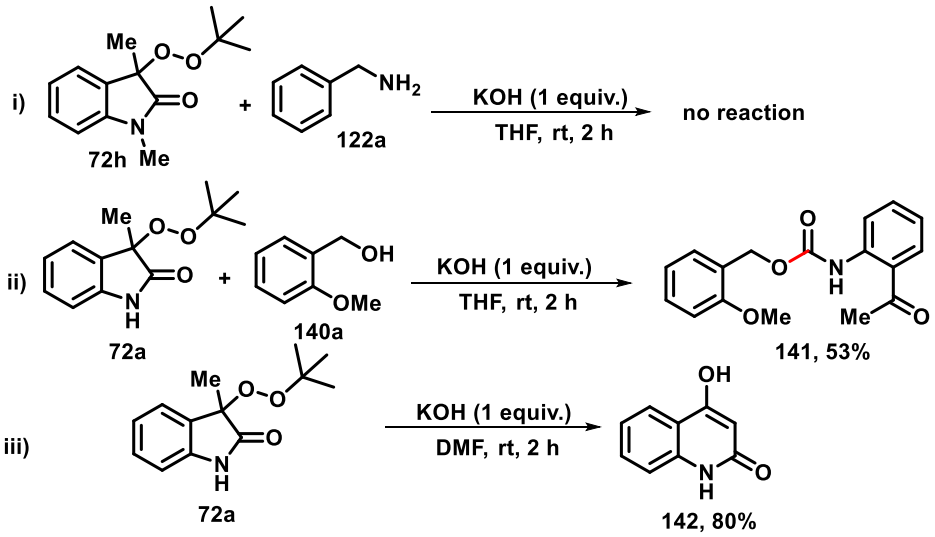
[a]**Reaction conditions**: KOH (1.5 eq, 0.525 mmol), compound **72** (0.35 mmol), compound **138** (1.2 equiv. 0.42 mmol), and THF (2 mL) were stirred at room temperature for 3 h. The mentioned yields are isolated yields.

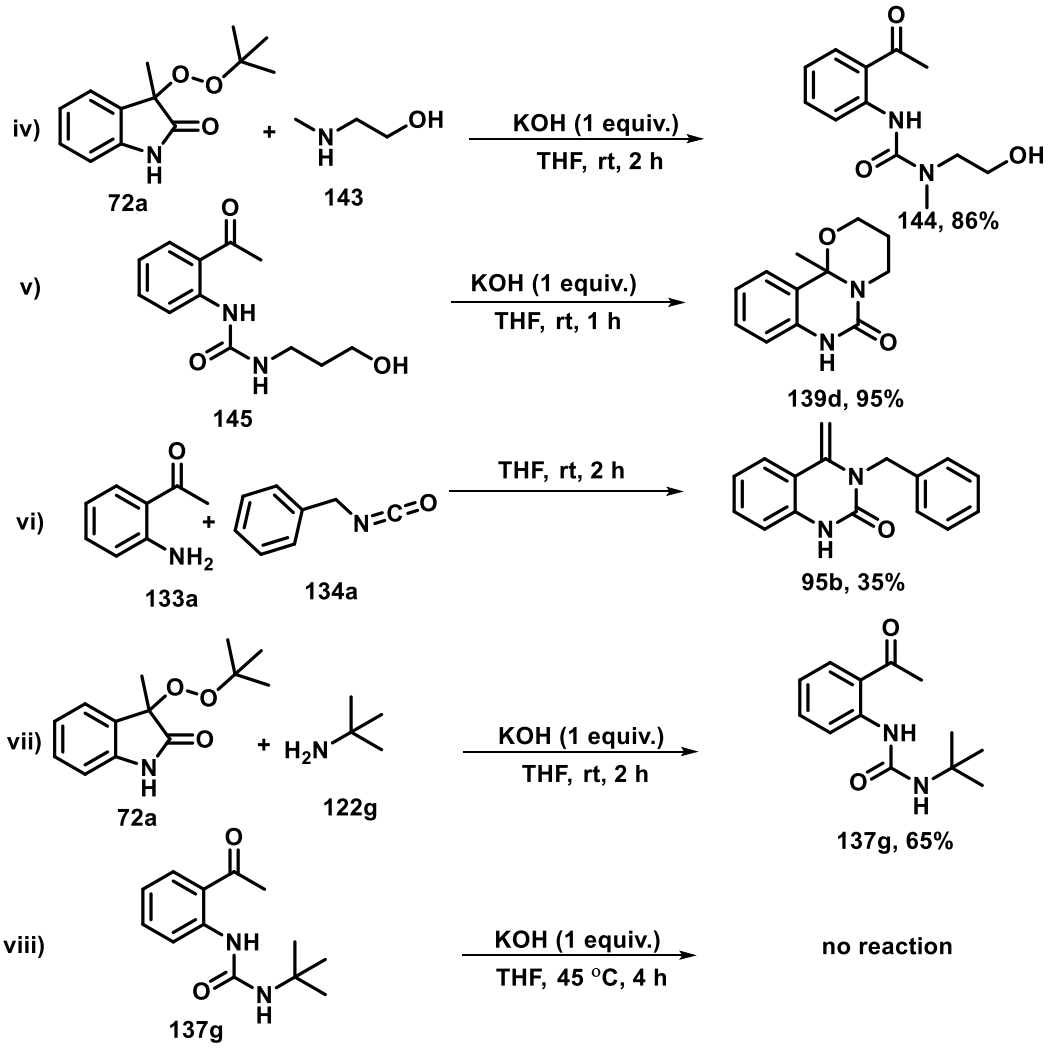
Subsequently, by utilizing amino alcohols, we expanded this idea to the molecular reconstructing of peroxyoxindole. Thus, the reaction of peroxyoxindole **72a** with 1.5 equiv. of

KOH and ethanolamine **138a** at room temperature gave the tricyclic compound **139a** in 81% isolated yield. To broaden the substrate scope, this reaction was carried out with other amino alcohols, giving the products **139b-139g** in moderate to good yields (Scheme 4.4.4.). Similarly, the synthesis of additional tricyclic compounds from peroxyoxindole derivatives proceeded smoothly in the presence of chiral amino alcohols to afford a diastereomeric mixture [**139h** (*de* = 97%)**: 139h'** (*de* = 90%), dr = 3.4:1], [**139i** (*de* = 94%): **139i'** (*de* = 95%), dr = 2.4:1] and [(**139j** (*de* 94%): **139j'** (*de* = 84%), dr = 1.3:1] in good yields. The structure and stereochemistry of compound **139h** were confirmed by using single-crystal XRD (Figure 4.9.24.). Moreover, the stereochemistry of all the additional tricyclic compounds **139h, 139h', 139i, 139i',** and **139j, 139j'** was comparatively assigned based on the crystal structure of **139h**.

4.5. Mechanistic investigations

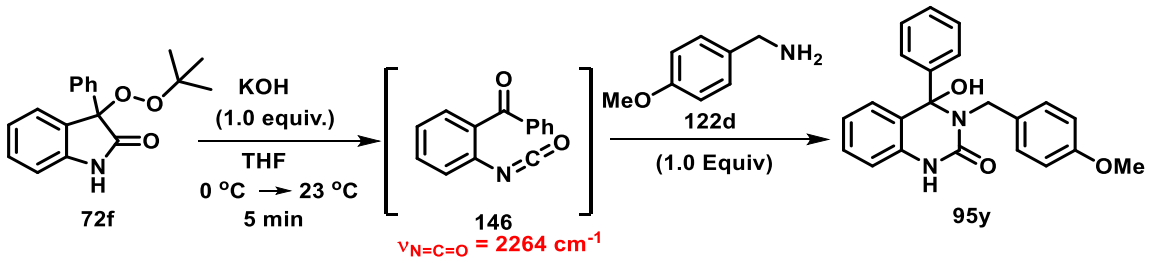
We have carried out various studies with peroxyoxindole to understand the reaction route for the synthesis of 4-methylene-3-substituted quinazolinone (Scheme 4.5.1.). Under optimized reaction conditions, the reaction of *N*-methylated peroxyoxindole **72h** was revealed to be chemically inactive (Scheme 4.5.1., i). This experiment implies that removing a proton from oxindole nitrogen was an important step in this transformation. A trapping experiment with various nucleophiles was carried out to determine the intermediate in this reaction. As a result, we performed the reaction of peroxyoxindole **72a** with alcohol **140a**, yielding carbamate **141** in 53% yield (Scheme 4.5.1., ii). This reaction confirmed the formation of isocyanate intermediate **146**, which was trapped by alcohol **140a** in situ. We hypothesized that an isocyanate intermediate was produced after deprotonation at oxindole nitrogen based on our experimental findings.





Scheme 4.5.1 Experiments for mechanistic studies

4.5.1. Detection of isocyanate intermediate using HRMS & IR analysis



Scheme 4.5.2. Detection of isocyanate intermediate using HRMS & IR analysis

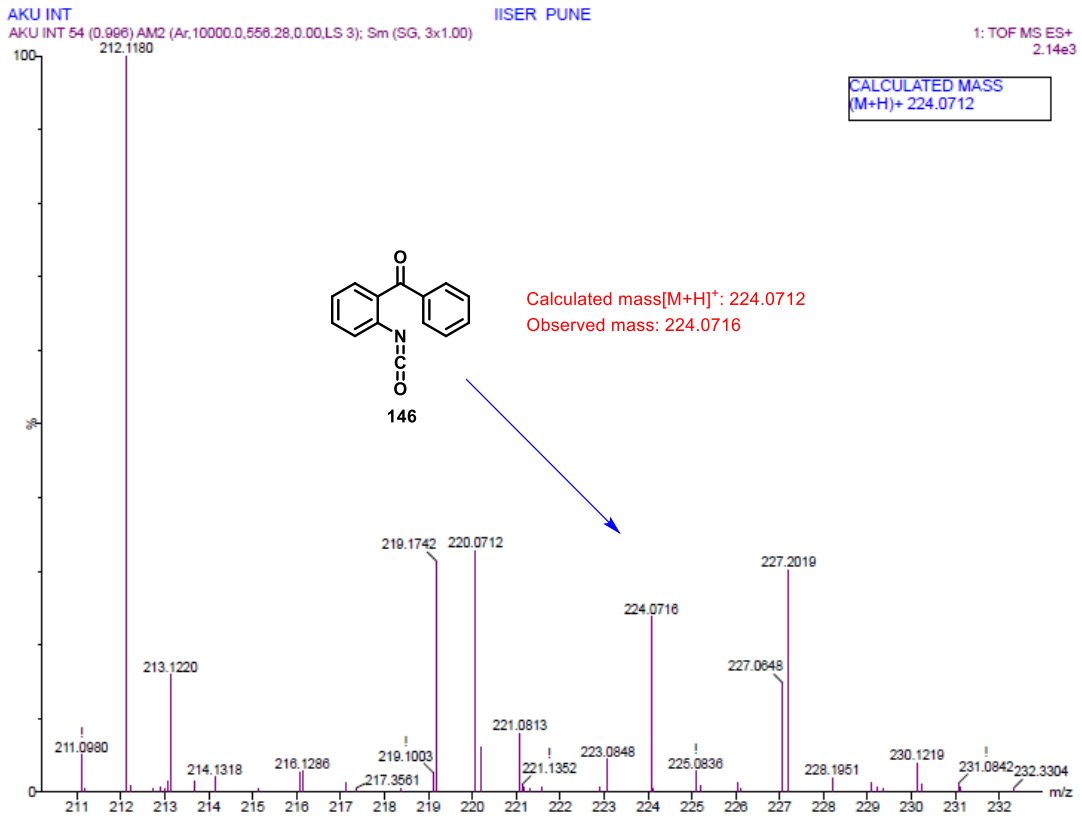


Figure 4.5.1.1. Detection of the isocyanate intermediate **146** by HRMS analysis

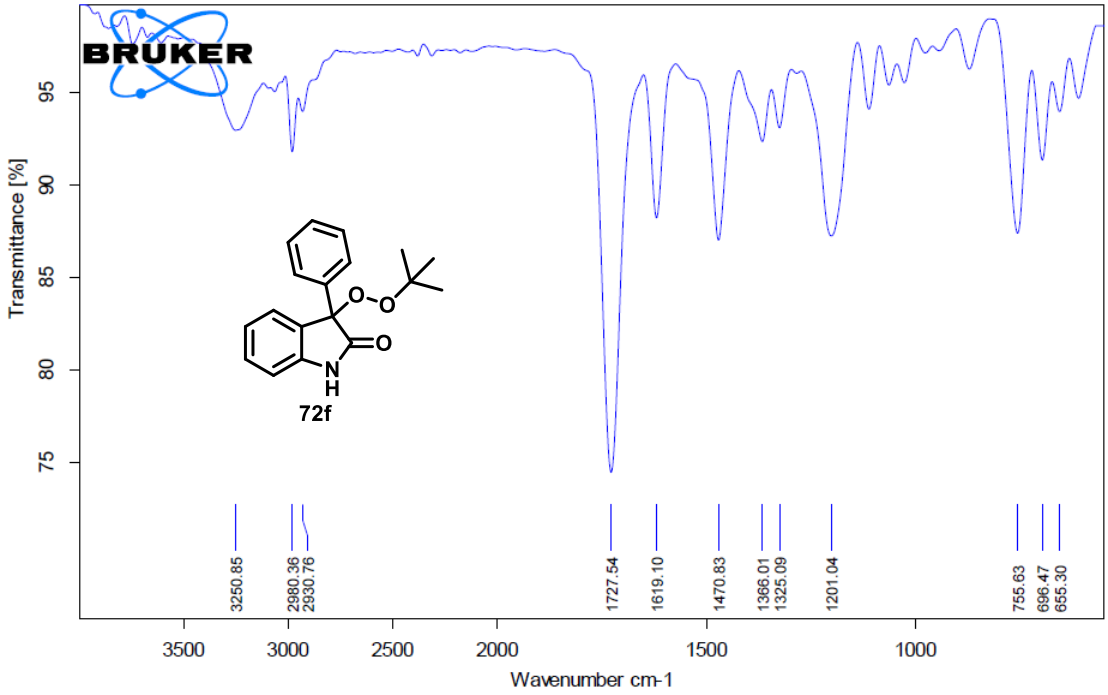


Figure 4.5.1.2. IR of 3-(*tert*-butylperoxy)-3-phenylindolin-2-one **72f**

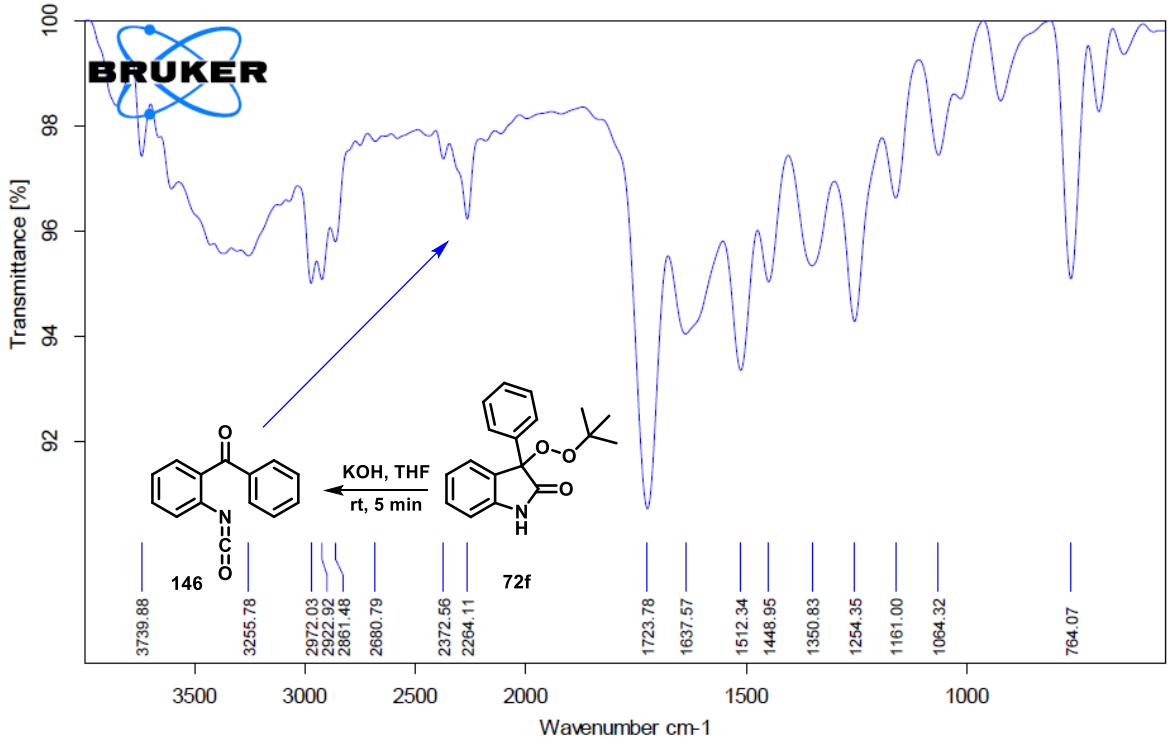


Figure 4.5.1.3. Detection of the isocyanate intermediate **146** by IR (**72f**+KOH) after 5 min

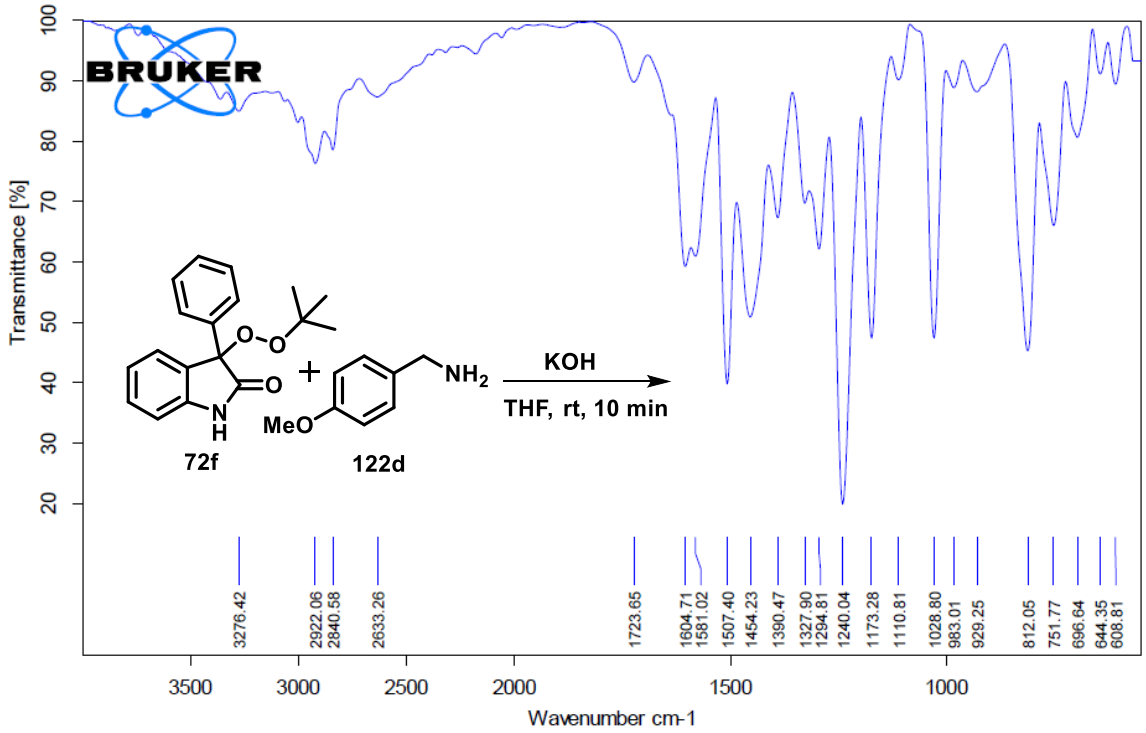


Figure 4.5.1.4. IR of reaction mixture containing (**72f**+KOH+**122d**) after 10 min

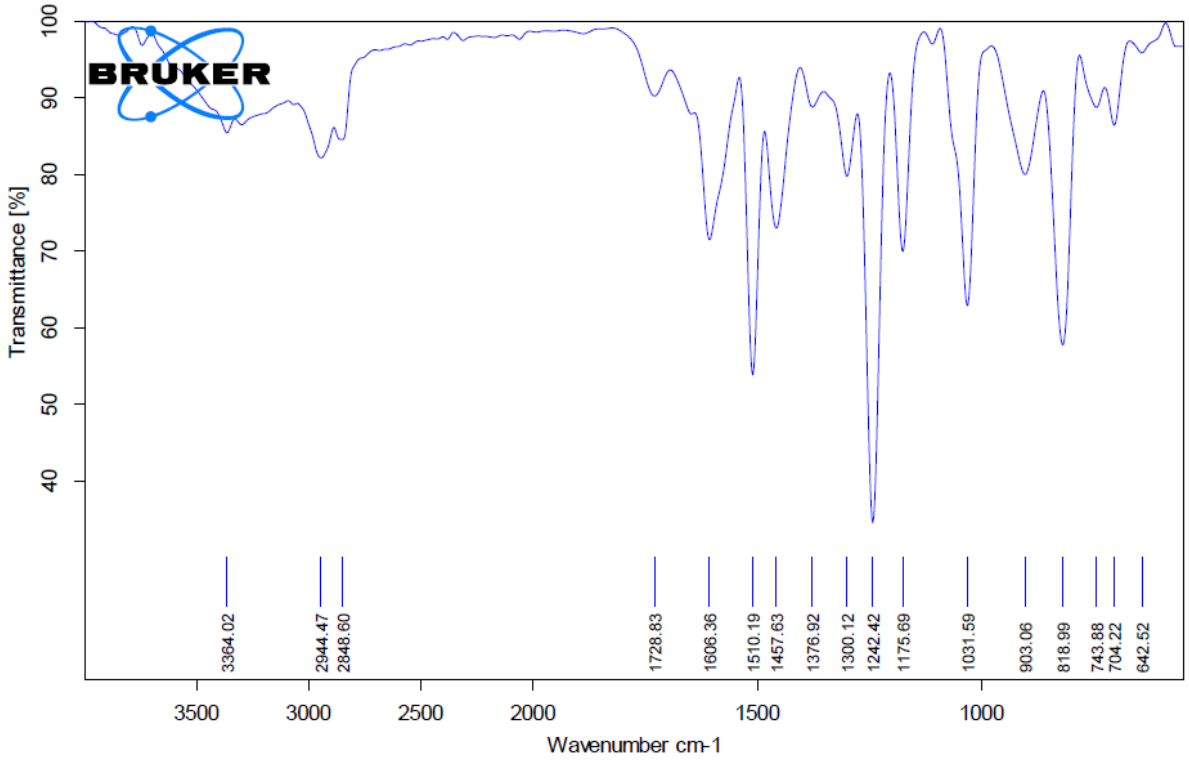


Figure 4.5.1.5. IR of reaction mixture containing (**72f**+KOH+**122d)** after 2 h

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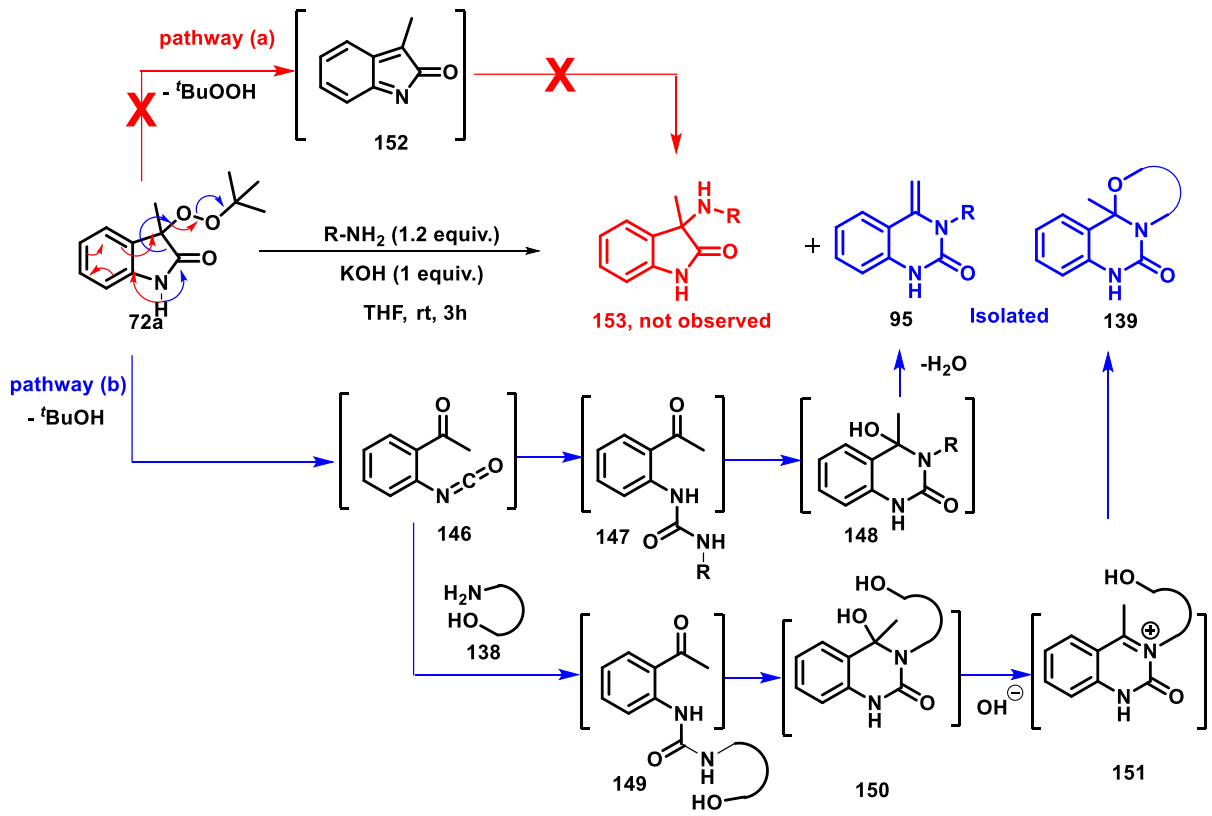
In the absence of an outside nucleophile, peroxyoxindole **72a** undertakes intramolecular cyclization, yielding 4-hydroxyquinolinone **142** (Scheme 4.5.1., iii).[46]

4.6. Plausible Mechanism

We presented the two possible pathways for this skeletal rearrangement depicted in Scheme 4.6.1. based on experimental observations and literature precedents. In pathway (a), we envisioned the complete elimination of *t*-BuOOH from peroxyoxindole **72a** that afforded *N*-alkylated product **153** *via* intermediate **152** (Scheme 4.6.1.). But pathway (a) failed to give product **153**. However, in the pathway (b) peroxyoxindole **72a** is followed by the Kornblum-DeLaMare rearrangement,[40] or which is similar to the 4-oxa-Grob fragmentation[77] and Stoltz group reported oxidative fragmentation.[46] This pathway (b) allowed fragmentation of the C2−C3 bond and elimination of *tert*-butyl alcohol resulting in the simultaneous formation of ketone, and isocyanate is an intermediate (**146**) generated in situ (Scheme 4.6.1.). The intermediate **146** was highly unstable even in the absence of amine and could not be isolated from the reaction, which immediately gave cyclized product **95**.



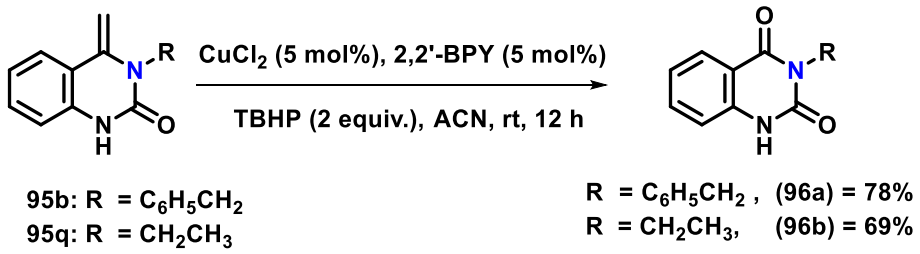
Scheme 4.6.1. Plausible mechanism for products **95** & **139**

To establish the isocyanate as the intermediate, we have performed the reaction of 2-amino acetophenone **133a** and benzylisocyanate **134a** in the presence or absence of KOH, which afforded product **95b** (Scheme 4.5.1., entry vi). Next, this intermediate (**146**) was also confirmed by trapping experiments with different secondary amine/oxygen-based nucleophiles (Scheme 4.4.3. and Scheme 4.5.1., entry ii). The examination of HRMS and IR were used to confirm the in-situ isocyanate formation in the reaction shown in Figure 4.5.1.1. and Figure 4.5.1.3. In the case of product **139**, intermediate **146** reacts with primary amine/ amino alcohol to obtain urea derivative **147/149**. Further, intermediate **147/149** contains a nitrogen atom, which is highly unstable (not able to isolate from the reaction mixture), and undergoes rapid intramolecular reaction with ketone to give the hemiaminol intermediate **148/150**. Interestingly, the intermediate **145** was isolated from the reaction of peroxide **72a** and 3-amino-1-propanol and performed the cyclization in the presence of KOH to afford the product **139d** (Scheme 4.5.1., entry v). Remarkably, we observed the urea derivative **137g** with bulky primary amine **122g,** and further urea derivative **137g** was unreacted under basic conditions when heated at 45 °C at 4 h. (Scheme 4.5.1., entry vii and entry viii). This

experiment also supported the conformation of urea derivatives **147** and **149** *via* isocyanates intermediate **146**. Finally, upon dehydration of **148** afforded the product **95**. Afterward, iminium cation **151** formed upon dehydration of **150** facilitates another intramolecular addition reaction, i.e. oxygen attack over the iminium cation to produce **139** (Scheme 4.6.1.).

4.7. Oxidation of 4-methylene-3-substituted quinazolinone derivative

Furthermore, the application of 4-methylene-3-substituted quinazolinone derivative has been examined toward the synthesis of 3-substituted quinazoline-2,4-diones by an oxidation reaction (Scheme 4.7.1.).



Scheme 4.7.1. Oxidation of 4-methylene-3-substituted quinazolinone derivative[a]

[a]**Reaction conditions:** compound **95a**/**95q** (0.25 mmol, 1 equiv.), $CuCl_2$ (5 mol%), 2,2'-bipyridine (5 mol%), and TBHP (2 equiv.) in 2 mL acetonitrile were stirred at room temperature for 12 h.

This oxidation reaction utilized **95a** and **95q** with $CuCl_2$ and TBHP,[95] resulting in the isolation of **96a** and **96b** in 78% and 69% yields, respectively (Scheme 4.6.2.). The synthesized quinazoline-2,4-diones can be used as precursors for the synthesis of bioactive molecules.[86]

4.8. Conclusion

In summary, we have discovered a new rearrangement for the synthesis of exo-olefinic-substituted quinazolinone or oxazoloquinazolinone by using peroxyoxindole and primary amine or amino alcohol under the basic conditions *via* isocyanate as a key intermediate. The broad substrate scope is demonstrated with various primary amine nucleophiles at room temperature in an excellent yield. In the presence of secondary amine, this oxidative fragmentation generated a variety of unsymmetrically substituted functionalized urea. Furthermore, with double nucleophilic scaffold such as amino alcohols, this reaction proceeded a sequential oxidative fragmentation and nucleophilic addition followed by intramolecular nucleophilic attack on tertiary alcohol, resulting in a variety of tricyclic quinazolinone derivatives as a diastereomeric mixture in one step. Unlike

conventional methods that often rely on transition metal catalysts, this protocol achieved quinazolinone synthesis without the need for transition metal-based catalysis. This has the potential to simplify the reaction set up and reduce the associated costs. The formation of the isocyanate as a key intermediate that accelerates oxidative-skeletal rearrangement has been confirmed by trapping experiments and spectroscopic evidence. The detailed mechanism has been established by experimental evidence.

4.9. Experimental section and characterization data

4.9.1. General information and data collection:

The amines, 2-oxindole, amino alcohols, KOH, cupric chloride, and *tert*-butyl hydroperoxide (TBHP) 5.0-6.0 M in decane solution were purchased from Sigma-Aldrich. All solvents used for the reactions were of dry grade. Column chromatographic separations were performed over silica gel with a mesh size of 100-200. Visualization with UV light, PMA, and CAM staining is accompanied by heating. A Bruker or JEOL spectrometer was used to record the ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra at 400 and 100 MHz, respectively. The values of the coupling constant (*J*) and chemical shift (δ) are expressed in hertz (Hz) and parts per million (ppm), respectively. Brief details of the NMR sequence experiments: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad; ddd, doublet of doublets of doublets. High-Resolution Mass Spectra were acquired with the waters-synapt G2 using electrospray ionization (ESI). Infrared spectra (ATR) were recorded using a Bruker Alpha-E infrared spectrometer. HPLC analysis was performed using an Agilent 1200 infinity series HPLC system with adiode array detector. Diastereomeric excess was determined by HPLC analysis on Chiralpak IA (4.6 mm × 250 mm) column compared to authentic racemic material using n-heptane and isopropanol as eluents. Data were analyzed using Agilent OpenLAB software. The melting point was measured using the BUCHI M-560 melting point instrument. All melting points were measured in an open glass capillary tube. Single-crystal diffraction analysis data were collected at 100 K with a BRUKER KAPPA APEX III CCD Duo diffractometer (operated at 1500 W power: 50 kV, 30 mA) using monochromatic Mo-Kα and Cu-Kα radiation from graphite. Further information on crystal structures can also be obtained from the Cambridge Crystallographic Data Centre (CCDC) with deposition numbers 2053446 (**95b**) and 2053447 (**139h**).

4.9.2. Experimental procedure

A. General experimental procedure for the synthesis of 4-methylene-3-substituted quinazolinone derivatives (95).

In a 20 mL re-sealable vial, KOH (19 mg, 0.35 mmol, 1 equiv.), peroxy compound (0.35 mmol, 1 equiv.), and amine (0.42 mmol, 1.2 equiv.) were added in THF (2 mL). Further, the tube was sealed with a rubber septum, and the reaction mixture was kept at room temperature with stirring for 3 h. After completion of the reaction, water was added, and the resulting mixture was extracted with ethyl acetate two times using 10 mL of solvent each time. The organic layers were combined and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by using column chromatography (EtOAc:*n*-hexane = 30:70 to 70:30).

B. Experimental procedure for the gram-scale synthesis of (95b).

In a 20 mL re-sealable vial, KOH (238 mg, 4.25 mmol, 1 equiv.), compound **72a** (1000 mg, 4.25 mmol, 1 equiv.), and benzylamine **122a** (546 mg, 5.1 mmol, 1.2 equiv.) were added in THF (10 mL). Further, the tube was sealed with a rubber septum, and the reaction mixture was kept at room temperature with stirring for 3 h. After completion of the reaction, water was added, and the resulting mixture was extracted with ethyl acetate two times using 20 mL of solvent each time. The organic layers were combined and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by using column chromatography (EtOAc:*n*-hexane = 30:70) to afford 3-benzyl-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one **95b** (694 mg, 65%) as a white solid.

C. General experimental procedure for the synthesis of urea derivatives.

In a 20 mL re-sealable vial, KOH (19 mg, 0.35 mmol, 1 equiv.), compound **72a** (0.35 mmol, 1 equiv.), and amine **122** (0.42 mmol, 1.2 equiv.) were added in THF (2 mL). Further, the tube was sealed with a rubber septum, and the reaction mixture was kept at room temperature with stirring for 2 h. After completion of the reaction, water was added, and the resulting mixture was extracted with ethyl acetate two times using 10 mL of solvent each time. The organic layers were combined and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by using column chromatography (EtOAc:*n*-hexane = 20:80 to 50:50).

D. Experimental procedure for the synthesis of carbamates (141).

In a 20 mL re-sealable vial, KOH (19 mg, 0.35 mmol, 1 equiv.), compound **72a** (82 mg, 0.35 mmol, 1 equiv.) and 2-methoxybenzyl alcohol **140a** (58 mg, 0.42 mmol, 1.2 equiv.) were added

in THF (2 mL). Further, the tube was sealed with a rubber septum, and the reaction mixture was kept at room temperature with stirring for 3 h. After completion of the reaction, water was added, and the resulting mixture was extracted with ethyl acetate two times using 10 mL of solvent each time. The organic layers were combined and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by using column chromatography (EtOAc:*n*-hexane = 10:90).

E. Experimental procedure for the synthesis of 1-(2-acetylphenyl)-3-(3-hydroxypropyl)urea (145).

In a 20 mL re-sealable vial, KOH (29.5 mg, 0.52 mmol, 1.5 equiv.), peroxy compound **72a** (0.35 mmol, 1 equiv.), and 3-aminopropan-1-ol **143** (0.42 mmol, 1.2 equiv.) was added in THF 2 (mL). Further, the tube was sealed with a rubber septum, and the reaction mixture was kept at room temperature with stirring for 20-30 min. Further water was added to the reaction mixture, and the resulting mixture was extracted with ethyl acetate two times using 10 mL of solvent each time. The organic layers were combined and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by using column chromatography (EtOAc:*n*-hexane = 30:70 to 70:30).

F. Experimental procedure for the synthesis 4-hydroxyquinolin-2(1*H*)-one (142).

Compound **142** was prepared according to the reported procedure by the Stoltz group.[46] In a 20 mL re-sealable vial, KOH (19 mg, 0.35 mmol, 1 equiv.), compound **72a** (82 mg, 0.35 mmol, 1 equiv.) was added in DMF (2 mL). Further, the tube was sealed with a rubber septum, and the reaction mixture was kept at room temperature with stirring for 2 h. After completion of the reaction, the resulting mixture was filtered through a plug of celite, and the filtrate was concentrated at reduced pressure. Finally, the residue was purified by using column chromatography (DCM:MeOH = 90:10).

G. General experimental procedure for the synthesis of poly heterocycle scaffold (139).

In a 20 mL re-sealable vial, KOH (29.5 mg, 0.52 mmol, 1.5 equiv.), peroxy compound **72** (0.35 mmol, 1 equiv.), and amino alcohols **138** (0.42 mmol, 1.2 equiv.) were charged in THF (2 mL). Further, the tube was sealed with a rubber septum. The reaction mixture was kept at room temperature with stirring for 3 h. After completion of the reaction, water was added, and the resulting mixture was extracted with ethyl acetate two times using 10 mL of solvent each time. The organic layers were combined and dried over Na_2SO_4. After removing the solvent under

reduced pressure, the residue was purified by using column chromatography (EtOAc:*n*-hexane = 30:70 to 70:30).

H. Experimental procedure for the oxidation of 4-methylene-3-substituted quinazolinone derivative (96).

In a 50 mL round-bottom flask, compound **95b** (0.25 mmol, 1 equiv.), $CuCl_2$ (5 mol%), 2,2'-bipyridine (5 mol%), and 5.0-6.0 M *tert*-butyl hydroperoxide (TBHP) **1c** in decane solution (0.50 mmol, 2 equiv.) were added in acetonitrile (2 mL). Further, the round-bottom flask was sealed using rubber septum without maintaining any special conditions like an inert atmosphere. The reaction mixture was kept at room temperature for 12 h. After completion of the reaction, a volatile component was evaporated using a vacuum. The residue was directly purified by silica gel chromatography (EtOAc:*n*-hexane = 30:70).

I. Experimental procedure for the detection of isocyanate intermediate using HRMS analysis.

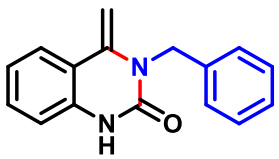
In a 20 mL re-sealable vial, compound **72f** (104 mg, 0.35 mmol, 1 equiv.) and KOH (20 mg, 0.35 mmol, 1 equiv.) were added at 0 ºC in dry THF (2 mL). Further, the tube was sealed with a rubber septum, and the reaction was performed under the nitrogen atmosphere. After 5 minutes, the reaction mixture was subjected to HRMS analysis. The presence of m/z= 224.0716 corresponds to isocyanate intermediate **146** (Figure 4.5.1.1.).

J. Experimental procedure for the observation of the isocyanate intermediate using IR analysis.

In a 20 mL re-sealable vial, compound **72f** (104 mg, 0.35 mmol, 1 equiv.) and KOH (20 mg, 0.35 mmol, 1 equiv.) were added at 0 ºC in dry THF (2 mL). Further, the tube was sealed with a rubber septum, and the reaction was performed under the nitrogen atmosphere. After 5 min. IR was recorded for the reaction mixture (4.5.1.3.). Further, 4-methoxybenzylamine **122d** (48 mg, 0.35 mmol, 1 equiv.) was added to the reaction mixture, and IR was recorded after 10 min. (4.5.1.4.) IR spectra indicate the disappearance of the isocyanate peak. Interestingly, after 2 h complete disappearance of the isocyanate peak was noticed (Figure 4.5.1.5.).

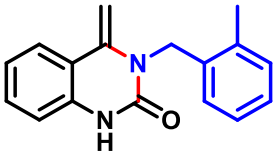
4.9.3. Analytical data for the product:

*3-benzyl-4-methylene-3,4-dihydroquinazolin-2(1H)-one (**95b**):*



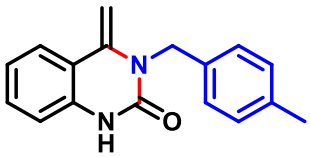
Prepared according to general procedure A, using benzylamine (45 mg, 0.42 mmol) to afford 3-benzyl-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one **95b** (76 mg, 87% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP: 198-201 °C. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.28 (s, 1H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.35 – 7.20 (m, 6H), 6.99 – 6.91 (m, 2H), 5.00 (s, 2H), 4.81 (d, *J* = 2.3 Hz, 1H), 4.12 (d, *J* = 2.3 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d$_6$) δ 150.1, 139.7, 137.0, 135.6, 130.1, 128.4, 126.7, 126.3, 123.9, 122.1, 115.9, 114.6, 85.2, 45.8. IR (neat): 3207, 2919, 1685, 1453 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{16}H_{15}N_2O$ $(M+H)^+$ 251.1184, found: 251.1184. The crystal of compound **95b** was grown using dichloromethane and pet ether (2:1) as a solvent by slow evaporation. A needle-shaped single crystal was mounted on a loop by applying a small amount of paraffin oil. Crystal data for the compound **95b**: $C_{16}H_{15}N_2O$, M = 249.28, Monoclinic, space group P21/n with a = 10.4745(5) Å, b = 5.5284(2) Å, c = 21.446(1) Å, α = 90°, β = 101.990(1)°, γ = 90°, V = 1214.79(9) Å^3, T = 296(2) K, R1 = 0.0490, wR2 =0.1282 on observed data, z = 4, D_{calcd} = 1.363 g cm^{-3}, F(000)= 524, Absorption coefficient = 0.127 mm^{-1}, λ= 0.71073 Å, 3014 reflections were collected on a Bruker APEX-II CCD single crystal diffractometer, 2362 observed reflections (I≥2σ (I)). The largest difference peak and hole = 0.875 and -0.267 eÅ^{-3}, respectively

3-(2-methylbenzyl)-4-methylene-3,4-dihydroquinazolin-2(1H)-one (***95c***):



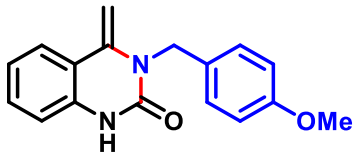
Prepared according to general procedure A, using 2-methylbenzylamine (51 mg, 0.42 mmol) to afford 3-(2-methylbenzyl)-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one **95c** (65 mg, 70% yield) as a yellow solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP: 249-252 °C. ^{1}H NMR (400 MHz, DMSO-d$_6$) δ 10.23 (s, 1H), 7.56 (d, *J* = 7.4 Hz, 1H), 7.25 – 7.20 (m, 1H), 7.16 – 7.12 (m, 1H), 7.09 – 7.01 (m, 2H), 6.94 – 6.86 (m, 3H), 4.88 (s, 2H), 4.73 (d, *J* = 2.4 Hz, 1H), 3.87 (d, *J* = 2.4 Hz, 1H), 2.29 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d$_6$) δ 149.9, 139.9, 135.6, 134.7, 133.8, 130.0, 126.3, 125.7, 124.1, 123.8, 122.0, 115.9, 114.6, 84.8, 44.3, 18.6. IR (neat): 3358, 2919, 1694, 1502 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{17}H_{17}N_2O$ $(M+H)^+$ 265.1341, found: 265.1349.

3-(4-methylbenzyl)-4-methylene-3,4-dihydroquinazolin-2(1H)-one (***95d***):



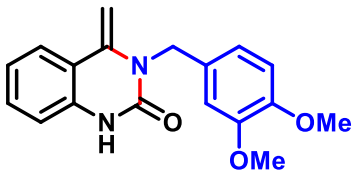
Prepared according to general procedure A, using 4-methylbenzylamine (59 mg, 0.42 mmol) to afford 3-(4-methylbenzyl)-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one **95d** (71 mg, 77% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP: 183-186 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.51 (d, *J* = 7.9 Hz, 1H), 7.24 –7.19 (m, 3H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.98 (t, *J* = 7.7 Hz, 1H), 6.77 (d, *J* = 7.9 Hz, 1H), 5.08 (s, 2H), 4.78 (d, *J* = 2.6 Hz, 1H), 4.24 (d, *J* = 2.6 Hz, 1H), 2.32 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 140.2, 136.7, 134.9, 133.5, 130.2, 129.4, 126.5, 124.1, 122.9, 117.1, 114.7, 86.5, 47.1, 21.2. IR (neat): 3204, 2921, 1979, 1630, 1508 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{17}H_{17}N_2O$ $(M+H)^+$ 265.1341, found: 265.1339.

3-(4-methoxybenzyl)-4-methylene-3,4-dihydroquinazolin-2(1H)-one (***95e***):



Prepared according to general procedure A, using 4-methoxybenzylamine (58 mg, 0.42 mmol) to afford 3-(4-methoxybenzyl)-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one **95e** (70 mg, 71 % yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP: 175-185 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 7.51 (d, *J* = 7.9 Hz, 1H), 7.24 – 7.21 (m, 3H), 7.00 – 6.95 (m, 1H), 6.89 – 6.84 (m, 2H), 6.80 (d, *J* = 8.0 Hz, 1H), 5.06 (s, 2H), 4.79 (d, *J* = 2.6 Hz, 1H), 4.26 (d, *J* = 2.6 Hz, 1H), 3.78 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.8, 151.8, 140.2, 135.0, 130.2, 128.7, 127.9, 124.0, 122.8, 117.1, 114.9, 114.2, 86.2, 55.4, 46.7. IR (neat): 3131, 2917, 1696, 1521, 1464 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{17}H_{17}N_2O_2$ $(M+H)^+$ 281.1290, found: 281.1297.

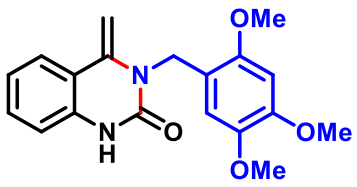
3-(3,4-dimethoxybenzyl)-4-methylene-3,4-dihydroquinazolin-2(1H)-one (***95f***):



Prepared according to general procedure A, using 3,4-dimethoxybenzylamine (70 mg, 0.42 mmol) to afford 3-(3,4-dimethoxybenzyl)-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one **95f** (70 mg, 64% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP: 209-211 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.25 – 7.22 (m, 1H), 7.01 – 6.96 (m, 1H), 6.89 – 6.79 (m, 4H), 5.06 (s, 2H), 4.80 (d, *J* = 2.6 Hz, 1H), 4.29 (d, *J* = 2.6 Hz, 1H), 3.85 (d, *J* = 2.7 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 151.8, 151.8, 149.3, 148.2, 140.3, 135.0, 130.2,

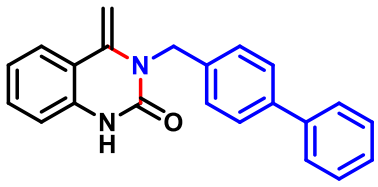
129.2, 124.0, 122.9, 118.8, 117.0, 114.8, 111.2, 110.0, 86.3, 56.0, 47.2. IR (neat): 3441, 2954, 1679, 1632, 1513 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{18}H_{19}N_2O_3$ $(M+H)^+$ 311.1395, found: 311.1388.

4-methylene-3-(2,4,5-trimethoxybenzyl)-3,4-dihydroquinazolin-2(1H)-one (***95g***):



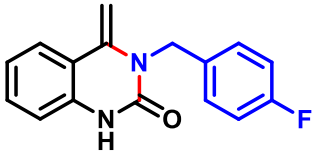
Prepared according to general procedure A, using 3,4,5-trimethoxybenzylamine (83 mg, 0.42 mmol) to afford 4-methylene-3-(2,4,5-trimethoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one **95g** (107 mg, 90% yield) as a yellow solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP: 225-227 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.53 (d, J = 7.9 Hz, 1H), 7.27 – 7.21 (m, 1H), 7.02 – 6.97 (m, 1H), 6.83 – 6.77 (m, 1H), 6.51 (s, 2H), 5.03 (s, 2H), 4.81 (d, J = 2.6 Hz, 1H), 4.28 (d, J = 2.7 Hz, 1H), 3.81 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.6, 151.7, 140.4, 137.0, 134.9, 132.5, 130.3, 124.1, 123.0, 117.0, 114.8, 103.4, 86.7, 61.0, 56.2, 47.8. IR (neat): 3273, 2925, 1651, 1519, 1460 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{19}H_{20}N_2O_4$ $(M+H)^+$ 341.1501, found: 341.1505.

3-([1,1'-biphenyl]-4-ylmethyl)-4-methylene-3,4-dihydroquinazolin-2(1H)-one (***95h***):



Prepared according to general procedure A, using 4-phenylbenzylamine (77 mg, 0.42 mmol) to afford 3-([1,1'-biphenyl]-4-ylmethyl)-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one **95h** (95 mg, 83% yield) as a fent yellow solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP: 228-231 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 10.30 (s, 1H), 7.62 (t, J = 7.2 Hz, 5H), 7.45 (t, J = 7.6 Hz, 2H), 7.38 – 7.26 (m, 4H), 6.96 (dd, J = 14.1, 7.7 Hz, 2H), 5.05 (s, 2H), 4.85 (d, J = 2.0 Hz, 1H), 4.18 (d, J = 2.1 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 150.1, 139.9, 139.7, 138.7, 136.3, 135.6, 130.2, 128.9, 127.3, 127.0, 126.8, 126.5, 123.9, 122.1, 115.9, 114.6, 85.3, 45.5. IR (neat): 1743, 1696, 1514 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{22}H_{19}N_2O$ $(M+H)^+$ 327.1497, found: 327.1490.

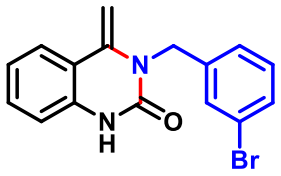
3-(4-fluorobenzyl)-4-methylene-3,4-dihydroquinazolin-2(1H)-one (***95i***):



Prepared according to general procedure A, using 4-fluorobenzylamine (53 mg, 0.42 mmol) to afford 3-(4-fluorobenzyl)-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one **95i** (65 mg, 69% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-

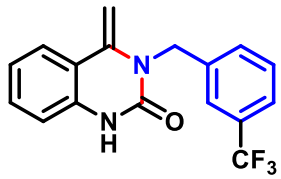
hexane = 30:70). MP: 180-183 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.29 (dd, *J* = 8.3, 5.2 Hz, 2H), 7.24 (*t*, J = 7.7 Hz, 1H), 7.05 – 6.97 (m, 3H), 6.83 – 6.79 (m, 1H), 5.09 (s, 2H), 4.79 (d, *J* = 2.8 Hz, 1H), 4.20 (d, *J* = 2.8 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.4, (d, *J* = 243.5 Hz), 151.9 (d, *J* = 6.5 Hz), 140.2, 135.0, 132.3 (d, *J* = 2.5 Hz), 130.3, 128.2 (d, *J* = 7.9 Hz), 124.0, 122.9, 116.9, 115.7, 115.5, 115.0 (d, *J* = 1.3 Hz), 86.2, 46.7. IR (neat): 2921, 1678, 1507 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{16}H_{14}FN_2O$ $(M+H)^+$ 269.1090, found: 269.1084.

3-(3-bromobenzyl)-4-methylene-3,4-dihydroquinazolin-2(1H)-one (***95j***):



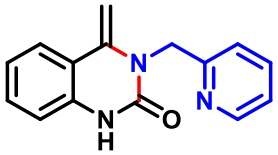
Prepared according to general procedure A, using 3-bromobenzylamine (78 mg, 0.42 mmol) to afford 3-(3-bromobenzyl)-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one **95j** (71 mg, 62% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP: 196-198 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 7.52 (d, *J* = 7.7 Hz, 1H), 7.45 (s, 1H), 7.38 (dt, *J* = 7.5, 1.6 Hz, 1H), 7.28 – 7.167(m, 4H), 7.03 – 6.99 (m, 1H), 6.80 (dd, *J* = 8.0, 0.9 Hz, 1H), 5.08 (s, 2H), 4.80 (d, *J* = 2.8 Hz, 1H), 4.17 (d, *J* = 2.9 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 151.6, 140.2, 139.1, 134.9, 130.4, 130.4, 130.3, 129.6, 125.2, 124.1, 123.0, 123.0, 116.9, 114.9, 86.5, 46.9. IR (neat): 3260, 2847, 1695, 1521 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{16}H_{14}BrN_2O$ $(M+H)^+$ 329.0289, found: 329.0294.

4-methylene-3-(4-(trifluoromethyl)benzyl)-3,4-dihydroquinazolin-2(1H)-one (***95k***):



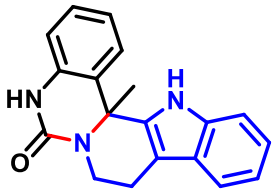
Prepared according to general procedure A, using 4-(trifluoromethyl)benzylamine (74 mg, 0.42 mmol) to afford 4-methylene-3-(4-(trifluoromethyl)benzyl)-3,4-dihydroquinazolin-2(1*H*)-one **95k** (75 mg, 67% yield) as a yellow solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP: 180-182 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 8.0 Hz, 2H), 7.28 – 7.24 (m, 1H), 7.03 (t, *J* = 7.4 Hz, 1H), 6.85 (d, *J* = 7.9 Hz, 1H), 5.20 (s, 2H), 4.82 (d, *J* = 2.8 Hz, 1H), 4.15 (d, *J* = 2.8 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.0, 140.9, 140.2, 134.9, 130.4, 129.5 (q, *J* = 32.0 Hz), 127.9 (q, *J* = 42.6 Hz), 125.7 (q, *J* = 3.4 Hz), 124.2 (q, *J* = 271.5 Hz), 124.0, 123.1, 116.7, 115.1, 86.3, 47.0. IR (neat): 2923, 1680, 1496, 1325 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{17}H_{14}F_3N_2O$ $(M+H)^+$ 319.1058, found: 319.1050.

4-methylene-3-(pyridin-2-ylmethyl)-3,4-dihydroquinazolin-2(1H)-one (***95l***):



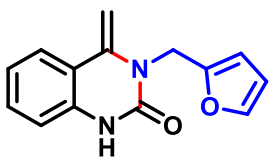
Prepared according to general procedure A, using 2-picolylamine (45 mg, 0.42 mmol) to afford 4-methylene-3-(pyridin-2-ylmethyl)-3,4-dihydroquinazolin-2(1*H*)-one **95l** (51 mg, 58% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP: 173-176 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.58 (ddd, *J* = 4.9, 1.7, 0.9 Hz, 1H), 7.62 (td, *J* = 7.7, 1.8 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.29 – 7.22 (m, 2H), 7.17 (dd, *J* = 6.9, 5.4 Hz, 1H), 6.99 (t, *J* = 7.7 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 5.24 (s, 2H), 4.78 (d, *J* = 2.8 Hz, 1H), 4.25 (d, *J* = 2.8 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.0, 151.6, 149.4, 140.2, 137.0, 134.9, 130.3, 124.0, 123.0, 122.2, 120.7, 117.0, 114.9, 86.7, 49.5. IR (neat): 3213, 2922, 1676, 1439 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{15}H_{14}N_3O$ $(M+H)^+$ 252.1137, found: 52.1138.

14b-methyl-8,9,14,14b-tetrahydroindolo[2',3':3,4]pyrido[1,2-c]quinazolin-6(5H)-one (***95m***):



Prepared according to general procedure A, using tryptamine (67 mg, 0.42 mmol) to afford 14*b*-methyl-8,9,14,14*b*-tetrahydroindolo[2',3':3,4]pyrido[1,2-*c*]quinazolin-6(5*H*)-one **95m** (65 mg, 61% yield) as a yellow solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 50:50). MP: 175-178 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.45 – 7.41 (m, 2H), 7.25 – 7.21 (m, 3H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.00 (t, *J* = 7.6 Hz, 1H), 6.80 (dd, *J* = 7.7, 3.4 Hz, 1H), 4.82 – 4.75 (m, 1H), 3.26 (ddd, *J* = 12.9, 10.9, 4.7 Hz, 1H), 2.93 – 2.79 (m, 2H), 1.85 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 154.6, 136.2, 136.0, 134.3, 128.7, 126.9, 125.3, 123.9, 122.6, 122.5, 120.1, 118.8, 114.7, 111.1, 110.7, 58.8, 38.6, 26.8, 21.1. IR (neat): 2900, 1657, 1520 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{19}H_{18}N_3O$ $(M+H)^+$ 304.1450, found: 304.1457.

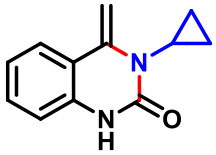
3-(furan-2-ylmethyl)-4-methylene-3,4-dihydroquinazolin-2(1H)-one (***95n***):



Prepared according to general procedure A, using furfurylamine (41 mg, 0.42 mmol) to afford 3-(furan-2-ylmethyl)-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one **95n** (57 mg, 67% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP: 180-183 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (s, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.36 – 7.30 (m, 1H), 7.22 (t, *J* = 7.2 Hz, 1H), 6.97 (t, *J* = 7.6 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 1H),

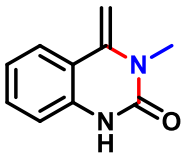
6.33 (d, J = 1.7 Hz, 2H), 5.07 (s, 2H), 4.84 (d, J = 2.7 Hz, 1H), 4.49 (d, J = 2.7 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 151.7, 150.3, 141.7, 140.2, 134.9, 130.1, 123.8, 122.7, 116.9, 115.0, 110.4, 108.0, 85.4, 40.5. IR (neat): 3612, 1696, 1520 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{14}H_{13}N_2O_2$ $(M+H)^+$ 241.0977, found: 241.0981.

3-cyclopropyl-4-methylene-3,4-dihydroquinazolin-2(1H)-one (***95o***):



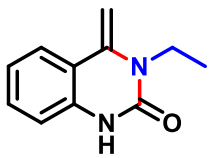
Prepared according to general procedure A, using cyclopropylamine (24 mg, 0.42 mmol) to afford 3-cyclopropyl-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one **95o** (40 mg, 58% yield) as a black solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP: 145-147 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 7.50 (d, J = 7.3 Hz, 1H), 7.25 – 7.20 (m, 1H), 7.00 – 6.95 (m, 1H), 6.86 – 6.83 (m, 1H), 4.89 (d, J = 1.6 Hz, 1H), 4.72 (d, J = 1.6 Hz, 1H), 2.66 – 2.60 (m, 1H), 1.16 – 1.09 (m, 2H), 0.79 – 0.74 (m, 2H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 153.0, 141.8, 135.2, 129.8, 123.9, 122.6, 118.2, 114.7, 88.4, 26.1, 10.3. IR (neat): 3214, 2922, 1683, 1517, 1415 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{12}H_{13}N_2O$ $(M+H)^+$ 201.1028, found: 201.1033.

3-methyl-4-methylene-3,4-dihydroquinazolin-2(1H)-one (***95p***):



Prepared according to general procedure A, using methylamine (13 mg, 0.42 mmol) to afford 3-methyl-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one **95p** (28 mg, 46% yield) as a yellow solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP: 155-157 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.26 (t, J = 7.6 Hz, 1H), 7.00 (t, J = 7.3 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 4.82 (d, J = 2.3 Hz, 1H), 4.26 (d, J = 2.3 Hz, 1H), 3.29 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 151.5, 141.8, 135.0, 130.2, 123.9, 122.7, 116.8, 114.9, 84.3, 30.6. IR (neat): 3344, 2924, 1637, 1559, 1454 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{10}H_{11}N_2O$ $(M+H)^+$ 175.0871, found:175.0878.

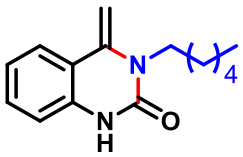
3-ethyl-4-methylene-3,4-dihydroquinazolin-2(1H)-one (***95q***):



Prepared according to general procedure A, using ethylamine (19 mg, 0.42 mmol) to afford 3-ethyl-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one **95q** (45 mg, 69% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP: 159-162 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.27 – 7.22 (m, 1H), 7.01 – 6.95 (m, 1H), 6.81 (d, J = 8.0 Hz, 1H), 4.83 (d, J = 2.5 Hz, 1H), 4.32 (d, J = 2.5 Hz, 1H), 3.93 (q, J = 7.1 Hz,

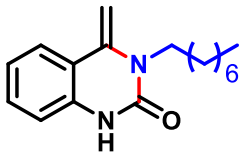
2H), 1.29 (t, J = 7.1 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 151.2, 140.1, 135.3, 130.1, 124.0, 122.6, 117.1, 114.8, 84.0, 38.4, 11.3. IR (neat): 3204, 2924, 1654, 1495, 1441 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{11}H_{13}N_2O$ $(M+H)^+$ 189.1028, found: 189.1030.

3-hexyl-4-methylene-3,4-dihydroquinazolin-2(1H)-one (***95r***):



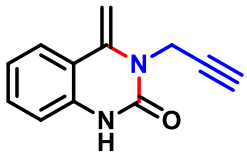
Prepared according to general procedure A, using hexylamine (43 mg, 0.42 mmol) to afford 3-hexyl-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one **95r** (63 mg, 73% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP: 108-110 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.26 – 7.22 (m, 1H), 7.00 – 6.96 (m, 1H), 6.84 (dd, J = 8.1, 0.9 Hz, 1H), 4.82 (d, J = 2.4 Hz, 1H), 4.28 (d, J = 2.5 Hz, 1H), 3.85 (t, J = 7.7 Hz, 2H) 1.74 – 1.67 (m, 2H), 1.43 – 1.31 (m, 6H), 0.90 (t, J = 7.1 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 151.6, 140.3, 135.4, 130.0, 123.9, 122.5, 117.0, 114.9, 84.0, 43.4, 31.7, 26.8, 25.6, 22.7, 14.2. IR (neat): 3202, 2929, 1684, 1629, 1497, 1424 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{15}H_{21}N_2O$ $(M+H)^+$ 245.1654, found: 245.1651.

4-methylene-3-octyl-3,4-dihydroquinazolin-2(1H)-one (***95s***):



Prepared according to general procedure A, using octylamine (54 mg, 0.42 mmol) to afford 4-methylene-3-octyl-3,4-dihydroquinazolin-2(1*H*)-one **95s** (71 mg, 75% yield) as a yellow solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP: 108-110 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (s, 1H), 7.54 (dd, J = 8.1, 1.1 Hz, 1H), 7.25 – 7.20 (m, 1H), 7.00 – 6.95 (m, 1H), 6.83 (dd, J = 7.9, 0.8 Hz, 1H), 4.82 (d, J = 2.5 Hz, 1H), 4.28 (d, J = 2.5 Hz, 1H), 3.87 – 3.80 (m, 2H), 1.74 – 1.66 (m, 2H), 1.33 – 1.25 (m, 10H), 0.86 (t, J = 7.0 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 151.4, 140.3, 135.3, 130.0, 123.9, 122.5, 117.0, 114.8, 84.1, 43.5, 31.9, 29.4, 29.4, 27.1, 25.6, 22.7, 14.2. IR (neat): 3204, 2921, 1679, 1433 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{17}H_{25}N_2O$ $(M+H)^+$ 273.1967, found: 273.1971.

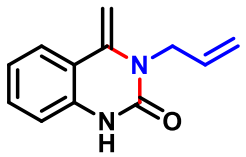
4-methylene-3-(prop-2-yn-1-yl)-3,4-dihydroquinazolin-2(1H)-one (***95t***):



Prepared according to general procedure A, using propargylamine (23.13 mg, 0.42 mmol) to afford 4-methylene-3-(prop-2-yn-1-yl)-3,4-dihydroquinazolin-2(1*H*)-one **95t** (45 mg, 65% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP: 170-172 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.59 (d, J = 7.9 Hz, 1H),

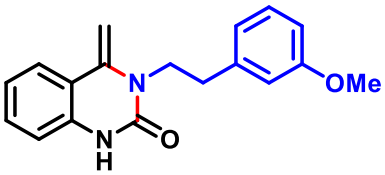
7.28 – 7.25 (m, 1H), 7.02 (t, *J* = 7.7 Hz, 1H), 6.79 (d, *J* = 7.9 Hz, 1H), 4.96 (d, *J* = 3.0 Hz, 1H), 4.65 (d, *J* = 2.4 Hz, 2H), 4.54 (d, *J* = 3.0 Hz, 1H), 2.24 (t, *J* = 2.4 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 150.4, 139.6, 134.6, 130.3, 124.1, 123.1, 117.0, 114.8, 86.1, 78.1, 77.1, 71.7, 33.2. IR (neat): 3284, 1686, 1521, 1462 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{12}H_{11}N_2O$ $(M+H)^+$ 199.0871, found: 199.0873.

3-allyl-4-methylene-3,4-dihydroquinazolin-2(1H)-one (***95u***):



Prepared according to general procedure A, using allylamine (28 mg, 0.42 mmol) to afford 3-allyl-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one **95u** (42 mg, 61% yield) as a white solid after purification using silica gel column chromatography (EtOAc:n-hexane = 30:70). MP: 127-130 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (s, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.26 – 7.22 (m, 1H), 6.99 (dd, *J* = 7.9, 7.4 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 5.93 – 5.84 (m, 1H), 5.30 – 5.21 (m, 2H), 4.83 (d, *J* = 2.5 Hz, 1H), 4.52 – 4.51 (m, 2H), 4.32 (d, *J* = 2.3 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 151.5, 140.4, 135.1, 132.0, 130.1, 123.9, 122.7, 117.0, 116.7, 115.0, 85.5, 46.1. IR (neat): 3242, 2923, 1654, 1496 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{12}H_{13}N_2O$ $(M+H)^+$ 201.1028, found: 201.1027.

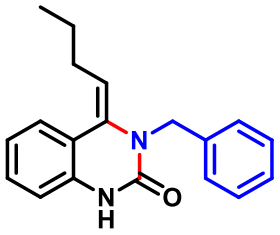
3-(3-methoxyphenethyl)-4-methylene-3,4-dihydroquinazolin-2(1H)-one (***95v***):



Prepared according to general procedure A, using 3-methoxyphenethylamine (52.92 mg, 0.42 mmol) to afford 3-(3-methoxyphenethyl)-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one **95v** (67 mg, 65 % yield) as a yellow solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP: 128-130 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.58 (d, *J* = 7.3 Hz, 1H), 7.28 – 7.22 (m, 2H), 7.03 – 6.99 (m, 1H), 6.93 – 6.85 (m, 2H), 6.78 (dd, *J* = 8.2, 1.7 Hz, 2H), 4.90 (d, *J* = 2.6 Hz, 1H), 4.43 (d, *J* = 2.7 Hz, 1H), 4.10 – 4.04 (m, 2H), 3.80 (s, 3H), 3.01 – 2.97 (m, 2H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 159.9, 150.9, 140.6, 140.2, 135.1, 130.2, 129.7, 124.1, 122.8, 121.2, 117.0, 114.7, 114.6, 112.0, 84.6, 55.3, 44.9, 32.0. IR (neat): 3616, 2927, 1680, 1517 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{18}H_{19}N_2O_2$ $(M+H)^+$ 295.1446, found: 295.1456.

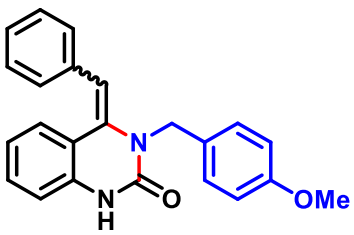
(E)-3-benzyl-4-butylidene-3,4-dihydroquinazolin-2(1H)-one (***95w***):

Prepared according to general procedure A, using benzylamine (45 mg, 0.42 mmol) to afford (*E*)-3-benzyl-4-butylidene-3,4-dihydroquinazolin-2(1*H*)-one **95w** (22 mg, 21% yield) as a yellow solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP: 122-124 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.39 (d, *J* = 7.9 Hz, 1H), 7.31 – 7.28 (m, 4H), 7.24 – 7.21 (m, 2H), 7.01– 6.97 (m, 1H), 6.79 (dd, *J* = 7.9, 0.8 Hz, 1H), 5.04 (s, 2H), 4.99 (t, *J* = 7.1 Hz, 1H), 2.28 (q, *J* = 7.2 Hz, 2H), 1.38 – 1.29 (m, 2H), 0.80 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 153.5, 137.5, 136.8, 133.0, 129.1, 128.6, 127.1, 126.9, 126.6, 121.7, 118.4, 114.1, 112.7, 48.2, 30.6, 23.9, 13.7. IR (neat): 3211, 2922, 1669, 1500, 1448 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{19}H_{21}N_2O$ $(M+H)^+$ 293.1654, found: 293.1660.



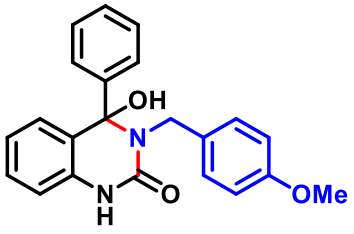
(E/Z)-4-benzylidene-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1H)-one (***95x***):

Prepared according to general procedure A, using 4-methoxybenzylamine (58 mg, 0.42 mmol) to afford (*E/Z*)-4-benzylidene-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one **95x** (62 mg, 50% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP: 236-238 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.21 (s, 1H), 7.49 (d, *J* = 7.4 Hz, 1H), 7.39 – 7.35 (m, 4H), 7.29 – 7.27 (m, 3H), 7.24 – 7.20 (m, 3H), 7.14 – 7.10 (m, 3H), 7.04 – 7.00 (m, 2H), 6.89 – 6.83 (m, 5H), 6.77 (t, *J* = 7.2 Hz, 2H), 6.67 – 6.62 (m, 3H), 6.31 (s, 1H), 6.08 (s, 1H), 5.13 (s, 2H), 4.70 (s, 2H), 3.79 (s, 3H), 3.70 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.7, 154.4, 152.9, 137.3, 136.6, 136.2, 135.3, 134.3, 134.1, 129.9, 129.8, 129.4, 129.2, 128.9, 128.8, 128.8, 128.6, 128.5, 128.4, 127.9, 127.2, 126.7, 123.0, 122.8, 121.8, 121.6, 117.0, 114.4, 114.4, 114.2, 113.8, 113.6, 111.8, 109.7, 55.4, 55.2, 49.5, 47.4. IR (neat): 2918, 1678, 1509, 1454 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{23}H_{21}N_2O_2$ $(M+H)^+$ 357.1603, found: 357.1604.



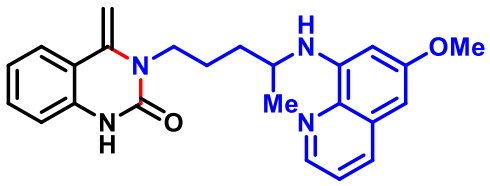
4-hydroxy-3-(4-methoxybenzyl)-4-phenyl-3,4-dihydroquinazolin-2(1H)-one (***95y***):

Prepared according to general procedure A, using 4-methoxybenzylamine (48 mg, 0.35 mmol) to afford 4-hydroxy-3-(4-methoxybenzyl)-4-phenyl-3,4-dihydroquinazolin-2(1*H*)-one **95y** (80 mg, 63% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 70:30). MP: 140-143 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.78 (s, 1H), 7.40 – 7.38 (m, 1H), 7.28 (t, *J* = 7.5 Hz, 2H),



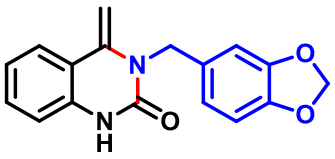
7.23 – 7.19 (m, 2H), 7.16 – 7.11 (m, 1H), 7.08 (d, *J* = 8.6 Hz, 2H), 6.97 (d, *J* = 7.7 Hz, 1H), 6.86 – 6.79 (m, 2H), 6.70 (d, *J* = 8.7 Hz, 2H), 4.30 (d, *J* = 15.1 Hz, 1H), 4.12 (d, *J* = 15.0 Hz, 1H), 3.67 (s, 3H). $^{13}C\{^{1}H\}$ NMR (101 MHz, DMSO-d_6) δ 157.5, 152.0, 145.6, 134.8, 132.0, 128.9, 128.6, 128.0, 127.7, 127.5, 125.8, 124.9, 120.9, 113.3, 112.8, 87.6, 54.9, 45.2. IR (neat): 1456, 1540, 1607, 1656, 2922, 2853 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{22}H_{20}N_2O_3Na$ $(M+Na)^+$ 383.1372, found 383.1382.

3-(4-((6-methoxyquinolin-8-yl)amino)pentyl)-4-methylene-3,4-dihydroquinazolin-2(1H)-one (***95z***):



Prepared according to general procedure A, using primaquine (109 mg, 0.42 mmol) to afford 3-(4-((6-methoxyquinolin-8-yl)amino)pentyl)-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one **95z** (64 mg, 45% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 60:40). MP: 90-93 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 1H), 8.50 (dd, *J* = 4.2, 1.6 Hz, 1H), 7.90 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.29 – 7.25 (m, 1H), 7.21 – 7.17 (m, 1H), 6.95 – 6.91 (m, 1H), 6.79 (d, *J* = 7.9 Hz, 1H), 6.31 (q, *J* = 2.5 Hz, 2H), 6.03 (s, 1H), 4.76 (d, *J* = 2.5 Hz, 1H), 4.24 (d, *J* = 2.6 Hz, 1H), 3.86 (s, 3H), 3.73 – 3.60 (m, 2H), 1.92 – 1.81 (m, 4H), 1.72 – 1.67 (m, 1H), 1.30 (d, *J* = 6.3 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 159.5, 151.5, 145.1, 144.3, 140.1, 135.5, 135.2, 134.8, 130.1, 130.0, 123.9, 122.6, 121.9, 116.9, 114.8, 96.8, 91.7, 84.4, 55.3, 48.0, 43.2, 34.0, 22.4, 20.6. IR (neat): 2956, 1661, 1519, 1453 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{24}H_{27}N_4O_2$ $(M+H)^+$ 403.2134, found: 403.2134.

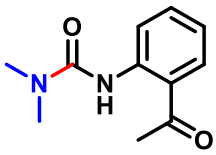
3-(benzo[d][1,3]dioxol-5-ylmethyl)-4-methylene-3,4-dihydroquinazolin-2(1H)-one (***95aa***):



Prepared according to general procedure A, using piperonylamine (64 mg, 0.42 mmol) to afford 3-(benzo[*d*][1,3]dioxol-5-ylmethyl)-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one **95aa** (60 mg, 58% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP: 173-175 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.25 (s, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.31 – 7.25 (m, 1H), 6.98 – 6.91 (m, 2H), 6.83 (dd, *J* = 9.0, 4.7 Hz, 2H), 6.74 (dd, *J* = 8.0, 1.4 Hz, 1H), 5.97 (s, 2H), 4.90 (s, 2H), 4.82 (d, *J* = 2.3 Hz, 1H), 4.17 (d, *J* = 2.4 Hz, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ 150.1, 147.4, 146.0, 139.6, 135.5, 130.9, 130.1, 123.9, 122.1, 119.6, 116.0, 114.6, 108.2, 107.0, 100.8, 85.3, 45.5. IR (neat): 3062,

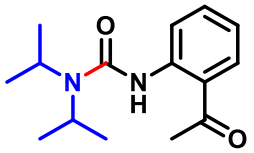
1681, 1626, 1546, 1440 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{17}H_{15}N_2O_3$ $(M+H)^+$ 295.1083, found: 295.1093.

3-(2-acetylphenyl)-1,1-dimethylurea (***137a***):



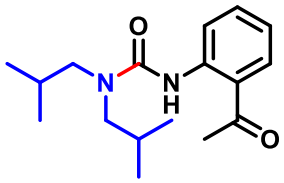
Prepared according to general procedure C, using dimethylamine (19 mg, 0.42 mmol) to afford 3-(2-acetylphenyl)-1,1-dimethylurea **137a** (43 mg, 60% yield) as a yellow solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 20:80). MP: 85-88 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.40 (s, 1H), 8.63 (dd, *J* = 8.6, 0.9 Hz, 1H), 7.84 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.49 (ddd, *J* = 8.6, 7.3, 1.5 Hz, 1H), 6.98 – 6.94 (m, 1H), 3.07 (s, 6H), 2.63 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 203.0, 155.8, 143.4, 135.2, 131.7, 120.9, 120.3, 119.7, 36.4, 28.5. IR (neat): 3616, 2921, 1738, 1524 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{11}H_{15}N_2O_2$ $(M+H)^+$ 207.1134, found: 207.1141.

3-(2-acetylphenyl)-1,1-diisopropylurea (***137b***):



Prepared according to general procedure C, using diisopropylamine (25 mg, 0.42 mmol) to afford 3-(2-acetylphenyl)-1,1-diisopropylurea **137b** (71 mg, 77% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 20:80). MP: 199-102 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.15 (s, 1H), 8.48 (dd, *J* = 8.6, 1.0 Hz, 1H), 7.83 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.47 (ddd, *J* = 8.7, 7.2, 1.6 Hz, 1H), 6.96 – 6.92 (m, 1H), 3.98 – 3.88 (m, 2H), 2.64 (s, 3H), 1.38 (s, 6H), 1.37 (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 202.9, 154.5, 143.7, 135.0, 131.7, 121.2, 120.5, 120.0, 46.5, 28.5, 21.2. IR (neat): 3264, 1734, 1645, 1521, 1309 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{15}H_{23}N_2O_2$ $(M+H)^+$ 263.1759, found: 263.1759.

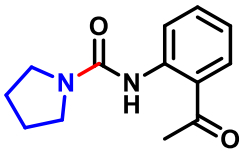
3-(2-acetylphenyl)-1,1-diisobutylurea (**137*c***):



Prepared according to general procedure C, using diisobutylamine (54 mg, 0.42 mmol) to afford 3-(2-acetylphenyl)-1,1-diisobutylurea **137c** (78 mg, 76% yield) as a red liquid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 20:80). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.39 (s, 1H), 8.68 (dd, *J* = 8.6, 0.8 Hz, 1H), 7.82 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.48 – 7.44 (m, 1H), 6.95 – 6.91 (m, 1H), 3.23 (s, 2H), 3.21 (s, 2H), 2.62 (s, 3H), 2.13 – 2.02 (m, 2H), 0.94 (s, 6H), 0.93 (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 202.7, 155.5, 143.4, 135.1, 131.6,

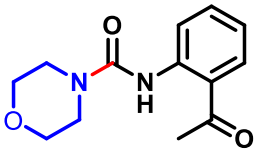
120.8, 120.1, 119.7, 55.9, 28.4, 27.7, 20.2. IR (neat): 1735, 1647, 1527, 1449, 1240 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{17}H_{27}N_2O_2$ $(M+H)^+$ 291.2072, found: 291.2072.

N-(2-acetylphenyl)pyrrolidine-1-carboxamide (***137d***):



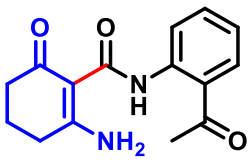
Prepared according to general procedure C, using pyrrolidine (30 mg, 0.42 mmol) to afford *N*-(2-acetylphenyl)pyrrolidine-1-carboxamide **137d** (65 mg, 80% yield) as a yellow solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 20:80). MP: 96-98 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 11.24 (s, 1H), 8.68 (dd, *J* = 8.6, 1.0 Hz, 1H), 7.82 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.48 (ddd, *J* = 8.7, 7.3, 1.5 Hz, 1H), 6.94 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1H), 3.53 – 3.50 (m, 4H), 2.62 (s, 3H), 1.95 (s, 4H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 202.9, 154.1, 143.4, 135.2, 131.7, 120.6, 120.1, 119.6, 45.8, 28.5. IR (neat): 3615, 2930, 1735, 1648, 1525 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{13}H_{17}N_2O_2$ $(M+H)^+$ 233.1290, found: 233.1297.

N-(2-acetylphenyl)morpholine-4-carboxamide (**137*e***):



Prepared according to general procedure C, using morpholine (37 mg, 0.42 mmol) to afford *N*-(2-acetylphenyl)morpholine-4-carboxamide **137e** (62 mg, 71% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 20:80). MP: 133-135 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 11.52 (s, 1H), 8.58 (dd, *J* = 8.6, 0.8 Hz, 1H), 7.84 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.50 (ddd, *J* = 8.7, 7.4, 1.5 Hz, 1H), 7.00 – 6.96 (m, 1H), 3.73 (t, *J* = 4.64 Hz, 4H), 3.56 (t, *J* = 5.12 Hz, 4H), 2.63 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 203.3, 154.9, 143.0, 135.3, 131.8, 120.9, 120.7, 119.8, 66.6, 44.0, 28.5. IR (neat): 2922, 1734, 1644, 1528, 1243 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{13}H_{17}N_2O_3$ $(M+H)^+$ 249.1239, found: 249.1248.

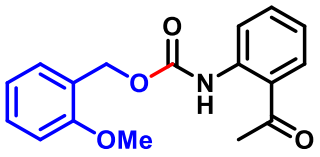
N-(2-acetylphenyl)-2-amino-6-oxocyclohex-1-ene-1-carboxamide (***137f***):



Prepared according to general procedure C, using 3-amino-2-cyclohexen-1-one (47 mg, 0.42 mmol) to afford N-(2-acetylphenyl)-2-amino-6-oxocyclohex-1-ene-1-carboxamide **137f** (15 mg, 16% yield) as a yellow solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 20:80). MP: 120-123 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (dd, *J* = 8.6, 0.8 Hz, 1H), 8.01 (dd, *J* = 8.5, 0.7 Hz, 1H), 7.77 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 7.56 (ddd, *J* = 8.3, 6.8, 1.3 Hz, 1H), 3.27 (t, *J* = 6.04 Hz 1H), 3.05 (s, 3H), 2.80 (t, *J* = 6.36 Hz, 2H), 2.24 – 2.16 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 200.8, 162.2, 150.1, 148.0, 131.6, 129.3, 127.8, 126.5, 125.6, 125.5,

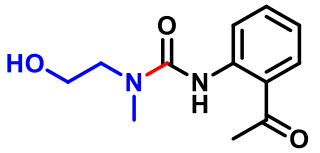
41.2, 34.9, 21.4, 16.2. IR (neat): 3616, 1739, 1695, 1524 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{15}H_{17}N_2O_3$ $(M+H)^+$ 273.1239, found: 273.1237.

2-methoxybenzyl (2-acetylphenyl)carbamate (***141***):



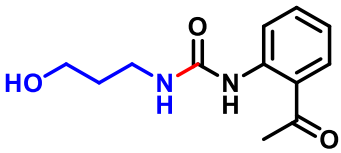
Prepared according to general procedure D, using 2-methoxybenzyl alcohol (58 mg, 0.42 mmol) to afford 2-methoxybenzyl (2-acetylphenyl)carbamate **141** (51 mg, 53% yield) as a faint green solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 10:90). MP: 108-110 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.22 (s, 1H), 8.52 (dd, *J* = 8.6, 0.9 Hz, 1H), 7.86 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.54 (ddd, *J* = 8.6, 7.4, 1.4 Hz, 1H), 7.41 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.31 (td, *J* = 8.1, 1.7 Hz, 1H), 7.06 (ddd, *J* = 8.3, 7.3, 1.2 Hz, 1H), 6.96 (td, *J* = 7.5, 0.9 Hz, 1H), 6.90 (d, *J* = 8.2 Hz, 1H), 5.28 (s, 2H), 3.86 (s, 3H), 2.64 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 202.3, 157.5, 154.0, 141.5, 135.1, 131.7, 129.6, 129.5, 124.6, 121.6, 121.4, 120.5, 119.4, 110.5, 62.4, 55.5, 28.6. IR (neat): 3615, 1732, 1650, 1522 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{17}H_{17}NO_4Na$ $(M+Na)^+$ 322.1055, found: 322.1060.

3-(2-acetylphenyl)-1-(2-hydroxyethyl)-1-methylurea (***144***):



Prepared according to general procedure C, using 2-(Methylamino)ethanol (31 mg, 0.42 mmol) to afford 3-(2-acetylphenyl)-1-(2-hydroxyethyl)-1-methylurea **144** (71 mg, 86% yield) as a white solid after purification using silica gel column chromatography (EtOAc:n-hexane = 30:70). MP: 112-115 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.46 (s, 1H), 8.58 (dd, *J* = 8.6, 1.1 Hz, 1H), 7.87 – 7.84 (m, 1H), 7.53 – 7.48 (m, 1H), 7.02 – 6.98 (m, 1H), 3.83 (s, 3H), 3.60 – 3.57 (m, 2H), 3.18 – 3.17 (m, 10H), 2.66 – 2.65 (m, 3H), 1.82 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 203.2, 157.1, 143.0, 135.3, 131.8, 121.2, 120.8, 120.0, 61.8, 52.1, 35.9, 28.6. IR (neat): 2923, 1644, 1452, 1203 cm^{-1} HRMS (ESI-TOF) m/z calculated for $C_{12}H_{16}N_2O_3Na$ $(M+Na)^+$ 259.1059, found: 259.1059.

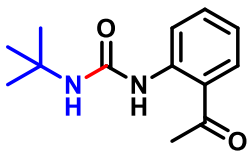
1-(2-acetylphenyl)-3-(3-hydroxypropyl)urea (***145***):



Prepared according to general procedure E, using 3-aminopropan-1-ol (32 mg, 0.42 mmol) to afford 1-(2-acetylphenyl)-3-(3-hydroxypropyl)urea **145** (25 mg, 31% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP: 111-113 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.34 (s, 1H), 8.12 (dd, *J* = 8.0,

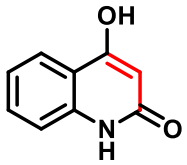
1.3 Hz, 1H), 7.61 (m, 1H), 7.25 – 7.21 (m, 1H), 7.12 (d, J = 8.1 Hz, 1H), 4.19 (m, 4H), 2.06 (m, 2H), 2.02 (s, 3H), 1.82 (bs, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 192.6, 171.3, 162.5, 152.1, 138.7, 135.2, 128.5, 123.5, 115.1, 114.6, 62.5, 38.3, 27.2, 21.0. IR (neat): 2921, 1733, 1715, 1660, 1243 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{12}H_{17}N_2O_3$ $(M+H)^+$ 237.1239, found: 237.1240.

1-(2-acetylphenyl)-3-(tert-butyl)urea (***137g***):



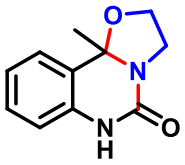
Prepared according to general procedure C, using *tert*-butylamine (31 mg, 0.42 mmol) to afford 1-(2-acetylphenyl)-3-(*tert*-butyl)urea **137g** (53 mg, 65% yield) as a yellow liquid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.95 (s, 1H), 8.52 (d, J = 8.7 Hz, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.47 (t, J = 7.9 Hz, 1H), 6.95 (t, J = 7.6 Hz, 1H), 2.63 (s, 3H), 1.39 (s, 9H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 203.0, 154.2, 143.4, 135.1, 131.7, 120.7, 120.2, 120.1, 119.9, 51.1, 29.3. IR (neat): 3350, 1715, 1649, 1539, 1014 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{13}H_{18}N_2O_2Na$ $(M+Na)^+$ 257.1265, found: 257.1247.

4-hydroxyquinolin-2(1H)-one (***142***):[46,96]



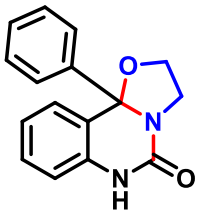
Prepared according to general procedure F, using 3-(*tert*-butylperoxy)-3-methylindolin-2-one (82 mg, 0.35 mmol) to afford 4-hydroxyquinolin-2(1*H*)-one **142** (45 mg, 80% yield) as a white solid after purification using silica gel column chromatography (DCM:MeOH = 90:10). The data for this compound are in agreement with reported compound.

10b-methyl-2,3,6,10b-tetrahydro-5H-oxazolo[3,2-c]quinazolin-5-one (**139*a***):



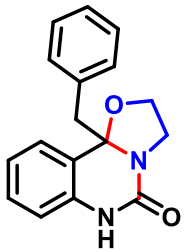
Prepared according to general procedure G, using ethanolamine (26 mg, 0.42 mmol) to afford 10b-methyl-2,3,6,10b-tetrahydro-5*H*-oxazolo[3,2-*c*]quinazolin-5-one **139a** (58 mg, 81 % yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP: 161-163 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.37 (d, J = 7.6 Hz, 1H), 7.25 – 7.22 (m, 1H), 7.04 (t, J = 7.5 Hz, 1H), 6.86 – 6.84 (m, 1H), 4.18 – 4.10 (m, 2H), 3.94 (dd, J = 14.3, 7.1 Hz, 1H), 3.66 (dt, J = 10.4, 7.0 Hz, 1H), 1.54 (s, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 151.6, 134.5, 129.3, 124.5, 123.1, 122.7, 114.2, 91.9, 63.5, 43.4, 27.6. IR (neat): 3616, 3061, 1673, 1517 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{11}H_{13}N_2O_2$ $(M+H)^+$ 205.0977, found: 205.0978.

10b-phenyl-2,3,6,10b-tetrahydro-5H-oxazolo[3,2-c]quinazolin-5-one (**139*b***):



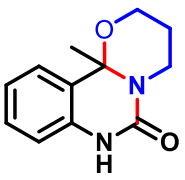
Prepared according to general procedure G, using ethanolamine (26 mg, 0.42 mmol) to afford 10b-phenyl-2,3,6,10b-tetrahydro-5*H*-oxazolo[3,2-*c*]quinazolin-5-one **139b** (75 mg, 78% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP: 170-173 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.51 (m, 2H), 7.38 – 7.30 (m, 3H), 7.30 – 7.27 (m, 1H), 7.19 (m, 1H), 6.97 (td, *J* = 7.7, 1.1 Hz, 1H), 6.82 (dd, *J* = 8.0, 0.7 Hz, 1H), 4.26 (ddd, *J* = 10.7, 8.2, 5.9 Hz, 1H), 4.08 (td, *J* = 8.2, 5.9 Hz, 1H), 3.95 (td, *J* = 8.3, 5.9 Hz, 1H) 3.36 (ddd, *J* = 10.7, 8.4, 5.9 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 151.7, 143.0, 134.0, 129.5, 128.8, 128.4, 126.6, 125.1, 122.9, 121.4, 114.4, 94.2, 62.8, 43.4. IR (neat): 3212, 2920, 1670, 1602, 1434, cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{16}H_{15}N_2O_2$ $(M+H)^+$ 267.1134, found: 267.1131.

10b-benzyl-2,3,6,10b-tetrahydro-5H-oxazolo[3,2-c]quinazolin-5-one (**139*c***):



Prepared according to general procedure G, using ethanolamine (26 mg, 0.42 mmol) to afford 10b-benzyl-2,3,6,10b-tetrahydro-5*H*-oxazolo[3,2-*c*]quinazolin-5-one **139c** (71 mg, 72% yield) as a yellow solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP: 154-156 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.28 (d, *J* = 7.6 Hz, 1H), 7.23 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.20 – 7.16 (m, 3H), 7.05 – 6.98 (m, 3H), 6.75 – 6.73 (m, 1H), 4.11 – 4.06 (m, 1H), 4.00 (m, 1H), 3.84 (q, *J* = 7.7 Hz, 1H), 3.16 (m, 1H), 3.01 3.05 (d, *J* = 13.5 Hz, 1H) 2.97 (d, *J* = 13.5 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 151.7, 135.1, 134.9, 130.7, 129.3, 128.1, 126.9, 124.8, 122.5, 122.1, 113.9, 94.1, 64.3, 47.0, 44.1. IR (neat): 3212, 2912, 1671, 1438 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{17}H_{17}N_2O_2$ $(M+H)^+$ 281.1290, found: 281.1289.

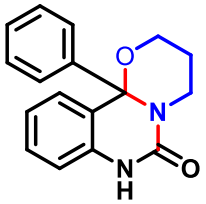
11b-methyl-3,4,7,11b-tetrahydro-2H,6H-[1,3]oxazino[3,2-c]quinazolin-6-one (**139*d***):



Prepared according to general procedure G, using 3-aminopropan-1-ol (32 mg, 0.42 mmol) to afford 11*b*-methyl-3,4,7,11b-tetrahydro-2*H*,6*H*-[1,3]oxazino[3,2-*c*]quinazolin-6-one **139d** (58 mg, 76% yield) as a yellow solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP: 140-142 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.37 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.24 – 7.20 (m, 1H), 7.02 (td, *J* = 7.6, 1.1 Hz, 1H), 6.72 (dd, *J* = 8.0, 0.8 Hz, 1H), 4.48 – 4.43 (m, 1H), 4.09 (td, *J* = 11.4, 3.6 Hz, 1H), 3.98 – 3.94 (m, 1H), 3.29 (td, *J* = 13.2, 4.0 Hz, 1H), 2.10 – 1.88 (m, 2H), 1.72 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.0, 134.0, 129.3, 124.9, 124.2, 122.6, 113.6, 86.3,

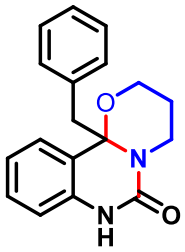
60.6, 35.8, 25.1, 23.0. IR (neat): 3615, 1716, 1657, 1520 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{12}H_{15}N_2O_2$ $(M+H)^+$ 219.1133, found: 219.1136.

11b-phenyl-3,4,7,11b-tetrahydro-2H,6H-[1,3]oxazino[3,2-c]quinazolin-6-one (**139*e***):



Prepared according to general procedure G, using 3-aminopropan-1-ol (32 mg, 0.42 mmol) to afford 11*b*-phenyl-3,4,7,11*b*-tetrahydro-2*H*,6*H*-[1,3]oxazino[3,2-*c*]quinazolin-6-one **139e** (75 mg, 76% yield) as a faint yellow solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP: 189-192 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 9.08 (s, 1H), 7.48 (d, *J* = 7.5 Hz, 2H), 7.41 – 7.36 (m, 3H), 7.28 (t, *J* = 7.3 Hz, 1H), 7.13 (td, *J* = 7.9, 1.3 Hz, 1H), 6.94 – 6.89 (m, 1H), 6.77 (d, *J* = 7.9 Hz, 1H), 4.61 (dd, *J* = 13.4, 3.2 Hz, 1H), 4.09 – 4.01 (m, 2H), 3.04 (td, *J* = 13.2, 3.1 Hz, 1H), 2.17 – 2.03 (m, 1H), 1.50 (d, *J* = 13.1 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.0, 140.9, 133.5, 129.3, 129.2, 128.2, 126.2, 123.1, 122.5, 114.1, 89.9, 62.6, 37.8, 25.3. IR (neat): 3204, 2922, 1666, 1605, 1425 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{17}H_{17}N_2O_2$ $(M+H)^+$ 281.1290, found: 281.1297.

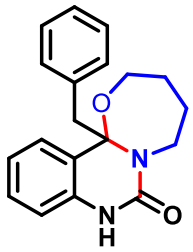
11b-benzyl-3,4,7,11b-tetrahydro-2H,6H-[1,3]oxazino[3,2-c]quinazolin-6-one (**139*f***):



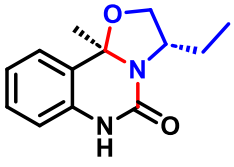
Prepared according to general procedure G, using 3-aminopropan-1-ol (32 mg, 0.42 mmol) to afford 11*b*-benzyl-3,4,7,11b-tetrahydro-2*H*,6*H*-[1,3]oxazino[3,2-*c*]quinazolin-6-one **139f** (73 mg, 71% yield) as a yellow solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP: 156-158 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.23 (d, *J* = 6.7 Hz, 1H), 7.18 – 7.14 (m, 1H), 7.12 (d, *J* = 7.3 Hz, 1H), 7.07 (t, *J* = 7.2 Hz, 2H), 6.96 (t, *J* = 7.6 Hz, 1H), 6.76 – 6.69 (m, 2H), 6.52 – 6.46 (m, 1H), 4.53 (dd, *J* = 13.6, 5.9 Hz, 1H), 4.27- 4.20 (m, 1H), 4.01 – 3.96 (m, 1H), 3.66 (d, *J* = 13.3 Hz, 1H), 3.38 (td, *J* = 13.0, 4.4 Hz, 1H), 3.00 (d, *J* = 13.3 Hz, 1H), 2.06 – 1.94 (m, 1H), 1.86 – 1.81 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.1, 135.1, 134.6, 130.4, 129.4, 127.9, 126.8, 125.6, 122.0, 121.5, 113.2, 89.2, 60.4, 41.8, 35.7, 24.9. IR (neat): 2920, 1664, 1437 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{18}H_{19}N_2O_2$ $(M+H)^+$ 295.1446, found: 295.1452.

12b-benzyl-2,3,4,5,8,12b-hexahydro-7H-[1,3]oxazepino[3,2-c]quinazolin-7-one (**139*g***):

Prepared according to general procedure G, using 4-amino-1-butanol (37 mg, 0.42 mmol) to afford 12*b*-benzyl-2,3,4,5,8,12b-hexahydro-7*H*-[1,3]oxazepino[3,2-*c*]quinazolin-7-one **139g** (67 mg, 62% yield) as a yellow solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP: 195-198 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.29 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.20 – 7.15 (m, 1H), 7.09 – 6.97 (m, 4H), 6.71 – 6.68 (m, 2H), 6.54 (dd, *J* = 8.0, 0.8 Hz, 1H), 4.39 (d, *J* = 13.3 Hz, 1H), 3.78 (d, *J* = 13.8 Hz, 1H), 3.60 (td, *J* = 12.2, 1.3 Hz, 1H), 3.30 (t, *J* = 12.5 Hz, 1H), 3.18 (d, *J* = 13.2 Hz, 1H), 2.98 (d, *J* = 13.2 Hz, 1H), 1.84 – 1.71 (m, 2H), 1.65 – 1.44 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.8, 136.5, 134.7, 130.4, 129.4, 127.7, 126.7, 125.7, 121.8, 120.6, 113.2, 92.8, 64.6, 47.3, 40.3, 29.2, 27.3. IR (neat): 1448, 1495, 1603, 1658, 2923, 3202 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{18}H_{19}N_2O_2$ $(M+H)^+$ 309.1603, found: 309.1596.



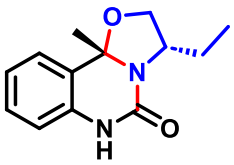
(3S,10bR)-3-ethyl-10b-methyl-2,3,6,10b-tetrahydro-5H-oxazolo[3,2-c]quinazolin-5-one (***139h***) & *(3S,10bS)-3-ethyl-10b-methyl-2,3,6,10b-tetrahydro-5H-oxazolo[3,2-c]quinazolin-5-one* (***139h'***)*:* Prepared according to general procedure G, using (S)-(+)-2-amino-1-propanol (37 mg, 0.42 mmol) to afford **(**3S,10bR)-3-ethyl-10*b*-methyl-2,3,6,10*b*-tetrahydro-5*H*-oxazolo[3,2-*c*]quinazolin-5-one **139h** (45 mg, 55% yield) as a faint pink solid after purification using silica gel column chromatography (EtOAc:n-hexane = 30:70). MP: 185-187 °C, & (3S,10*b*S)-3-ethyl-10*b*-methyl-2,3,6,10*b*-tetrahydro-5*H*-oxazolo[3,2-*c*]quinazolin-5-one **139h'** (13 mg, 16% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 70:30). MP: 184-186 °C. Diastereomers **139h** & **139h′** having a ratio of 3.4:1. HPLC for **139h** (CHIRALPAK IA column, *n*-heptane/isopropanol=80/20, flow rate = 0.7 mL/min, l = 254 nm) t_R = 9.62 min (major), t_R = 7.23 min (minor), 97% *de*. HPLC for **139h'** (CHIRALPAK IA column, *n*-heptane/isopropanol=80/20, flow rate = 0.7 mL/min, l = 254 nm) t_R = 9.88 min (major), t_R = 9.61 min (minor), 90% *de*. *(3S,10bR)-3-ethyl-10b-methyl-2,3,6,10b-tetrahydro-5H-oxazolo[3,2-c]quinazolin-5-one* (***139h***):



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.22 (td, *J* = 8.1, 1.3 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.79 (t, *J* = 7.1 Hz, 1H), 4.10 (td, *J* = 10.5, 5.5 Hz, 1H), 4.01 (dd, *J* = 8.4, 6.6 Hz, 1H), 3.91 (dd, *J* = 8.5, 4.6 Hz, 1H), 2.23 – 2.12 (m, 1H), 1.74 – 1.63 (m, 1H), 1.56 (s, 3H), 1.03 (t, *J* = 7.5 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.4, 134.8, 129.1, 124.0, 122.7, 114.0, 113.9,

92.4, 69.1, 59.1, 29.5, 28.0, 10.7. IR (neat): 3616, 1739, 1690, 1524 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{13}H_{17}N_2O_2$ $(M+H)^+$ 233.1290, found: 233.1295. The crystal of compound **139h** was grown using dichloromethane and pet ether (2:1) as a solvent by slow evaporation. A needle-shaped single crystal was mounted on a loop by applying a small amount of paraffin oil. Crystal data for the compound **139h**: C_{13} H_{15} N_2 O_2, M = 231.27, orthorhombic, space group P 21 21 21 with a = 7.5792(3)Å, b = 7.7672(3)Å, c = 19.9951(7)Å, α = 90°, β = 90°, γ = 90°, V = 1177.09(8) Å3, T = 296(2) K, R1 = 0.0306, wR2 =0.0814 on observed data, z = 4, Dcalcd = 1.305 g cm–3, F(000) = 492, Absorption coefficient = 0.725 mm–1, λ = 1.54178Å, 1999 reflections were collected on a Bruker APEX-II CCD single crystal diffractometer, 1964 observed reflections (I≥2σ (I)). The largest difference peak and hole = 0.510 and -0.142 eÅ–3, respectively.

(3S,10bS)-3-ethyl-10b-methyl-2,3,6,10b-tetrahydro-5H-oxazolo[3,2-c]quinazolin-5-one (***139h'***):

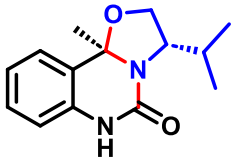


^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.32 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.22 (td, *J* = 7.8, 1.4 Hz, 1H), 7.04 (td, *J* = 7.5, 0.9 Hz, 1H), 6.80 (d, *J* = 7.9 Hz, 1H), 4.37 (dd, *J* = 8.8, 7.0 Hz, 1H), 4.14 – 4.08 (m, 1H), 3.99 (dd, *J* = 8.9, 2.7 Hz, 1H), 2.07 – 1.96 (m, 1H), 1.67 – 1.60 (m, 1H), 1.45 (s, 3H), 0.80 (t, *J* = 7.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.2, 134.8, 128.8, 125.5, 123.0, 122.8, 114.0, 92.4, 69.0, 56.4, 25.5, 24.1, 9.3. IR (neat): 3615, 1674, 1520 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{13}H_{17}N_2O_2$ $(M+H)^+$ 233.1290, found: 233.1295.

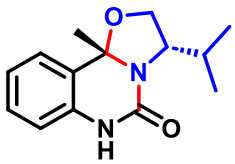
(3S,10bR)-3-isopropyl-10b-methyl-2,3,6,10b-tetrahydro-5H-oxazolo[3,2-c]quinazolin-5-one (***139i***) *&* *(3S,10bS)-3-isopropyl-10b-methyl-2,3,6,10b-tetrahydro-5H-oxazolo[3,2-c]quinazolin-5-one* (***139i'***):

Prepared according to general procedure G, using (S)-(+)-2-amino-3-methyl-1-butanol (43 mg, 0.42 mmol) to afford (3S,10*b*R)-3-isopropyl-10*b*-methyl-2,3,6,10*b*-tetrahydro-5*H*-oxazolo[3,2-*c*]quinazolin-5-one **139i** (41 mg, 48% yield) as a gray solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP: 205-208 °C, & **(**3S,10*b*S)-3-isopropyl-10b-methyl-2,3,6,10b-tetrahydro-5*H*-oxazolo[3,2-*c*]quinazolin-5-one **139i'** (17 mg, 20% yield) as a white solid after purification using silica gel column chromatography (EtOAc:n-hexane = 70:30). MP: 204-207 °C. Diastereomers **139i** & **139i′** having a ratio of 2.4:1. HPLC for **139i** (CHIRALPAK IA column, *n*-heptane/isopropanol = 80/20, flow rate = 0.7 mL/min, l = 254 nm) t_R = 8.03 min (major), t_R = 6.82 min (minor), 94% *de*. HPLC for **139i'** (CHIRALPAK IA column, *n*-heptane/isopropanol = 80/20, flow rate = 0.7 mL/min, l = 254 nm) t_R = 13.63 min (major), t_R =

8.12 min (minor), 95% *de*. *(3S,10bR)-3-isopropyl-10b-methyl-2,3,6,10b-tetrahydro-5H-oxazolo[3,2-c]quinazolin-5-one* (***139i***): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.38 – 7.34 (m, 1H), 7.22 (td, *J* = 7.7, 1.5 Hz, 1H), 7.03 (td, *J* = 7.5, 1.1 Hz, 1H), 6.77 (dd, *J* = 8.0, 0.7 Hz, 1H), 3.98 (dd, *J* = 8.4, 2.9 Hz, 1H), 3.93 – 3.88 (m, 1H), 3.76 (dd, *J* = 8.4, 5.9 Hz, 1H), 2.17 – 2.04 (m, 1H), 1.56 (s, 3H), 1.15 (d, *J* = 6.9 Hz, 3H), 1.03 (d, *J* = 6.6 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 153.2, 135.0, 129.1, 124.3, 124.0, 122.6, 113.8, 92.5, 67.7, 64.2, 31.8, 30.0, 19.9, 19.6. IR (neat): 3616, 1739, 1693, 1524 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{14}H_{19}N_2O_2$ $(M+H)^+$ 247.1446, found: 247.1444.

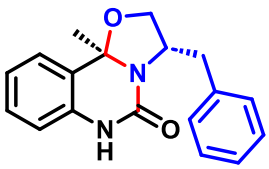


(3S,10bS)-3-isopropyl-10b-methyl-2,3,6,10b-tetrahydro-5H-oxazolo[3,2-c]quinazolin-5-one (***139i'***): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, *J* = 7.0 Hz, 1H), 7.23 (td, *J* = 7.8, 1.4 Hz, 1H), 7.05 (td, *J* = 7.5, 0.9 Hz, 1H), 6.98 (s, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 4.26 – 4.21 (m, 1H), 4.13 – 4.09 (m, 2H), 2.69 – 2.59 (m, 1H), 1.45 (s, 3H), 0.89 (d, *J* = 7.1 Hz, 3H), 0.58 (d, *J* = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 150.7, 128.7, 125.6, 125.5, 123.1, 122.9, 113.7, 92.4, 64.8, 60.0, 26.2, 25.2, 19.5, 14.7. IR (neat): 3613, 3062, 1670, 1605, 1511 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{14}H_{19}N_2O_2$ $(M+H)^+$ 247.1446, found: 247.1451.



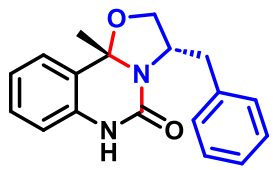
(3S,10bR)-3-benzyl-10b-methyl-2,3,6,10b-tetrahydro-5H-oxazolo[3,2-c]quinazolin-5-one (***139j***) *& (3S,10bS)-3-benzyl-10b-methyl-2,3,6,10b-tetrahydro-5H-oxazolo[3,2-c]quinazolin-5-one* (***139j'***)**:** Prepared according to general procedure G, using (S)-2-amino-3-phenylpropan-1-ol (64 mg, 0.42 mmol) to afford (3S,10*b*R)-3-benzyl-10*b*-methyl-2,3,6,10*b*-tetrahydro-5*H*-oxazolo[3,2-*c*]quinazolin-5-one **139j** (47 mg, 45% yield) as a white solid after purification using silica gel column chromatography (EtOAc:n-hexane = 30:70). MP: 122-125 °C, & (3S,10*b*S)-3-benzyl-10*b*-methyl-2,3,6,10*b*-tetrahydro-5*H*-oxazolo[3,2-*c*]quinazolin-5-one **139j'** (36 mg, 35% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 70:30). MP: 92-95 °C. Diastereomers **139j** & **139j'** having a ratio of 1.3:1. HPLC for **139j** (CHIRALPAK IA column, *n*-heptane/isopropanol = 80/20, flow rate = 0.7 mL/min, l = 254 nm) t_R = 11.84 min (major), t_R = 4.72 min (minor), 94% *de*. HPLC for **139j'** (CHIRALPAK IA column, *n*-heptane/isopropanol = 80/20, flow rate = 0.7 mL/min, l = 254 nm) t_R = 13.47 min (major), t_R = 11.81 min (minor), 84% *de*. *(3S,10bR)-3-benzyl-10b-methyl-2,3,6,10b-tetrahydro-5H-oxazolo[3,2-c]quinazolin-5-one* (***139j***): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1H), 7.38 – 7.33

(m, 5H), 7.30 – 7.22 (m, 2H), 7.04 (t, J = 7.5 Hz, 1H), 6.90 – 6.89 (m, 1H), 4.47 – 4.43 (m, 1H), 4.00 (dd, J = 8.8, 5.4 Hz, 1H), 3.90 (t, J = 7.8 Hz, 1H), 3.54 (d, J = 13.2 Hz, 1H), 3.06 – 2.99 (m, 1H), 1.48 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.9, 137.6, 134.9, 129.7, 129.1, 128.7, 126.8, 124.0, 123.9, 122.6, 114.2, 92.7, 68.2, 58.7, 40.4, 29.2. IR (neat): 3617, 1685, 1524 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{18}H_{19}N_2O_2$ $(M+H)^+$ 295.1446, found: 295.1444.



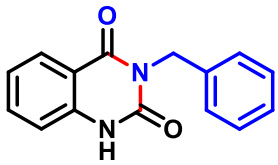
(3S,10bS)-3-benzyl-10b-methyl-2,3,6,10b-tetrahydro-5H-oxazolo[3,2-c]quinazolin-5-one (***139j'***):

^1H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 7.34 – 7.17 (m, 8H), 7.02 (td, J = 7.5, 1.0 Hz, 1H), 6.91 (d, J = 8.0 Hz, 1H), 4.41– 4.36 (m, 1H), 4.18 (dd, J = 8.9, 6.9 Hz, 1H), 4.03 (dd, J = 9.3, 2.4 Hz, 1H), 3.66 (dd, J = 13.2, 2.7 Hz, 1H), 2.51 (dd, J = 13.2, 10.3 Hz, 1H), 1.46 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.9, 138.0, 135.0, 129.4, 128.8, 128.7, 126.6, 125.5, 122.8, 122.7, 114.2, 92.6, 68.5, 56.8, 37.7, 25.6. IR (neat): 3615, 1685, 1523 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{18}H_{19}N_2O_2$ $(M+H)^+$ 295.1446, found: 295.1443.



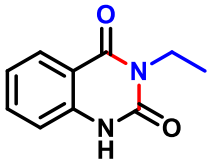
3-benzylquinazoline-2,4(1H,3H)-dione (***96a***):

Prepared according to general procedure H, using 3-benzyl-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one **95b** (63 mg, 0.25 mmol) to afford 3-benzylquinazoline-2,4(1*H*,3*H*)-dione **96a** (49 mg, 78% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP: 203-205 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 9.93 (s, 1H), 8.13 (d, J = 7.9 Hz, 1H), 7.58 (t, J = 7.7 Hz, 1H), 7.54 – 7.52 (m, 2H), 7.33 – 7.29 (m, 2H), 7.25 – 7.20 (m, 2H), 7.04 (d, J = 8.1 Hz, 1H), 5.27 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.4, 152.0, 138.6, 137.0, 135.2, 129.0, 128.7, 128.6, 127.8, 123.5, 115.0, 114.7, 44.3. IR (neat): 3282, 2922, 1735, 1645, 1459 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{15}H_{13}N_2O_2$ $(M+H)^+$ 253.0977, found: 253.0968.



3-ethylquinazoline-2,4(1H,3H)-dione (***96b***):

Prepared according to general procedure H, using 3-ethyl-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one **95q** (47 mg, 0.25 mmol) to afford 3-ethylquinazoline-2,4(1*H*,3*H*)-dione **96b** (33 mg, 69% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP: 190-192 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 10.35 (s, 1H), 8.14 (d, J = 7.9 Hz, 1H),



7.61 (ddd, J = 8.2, 7.3, 1.5 Hz, 1H), 7.25 – 7.21 (m, 1H), 7.14 (d, J = 8.1 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 162.3, 52.1, 138.7, 135.0, 128.4, 123.4, 115.1, 114.8, 36.3, 13.3. IR (neat): 3058, 2919, 1715, 1659, 1455 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{10}H_{11}N_2O_2$ $(M+H)^+$ 191.0820, found: 191.0824.

4.10. Appendix III: Copies of ^{1}H, $^{13}C\{^{1}H\}$ NMR spectra and HPLC Chromatograms of representative compounds

Entry	Figure No	NMR Data	Page No
95b	4.10.1. & 4.10.2.	^{1}H and $^{13}C\{^{1}H\}$	181
95e	4.10.3. & 4.10.4.	^{1}H and $^{13}C\{^{1}H\}$	182
95v	4.10.5. & 4.10.6.	^{1}H and $^{13}C\{^{1}H\}$	183
137b	4.10.7. & 4.10.8.	^{1}H and $^{13}C\{^{1}H\}$	184
141	4.10.9. & 4.10.10.	^{1}H and $^{13}C\{^{1}H\}$	185
142	4.10.11. & 4.10.12.	^{1}H and $^{13}C\{^{1}H\}$	186
139f	4.10.13. & 4.10.14.	^{1}H and $^{13}C\{^{1}H\}$	187
139j	4.10.15. & 4.10.16.	^{1}H and $^{13}C\{^{1}H\}$	188
139j'	4.10.17. & 4.10.18.	^{1}H and $^{13}C\{^{1}H\}$	189
96a	4.10.19. & 4.10.20.	^{1}H and $^{13}C\{^{1}H\}$	190
139j	4.10.21.	HPLC Chromatogram	191
139j'	4.10.22.	HPLC Chromatogram	191
96b	4.10.23.	Crystal structure	192
139h	4.10.24.	Crystal structure	192

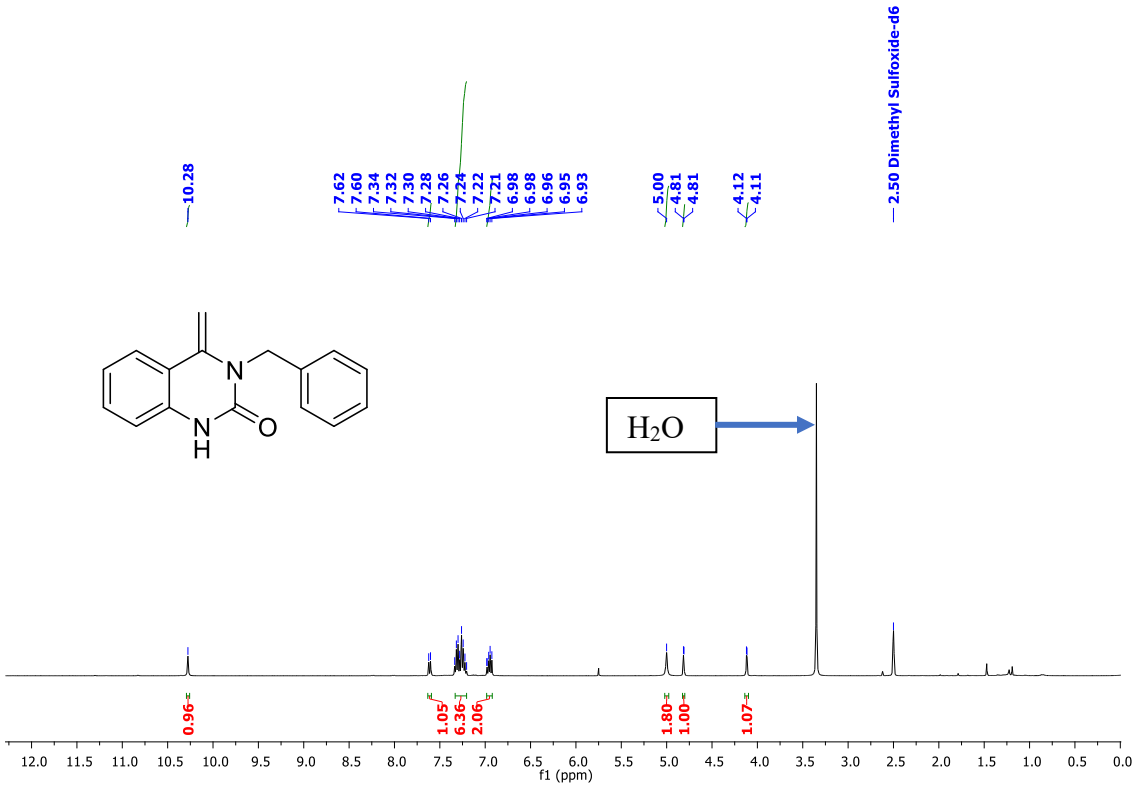


Figure 4.10.1. ^{1}H NMR (400 MHz, DMSO-d$_6$) of **95b**

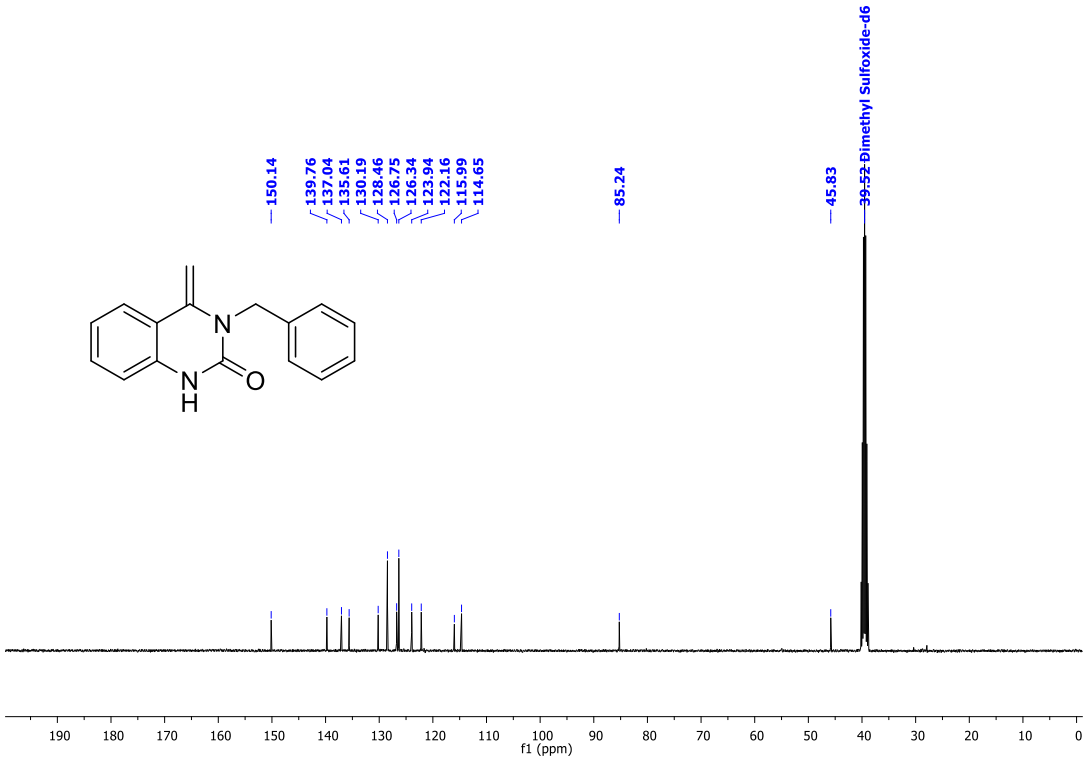


Figure 4.10.2. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d$_6$) of **95b**

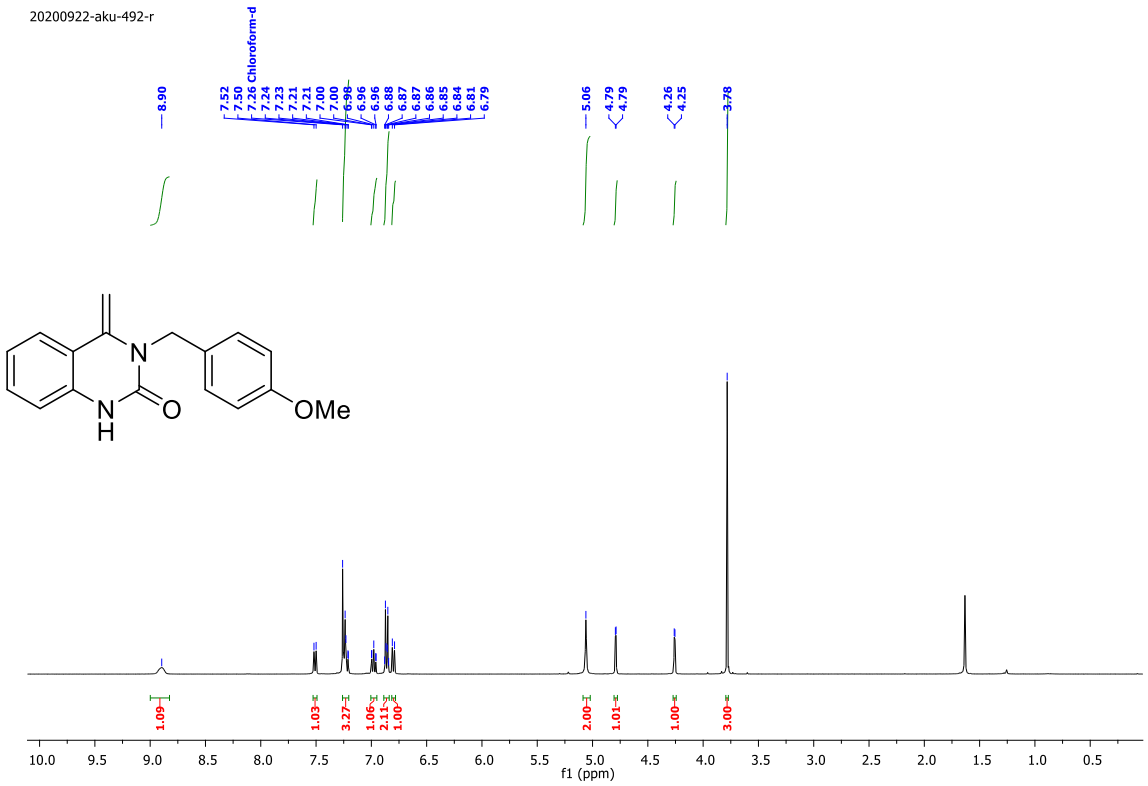


Figure 4.10.3. ^{1}H NMR (400 MHz, $CDCl_3$) of **95e**

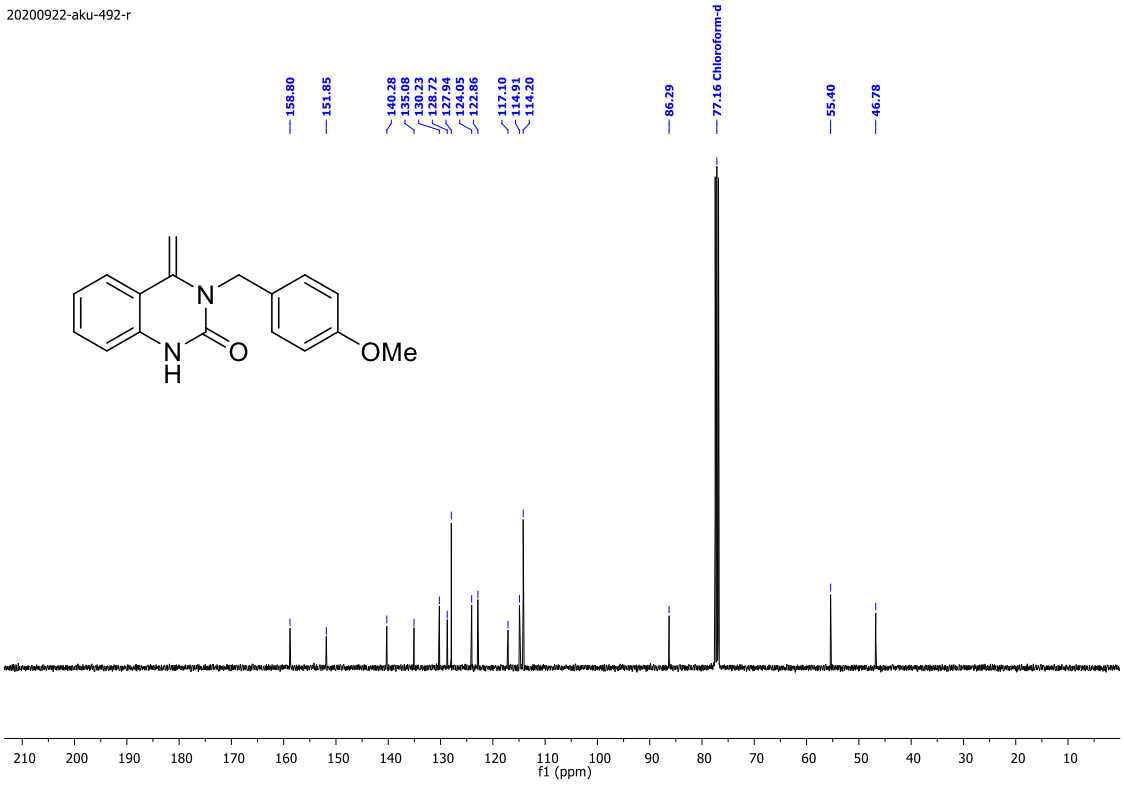


Figure 4.10.4. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) of **95e**

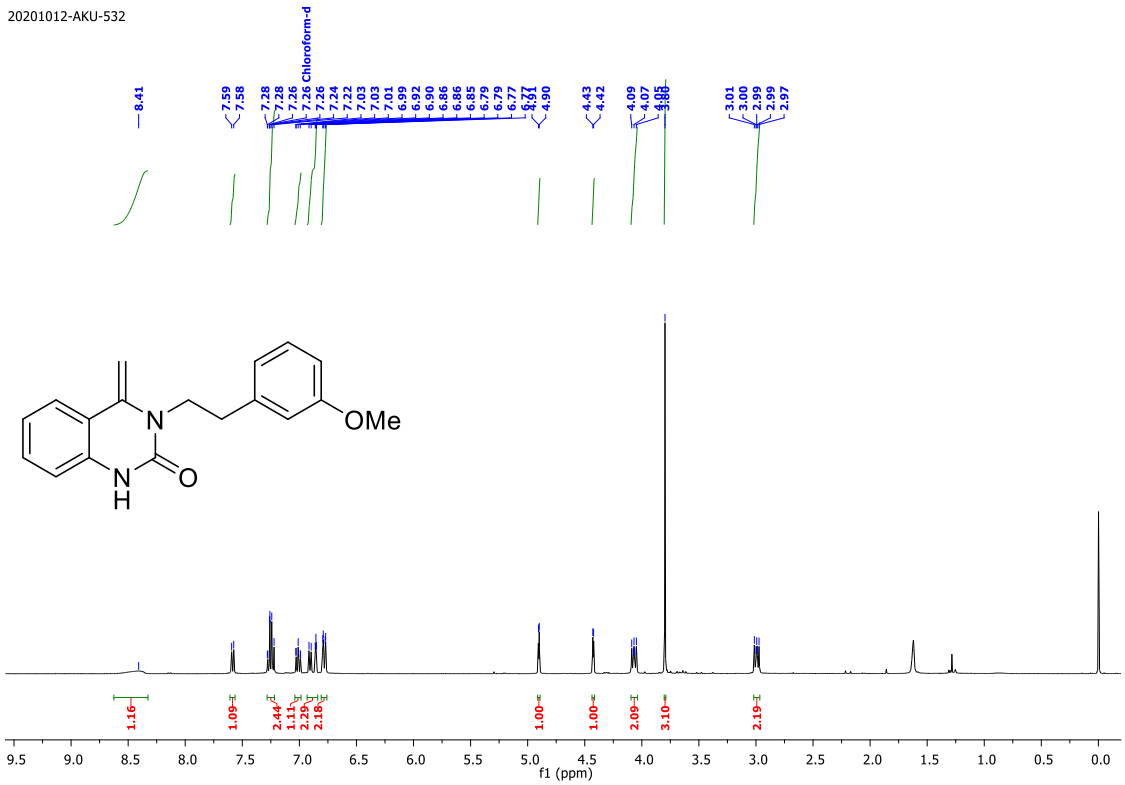


Figure 4.10.5. ^{1}H NMR (400 MHz, $CDCl_3$) of **95v**

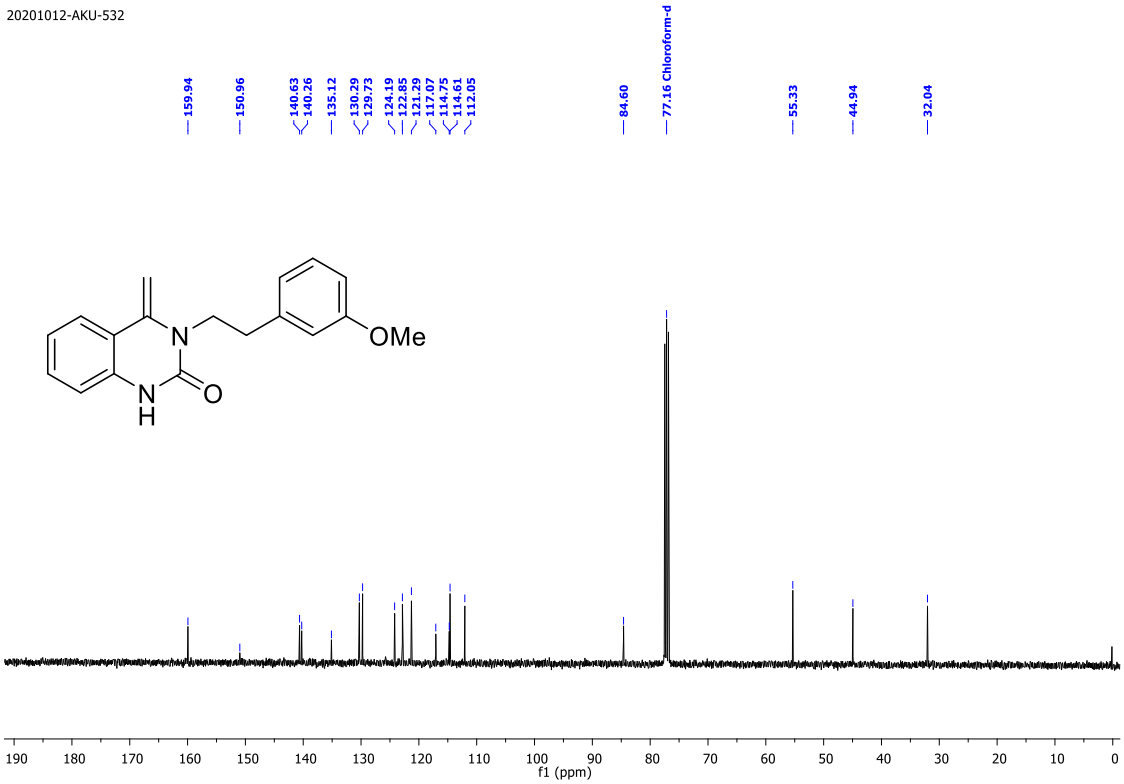


Figure 4.10.6. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) of **95v**

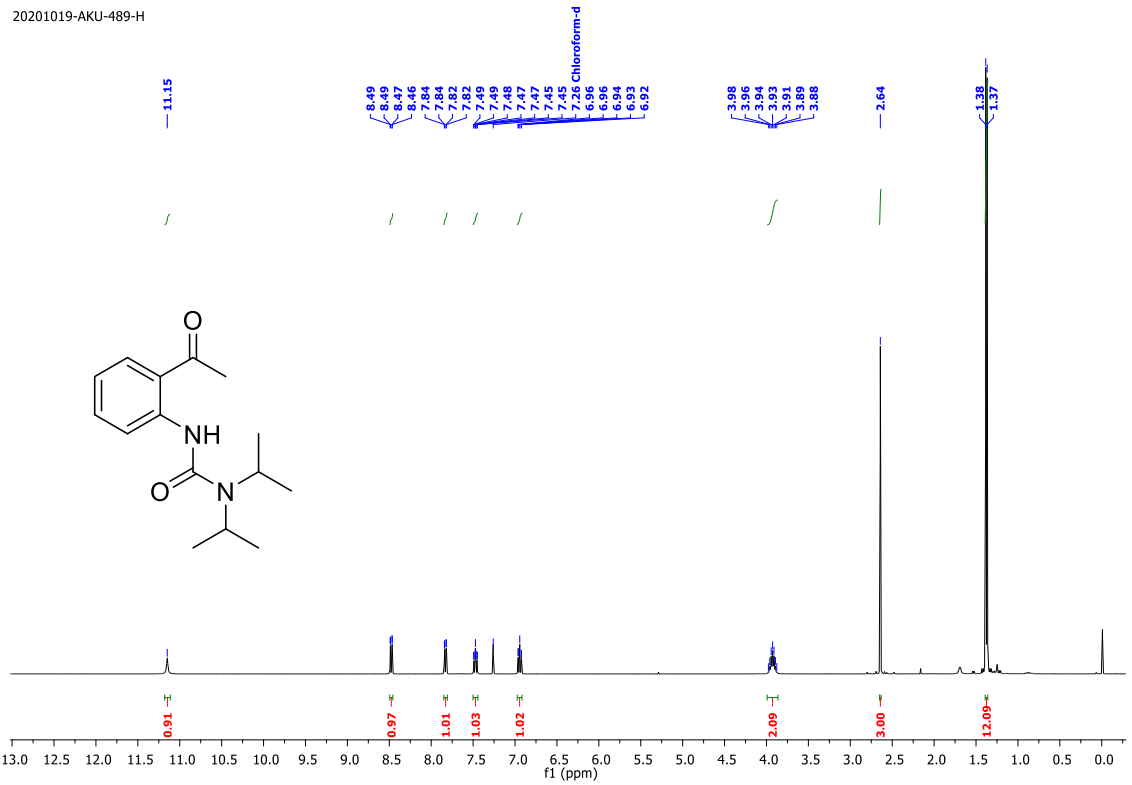


Figure 4.10.7. ^{1}H NMR (400 MHz, $CDCl_3$) of **137b**

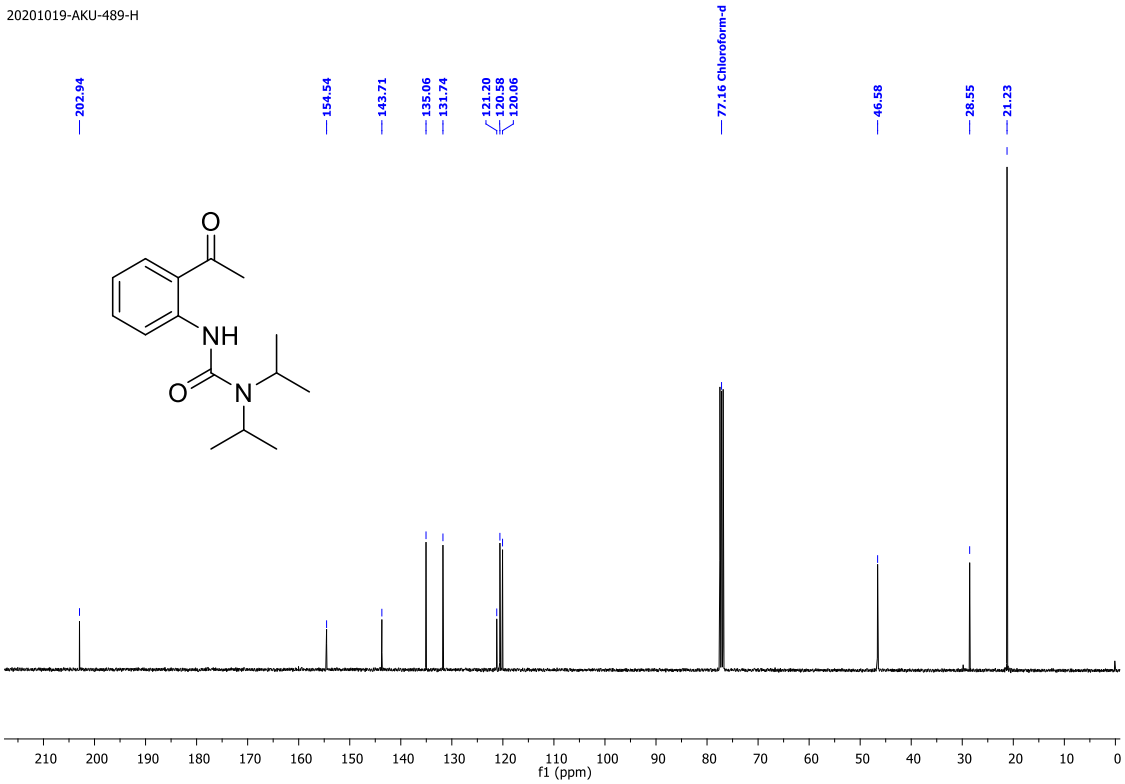


Figure 4.10.8. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) of **137b**

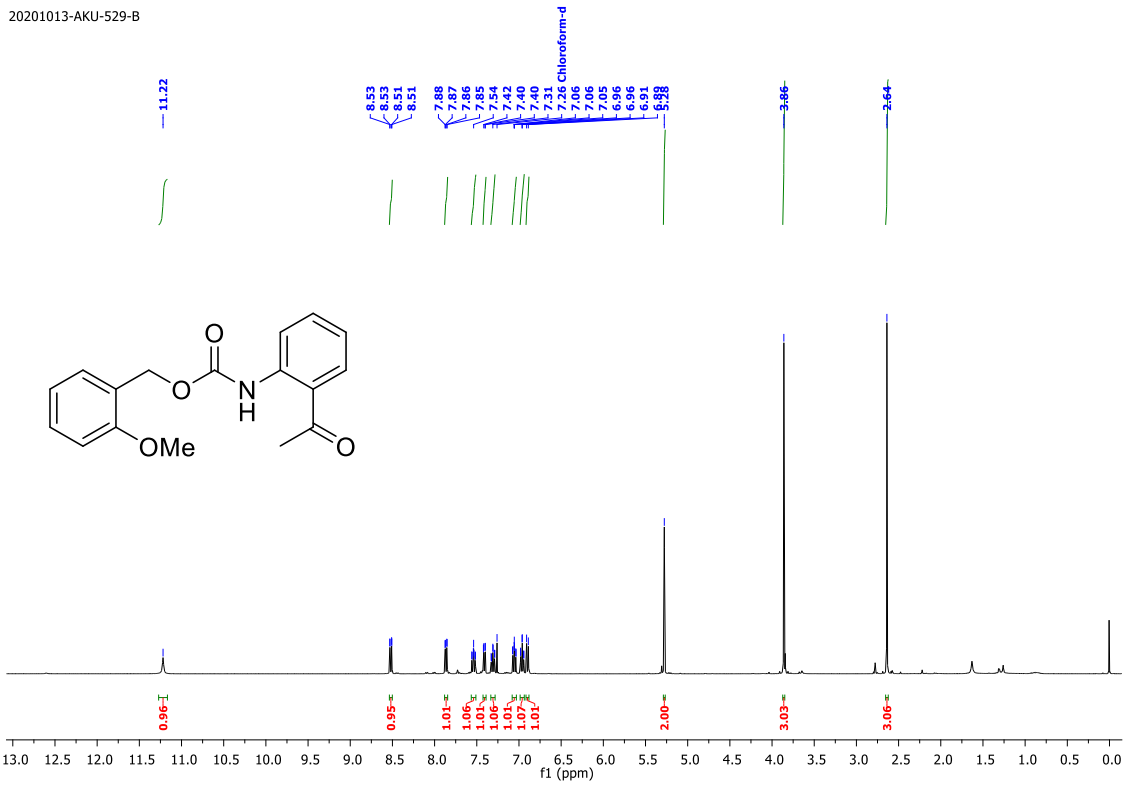


Figure 4.10.9. ^{1}H NMR (400 MHz, $CDCl_3$) of **141**

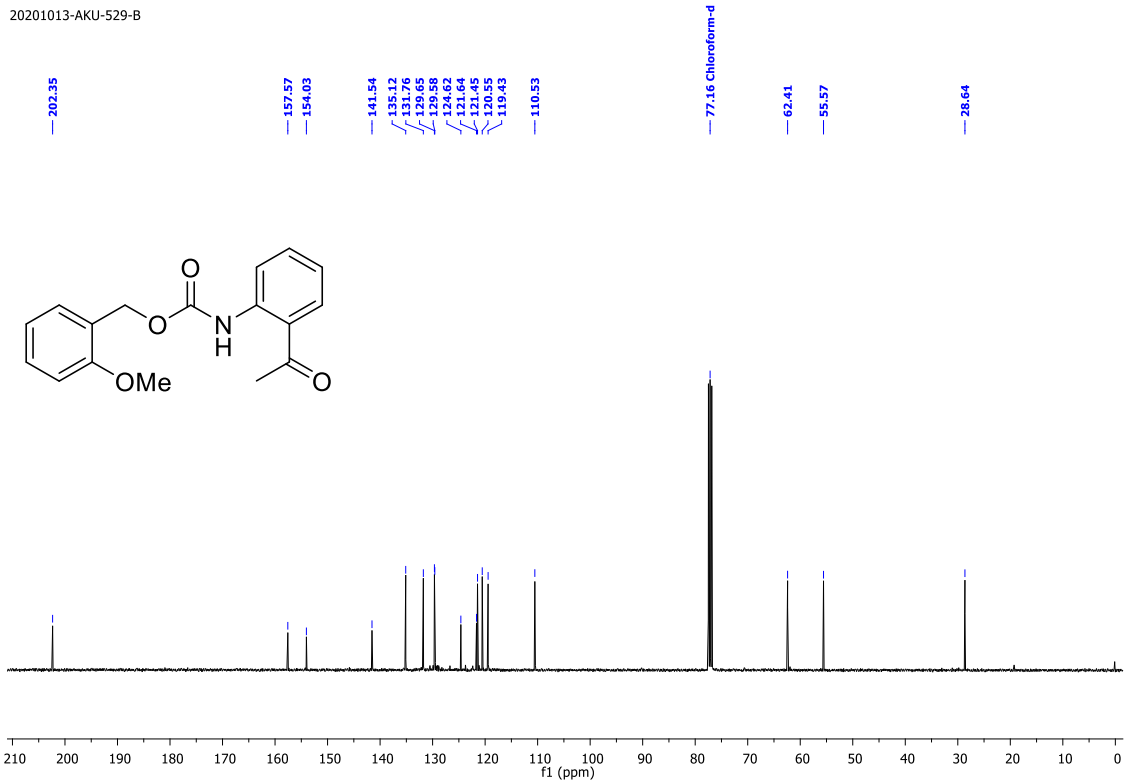


Figure 4.10.10. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) of **141**

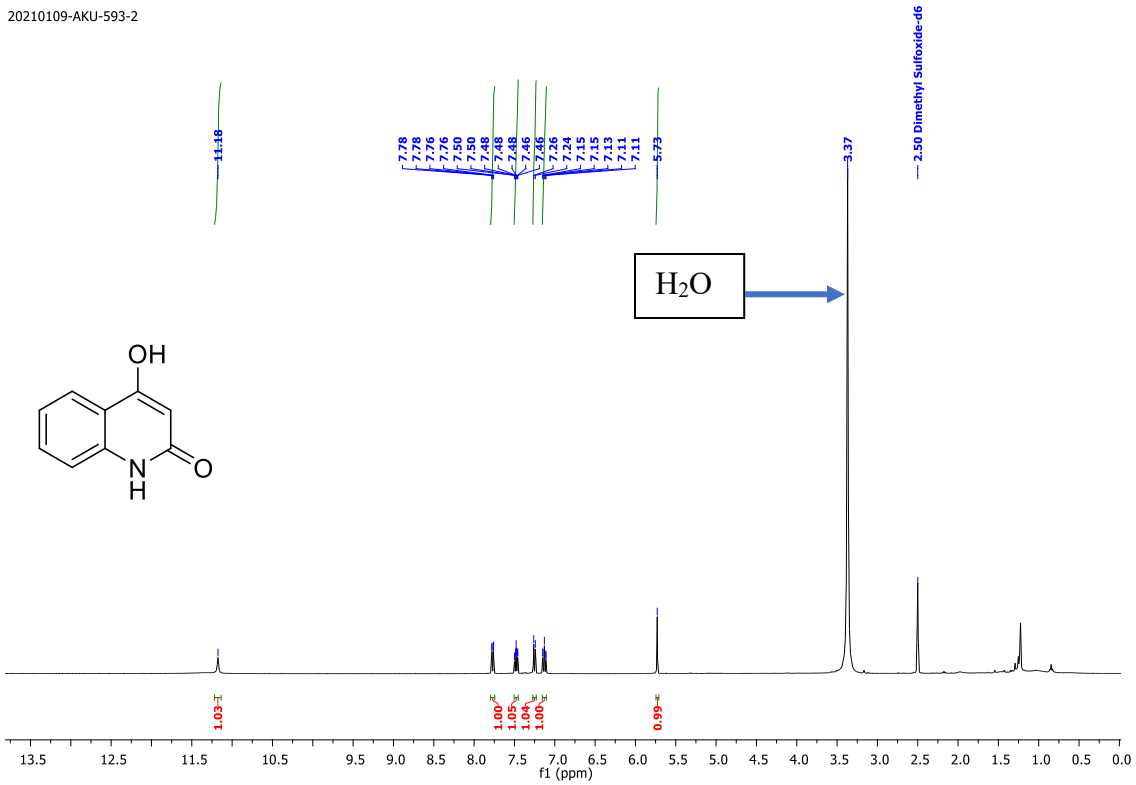


Figure 4.10.11. ^{1}H NMR (400 MHz, DMSO-d$_6$) of **142**

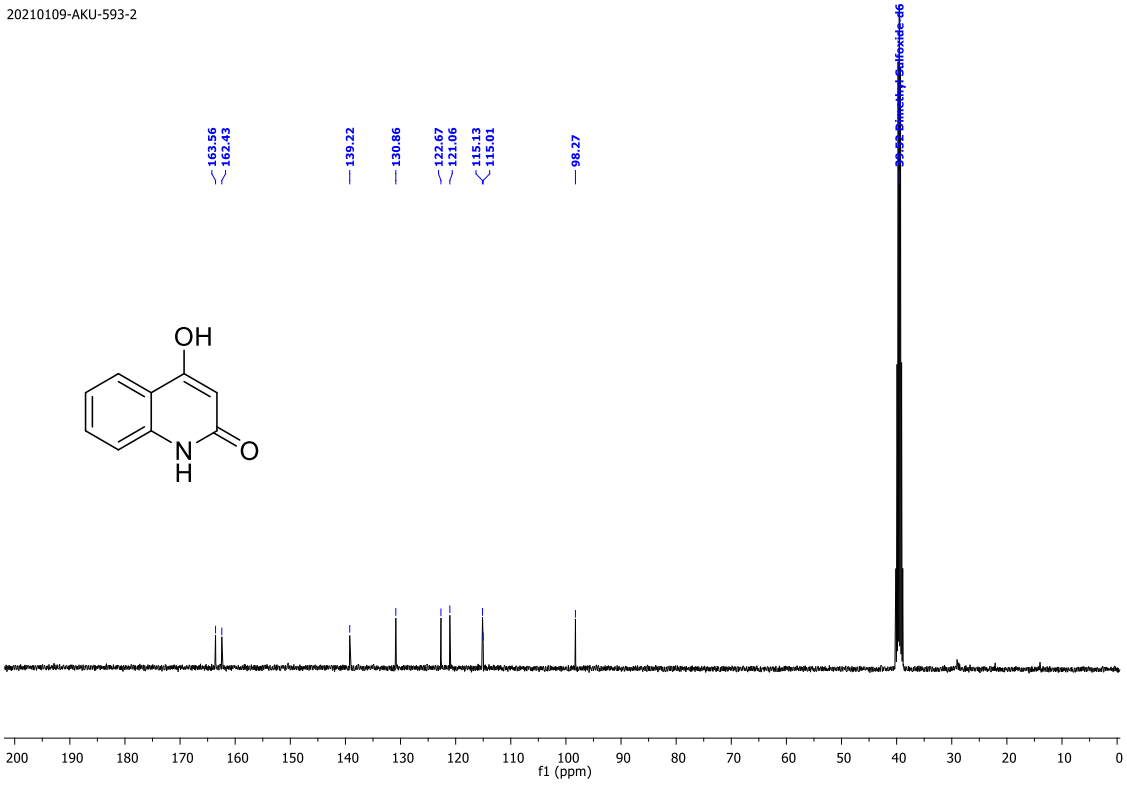


Figure 4.10.12. ^{13}C{^{1}H} NMR (100 MHz, DMSO-d$_6$) of **142**

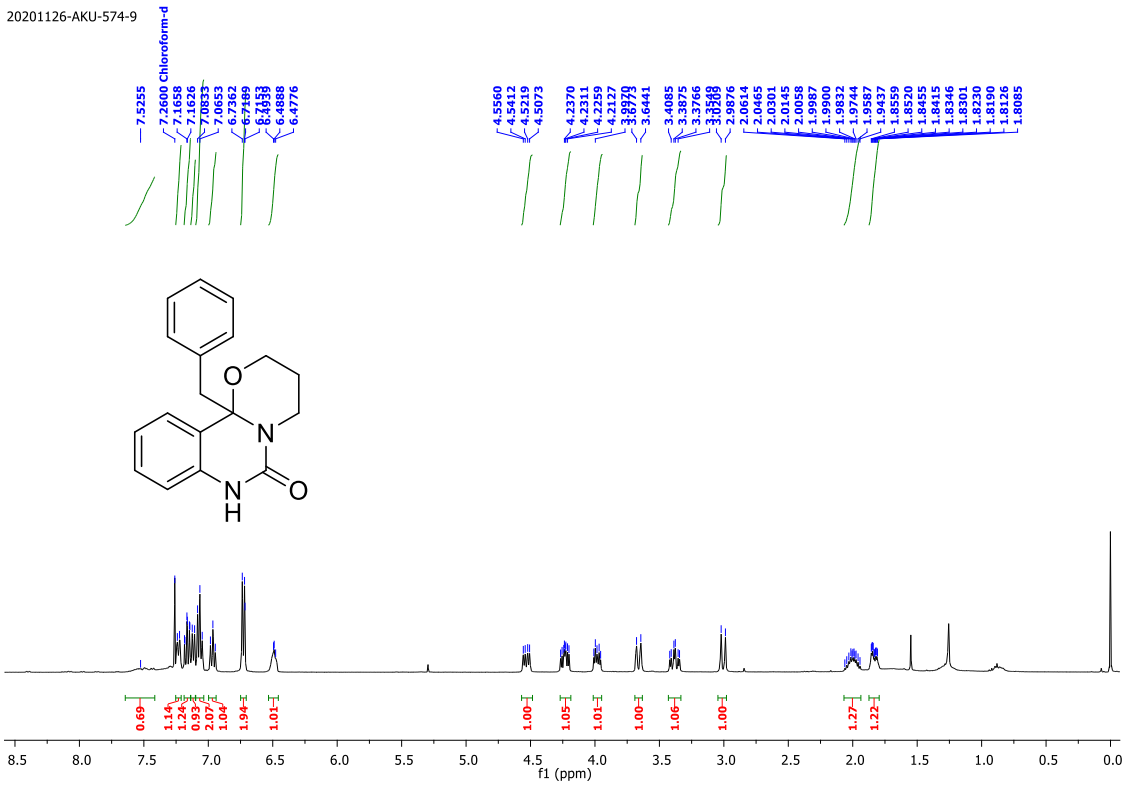


Figure 4.10.13. ^{1}H NMR (400 MHz, $CDCl_3$) of **139f**

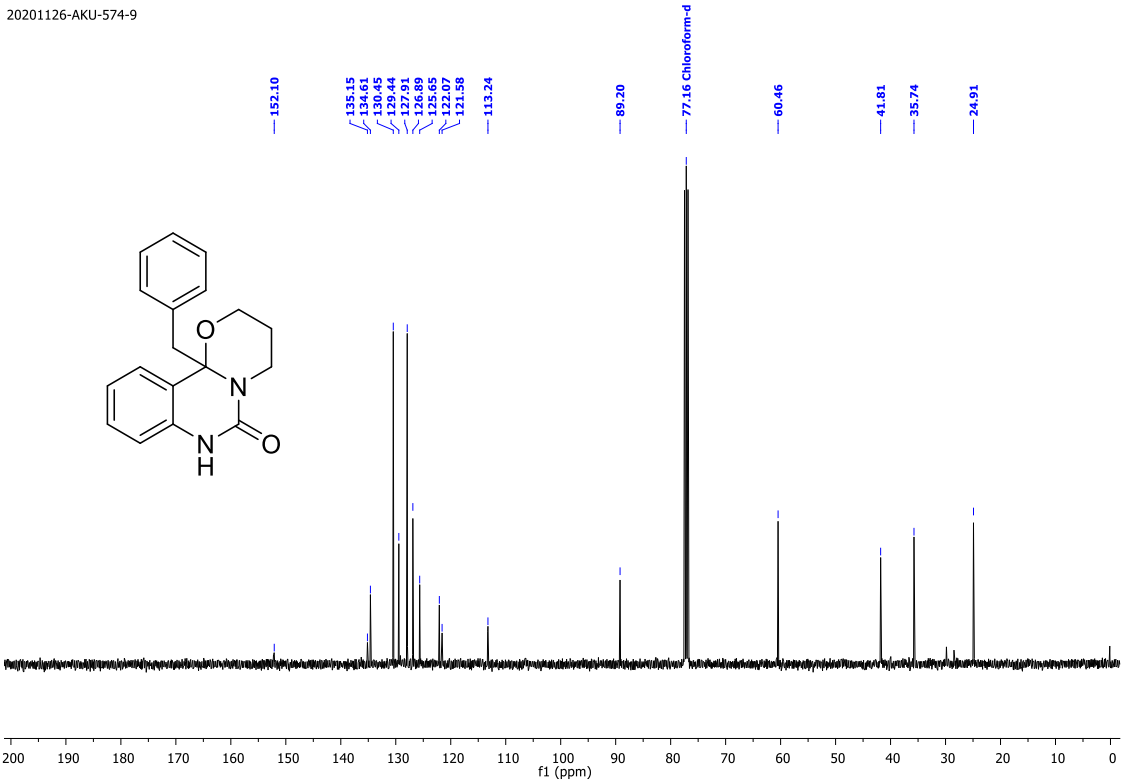


Figure 4.10.14. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) of **139f**

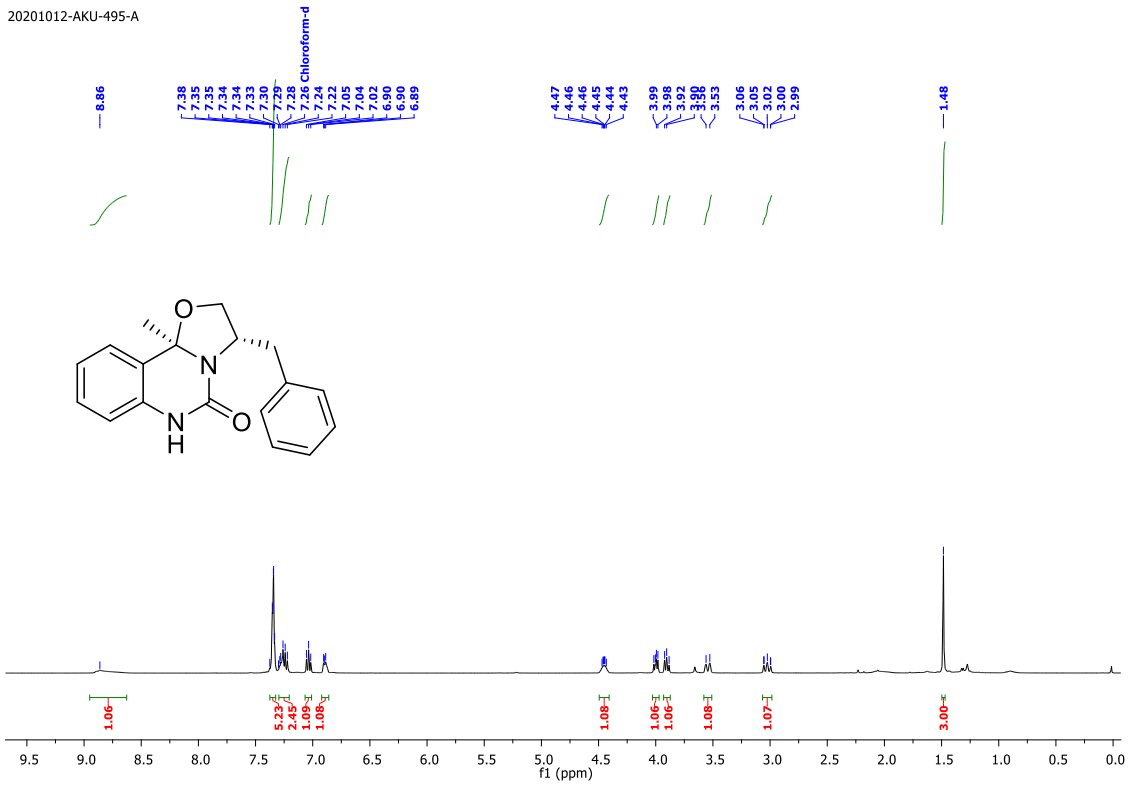


Figure 4.10.15. ^{1}H NMR (400 MHz, $CDCl_3$) of **139j**

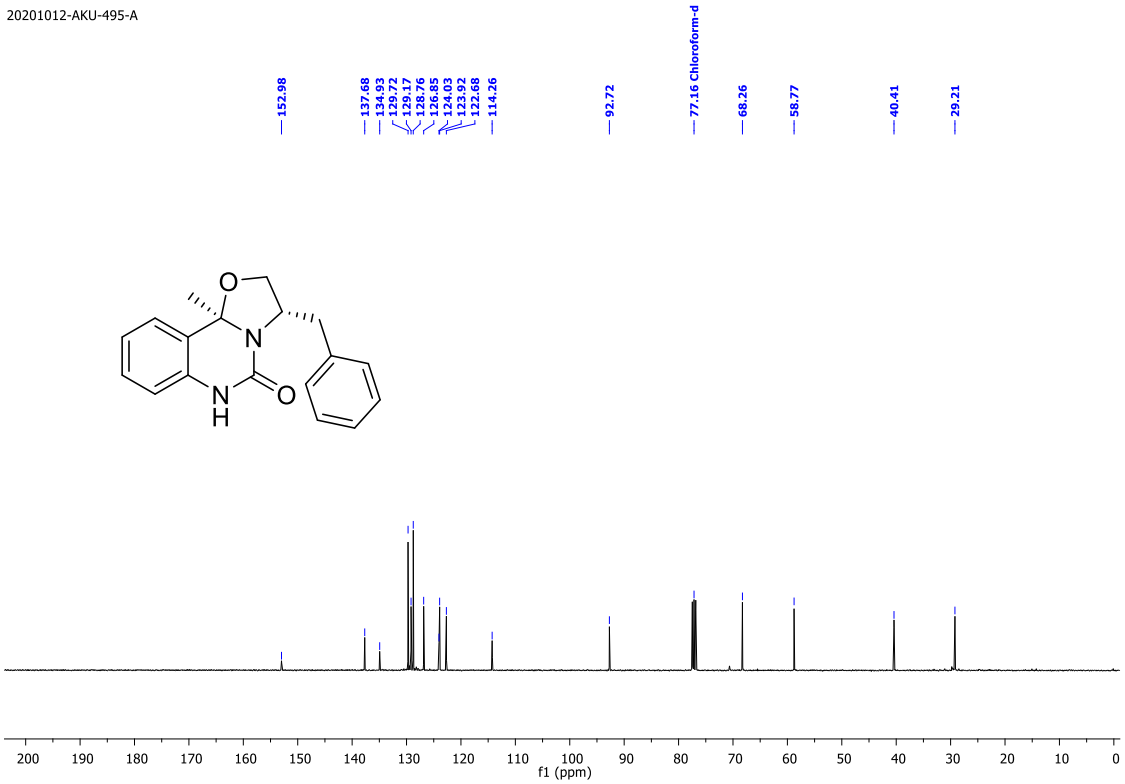


Figure 4.10.16. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) of **139j**

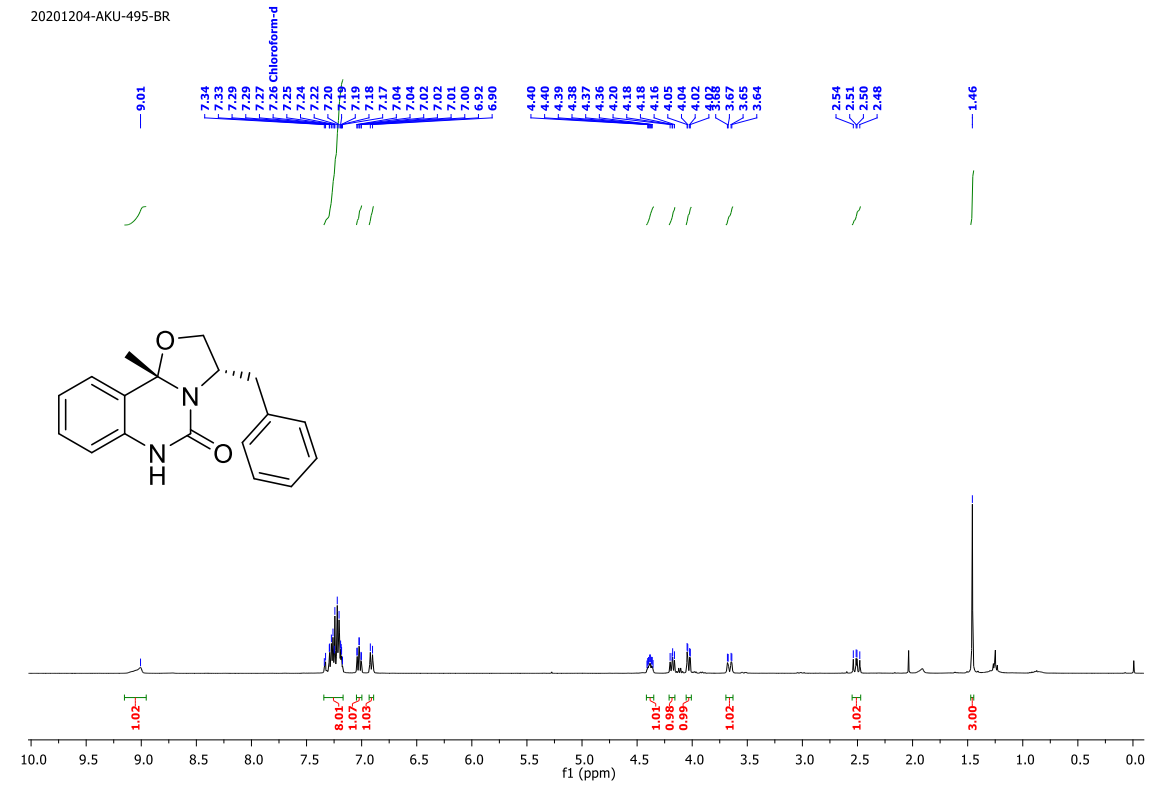


Figure 4.10.17. ^{1}H NMR (400 MHz, $CDCl_3$) of **139j'**

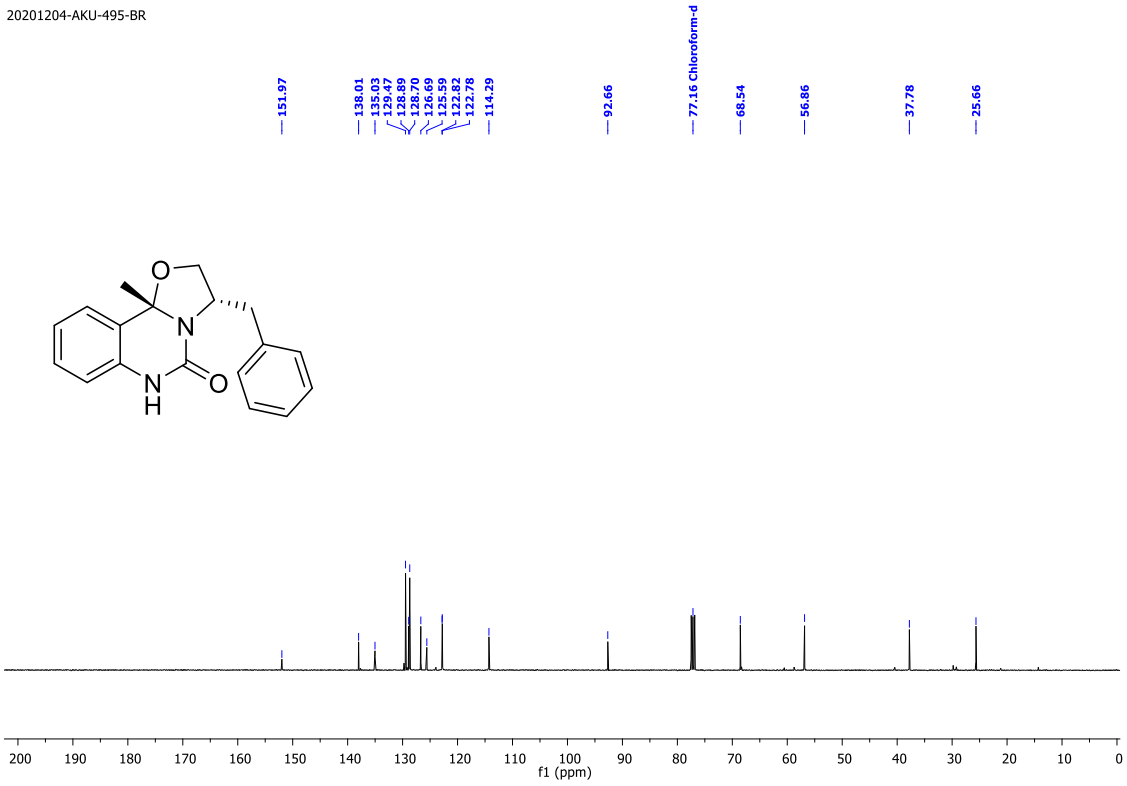


Figure 4.10.18. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) of **139j'**

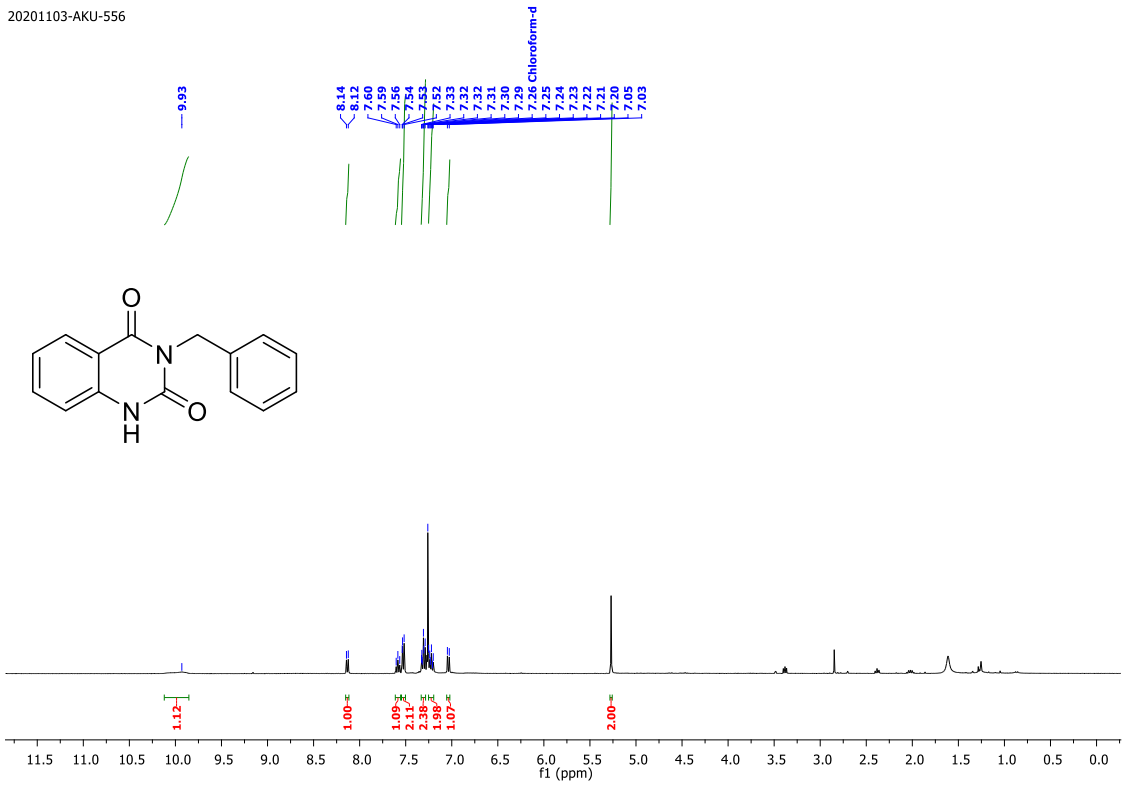


Figure 4.10.19. ^{1}H NMR (400 MHz, $CDCl_3$) of **96a**

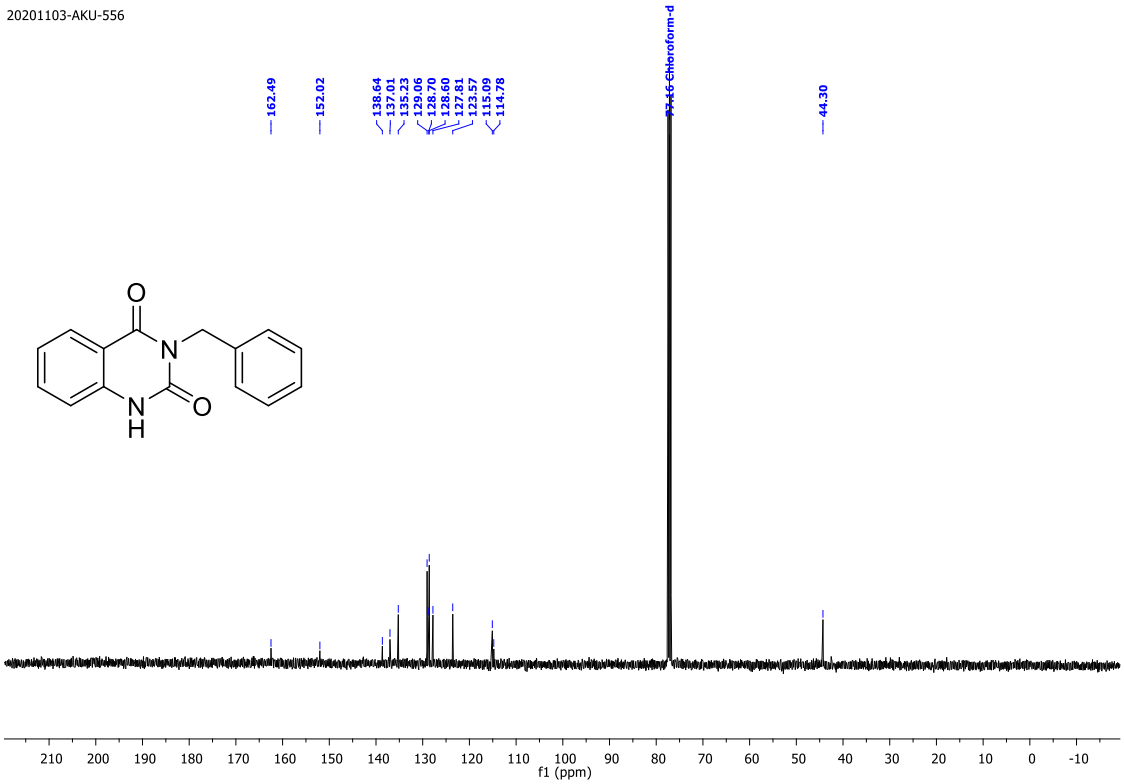
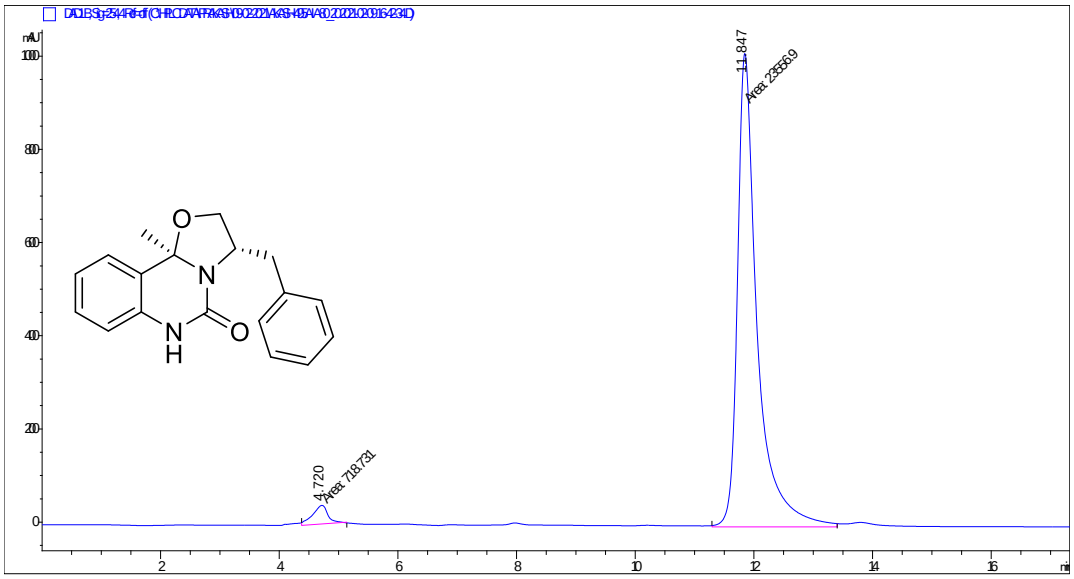


Figure 4.10.20. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) of **96a**

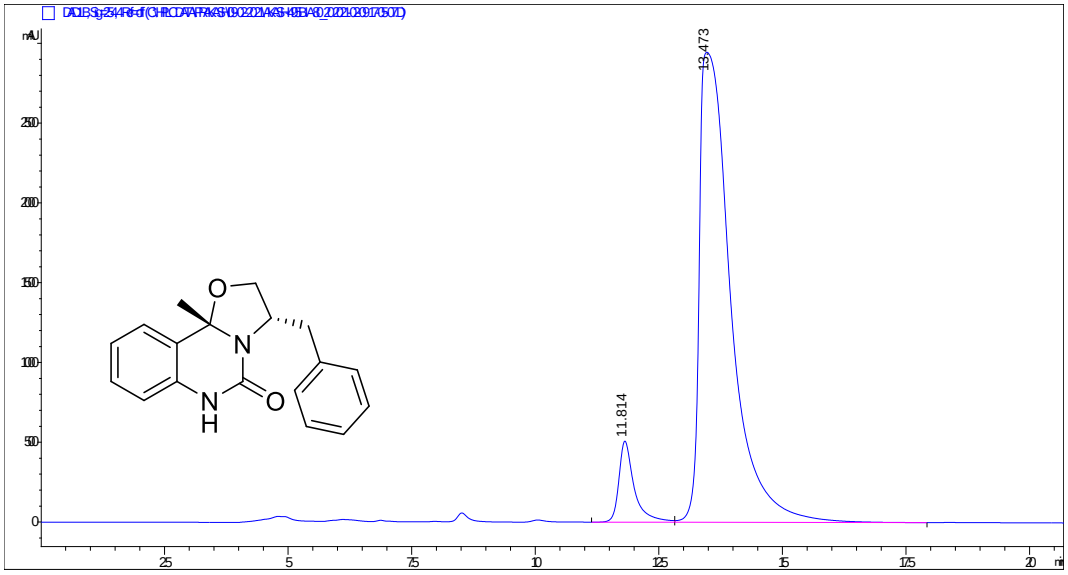
HPLC Chromatograms (**139j** and **139j'**): Column Detail:

Column DAICEL - CHIRALPAK-IA, Dimensions- 4.6 mmϕ X 250 mmL, Particle Size- 5 µm



#	Time	Area	Height	Width	Area%	Symmetry
1	4.72	718.7	39.9	0.2999	2.961	1.577
2	11.847	23556.9	1016.4	0.3863	97.039	0.566

Figure 4.10.21. HPLC Chromatogram of **139j**



#	Time	Area	Height	Width	Area%	Symmetry
1	11.814	10983.4	508.4	0.3141	7.761	0.588
2	13.473	130536.1	2947	0.5728	92.239	0.295

Figure 4.10.22. HPLC Chromatogram of **139j'**

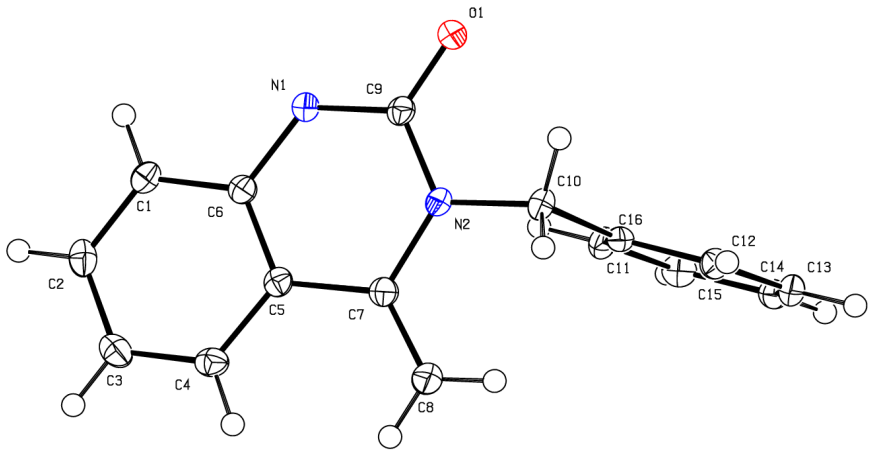


Figure 4.10.23. ORTEP crystal structure of **95b** showing thermal ellipsoids at the 50% probability level**.**

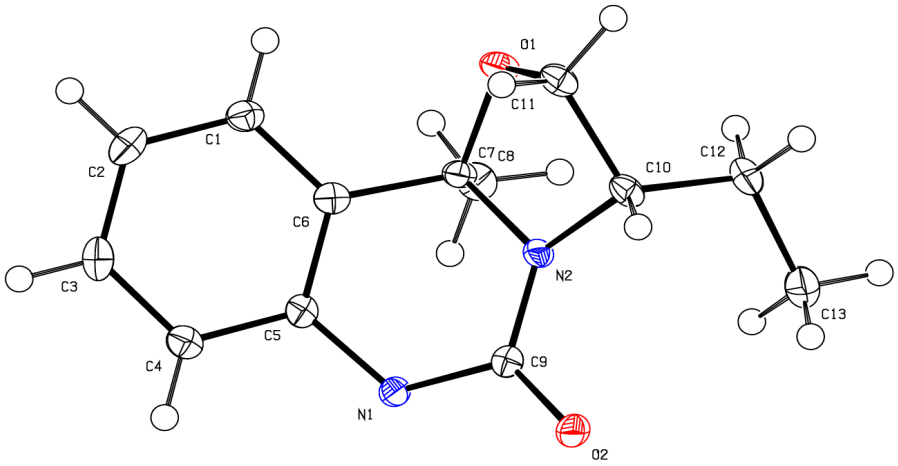


Figure 4.10.24. ORTEP crystal structure of **139h** showing thermal ellipsoids at the 50% probability level.

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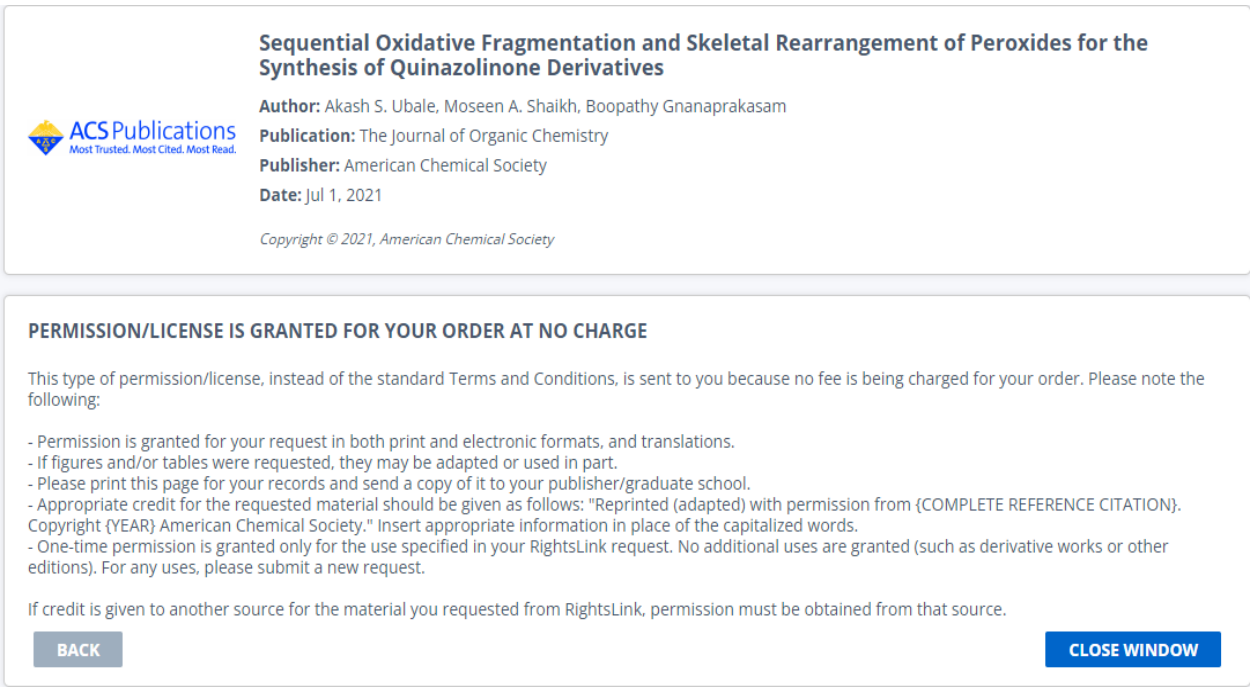

Sequential Oxidative Fragmentation and Skeletal Rearrangement of Peroxides for the Synthesis of Quinazolinone Derivatives

Author: Akash S. Ubale, Moseen A. Shaikh, Boopathy Gnanaprakasam
Publication: The Journal of Organic Chemistry
Publisher: American Chemical Society
Date: Jul 1, 2021

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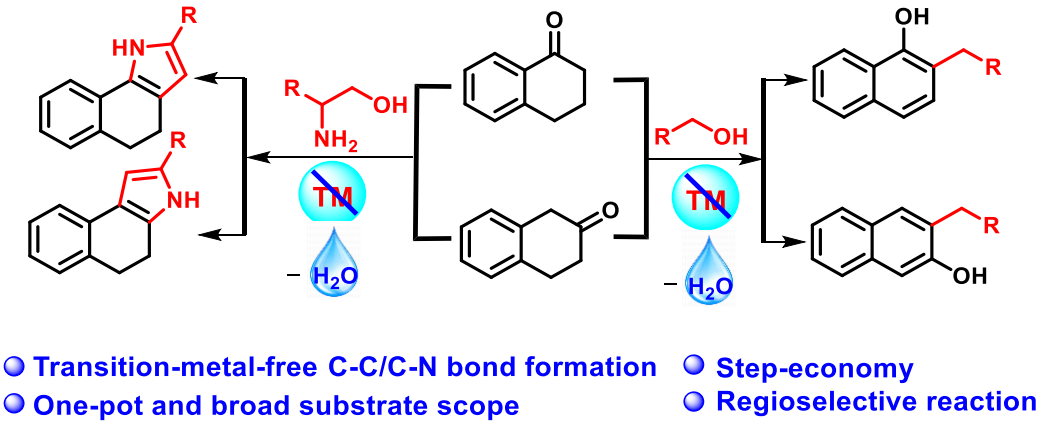
Chapter 5

Transition-Metal-Free Alkylative Aromatization of Tetralone using Alcohol/Amino Alcohol Towards the Synthesis of Bioactive Naphthol and Benzo[*e/g*]indole Derivatives

5. Transition-Metal-Free Alkylative Aromatization of Tetralone using Alcohol/Amino Alcohol Towards the Synthesis of Bioactive Naphthol and Benzo[*e/g*]indole Derivatives

5.1. Abstract

In this chapter, we have shown how tetralone can be alkylated to synthesize naphthols and benzo[*e/g*]indole derivatives using alcohols in the presence of NaOH through an aerobic oxidative cross-coupling protocol. This method is general and applicable for alkylative aromatization without any transition metal, requires an inexpensive base, does not necessitate inert conditions, and produces water alongside hydrogen peroxide as byproducts. Furthermore, this method exhibited a broad substrate scope and yielded regioselectivity.



Scheme 5.1. Present finding alkylative aromatization of tetralone for the synthesis of bioactive naphthols and benzo[*e/g*]indole

5.2. Introduction to the naphthols and benzo[*e*]indoles

The naphthols and benzo[*e*]indoles are important structural motifs in organic chemistry, and they have been discovered in a variety of functionalized molecules, including naturally occurring bioactive compounds.[97,98,114] This type of compound exhibits broad therapeutic applications such as anticancer, antioxidant, antipsoriatic agent and 5-lipoxygenase inhibitor properties, which make it a valuable addition to the field of biology (Figure 5.2.1).[99a-f] Moreover,

functionalized naphthols are useful precursors for the synthesis of chiral binaphthol, which serves as a chiral ligand in asymmetric synthesis.[100] The intense use of this important subunit has led to many methods for its construction.

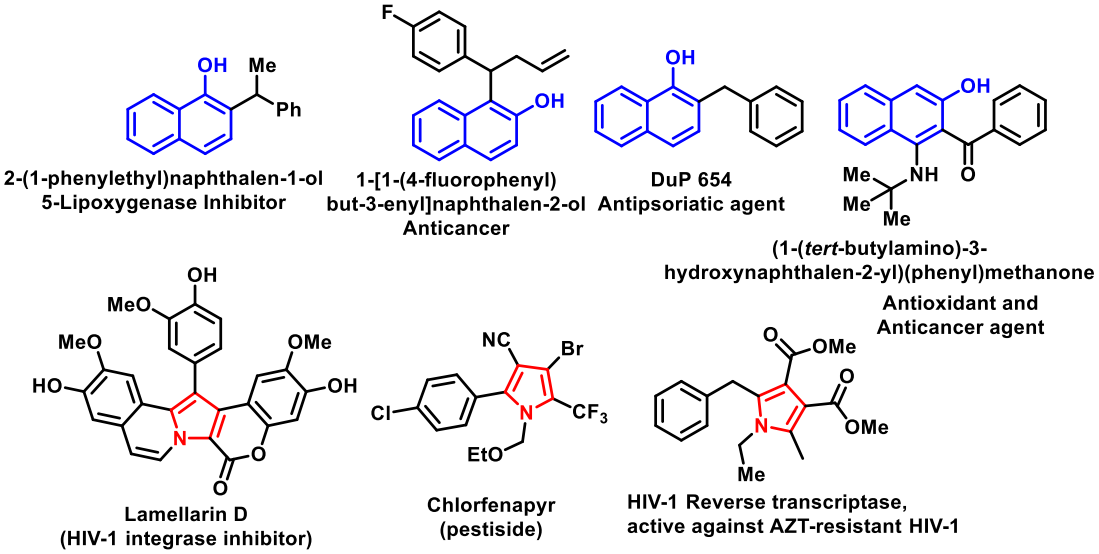
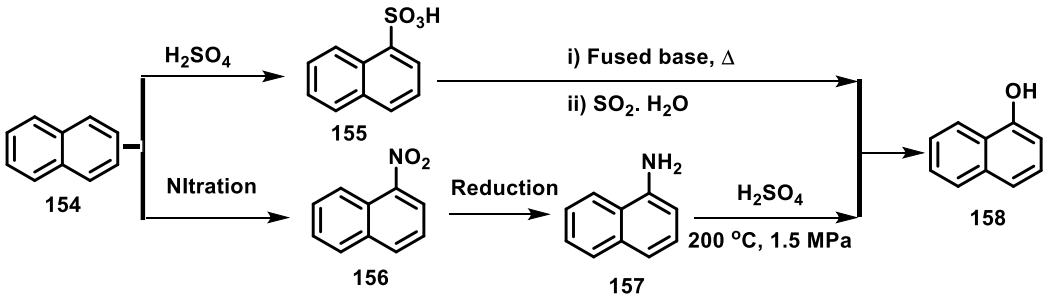


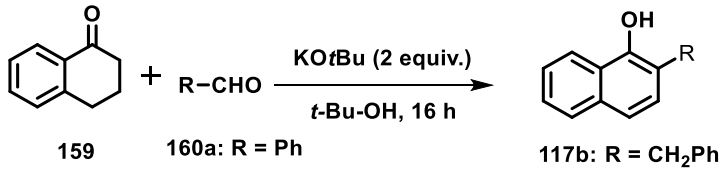
Figure 5.2.1 Naphthol and pyrrole derivatives in bioactive molecules

The common classical processes that are widely used in the industrial-scale synthesis of naphthol derivatives from naphthalene involve multistep reactions such as sulfonation-hydrolysis or nitration-reduction-hydrolysis at extreme temperature and pressure (Scheme 5.2.1.).[101] These approaches are associated with high toxicity, harsh conditions, and large-scale waste generation.



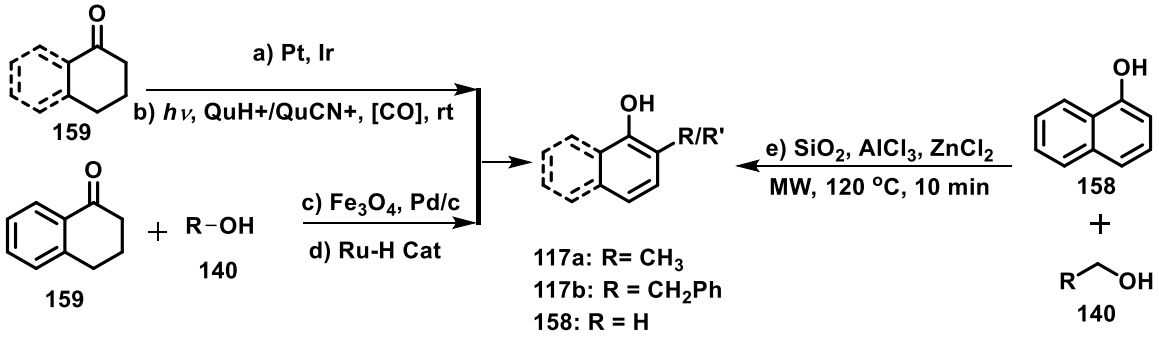
Scheme 5.2.1. The classical approaches for the synthesis of naphthol

Further, several methods were documented in the literature for the synthesis of naphthols. For instance, in 1990, Batt *et al*. reported the base-catalyzed condensation of 1-tetralone **159** with an aromatic aldehyde **160** to afford the benzylidene ketone, which undergoes further isomerization to form the derivative of naphthol.[102]



Scheme 5.2.2. Synthesis of naphthol by Batt research group

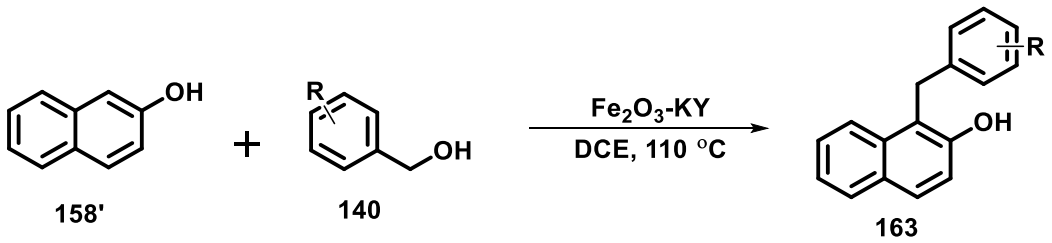
A catalytic olefin-isomerization process was also reported for the synthesis of naphthols by using benzylidene ketone in the presence of Rh and Ir-catalyst along with a strong base.[103] Next, the catalytic dehydrogenation methods have been reported for the synthesis of a variety of substituted phenols and naphthols by using cyclohexanone and tetralone in the presence of Pt and Ir-catalyst (Scheme 5.2.3. (a)).[104]



Scheme 5.2.3. Previous approaches to naphthol derivatives from ketones, tetralones, and naphthol

Recently, He *et al.* reported a photocatalytic dehydrogenative method for α-naphthols **158** from 1-tetralones **159** under ambient conditions (Scheme 5.2.3. (b)).[105] Moreover, 2-methyl-1-tetralone **117a** and 1-naphthol **158** were synthesized from 1-tetralone **159** *via* methylation and dehydrogenation proceeded by modified iron oxide and Pd-supported on activated carbon, at high temperature (Scheme 5.2.3. (c)).[106a] Later, Koltunov *et al*. reported the dehydrogenation of tetralones and tetralin to form naphthols and naphthalene under supercritical (T = 400°C, ρ =0.2 g/cm^3) water.[106b] Recently, the Yi research group established Ru-H catalyzed tandem dehydrogenation-alkylation using tetralone **159** and alcohols **140** at 200 °C (Scheme 5.2.3. (d)).[107] Moreover, this type of catalytic borrowing alkylation strategy has been reported for the synthesis of various annulated heterocycles.[108] The Friedel-Craft alkylation strategy has also been reported for the synthesis of alkylnaphthol derivatives **117b** using naphthol **158** and alcohols **140** in the presence of $ZnCl_2$ and $AlCl_3$ on silica gel under microwave irradiation (Scheme 5.2.3. (e)).[109a]

Recently, Kusum and coworkers reported the selective α-H functionalization of 2-naphthols **158'** with a variety of aromatic primary alcohols **140**, an effective and reusable catalyst is an iron oxide nanocatalyst based on a potassium exchanged zeolite-Y (Fe_2O_3-KY) (Scheme 5.2.4.)[109b]



Scheme 5.2.4. α-H functionalization of 2-naphthols **158'** by Kusum and coworkers group

---

5.3. The rationale of the present work

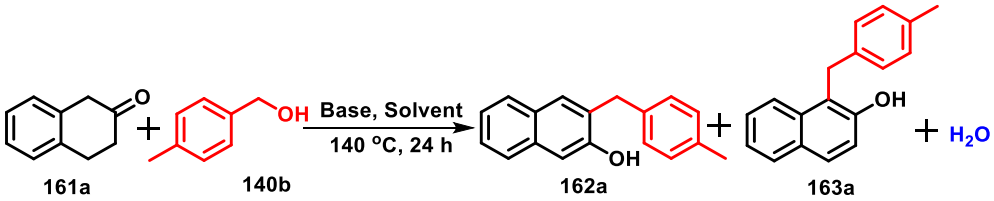
Most of the modern synthetic reactions are catalyzed by a specially designed catalyst and multidentate ligands[110] that require stoichiometric bases for the synthesis of naphthols. These transition metal complexes are typically expensive, less abundant in nature, and much more sensitive to air and moisture. In addition, transition metal residues are difficult to separate from the desired products, which are not suitable for pharmaceuticals. Consequently, various chemical transformations promoted by different bases under transition metal-free conditions have been reported in recent decades.[111] Interestingly, NaOH has been widely used for metal-free coupling reactions of alcohols with ketones.[111a] In addition, KO*t*Bu has been widely used for one-electron transfer reactions and metal-free cross-coupling reactions of aryl halides with arenes.[111b] In this context, we wondered an alternative and efficient transition metal-free synthetic methods for the synthesis of naphthols and benzo[*e/g*]indols derivatives from tetralone using alcohols.

5.4. Results and discussion

In this chapter, we have reported the transition metal-free reaction of tetralones and alcohol/amino alcohol for the synthesis of bioactive naphthol and benzo[*e/g*]indole derivatives promoted by a low-cost base.

5.4.1. Optimization studies

Table 5.4.1. Optimization table for the alkylative aromatization of 2-tetralone[a]



161a 140b 162a 163a

Entry	Base (equiv.)	Solvent	Yield [%][b] (**162a**+**163a**)	Ratio[c] (**162a**:**163a**)
1	-	Toluene	-	-
2[d,e]	NaOH (1)	Toluene	34	25:1
3[e]	NaOH (3)	Toluene	41	50:1
4[e]	NaOH (5)	Toluene	47	50:1
5[f]	NaOH (3)	Toluene	62	100:1
6	NaOH (3)	Toluene	93	100:1
7	NaOH (2)	Toluene	78	100:1
8	NaOH (1)	Toluene	67	100:1
9	NaOH (0.2)	Toluene	26	100:1
10[g]	NaOH (3)	Toluene	82	100:1
11	KO*t*Bu (3)	Toluene	70	20:1
12	KOH (3)	Toluene	65	4:1
13	Cs_2CO_3 (3)	Toluene	35	100:1
14	K_2CO_3 (3)	Toluene	-	-
15	NaOH (3)	1.4-dioxane	86	100:1
16	NaOH (3)	Xylene	81	100:1
17	NaOH (3)	DMF	trace	-
18	NaOH (3)	DMSO/H_2O	-	-
19[h]	NaOH (3)	Toluene	78	100:1

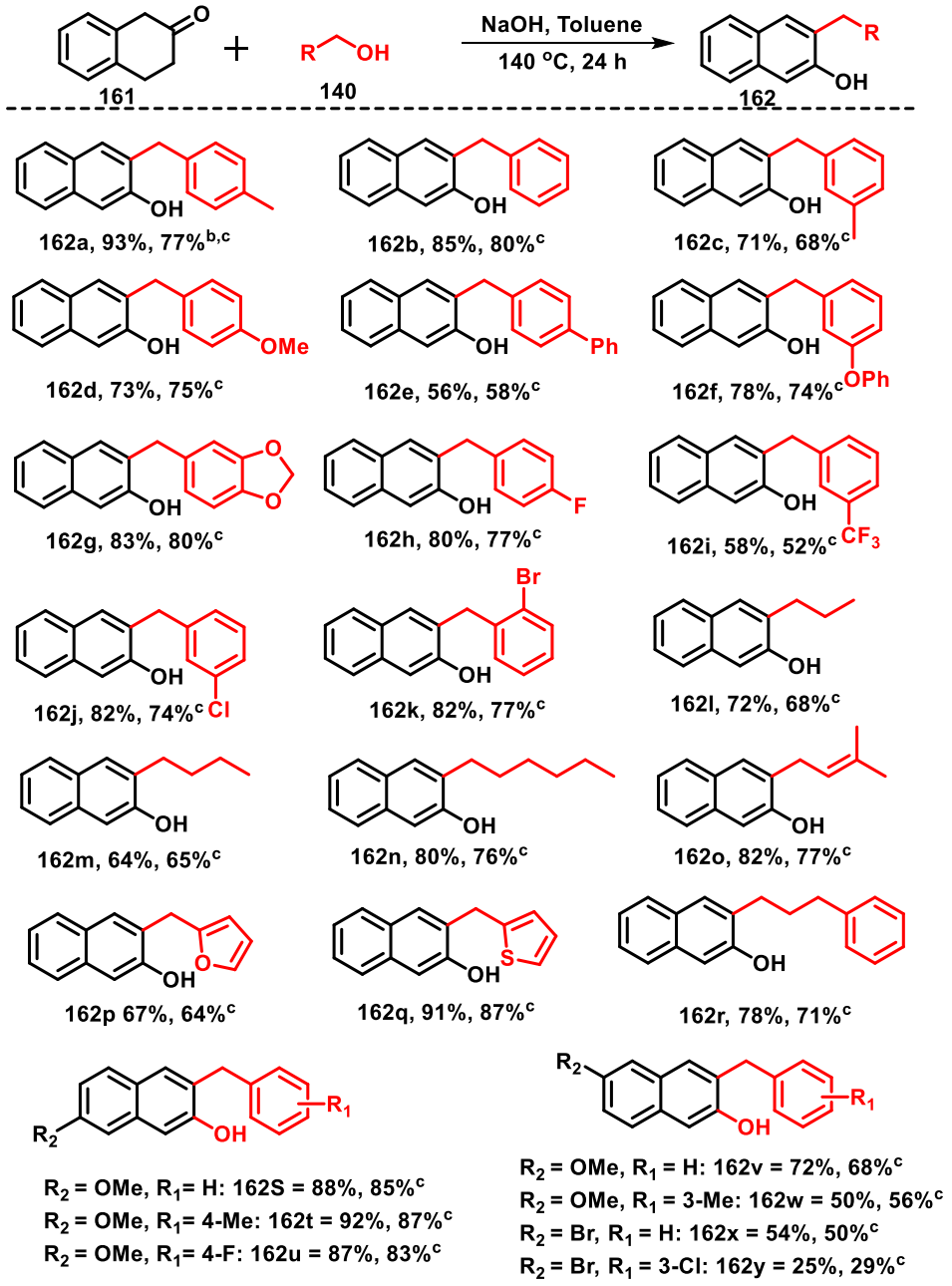
[a]**Reaction condition:** compound **161a** (0.70 mmol), **140b** (0.35 mmol), and solvent (2 mL) were stirred in a preheated oil bath to 140 °C. Base equiv. (see table), [b]isolated yields. [c]ratios **162a/163a** were determined by ^{1}H NMR analysis; [d]with 1 mol% $RuHCl(CO)(PPh_3)_3$. [e]Compound (**161a**:**140b** = 0.35:0.35); [f]compound (**161a**:**140b** = 0.52:0.35); [g]after 16 h; [h]at 120 °C.

To establish a transition-metal-free alkylative aromatization, an initial optimization was performed with 2-tetralone **161a** and **140b**. A control experiment with **161a** and **140b** in the absence of a base at 140 °C in toluene did not give the desired products **162a** and **163a** (Table 5.4.1., entry 1). Next, we performed the reaction of **161a** and **140b** in the presence of 1 mol% $RuHCl(CO)(PPh_3)_3$ and 1 equiv. of NaOH, and 34% of **162a** and **163a** were observed in a 25:1 ratio (Table 5.4.1., entry 2). In the absence of the Ru catalyst, 41% of **162a** and **163a** were observed in a 50:1 ratio (Table 5.4.1., entry 3). We then increased the base equivalent, resulting in a slight increase in yield. The effect of base equivalents for this reaction are summarized in Table 5.4.1. (entries 4-10). In particular, when the equivalent of **161a** was increased (i.e., **161a**:**140b** = 0.70:0.35), a yield of 93% was observed (Table 5.4.1., entry 6). We also studied a number of bases, such as KO*t*Bu, KOH, Cs_2CO_3, and K_2CO_3, for this reaction, and the results are shown in Table 5.4.1. (entries 11-14). From the study of bases, NaOH was found to be the best base for this transformation. Also, different solvents were used to increase the yield of product **162a**, but no improvement was observed (Table 5.4.1., entries 15−18). In the case of DMSO and water, the desired products **162a** and **163a** could not be detected. From these experimental solvent studies, toluene is the best solvent for this conversion. A decrease in yield was observed when the reaction temperature was lowered (Table 5.4.1., entry 19). In addition, hydrogen peroxide and water are by-products of this conversion.

5.4.2. Substrate scope for 3-substituted-2-naphthols and 2-substituted-l-naphthol derivatives

To generalize the substrate scope for 3-substituted 2-naphthol derivatives, the alkylative aromatization of 2-tetralone **161a** with **140b** led to **162a** in 93% yield. A variety of alcohols were satisfactorily reacted with 2-tetralone **161a** to produce the corresponding 3-substituted 2-naphthol derivatives in good to excellent yields (Scheme 5.4.1.). Electron-neutral benzyl alcohol afforded product **162b** in 85% yield. Electron-rich benzyl alcohol gave 56% to 83% yield of products **162c-162g** (Scheme 5.4.1.). Benzyl alcohol having electron-withdrawing substituents such as 4-F, 4-CF_3, 3-Cl, and 2-Br, on the benzene ring gave moderate to good yields of the corresponding products **162h**−**162k** (Scheme 5.4.1.). Fortunately, aliphatic and heteroaryl alcohols were well

tolerated under optimized experimental conditions. Aliphatic alcohols such as propan-1-ol, 1-butanol, 1-hexanol, 3-methyl-2-buten-1-ol, were successfully converted into products **162l-162o** in 64%-82% yields. Next, furfuryl alcohol and 2-thiophenemethanol successfully afforded the

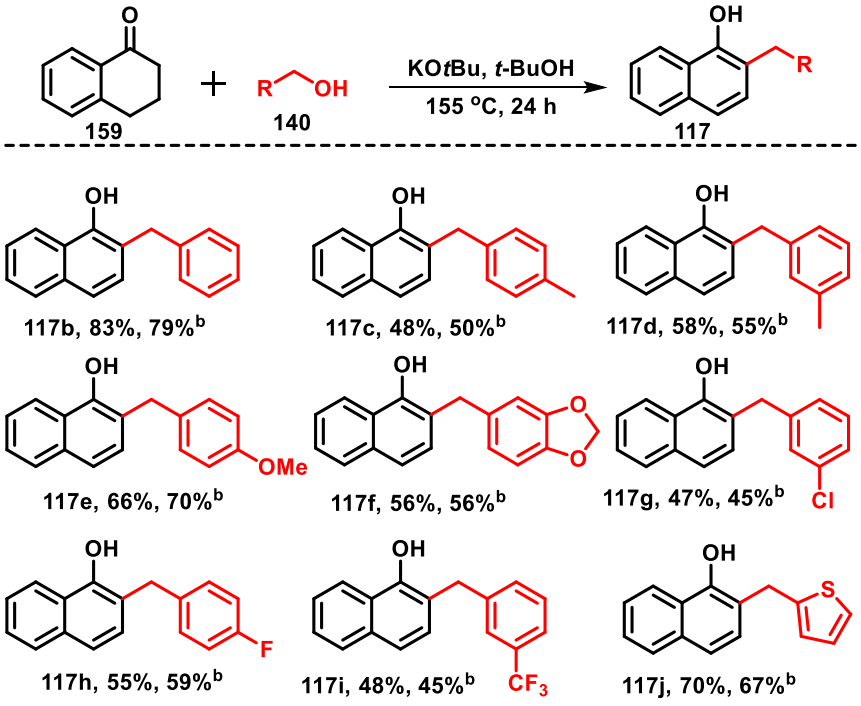


Scheme 5.4.1. Substrate scope for 3-substituted-2-naphthols[a]

[a]**Reaction condition:** compound **161** (0.70 mmol), **140** (0.35 mmol), NaOH (3 equiv.), and toluene (2 mL) were stirred in a preheated oil bath at 140 °C for 24 h. [b]Gram scale, [c]with (1 mmol scale). The mentioned yields are isolated yields.

desired products **162p** and **162q** in 67% and 91% respectively. In particular, 3-phenyl-1-propanol afforded naphthol product **162r** in 78% yield. In addition, the substrate scope is extended to naphthol derivatives with substituents on 2-tetralone **161a** as well as on benzyl alcohol. The reaction of 7-methoxy-2-tetralone, 6-methoxy-2-tetralone, and 6-bromo-2-tetralone with the respective alcohol gave the corresponding products **162s**–**162y** in good to excellent yields (Scheme 5.4.1.). The product **162s** was characterized by spectroscopic techniques and single-crystal XRD (Figure 5.9.17.). We were delighted to observe a gram-scale reaction that produced 77% of product **162a**.

Next, the alkylative aromatization of 1–tetralone **159** with alcohols **140** was investigated (Scheme 5.4.2.). Thus, the reaction of 1-tetralone **159** and benzyl alcohol **140a** under slightly modified standard conditions (**159**:**140**= 0.35:0.70) with *tert*-butyl alcohol as solvent gave the product **117b** in 83% yield. Other electron-rich benzyl alcohols gave **117c**-**117f** in 48% to 66% yields (Scheme 5.4.2.). The electron-withdrawing benzyl alcohol gave the desired products **117g**, **117h**, and **117i** in 47%, 55%, and 48% yields, respectively. 2-Thiophenemethanol afforded product **117j** in 70% yield (Scheme 5.4.2.). All the above reactions were also carried out in 1.0 mmol, and the results are summarized in Scheme 5.4.1. and Scheme 5.4.2.

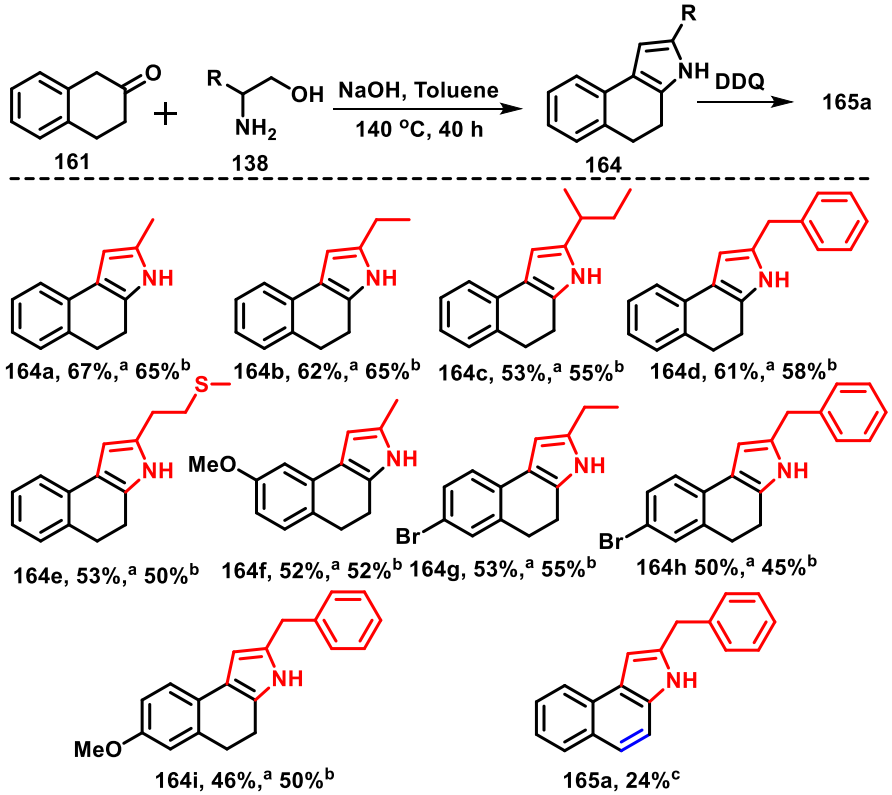


Scheme 5.4.2. Substrate scope for 2-substituted-l-naphthols[a]

[a]**Reaction condition**: compound **159** (0.35 mmol), **140** (0.70 mmol), KO*t*Bu (4 equiv.), and *t*-BuOH (4 mL) were stirred in a preheated oil bath at 155 °C for 24 h. [b]With 1 mmol scale. Isolated yields.

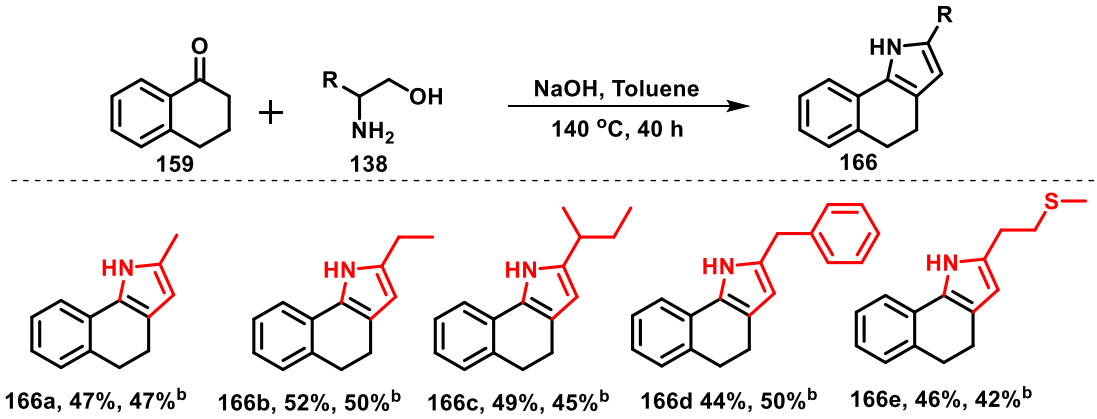
5.4.3. Substrate scope for Benzo[*e*/*g*]indoles derivatives

Subsequently, this concept was extended to the synthesis of benzo[*e*]indole derivatives. Thus, the transition-metal-free reaction of 2-tetralone **161a** and 2-aminopropan-1-ol **138** in the presence of NaOH gave the benzo[*e*]indole derivative **164a** in an isolated yield of 67%. Other amino alcohols also reacted well with this reaction to gave **164b**–**164i** in moderate to good yield (Scheme 5.4.3.). Further oxidation of **164d** with DDQ gave the corresponding product **165a** in 24% yield (Scheme 5.4.3.). Next, the formation of benzo[*g*]indole derivatives from 1-tetralone **159** and amino alcohols **138** also proceeded well to give the desired products **166a-166e** in moderate to good yields (Scheme 5.4.4). In addition, a slight decrease in yield was observed in the 1 mmol scale reaction (Scheme 5.4.3. and Scheme 5.4.4.).



Scheme 5.4.3. Benzo[*e*]indoles from 2-tetralone and amino alcohols[a]

[a]**Reaction condition**: compound **161** (0.70 mmol), **138** (0.35 mmol), NaOH (3 equiv.), and toluene (2 mL) were stirred in a preheated oil bath at 140 °C for 40 h. [b] With 1 mmol scale. [c]DDQ (2 equiv.) The mentioned yields are isolated yields.

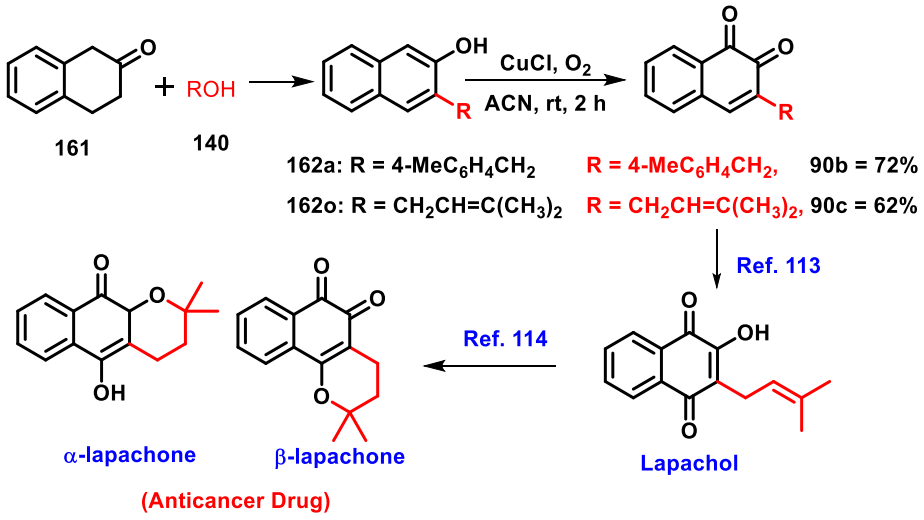


Scheme 5.4.4. Benzo[*g*]indoles from 1-tetralone[a]

[a]**Reaction condition** compound 1**59** (0.35 mmol), **138** (0.70 mmol), NaOH (3 equiv.), and toluene (2 mL) were stirred in a preheated oil bath at 140 °C for 40 h. [b] With 1 mmol scale. The mentioned yields are isolated yields.

Moreover, the synthesized 2-benzyl-3*H*-benzo[*e*]indole **165a** can be used as a valuable precursor for the synthesis of various bioactive molecules.[112]

5.4.4. Synthesis of an *α/β*-lapachone drug intermediate

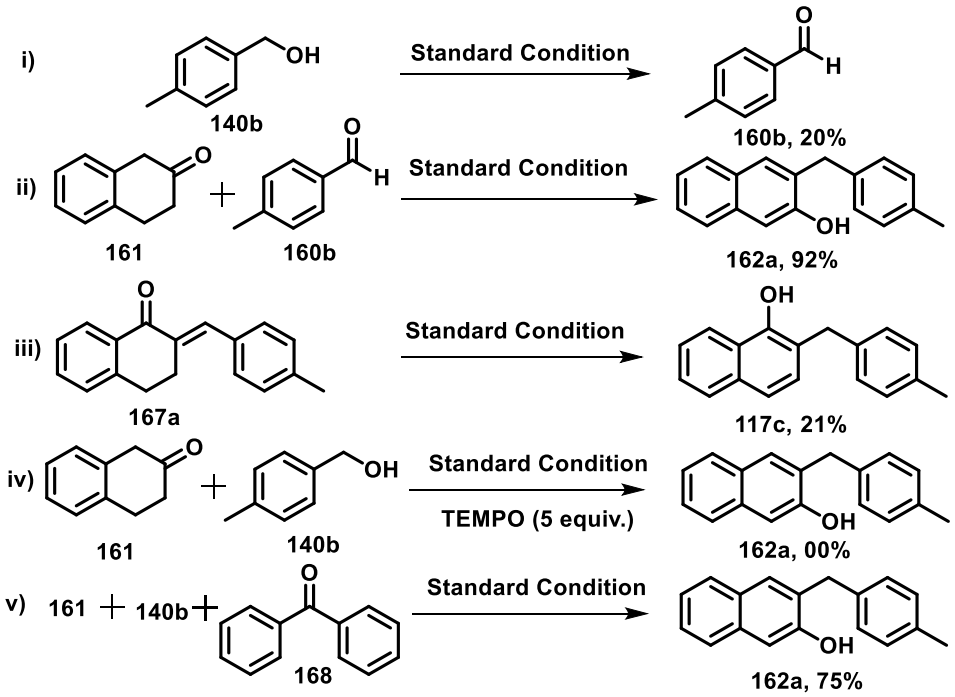


Scheme 5.4.5. Synthesis of *α/β*-lapachone drug intermediate

Next, the use of 3-substituted 2-naphthol derivatives for the synthesis of the important intermediate naphthalene-1,2-dione by an oxidation reaction was investigated. This oxidation was carried out by using **162a** and **162o** with CuCl as a catalyst and an oxygen balloon.[113]After completion of the reaction, the corresponding products **90b** and **90c** were isolated in 72% and 62% yields, respectively (Scheme 5.4.5.). Moreover, the synthesized naphthalene-1,2-diones can be used as valuable precursors for the synthesis of *α/β*-lapachone drug.[114]

5.5. Mechanistic investigations

To understand the reaction pathway, a series of control experiments were performed (Scheme 5.5.1.). In the absence of tetralone, 4-methylbenzyl alcohol **140b** gave methylbenzaldehyde **160b** (Scheme 5.5.1. (i)).[111a]



Scheme 5.5.1 Control experiments for mechanistic studies

Reaction of 2-tetralone **161a** with 4-methylbenzaldehyde **160b** gave **162a** in 92% yield under optimized reaction conditions (Scheme 5.5.1. (ii)).[102] This experiment suggests that oxidation of the alcohol to aldehyde was a crucial step for this transformation. To identify the intermediate of this reaction, benzylidene **167** was subjected to the standard reaction conditions and gave product **162a** in 20% yield (Scheme 5.5.1. (iii)).[103] This experiment confirmed the *in-situ* generation of benzylidene **167a** as an intermediate during this reaction.[111c] Furthermore, we hypothesized that NaOH-mediated deprotonated isomerization of benzylidene **167a** leads to

aromatization and formation of product **117c**. To prove the presence of a radical pathway for the oxidation of the alcohol, the reaction was carried out in the presence of the radical scavenger TEMPO, and no product **162a** was detected. The absence of product **162a** indicates the radical nature of the reaction (Scheme 5.5.1. (iv)). The reaction of tetralone **161a**, alcohol **140b**, and benzophenone **168** under optimized conditions did not give benzhydrol, indicating that this reaction did not proceed by Oppernauer-type oxidation (Scheme 5.5.1. (v)).

5.5.1. Detection of imines intermediate using HRMS

To determine the reaction intermediate of transition metal-free oxidation-condensation-isomerization-aromatization reaction, we performed the HRMS analysis experiment.

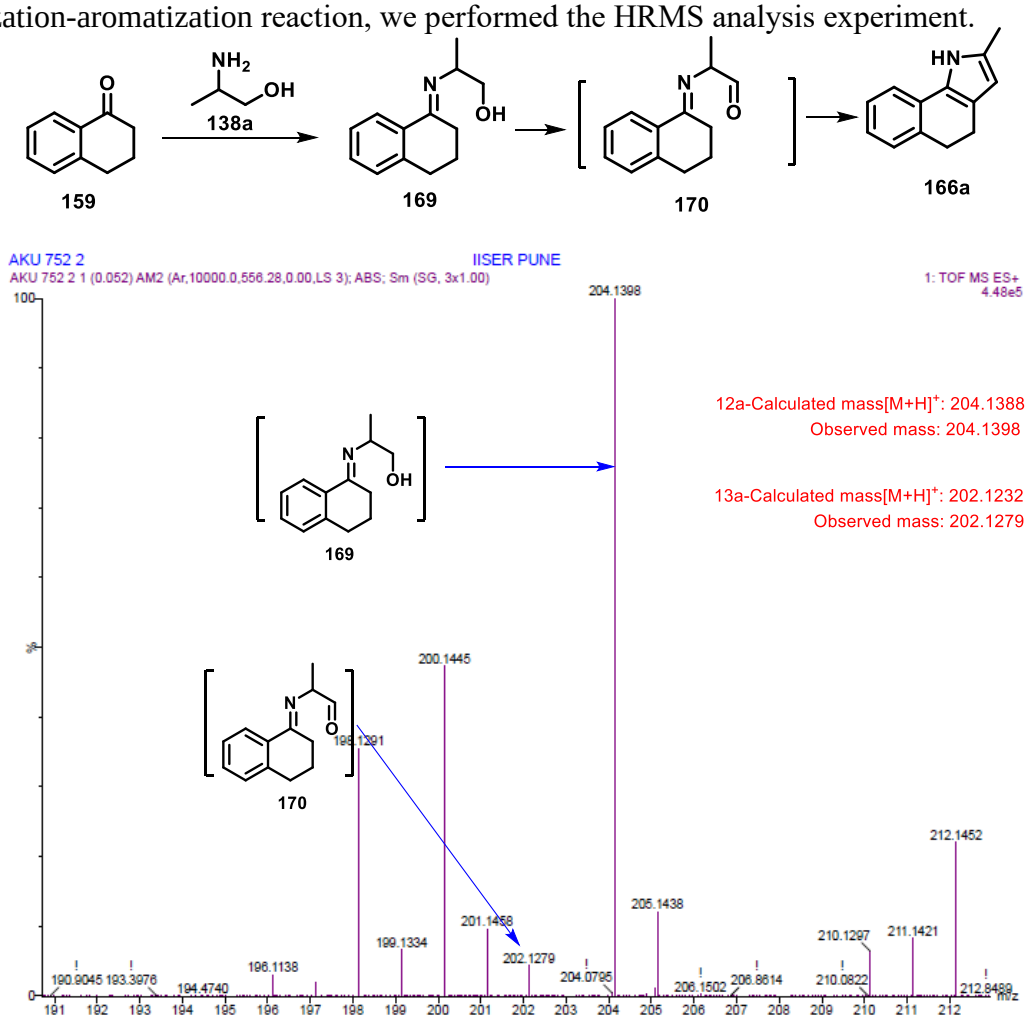


Figure 5.5.1. Detection of the intermediate **169** and **170** by HRMS analysis

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NaOH (42 mg, 1.05 mmol, 3 equiv.), α-tetralone compound **159** (0.35 mmol, 1 equiv.), and amino alcohol **138a** (0.35 mmol, 1 equiv.) in toluene (2 mL) were added to a resealable 20-

mL vial. Later, the tube was sealed with a cap using a crimper. The reaction mixture was stirred for 3 h at 140 °C in a preheated oil bath. After 3 h, the reaction mixture was injected into the HRMS instrument. The presence of m/z = 204.1398 and m/z = 202.1979 corresponds to intermediates **169** and **170**, respectively (Figure 5.5.1.).

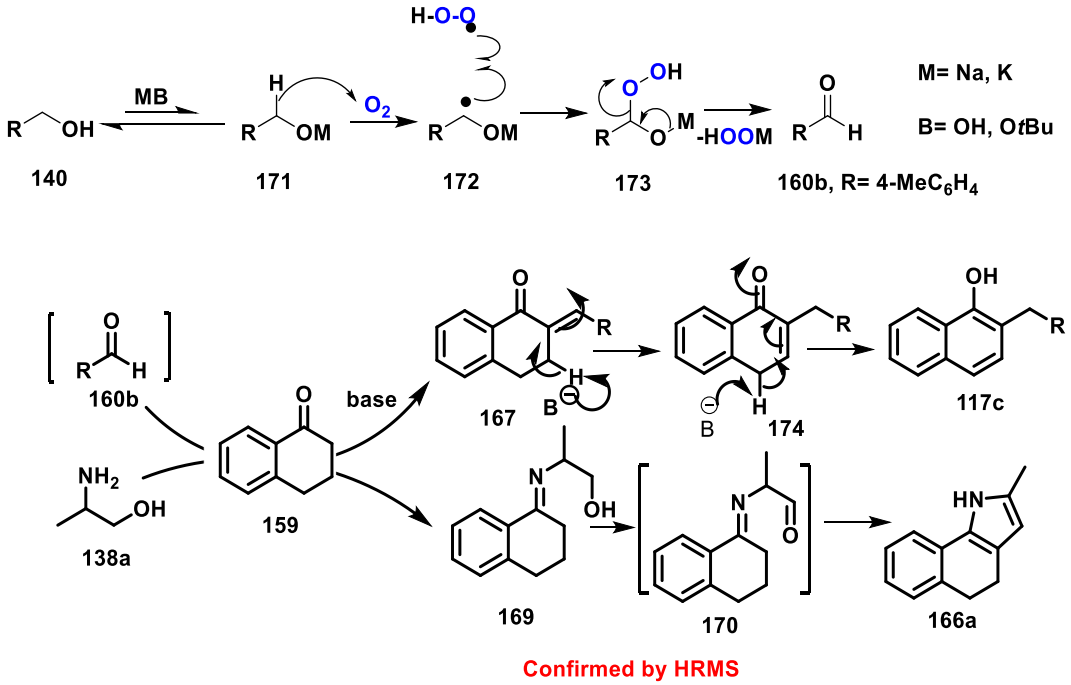
5.5.2. MP-AES (Microwave Plasma Atomic Emission Spectroscopy) analysis:

Ag	Co	Cu	Ni	Fe	Mn	Ru
Not detected	-0.01u (ppm)	0.04 ppm	0.10 ppm	0.23 ppm	Not detected	0.06 ppm

To determine the content of trace metals in the base, we performed the MP-AES (Microwave Plasma Atomic Emission Spectroscopy) analysis. The analysis was performed to determine the trace metal content and indicates that all metals are < 0.1 ppm or ~ 0.23 ppm. In addition, we confirmed our established reaction conditions in a new resealable 20-mL vial, and to our delight, we obtained the same results as before. These results indicate that the synthesis of bioactive naphthol and benzo[*e/g*]indole derivatives was promoted by the base itself rather than by contamination with trace metals.

5.6. Plausible Mechanism

Based on experimental observations and literature examples,[111a-e] we proposed a possible mechanism for the transition metal-free reaction (Scheme 5.6.1.). First, the aerobic oxidation of alcohols was carried out in the presence of the base.[111d] Then the alcohol **140b** was in equilibrium with the corresponding Na/K alkoxide **171**. The alkoxide anion facilitated the abstraction of the oxygen-bonded α-CH from **171** by O_2 to form a carbon-centered radical **172** and a hydrogen peroxide radical. The combination of these two radicals led to the formation of intermediate **173**, and the elimination of HOOM from **173** gave the aldehyde **160b**. Subsequently, the aldehyde condenses with tetralone in the presence of a base to give the intermediate **167** by aldol condensation. After the isomerization of benzylidene **167**, product **117c** is formed.[103,111c] In the case of product **166a**, the reaction of aminoalcohol **138a** and 1-tetralone **159** leads to the formation of imine as the starting intermediate **169**. Subsequently, imine **169** oxidizes the alcohol by a base to form **170**,[111d.e,] which was confirmed by HRMS (Figure 5.5.1). Finally, **170** allows intramolecular aldol condensation to form **166a** (Scheme 5.6.1.).



Scheme 5.6.1. Plausible mechanism for the alkylative aromatization under basic condition

5.7. Conclusion

In summary, in this chapter, we have described the transition metal-free oxidation-condensation-isomerization-aromatization method for the synthesis of bioactive naphthol and benzo[*e*/*g*]indole derivatives. This method is sequential, regioselective, and occurred with inexpensive benchtop NaOH and KO*t*Bu bases and using environmentally friendly alcohol as an alkylating reagent, This approach avoided halogenated reagents and provided water and hydrogen peroxide as by-products. All the naphthols and benzo[*e*/*g*]indoles demonstrated broad substrate scope with good to excellent yields. Moreover, an α/β-lapachone drug could be achieved using this protocol. Finally, based on preliminary experimental results and previous literature studies, a plausible mechanism was proposed for the alkylative aromatization of tetralone.

5.8. Experimental section and characterization data

5.8.1. General information and data collection.

The *α*-tetralone (**159**), *β*-tetralone (**161a**), alcohol (**140**), amino alcohol (**138**), KO*t*Bu, and NaOH were purchased from Sigma-Aldrich or Alfa-Aesar. All the solvents used in the reactions were dry grade. The column chromatographic separation separations were achieved over 100-200 mesh size silica-gel. Visualization completed with UV light, PMA, and CAM stain goes along

with heating. By using a Bruker or JEOL spectrometer, the ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded at 400 and 100 MHz, respectively. The values of the coupling constant (*J*) and chemical shift (δ) are expressed in hertz (Hz) and parts per million (ppm), respectively. Brief information used in NMR follow-up experiments: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad; ddd, doublet of doublets of doublets. High-Resolution Mass Spectra were recorded by waters-synapt G2 applying electrospray ionization (ESI-TOF). Infrared (ATR) spectra were obtained with a Bruker Alpha-E infrared spectrometer. The melting point was measured using the BUCHI M-560 melting-point instrument. All melting points were measured in an open glass capillary tube. Single-crystal diffraction analysis data were collected at 100 K with a Bruker Kappa Apex IIICCD Duo diffractometer (operated at 1500 W power: 50 kV, 30 mA) using graphite monochromatic Mo Kα radiation. More information on crystal structures (**162s**) can also be obtained from the Cambridge Crystallographic Data Centre (CCDC) *via* deposition number 2150250.

5.8.2. Experimental procedure

A. General experimental procedure for the synthesis of 3-substituted-2-naphthol derivatives.

In a 20 mL re-sealable vial were added NaOH (42 mg, 1.05 mmol, 3 equiv.), 2-tetralone compound **161** (0.70 mmol, 2 equiv.), and alcohol **140** (0.35 mmol, 1 equiv.) in toluene (2 mL). Further, the tube was sealed with a cap using a crimper. The reaction mixture was stirred at 140 °C for 24 h in a preheated oil bath. After completion of the reaction, 1 mL of 1 M HCl solution was added, and the resulting mixture was extracted with ethyl acetate two times using 10 mL of solvent each time. The organic layers were combined and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by using silica gel column chromatography (EtOAc:*n*-hexane =10:90).

A'. General experimental procedure for the synthesis of 3-substituted-2-naphthol derivatives on a (1.0 mmol) scale.

In a 20 mL re-sealable vial were added NaOH (120 mg, 3 mmol, 3 equiv.), 2-tetralone compound **161** (2 mmol, 2 equiv.), and alcohol **140** (1 mmol, 1 equiv.) in toluene (3 mL). Further, the tube was sealed with a cap using a crimper. The reaction mixture was stirred at 140 °C for 24 h in a preheated oil bath. After completion of the reaction, 2 mL of 1 M HCl solution was added, and the resulting mixture was extracted with ethyl acetate two times using 10 mL of solvent each time. The organic layers were combined and dried over Na_2SO_4. After removing the solvent under

reduced pressure, the residue was purified by using silica gel column chromatography (EtOAc:*n*-hexane =10:90).

B. Experimental procedure for the synthesis of (162a) (gram-scale synthesis).

In a 20 mL re-sealable vial were added NaOH (983 mg, 24.6 mmol, 3 equiv.), 2-tetralone compound **161a** (2.396 g, 16.4 mmol, 2 equiv.), and alcohol **140b** (1 g, 8.2 mmol, 1 equiv.) in toluene (10 mL). Further, the tube was sealed with a cap using a crimper. The reaction mixture was stirred at 140 °C for 24 h in a preheated oil bath. After completion of the reaction, 5 mL of 1 M HCl solution was added, and the resulting mixture was extracted with ethyl acetate two times using 25 mL of solvent each time. The organic layers were combined and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by using silica gel column chromatography (EtOAc:*n*-hexane =10:90) to furnish **162a** in a 77% (1.55 g) yield.

C. General experimental procedure for the synthesis of 2-substituted-l-naphthol derivatives.

In a 20 mL re-sealable vial were added KO*t*Bu (157 mg, 1.40 mmol, 4 equiv.), 1-tetralone **159** (0.35 mmol, 1 equiv.), and alcohol **140** (0.70 mmol, 2 equiv.) in *t*-BuOH (4 mL). Further, the tube was sealed with a cap using a crimper. The reaction mixture was stirred at 155 °C for 24 h in a preheated oil bath. After completion of the reaction, 1 mL of 1 M HCl solution was added, and the resulting mixture was extracted with ethyl acetate two times using 10 mL of solvent each time. The organic layers were combined and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by using silica gel column chromatography (EtOAc:*n*-hexane = 10:90).

C'. General experimental procedure for the synthesis of 2-substituted-l-naphthols derivatives on a (1.0 mmol) scale.

In a 20 mL re-sealable vial were added KO*t*Bu (448 mg, 4 mmol, 4 equiv.), 1-tetralone **159** (1 mmol, 1 equiv.), and alcohol **140** (2 mmol, 2 equiv.) in *t*-BuOH (6 mL). Further, the tube was sealed with a cap using a crimper. The reaction mixture was stirred at 155 °C for 24 h in a preheated oil bath. After completion of the reaction, 3 mL of 1 M HCl solution was added, and the resulting mixture was extracted with ethyl acetate two times using 20 mL of solvent each time. The organic layers were combined and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by using silica gel column chromatography (EtOAc:*n*-hexane = 10:90).

D. General experimental procedure for the synthesis of benzo[*e*]indole derivatives from 2-tetralone:

In a 20 mL re-sealable vial were added NaOH (42 mg, 1.05 mmol, 3 equiv.), 2-tetralone compound **161** (0.70 mmol, 2 equiv.), and amino alcohol **138** (0.35 mmol, 1 equiv.) in toluene (2 mL). Further, the tube was sealed with a cap using a crimper. The reaction mixture was stirred at 140 °C for 40 h in a preheated oil bath. After completion of the reaction, 1 mL of 1 M HCl solution was added, and the resulting mixture was extracted with ethyl acetate two times using 10 mL of solvent each time. The organic layers were combined and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by using silica gel column chromatography (EtOAc:*n*-hexane =10:90).

D'. General experimental procedure for the synthesis of benzo[*e*]indole derivatives from 2-tetralone on a (1.0 mmol) scale.

In a 20 mL re-sealable vial were added NaOH (120 mg, 3 mmol, 3 equiv.), 2-tetralone compound **161** (2 mmol, 2 equiv.), and amino alcohol **138** (1 mmol, 1 equiv.) in toluene (3 mL). Further, the tube was sealed with a cap using a crimper. The reaction mixture was stirred at 140 °C for 40 h in a preheated oil bath. After completion of the reaction, 2 mL of 1 M HCl solution was added, and the resulting mixture was extracted with ethyl acetate two times using 10 mL of solvent each time. The organic layers were combined and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by using silica gel column chromatography (EtOAc:*n*-hexane =10:90).

E. General experimental procedure for the synthesis of benzo[*g*]indole derivatives from 1-tetralone.

In a 20 mL re-sealable vial were added NaOH (42 mg, 1.05 mmol, 3 equiv.), 1-tetralone compound **159** (0.35 mmol, 1 equiv.), and amino alcohol **138** (0.35 mmol, 1 equiv.) in toluene (2 mL). Further, the tube was sealed with a cap using a crimper. The reaction mixture was stirred at 140 °C for 40 h in preheated oil bath. After completion of the reaction, 1 mL of 1 M HCl solution was added, and the resulting mixture was extracted with ethyl acetate two times using 10 mL of solvent each time. The organic layers were combined and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by using silica gel column chromatography (EtOAc:*n*-hexane = 20:80).

E'. General experimental procedure for the synthesis of benzo[*g*]indole derivatives from 1-tetralone on a (1.0 mmol) scale.

In a 20 mL re-sealable vial were added NaOH (120 mg, 3 mmol, 3 equiv.), 1-tetralone compound **159** (1 mmol, 1 equiv.), and amino alcohol **138** (1 mmol, 1 equiv.) in toluene (3 mL). Further, the tube was sealed with a cap using a crimper. The reaction mixture was stirred at 140 °C for 40 h in a preheated oil bath. After completion of the reaction, 2 mL of 1 M HCl solution was added, and the resulting mixture was extracted with ethyl acetate two times using 10 mL of solvent each time. The organic layers were combined and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by using silica gel column chromatography (EtOAc:*n*-hexane = 20:80).

F. General experimental procedure for the synthesis of 2-benzyl-3*H*-benzo[*e*]indole (165a) from 2-benzyl-4,5-dihydro-3*H*-benzo[*e*]indole (164d).

The compound **164d** (39 mg, 0.15 mmol) was dissolved in 5 mL of 1,4-dioxane in a 25 mL RB then DDQ (68 mg, 2.0 mmol) was added slowly, and RB closed with a glass stopper. The reaction mixture was stirred at room temperature for 12 h. After completion of the reaction, 5 mL water was added, and the resulting mixture was extracted with ethyl acetate two times using 10 mL of solvent each time. The organic layers were combined and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by using silica gel column chromatography (EtOAc:*n*-hexane = 10:90).

G. Experimental procedure for the synthesis (*E*)-2-(4-methylbenzylidene)-3,4-dihydronaphthalen-1(2*H*)-one (167).[115]

According to the reported procedure by Esguerra, K. et al.[115] A 50-mL round-bottom flask equipped with a Teflon-coated stir bar were charged with the appropriate 1-tetralone (1 equiv.), 4-methylbenzaldehyde (1.2 equiv.), and degassed ethanol/water (9:1, 0.25 M with respect to the 1-tetralone), Sodium hydroxide (2 equiv.) was then added, and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was quenched by the addition of $NaHSO_4$ (10 mL, 10% by weight aqueous solution) and diluted with CH_2Cl_2 (5 mL). Then, the phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic fractions were dried over $MgSO_4$, and after removing the solvent under reduced pressure, the residue was purified by using silica gel column chromatography (EtOAc:*n*-hexane = 20:80).

H. Experimental procedure for the synthesis of naphthalene-1,2-dione derivatives (90).[113]

According to the reported procedure by Ghera, E. et al.[113] A 50-mL round-bottom flask with dry oxygen was immersed in dry CH_3CN (6 mL) in a suspension of CuCl (2.47 mg, 10 mol%) for 30

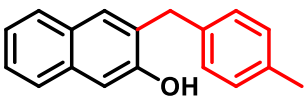
min at room temperature. A solution of the corresponding naphthalen-2-ol **(162a/162o)** (0.25 mmol) in dry CH_3CN (3 mL) was added dropwise, and the mixture was constantly stirred with oxygen bubbling until TLC showed no further starting material (2 h). After completion of the reaction, 5% $NaHCO_3$ solution was added, and the resulting mixture was extracted twice with chloroform using 10 mL of solvent each time. The organic layers were combined and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by using silica gel column chromatography (EtOAc:*n*-hexane = 10:90). Afforded the yellow-colored quinone **90**.

I. Experimental procedure for radical quenching.

In a 20 mL re-sealable vial were added NaOH (42 mg, 1.05 mmol, 3 equiv.), *β*-tetralone compound **161** (0.70 mmol, 2 equiv.), alcohol **140** (0.35 mmol, 1 equiv.) in toluene (2 mL), and finally 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) (5 equiv.). Further, the tube was sealed with a cap using a crimper. The reaction mixture was stirred at 140 °C for 24 h in preheated oil bath. After completion of the reaction, 1 mL of 1 M HCl solution was added, and the resulting mixture was extracted with ethyl acetate two times using 10 mL of solvent each time. The organic layers were combined and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by using silica gel column chromatography (EtOAc:*n*-hexane = 10:90). From this experiments, no detection of product **162a** signifies the radical nature of the reaction.

5.8.3. Analytical data for the product:

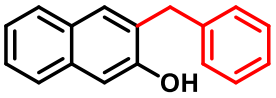
*3-(4-methylbenzyl)naphthalen-2-ol (**162a**):*



Prepared according to general procedures A and A', using 4-methylbenzyl alcohol (43 mg, 0.35 mmol)/(122 mg, 1 mmol) to afford 3-(4-methylbenzyl)naphthalen-2-ol **162a** (81 mg, 93%) using (0.35 mmol) and (191 mg, 77%) using (1 mmol) as a white solid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). Melting point: 113−115 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.1 Hz, 1H), 7.65 (d, *J* = 7.8 Hz, 1H), 7.59 (s, 1H), 7.38 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.33-7.29 (m,1H), 7.18 – 7.11 (m, 5H), 4.96 (s, 1H), 4.13 (s, 2H), 2.33 (s, 3H).^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.6, 136.6, 136.1, 133.7, 129.7, 129.6, 129.5, 129.2, 128.8, 127.4, 126.0, 125.9, 123.7, 110.2, 36.6, 21.1. IR (neat): 3526, 3053, 1633, 1264 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{18}H_{17}O$ $(M+H)^+$ 249.1279, found: 249.1284.

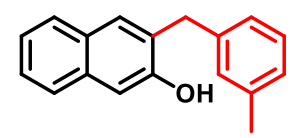
*3-benzylnaphthalen-2-ol (**162b**):*[102]

Prepared according to general procedures A and A', using benzyl alcohol (38 mg, 0.42 mmol)/ (108 mg, 1 mmol) to afford 3-benzylnaphthalen-2-ol **162b** (70 mg, 85%) using (0.35 mmol) and (187 mg, 80%) using (1 mmol) as a yellow solid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). Melting point: 80−82 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.0 Hz, 1H), 7.68 – 7.62 (m, 2H), 7.43 (t, *J* = 7.4 Hz, 1H), 7.38 – 7.25 (m, 6H), 7.09 (s, 1H), 5.27 (s, 1H), 4.20 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.6, 139.9, 133.8, 129.8, 129.6, 129.2, 129.0, 128.7, 127.5, 127.5, 126.5, 126.0, 123.8, 110.1, 36.9. IR (neat): 3527, 3056, 1633, 1236 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{17}H_{15}O$ $(M+H)^+$ 235.1123, found: 235.1117.



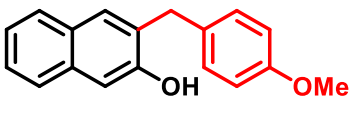
*3-(3-methylbenzyl)naphthalen-2-ol (**162c**):*

Prepared according to general procedure A and A', using 3-methylbenzyl alcohol (43 mg, 0.35 mmol)/(122 mg, 1 mmol) to afford 3-(3-methylbenzyl)naphthalen-2-ol **162c** (62 mg, 71%) using (0.35 mmol) and (170 mg, 68%) using (1 mmol) as a yellow semisolid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.8 Hz, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.62 (s, 1H), 7.45 – 7.40 (m, 1H), 7.38 – 7.33 (m, 1H), 7.25 – 7.22 (m, 1H), 7.12 – 7.08 (m, 4H), 5.29 (s, 1H), 4.16 (s, 2H), 2.34 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.6, 139.7, 138.4, 133.7, 129.7, 129.6, 129.2, 128.6, 127.4, 127.3, 126.0, 125.9, 123.7, 110.1, 36.9, 21.5. IR (neat): 3524, 3054, 2921, 1604, 1224 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{18}H_{17}O$ $(M+H)^+$ 249.1279, found: 249.1277.

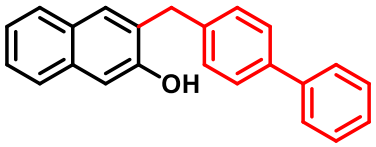


*3-(4-methoxybenzyl)naphthalen-2-ol (**162d**):*[97]

Prepared according to general procedure A and A', using 4-methoxybenzyl alcohol (48 mg, 0.35 mmol)/(138 mg, 1 mmol) to afford 3-(4-methoxybenzyl)naphthalen-2-ol **162d** (67 mg, 73%) using (0.35 mmol) and (197 mg, 75%) using (1 mmol) as a yellow solid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). Melting point: 98−100 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.1 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 1H), 7.58 (s, 1H), 7.39 (m, 1H), 7.34 – 7.30 (m, 1H), 7.21 (d, *J* = 8.6 Hz, 2H), 7.11 (s, 1H), 6.88 – 6.86 (m, 2H), 5.23 (s, 1H), 4.12 (s, 2H), 3.80 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.3, 152.6, 133.7, 131.8, 129.9, 129.6, 129.2, 127.4, 126.0, 125.9, 123.7, 114.2, 110.1, 55.4, 36.1. IR (neat): 3401, 2921, 1611, 1214 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{18}H_{17}O_2$ $(M+H)^+$ 265.1229, found: 265.1237.

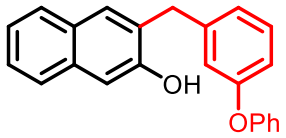


*3-([1,1'-biphenyl]-4-ylmethyl)naphthalen-2-ol (**162e**):*



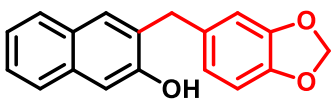
Prepared according to general procedure A and A', using biphenyl-4-methanol (64 mg, 0.35 mmol)/(184 mg, 1 mmol) to afford 33-([1,1'-biphenyl]-4-ylmethyl)naphthalen-2-ol **162e** (61 mg, 56%) using (0.35 mmol) and (180 mg, 58%) using (1 mmol) as a yellow solid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). Melting point: 145−147 °C.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.1 Hz, 1H), 7.69 – 7.64 (m, 2H), 7.61 – 7.55 (m, 4H), 7.47 – 7.40 (m, 3H), 7.38 – 7.32 (m, 4H), 7.14 (s, 1H), 5.14 (s, 1H), 4.22 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.57, 141.06, 139.45, 139.06, 133.82, 129.89, 129.47, 129.37, 129.30, 128.87, 127.51, 127.47, 127.26, 127.16, 126.08, 126.04, 123.84, 110.17, 36.63. IR (neat): 3527, 3054, 1632, 1264 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{23}H_{19}O$ $(M+H)^+$ 311.1436, found: 311.1442.

*3-(3-phenoxybenzyl)naphthalen-2-ol (**162f**):*



Prepared according to general procedure A and A', using 3-phenoxybenzyl alcohol (70 mg, 0.35 mmol)/(200 mg, 1 mmol) to afford 3-(3-phenoxybenzyl)naphthalen-2-ol **162f** (89 mg, 78%) using (0.35 mmol) and (240 mg, 74%) using (1 mmol) as a yellow solid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). Melting point: 100−102 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.72 (m, 1H), 7.67–7.61 (m, 2H), 7.47 – 7.27 (m, 5H), 7.16 – 7.07 (m, 6H), 6.93– 6.92 (m, 1H). 5.49 (s, 1H), 4.18 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.4, 157.2, 152.4, 142.2, 133.7, 129.8, 129.7, 129.3, 129.2, 128.6, 127.4, 126.0, 125.9, 123.9, 123.8, 123.2, 119.7, 118.9, 116.7, 109.9, 36.7. IR (neat): 3526, 3055, 1486, 1236 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{23}H_{19}O_2$ $(M+H)^+$ 327.1385, found: 327.1384.

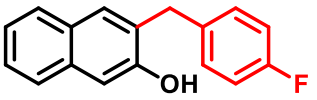
*3-(benzo[d][1,3]dioxol-5-ylmethyl)naphthalen-2-ol (**162g**):*



Prepared according to general procedure A and A', using piperonyl alcohol (53 mg, 0.35 mmol)/(152 mg, 1 mmol) to afford 3-(benzo[*d*][1,3]dioxol-5-ylmethyl)naphthalen-2-ol **162g** (81 mg, 83%) using (0.35 mmol) and (224 mg, 80%) using (1 mmol) as a yellow solid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). Melting point: 78−80 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.59 (s, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 7.36 – 7.32 (m, 1H), 7.09 (s, 1H), 6.80 – 6.78 (m, 3H), 5.93 (s, 2H), 5.60 (s, 1H), 4.10 (s, 2H). ^{13}C{^{1}H}

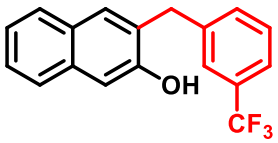
NMR (100 MHz, $CDCl_3$) δ 152.5, 147.8, 146.1, 133.8, 133.7, 129.7, 129.5, 129.1, 127.4, 125.9, 123.7, 121.7, 110.0, 109.4, 108.3, 100.9, 36.5. IR (neat): 3664, 2916, 1633, 1491, 1244 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{18}H_{15}O_3$ $(M+H)^+$ 279.1021, found: 279.1021.

*3-(4-fluorobenzyl)naphthalen-2-ol (**162h**):*



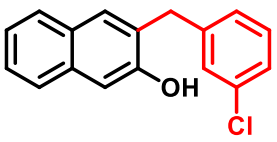
Prepared according to general procedure A and A', using 4-fluorobenzyl alcohol (44 mg, 0.35 mmol)/(126 mg, 1 mmol) to afford 3-(4-fluorobenzyl)naphthalen-2-ol **162h** (70 mg, 80%) using (0.35 mmol) and (195 mg, 77%) using (1 mmol) as a white solid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). Melting point: 77−79 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.4 Hz, 1H), 7.66 (d, *J* = 8.2 Hz, 1H), 7.57 (s, 1H), 7.42 m, 1H), 7.37 – 7.32 (m, 1H), 7.25 (m, 2H), 7.10 (s, 1H), 7.03 – 6.98 (m, 2H), 5.05 (s, 1H), 4.14 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.7 (d, *J* = 244.2 Hz), 152.4, 135.7 (d, *J* = 2.7 Hz), 133.8, 130.4 (d, *J* = 7.7 Hz), 129.7, 129.5, 129.3, 127.5, 126.1 (d, *J* = 14.5 Hz), 123.9, 115.5, 115.3, 110.1, 36.1. IR (neat): 3649, 3054, 1508, 1222 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{18}H_{17}O_2$ $(M+H)^+$ 265.1229, found: 265.1237.

*3-(3-(trifluoromethyl)benzyl)naphthalen-2-ol (**162i**):*



Prepared according to general procedure A and A', using 3-(trifluoromethyl)benzyl alcohol (62 mg, 0.35 mmol)/(176 mg, 1 mmol) to afford 3-(3-(trifluoromethyl)benzyl)naphthalen-2-ol **162i** (62 mg, 58%) using (0.35 mmol) and (156 mg, 52%) using (1 mmol) as a yellow solid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). Melting point: 90−92 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.1 Hz, 1H), 7.65 (d, *J* = 8.1 Hz, 1H), 7.58 (m, 2H), 7.49 – 738 (m, 4H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.10 (s, 1H), 5.05 (s, 1H), 4.21 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.2, 141.3, 133.8, 132.4, 130.9 (q, *J* = 32.0 Hz),130.0, 129.3, 129.0, 128.9, 127.6, 126.3, 126.0, 125.8 (q, *J* = 3.6 Hz), 124.4 (q, *J* = 270.5 Hz), 124.0, 123.2 (q, *J* = 3.8 Hz), 110.0, 36.7. IR (neat): 3528, 3056, 1358, 1122 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{18}H_{14}F_3O$ $(M+H)^+$ 303.0997, found: 303.1008.

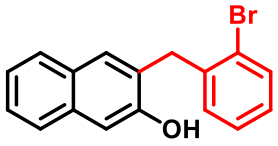
*3-(3-chlorobenzyl)naphthalen-2-ol (**162j**):*



Prepared according to general procedure A and A', using 3-chlorobenzyl alcohol (50 mg, 0.35 mmol)/(143 mg, 1 mmol) to afford 3-(3-chlorobenzyl)naphthalen-2-ol **162j** (77 mg, 82%) using (0.35 mmol) and (200 mg, 74%) using (1 mmol) as a white solid after silica gel column

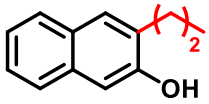
chromatography (EtOAc:*n*-hexane =10:90). Melting point: 85−87 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.1 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 1H), 7.58 (s, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.35 – 7.31 (m, 1H), 7.27 (s, 1H), 7.25 – 7.16 (m, 3H), 7.09 (s, 1H), 5.15 (s, 1H), 4.13 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.3, 142.3, 134.4, 133.8, 129.9, 129.8, 129.2, 129.0, 128.9, 127.5, 127.1, 126.5, 126.2, 125.9, 123.9, 110.0, 36.5. IR (neat): 3672, 3056, 1515, 1264 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{17}H_{14}ClO$ $(M+H)^+$ 269.0733, found: 269.0725.

*3-(2-bromobenzyl)naphthalen-2-ol (**162k**):*



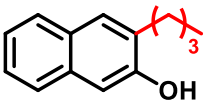
Prepared according to general procedure A and A', using 2-bromobenzyl alcohol (65 mg, 0.35 mmol)/(187 mg, 1 mmol) to afford 3-(2-bromobenzyl)naphthalen-2-ol **162k** (90 mg, 82%) using (0.35 mmol) and (240 mg, 77%) using (1 mmol) as a yellow semisolid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.62 (m, 3H), 7.48 (s, 1H), 7.43 – 7.39 (m, 1H), 7.34 –7.30 (m, 1H), 7.25 – 7.21 (m, 1H), 7.15 – 7.11 (m, 3H), 5.31 (s, 1H), 4.28 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.5, 139.3, 133.8, 132.9, 130.8, 129.9, 129.2, 128.1, 128.1, 127.7, 127.6, 126.1, 126.0, 125.1, 123.8, 109.8, 36.7. IR (neat): 3527, 3056, 1632, 1225 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{17}H_{14}BrO$ $(M+H)^+$ 313.0228, found: 313.0221.

*3-propylnaphthalen-2-ol (**162l**):*



Prepared according to general procedure A and A', using propyl alcohol (21 mg, 0.35 mmol)/(60 mg, 1 mmol) to afford 3-propylnaphthalen-2-ol **162l** (47 mg, 72%) using (0.35 mmol) and (127 mg, 68%) using (1 mmol) as a yellow solid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). Melting point: 34−36 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.1 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 1H), 7.61 (s, 1H), 7.40 (m, 1H), 7.35– 7.31 (m, 1H), 7.08 (s, 1H), 5.41 (s, 1H), 2.79 (t, *J* = 7.2 Hz, 2H), 1.85 – 1.73 (m, 2H), 1.05 (t, *J* = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.7, 133.4, 131.1, 129.2, 128.8, 127.3, 125.9, 125.7, 123.6, 109.4, 32.7, 23.0, 14.2. IR (neat): 3528, 2959, 2928, 1633, 1454, 1221 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{13}H_{15}O$ $(M+H)^+$ 187.1123, found: 187.1125.

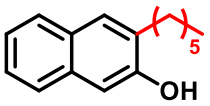
*3-butylnaphthalen-2-ol (**162m**):*



Prepared according to general procedures A and A', using butyl alcohol (26 mg, 0.35 mmol)/(72 mg, 1 mmol) to afford 3-butylnaphthalen-2-ol **162m** (45 mg, 64%) using (0.35 mmol) and (130 mg, 65%) using (1 mmol) as a white

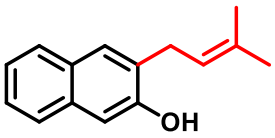
solid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). Melting point: 78−80 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.1 Hz, 1H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.59 (s, 1H), 7.40 – 7.36 (m, 1H), 7.33 – 7.31 (m, 1H), 7.08 (s, 1H), 5.16 (s, 1H), 2.79 (t, *J* = 7.6 Hz, 2H), 1.75-1.67 (m, 2H), 1.50 – 1.40 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H).^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 152.6, 133.4, 131.2, 129.3, 128.7, 127.3, 125.9, 125.7, 123.6, 109.4, 32.0, 30.4, 22.8, 14.2. IR (neat): 3510, 2925, 1632, 1515, 1193 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{14}H_{17}O$ $(M+H)^+$ 201.1279, found: 201.1272.

*3-hexylnaphthalen-2-ol (**162n**):*



Prepared according to general procedure A and A', using hexyl alcohol (36 mg, 0.35 mmol)/(102 mg, 1 mmol) to afford 3-hexylnaphthalen-2-ol **162n** (64 mg, 80%) using (0.35 mmol) and (174 mg, 76%) using (1 mmol) as a yellow solid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). Melting point: 78−80 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.1 Hz, 1H), 7.64 (d, *J* = 8.1 Hz, 1H), 7.58 (s, 1H), 7.37 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.30 (ddd, *J* = 8.0, 6.9, 1.2 Hz, 1H), 7.09 (s, 1H), 4.96 (s, 1H), 2.77 (t, *J* = 7.6 Hz, 2H), 1.71 (m, 2H), 1.44 – 1.32 (m, 6H), 0.90 (t, *J* = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.6, 133.4, 131.2, 129.3, 128.7, 127.3, 125.9, 125.7, 123.6, 109.4, 31.9, 30.7, 29.8, 29.4, 22.8, 14.2. IR (neat): 3515, 2927, 1515, 1264 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{16}H_{21}O$ $(M+H)^+$ 229.1592, found: 229.1610.

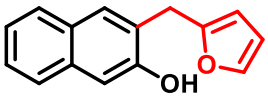
*3-(3-methylbut-2-en-1-yl)naphthalen-2-ol (**162o**):*



Prepared according to general procedure A and A', using 3-methylbut-2-en-1-ol (30 mg, 0.35 mmol)/(86 mg, 1 mmol) to afford 3-(3-methylbut-2-en-1-yl)naphthalen-2-ol **162o** (61 mg, 82%) using (0.35 mmol) and (164 mg, 77%) using (1 mmol) as a yellow solid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). Melting point: 78−80 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.1 Hz, 1H), 7.66 (d, *J* = 8.1 Hz, 1H), 7.61 (s, 1H), 7.43 – 7.38 (m, 1H), 7.34 (ddd, *J* = 8.1, 6.9, 1.3 Hz, 1H), 7.14 (s, 1H), 5.61 (s, 1H), 5.48 – 5.43 (m, 1H), 3.56 (d, *J* = 7.1 Hz, 2H), 1.84 (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 153.1, 135.0, 133.6, 129.6, 129.2, 128.5, 127.3, 126.1, 125.8, 123.6, 121.8, 110.0, 30.1, 26.0, 18.1. IR (neat): 3443, 2921, 1664, 1376 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{15}H_{17}O$ $(M+H)^+$ 213.1279, found: 213.1270.

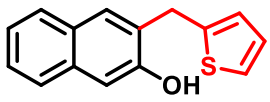
*3-(furan-2-ylmethyl)naphthalen-2-ol (**162p**):*

Prepared according to general procedure A and A', using furfuryl alcohol (34 mg, 0.35 mmol)/(98 mg, 1 mmol) to afford 3-(furan-2-ylmethyl)naphthalen-2-ol **162p** (53 mg, 67%) using (0.35 mmol) and (143 mg, 64%) using (1 mmol) as a yellow semisolid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.1 Hz, 1H), 7.66 (d, *J* = 8.3 Hz, 1H), 7.63 (s, 1H), 7.44 – 7.31 (m, 3H), 7.15 (s, 1H), 6.35 (s, 1H), 6.12 (d, *J* = 3.1 Hz, 1H), 5.55 (s, 1H), 4.18 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 153.6, 152.3, 141.6, 133.9, 129.6, 129.2, 127.5, 126.9, 126.2, 126.1, 123.8, 110.6, 110.5, 106.6, 29.7. IR (neat): 3526, 3055, 1699, 1511, 1229 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{15}H_{13}O_2$ $(M+H)^+$ 225.0916, found: 225.0918.



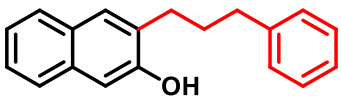
*3-(thiophen-2-ylmethyl)naphthalen-2-ol (**162q**):*

Prepared according to general procedure A and A', using 2-thiophenemethanol (40 mg, 0.35 mmol)/(114 mg, 1 mmol) to afford 3-(thiophen-2-ylmethyl)naphthalen-2-ol **162q** (77 mg, 91%) using (0.35 mmol) and (201 mg, 87%) using (1 mmol) as a yellow semisolid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.1 Hz, 1H), 7.66 (d, *J* = 5.5 Hz, 2H), 7.45 – 7.41 (m, 1H), 7.37 – 7.34 (m, 1H), 7.21 (d, *J* = 4.8 Hz, 1H), 7.11 (s, 1H), 6.99 – 6.92 (m, 2H), 5.30 (s, 1H), 4.37 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.3, 142.9, 133.9, 129.4, 129.2, 129.0, 127.6, 127.0, 126.2, 126.0, 125.6, 124.4, 123.9, 110.2, 31.2. IR (neat): 3524, 3054, 1632, 1262 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{15}H_{13}OS$ $(M+H)^+$ 241.0687, found: 241.0686.

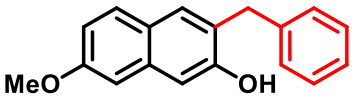


*3-(3-phenylpropyl)naphthalen-2-ol (**162r**):*[118]

Prepared according to general procedure A and A', using 3-phenyl-1-propanol (48 mg, 0.35 mmol)/(136 mg, 1 mmol) to afford 3-(3-phenylpropyl)naphthalen-2-ol **162r** (72 mg, 78%) using (0.35 mmol) and (185 mg, 71%) using (1 mmol) as a white solid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). Melting point: 60−62 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.9 Hz, 1H), 7.49 (d, *J* = 8.1 Hz, 1H), 7.45 (s, 1H), 7.19 (m, 7H), 6.88 (s, 1H), 4.96 (s, 1H), 2.70 (t, *J* = 7.6 Hz, 2H), 2.61 (t, *J* = 7.7 Hz, 2H), 1.98 – 1.86 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.6, 142.4, 133.4, 130.8, 129.3, 128.8, 128.6, 128.5, 127.3, 125.9, 125.8, 123.7, 109.5, 35.8, 31.3, 30.2. IR (neat): 3527, 2930, 1515, 1264 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{19}H_{19}O$ $(M+H)^+$ 263.1436, found: 263.1429.

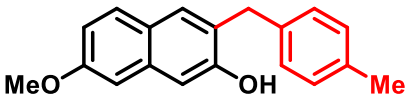


*3-benzyl-7-methoxynaphthalen-2-ol (**162s**):*



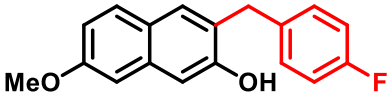
Prepared according to general procedure A and A', using benzyl alcohol (38 mg, 0.35 mmol)/(108 mg, 1 mmol) to afford 3-benzyl-7-methoxynaphthalen-2-ol **162s** (81 mg, 88%) using (0.35 mmol) and (225 mg, 85%) using (1 mmol) as a white solid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). Melting point: 136−138 °C.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.6 Hz, 1H), 7.49 (s, 1H), 7.32 – 7.21 (m, 5H), 7.02 (s, 1H), 6.98 – 6.95 (m, 2H), 4.97 (s, 1H), 4.12 (s, 2H), 3.88 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.0, 153.2, 140.0, 135.0, 129.7, 129.0, 128.9, 128.8, 126.8, 126.5, 124.7, 116.4, 109.5, 104.4, 55.4, 36.9. IR (neat): 3360, 2920, 2354, 1593, 1227 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{18}H_{17}O_2$ $(M+H)^+$ 265.1229, found: 265.1223.

*7-methoxy-3-(4-methylbenzyl)naphthalen-2-ol (**162t**):*



Prepared according to general procedure A and A', using 4-methylbenzyl alcohol (43 mg, 0.35 mmol)/(122 mg, 1 mmol) to afford 7-methoxy-3-(4-methylbenzyl)naphthalen-2-ol **162t** (90 mg, 92%) using (0.35 mmol) and (242 mg, 87%) using (1 mmol) as a brown solid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). Melting point: 135−134 °C.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.8 Hz, 1H), 7.51 (s, 1H), 7.14 (q, *J* = 8.1 Hz, 4H), 7.03 (s, 1H), 7.00 – 6.95 (m, 2H), 5.03 (s, 1H), 4.09 (s, 2H), 3.90 (s, 3H), 2.33 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.9, 153.2, 136.8, 136.1, 135.0, 129.6, 129.5, 129.0, 128.8, 127.0, 124.6, 116.4, 109.6, 104.4, 55.3, 36.5, 21.2. IR (neat): 3673, 2925, 1635, 1514, 1219 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{19}H_{19}O_2$ $(M+H)^+$ 279.1385, found: 279.1380.

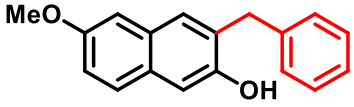
*3-(4-fluorobenzyl)-7-methoxynaphthalen-2-ol (**162u**):*



Prepared according to general procedure A and A', using 4-fluorobenzyl alcohol (44 mg, 0.35 mmol)/(126 mg, 1 mmol) to afford 3-(4-fluorobenzyl)-7-methoxynaphthalen-2-ol **162u** (86 mg, 87%) using (0.35 mmol) and (235 mg, 83%) using (1 mmol) as a white solid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). Melting point: 136−138 °C.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.8 Hz, 1H), 7.47 (s, 1H), 7.24 – 7.19 (m, 2H), 7.01 (s, 1H), 7.00 – 6.94 (m, 4H), 5.00 (s, 1H), 4.08 (s, 2H), 3.89 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.7 (d, *J* = 244.1 Hz), 158.1, 153.0, 135.9 (d, *J* = 3.1 Hz), 135.1, 130.3 (d, *J* = 7.8 Hz), 129.6, 129.0,

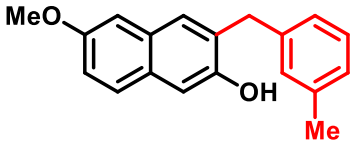
126.8, 124.7, 116.5, 115.4 (d, J = 21.2 Hz).109.4, 104.4, 55.4, 36.0. IR (neat): 3524, 2853, 1636, 1507, 1221 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{18}H_{16}FO_2$ $(M+H)^+$ 283.1134, found: 283.1129.

*3-benzyl-6-methoxynaphthalen-2-ol (**162v**):*



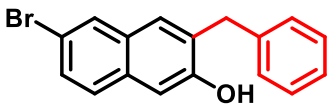
Prepared according to general procedures A and A', using benzyl alcohol (38 mg, 0.35 mmol)/(108 mg, 1 mmol) to afford 3-benzyl-6-methoxynaphthalen-2-ol **162v** (66 mg, 72%) using (0.35 mmol) and (180 mg, 68%) using (1 mmol) as a white solid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). Melting point: 95−97 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 8.9 Hz, 1H), 7.38 (s, 1H), 7.29 (d, J = 4.5 Hz, 1H), 7.25 – 7.15 (m, 5H), 7.00 – 6.95 (m, 2H), 4.89 (s, 1H), 4.06 (s, 2H), 3.79 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 156.3, 150.9, 140.0, 130.1, 130.0, 129.0, 129.0, 128.8, 128.6, 127.5, 126.5, 118.8, 110.4, 105.8, 55.4, 37.0. IR (neat): 3672, 2927, 1609, 1515, 1263 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{18}H_{17}O_2$ $(M+H)^+$ 265.1229, found: 265.1217.

*6-methoxy-3-(3-methylbenzyl)naphthalen-2-ol (**162w**):*



Prepared according to general procedures A and A', using 3-methylbenzyl alcohol (43 mg, 0.35 mmol)/(122 mg, 1 mmol) to afford 6-methoxy-3-(3-methylbenzyl)naphthalen-2-ol **162w** (49 mg, 50%) using (0.35 mmol) and (155 mg, 56%) using (1 mmol) as a yellow semisolid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 8.8 Hz, 1H), 7.49 (s, 1H), 7.23 (m, 1H), 7.11 – 7.07 (m, 6H), 5.11 (s, 1H), 4.13 (s, 2H), 3.90 (s, 3H), 2.34 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 156.2, 151.0, 139.8, 138.4, 130.1, 130.0, 129.7, 129.0, 128.7, 128.6, 127.5, 127.3, 126.0, 118.7, 110.4, 105.8, 55.4, 37.0, 21.5. IR (neat): 3398, 2918, 1609, 1249 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{19}H_{18}O_2$ $(M)^+$ 278.1307, found: 278.1295.

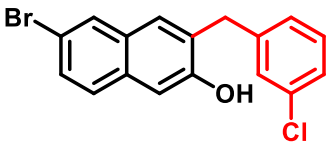
*3-benzyl-6-bromonaphthalen-2-ol (**162x**):*



Prepared according to general procedure A and A', using benzyl alcohol (38 mg, 0.35 mmol)/(108 mg, 1 mmol) to afford 3-benzyl-6-bromonaphthalen-2-ol **162x** (60 mg, 54%) using (0.35 mmol) and (156 mg, 50%) using (1 mmol) as a white solid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). Melting point: 95−97 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.40 – 7.31

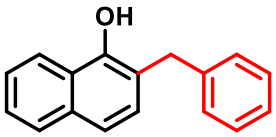
(m, 3H), 7.25 – 7.09 (m, 5H), 6.94 (m, 1H), 5.06 (s, 1H), 4.03 (s, 2H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 152.9, 139.5, 132.2, 130.8, 130.3, 129.5, 129.3, 129.0, 128.9, 128.8, 127.7, 126.7, 117.3, 110.1, 36.9. IR (neat): 3563, 3057, 1514, 1264 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{17}H_{14}BrO$ $(M+H)^+$ 313.0228, found: 313.0235.

*6-bromo-3-(3-chlorobenzyl)naphthalen-2-ol (**162y**):*



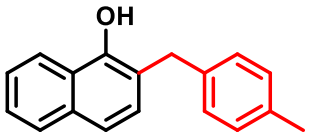
Prepared according to general procedure A and A', using 3-chlorobenzyl alcohol (50 mg, 0.35 mmol)/(142 mg, 1 mmol) to afford 6-bromo-3-(3-chlorobenzyl)naphthalen-2-ol **162y** (30 mg, 25%) using (0.35 mmol) and (100 mg, 29%) using (1 mmol) as a white solid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). Melting point: 118−120 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 1.6 Hz, 1H), 7.51 (d, *J* = 8.7 Hz, 1H), 7.46 – 7.44 (m, 2H), 7.26 – 7.20 (m, 3H), 7.15 – 7.12 (m, 1H), 7.07 (s, 1H), 5.26 (s, 1H), 4.11 (s, 2H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 152.7, 141.9, 134.5, 132.2, 130.3, 130.2, 129.9, 129.5, 129.5, 129.1, 129.0, 127.6, 127.2, 126.7, 117.4, 110.0, 36.5. IR (neat): 3360, 2920, 1593, 1227 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{17}H_{13}BrClO$ $(M+H)^+$ 346.9838, found: 346.9853.

*2-benzylnaphthalen-1-ol (**117b**):*[102]



Prepared according to general procedures C and C', using benzyl alcohol (76 mg, 0.70 mmol)/(216 mg, 2 mmol) to afford 2-benzylnaphthalen-1-ol **117b** (68 mg, 83%) using (0.35 mmol) and (185 mg, 79%) using (1 mmol) as a white solid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). Melting point: 72−74 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 – 8.01 (m, 1H), 7.74 – 7.70 (m, 1H), 7.37 (m, 3H), 7.25 – 7.15 (m, 6H), 5.06 (s, 1H), 4.09 (s, 2H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 149.1, 139.4, 133.9, 129.1, 129.0, 128.7, 127.8, 126.9, 125.9, 125.5, 125.0, 121.2, 120.7, 120.0, 36.9. IR (neat): 3649, 3055, 1699, 1264 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{17}H_{15}O$ $(M+H)^+$ 235.1123, found: 235.1121.

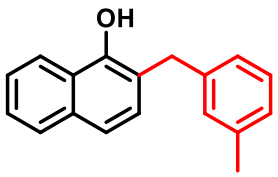
*2-(4-methylbenzyl)naphthalen-1-ol (**117c**):*[102]



Prepared according to general procedure C and C', using 4-methylbenzyl alcohol (86 mg, 0.70 mmol)/(244 mg, 2 mmol) to afford 2-(4-methylbenzyl)naphthalen-1-ol **117c** (42 mg, 48%) using (0.35 mmol) and (125 mg, 50%) using (1 mmol) as a yellow solid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). Melting point: 68−70 °C. ^{1}H NMR (400

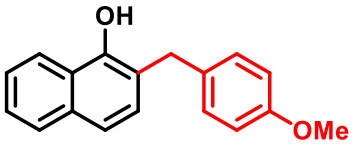
MHz, $CDCl_3$) δ 8.12 – 8.10 (m, 1H), 7.81 – 7.79 (m, 1H), 7.48 – 7.43 (m, 3H), 7.29 (d, *J* = 8.3 Hz, 1H), 7.14 (q, *J* = 8.2 Hz, 4H), 5.18 (s, 1H), 4.14 (s, 2H), 2.33 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 149.2, 136.6, 136.2, 133.9, 129.8, 129.1, 128.6, 127.8, 125.9, 125.5, 125.0, 121.3, 120.5, 120.2, 36.6, 21.1. IR (neat): 3665, 2924, 1652, 1264 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{18}H_{17}O$ $(M+H)^+$ 249.1279, found: 249.1275.

*2-(3-methylbenzyl)naphthalen-1-ol (**117d**):*



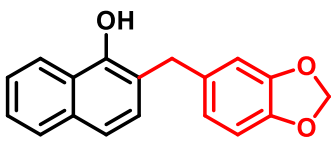
Prepared according to general procedure C and C', using 3-methylbenzyl alcohol (86 mg, 0.70 mmol)/(244 mg, 2 mmol) to afford 2-(3-methylbenzyl)naphthalen-1-ol **117d** (50 mg, 58%) using (0.35 mmol) and (136 mg, 55%) using (1 mmol) as a yellow semisolid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 – 7.99 (m, 1H), 7.70 – 7.66 (m, 1H), 7.36 – 7.31 (m, 3H), 7.17 (d, *J* = 8.3 Hz, 1H), 7.10 – 7.06 (m, 1H), 6.94 (d, *J* = 7.5 Hz, 3H), 5.10 (s, 1H), 4.00 (s, 2H), 2.18 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 149.2, 139.3, 138.8, 133.9, 129.4, 129.1, 129.0, 127.8, 127.7, 125.9, 125.7, 125.4, 125.0, 121.3, 120.6, 120.1, 36.9, 21.5. IR (neat): 3525, 2921, 1657, 1263 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{18}H_{17}O$ $(M+H)^+$ 249.1279, found: 249.1283.

*2-(4-methoxybenzyl)naphthalen-1-ol (**117e**):*[102]



Prepared according to general procedure C and C', using 4-methoxybenzyl alcohol (97 mg, 0.70 mmol)/(276 mg, 2 mmol) to afford 2-(4-methoxybenzyl)naphthalen-1-ol **117e** (61 mg, 66%) using (0.35 mmol) and (185 mg, 70%) using (1 mmol) as a yellow solid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). Melting point: 79−81 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 – 8.06 (m, 1H), 7.78 – 7.75 (m, 1H), 7.44 – 7.39 (m, 3H), 7.23 (d, *J* = 5.8 Hz, 1H), 7.14 (d, *J* = 8.8 Hz, 2H), 6.83 – 6.80 (m, 2H), 5.15 (s, 1H), 4.08 (s, 2H), 3.75 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 158.6, 149.2, 133.9, 131.2, 129.7, 129.0, 127.8, 125.9, 125.5, 125.0, 121.3, 120.5, 120.2, 114.5, 55.4, 36.2. IR (neat): 3471, 2921, 1595, 1242 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{18}H_{17}O_2(M+H)^+$ 265.1229, found: 265.1223.

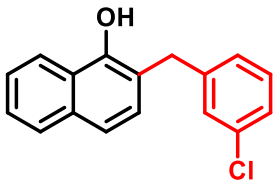
*2-(benzo[d][1,3]dioxol-5-ylmethyl)naphthalen-1-ol (**117f**):*[102]



Prepared according to general procedure C and C', using piperonyl alcohol (106 mg, 0.70 mmol)/(304 mg, 2 mmol) to afford 2-(benzo[*d*][1,3]dioxol-5-ylmethyl)naphthalen-1-ol **117f** (54 mg, 56%)

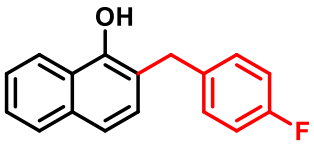
using (0.35 mmol) and (156 mg, 56%) using (1 mmol) as a yellow solid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). Melting point: 94−96 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 – 8.09 (m, 1H), 7.80 – 7.82 (m, 1H), 7.49 – 7.43 (m, 3H), 7.28 (d, *J* = 8.3 Hz, 1H), 6.75 (s, 2H), 6.71 (s, 1H), 5.92 (s, 2H), 5.25 (s, 1H), 4.08 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 149.2, 148.4, 146.6, 133.9, 133.2, 128.9, 127.8, 125.9, 125.5, 124.9, 121.4, 121.2, 120.6, 120.1, 109.2, 108.6, 101.2, 36.8. IR (neat): 3400, 2923, 1486, 1391, 1239 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{18}H_{15}O_3(M+H)^+$ 279.1021, found: 279.1021.

*2-(3-chlorobenzyl)naphthalen-1-ol (**117g**):*[102]



Prepared according to general procedures C and C', using hexylalcohol (97 mg, 0.70 mmol)/(285 mg, 2 mmol) to afford 2-(3-chlorobenzyl)naphthalen-1-ol **117g** (100 mg, 47%) using (0.35 mmol) and (120 mg, 45%) using (1 mmol) as a white solid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). Melting point: 74−76 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 – 8.03 (m, 1H), 7.82 (dd, *J* = 6.7, 2.7 Hz, 1H), 7.52 – 7.43 (m, 3H), 7.23 (m, 4H), 7.14 – 7.12 (m, 1H), 5.15 (s, 1H), 4.15 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 148.9, 141.9, 134.8, 133.9, 130.1, 129.1, 128.8, 128.0, 126.9, 126.8, 126.1, 125.7, 124.8, 121.0, 120.8, 119.6, 36.3. IR (neat): 3400, 2926, 1716, 1575, 1396, 1264 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{17}H_{13}ClO(M)^+$ 268.0655, found: 268.0637.

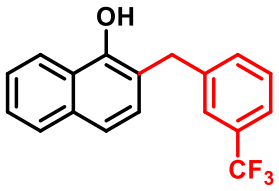
*2-(4-fluorobenzyl)naphthalen-1-ol (**117h**):*[102]



Prepared according to general procedure C and C', using 4-fluorobenzyl alcohol (88 mg, 0.70 mmol)/(252 mg, 2 mmol) to afford 2-(4-fluorobenzyl)naphthalen-1-ol **117h** (48 mg, 55%) using (0.35 mmol) and (150 mg, 59%) using (1 mmol) as a yellow solid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). Melting point: 75−77 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.9 – 8.07 (m, 1H), 7.83 – 7.80 (m, 1H), 7.51 – 7.43 (m, 3H), 7.27 – 7.25 (m, 1H), 7.22 – 7.19 (m, 2H), 7.01 – 6.97 (m, 2H), 5.13 (s, 1H), 4.14 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.8 (d, *J* = 245.0 Hz), 148.9, 135.2 (d, *J* = 3.2 Hz), 133.9, 130.1 (d, *J* = 7.8 Hz), 128.8, 127.9, 126.0, 125.7, 124.8, 121.0, 120.8, 120.0, 115.8 (d, *J* = 21.4 Hz), 35.9. IR (neat): 3565, 3058, 1652, 1507, 1266 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{17}H_{14}FO$ $(M+H)^+$ 253.1028, found: 253.1027.

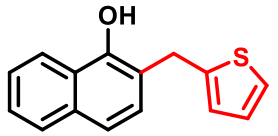
*2-(3-(trifluoromethyl)benzyl)naphthalen-1-ol (**117i**):*[102]

Prepared according to general procedure C and C', using 3-(trifluoromethyl)benzyl alcohol (123 mg, 0.70 mmol)/(352 mg, 2 mmol) to afford 2-(3-(trifluoromethyl)benzyl)naphthalen-1-ol **117i** (51 mg, 48%) using (0.35 mmol) and (136 mg, 45%) using (1 mmol) as a white solid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). Melting point: 85−87 °C.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (m, 1H), 7.83 (dd, *J* = 7.0, 2.3 Hz, 1H), 7.54 – 7.45 (m, 5H), 7.40 (m, 2H), 7.26 (m, 1H), 5.17 (s, 1H), 4.23 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 148.7, 141.0, 133.9, 132.1, 131.1 (q, *J* = 32 Hz), 129.2, 128.7, 128.1, 126.1, 125.8, 125.5 (q, *J* = 3.5 Hz), 124.7, 124.3 (q, *J* = 271 Hz), 123.5 (q, *J* = 3.6 Hz), 121.1, 120.2, 119.8, 36.2. IR (neat): 3500, 2923, 1574, 1486, 1239, 1034 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{18}H_{14}F_3O(M+H)^+$ 303.0997, found: 303.0996.



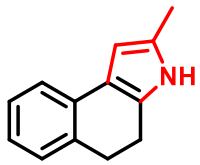
*2-(thiophen-2-ylmethyl)naphthalen-1-ol (**117j**):*

Prepared according to general procedure C and C', using 2-thiophenemethanol (80 mg, 0.70 mmol)/(228 mg, 2 mmol) to afford 2-(thiophen-2-ylmethyl)naphthalen-1-ol **117j** (59 mg, 70%) using (0.35 mmol) and (151 mg, 67%) using (1 mmol) as a yellow solid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). Melting point: 56−58 °C.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 – 8.12 (m, 1H), 7.82 (m, 1H), 7.50 – 7.46 (m, 3H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.21 (d, *J* = 4.7 Hz, 1H), 6.95 (t, *J* = 4.2 Hz, 1H), 6.90 (d, *J* = 2.4 Hz, 1H), 5.36 (d, *J* = 3.2 Hz, 1H), 4.35 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 149.2, 142.6, 134.0, 128.4, 127.9, 127.1, 126.1, 125.6, 125.6, 125.0, 121.2, 120.8, 119.8, 31.5. IR (neat): 3612, 3059, 1512, 1392, 1266 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{15}H_{13}SO(M+H)^+$ 241.0687, found: 241.0668.



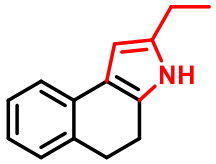
*2-methyl-4,5-dihydro-3H-benzo[e]indole (**164a**):*[119]

Prepared according to general procedures D and D', using 2-aminopropan-1-ol (26 mg, 0.35 mmol)/(75 mg, 1 mmol) to afford 2-methyl-4,5-dihydro-3*H*-benzo[*e*]indole **164a** (43 mg, 67%) using (0.35 mmol) and (120 mg, 65%) using (1 mmol) as a brown liquid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.20 (dd, *J* = 15.1, 7.4 Hz, 2H), 7.06 – 7.02 (m, 1H), 6.17 (s, 1H), 3.01 (t, *J* = 7.8 Hz, 2H), 2.76 (t, *J* = 7.8 Hz, 2H), 2.29 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 133.6, 132.9, 128.0, 127.9, 127.2, 126.7,



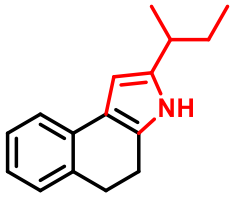
124.1, 121.4, 118.5, 101.2, 29.8, 21.8, 13.2. IR (neat): 3401, 2925, 1699, 1536, 1375 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{13}H_{13}N$ $(M)^+$183.1048, found: 183.1042.

*2-ethyl-4,5-dihydro-3H-benzo[e]indole (**164b**):*



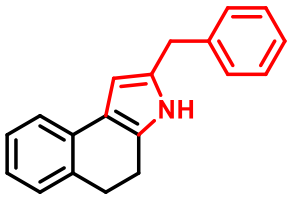
Prepared according to general procedure D and D', using 2-amino-1-butanol (31 mg, 0.35 mmol)/(89 mg, 1 mmol) to afford 2-ethyl-4,5-dihydro-3*H*-benzo[*e*]indole **164b** (43 mg, 62%) using (0.35 mmol) and (128 mg, 65%) using (1 mmol) as a brown solid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). Melting point: 89−91 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.35 (d, *J* = 7.6 Hz, 1H), 7.20 (dd, *J* = 15.7, 7.8 Hz, 2H), 7.05 – 7.01 (m, 1H), 6.20 (d, *J* = 2.2 Hz, 1H), 3.02 (t, *J* = 7.7 Hz, 2H), 2.78 (t, *J* = 7.7 Hz, 2H), 2.65 (q, *J* = 7.6 Hz, 2H), 1.30 (d, *J* = 7.6 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 133.9, 133.6, 132.9, 127.9, 127.8, 126.7, 124.1, 121.4, 118.3, 99.5, 29.8, 21.9, 21.1, 13.8. IR (neat): 3402, 2925, 1699, 1538, 1456 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{14}H_{15}N$ $(M)^+$ 197.1204, found: 197.1188.

*2-(sec-butyl)-4,5-dihydro-3H-benzo[e]indole (**164c**):*



Prepared according to general procedure D and D', using 2-amino-3-methylpentan-1-ol (41 mg, 0.35 mmol)/(117 mg, 1 mmol) to afford 2-(*sec*-butyl)-4,5-dihydro-3*H*-benzo[*e*]indole **164c** (42 mg, 53%) using (0.35 mmol) and (125 mg, 55%) using (1 mmol) as a yellow semisolid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.33 (d, *J* = 7.7 Hz, 1H), 7.17 (dd, *J* = 16.2, 7.9 Hz, 2H), 7.00 (td, *J* = 7.4, 1.1 Hz, 1H), 6.17 (d, *J* = 2.5 Hz, 1H), 3.01 (t, *J* = 7.7 Hz, 2H), 2.79 (m, 2H), 2.68 (h, *J* = 7.0 Hz, 1H), 1.70 – 1.53 (m, 2H), 1.29 (d, *J* = 6.9 Hz, 3H), 0.95 (t, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 137.5, 133.7, 132.7, 127.9, 127.5, 126.7, 124.1, 121.4, 118.1, 99.0, 34.5, 30.3, 29.8, 22.0, 20.2, 12.0. IR (neat): 3407, 2961, 1698, 1514, 1278 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{16}H_{19}N$ $(M)^+$ 225.1517, found: 225.1511.

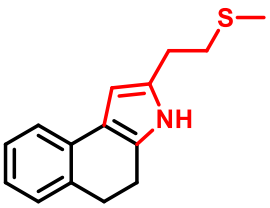
*2-benzyl-4,5-dihydro-3H-benzo[e]indole (**164d**):*



Prepared according to general procedure D and D', using (S)-(−)-2-Amino-3-phenyl-1-propanol (53 mg, 0.35 mmol)/(151 mg, 1 mmol) to afford 2-benzyl-4,5-dihydro-3*H*-benzo[*e*]indole **164d** (55 mg, 61 %) using (0.35 mmol) and (150 mg, 58%) using (1 mmol) as a pink solid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). Melting point: 88−90 °C. ^{1}H

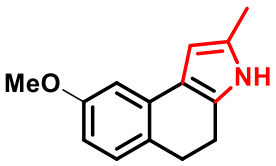
NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.34 –7.26 (m, 6H), 7.19 – 7.13 (m, 2H), 7.03 – 6.99 (m, 1H), 6.25 (s, 1H), 3.99 (s, 2H), 2.98 (t, *J* = 7.7 Hz, 2H), 2.73 (t, *J* = 7.7 Hz, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 139.6, 133.5, 132.9, 130.3, 128.9, 128.8, 128.7, 128.0, 126.8, 126.6, 124.3, 121.5, 118.5, 102.0, 34.4, 29.8, 21.9. IR (neat): 1453, 1516, 1699, 2927, 3402 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{19}H_{18}N$ $(M+H)^+$ 260.1439, found 260.1429.

*2-(2-(methylthio)ethyl)-4,5-dihydro-3H-benzo[e]indole (**164e**):*



Prepared according to general procedure D and D', using (S)-(-)-methioninol (47 mg, 0.35 mmol)/(135 mg, 1 mmol) to afford 2-(2-(methylthio)ethyl)-4,5-dihydro-3*H*-benzo[*e*]indole **164e** (45 mg, 53%) using (0.35 mmol) and (122 mg, 50%) using (1 mmol) as a yellow semisolid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.32 (d, *J* = 7.5 Hz, 1H), 7.18 (dd, *J* = 15.4, 7.4 Hz, 2H), 7.04 – 7.00 (m, 1H), 6.21 (s, 1H), 3.00 (t, *J* = 7.7 Hz, 2H), 2.91 (t, *J* = 7.0 Hz, 2H), 2.82 – 2.76 (m, 4H), 2.17 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 133.5, 132.9, 130.6, 128.4, 127.9, 126.7, 124.2, 121.4, 118.3, 101.1, 34.7, 29.8, 27.6, 21.9, 15.7. IR (neat): 3397, 2918, 1699, 1515, 1367 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{15}H_{18}NS$ $(M+H)^+$ 244.1160, found: 244.1149.

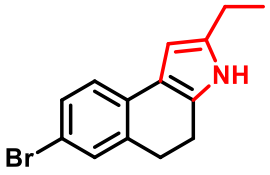
*8-methoxy-2-methyl-4,5-dihydro-3H-benzo[e]indole (**164f**):*



Prepared according to general procedures D and D', using 2-aminopropan-1-ol (26 mg, 0.35 mmol)/(75 mg, 1 mmol) to afford 8-methoxy-2-methyl-4,5-dihydro-3*H*-benzo[*e*]indole **164f** (39 mg, 52%) using (0.35 mmol) and (111 mg, 52%) using (1 mmol) as a yellow semisolid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.06 (d, *J* = 8.2 Hz, 1H), 6.88 (d, *J* = 2.6 Hz, 1H), 6.56 (dd, *J* = 8.1, 2.6 Hz, 1H), 6.13 (d, *J* = 1.3 Hz, 1H), 3.83 (s, 3H), 2.93 (t, *J* = 7.7 Hz, 2H), 2.74 (t, *J* = 7.7 Hz, 2H), 2.29 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 158.8, 134.8, 128.6, 128.5, 127.3, 125.3, 118.6, 109.0, 107.6, 101.3, 55.4, 29.0, 22.1, 13.3. IR (neat): 3197, 2931, 1617, 1507, 1277 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{14}H_{16}NO$ $(M+H)^+$ 214.1232, found: 214.1224.

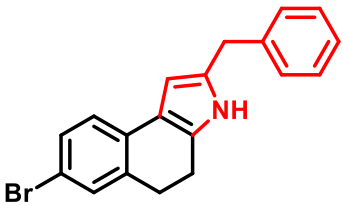
*7-bromo-2-ethyl-4,5-dihydro-3H-benzo[e]indole (**164g**):*

Prepared according to general procedure D and D', using 2-amino-1-butanol (31 mg, 0.35 mmol)/(89 mg, 1 mmol) to afford 2-benzyl-7-bromo-4,5-dihydro-3*H*-benzo[*e*]indole **164g** (51 mg, 53%) using (0.35 mmol) and (152 mg, 55%) using (1 mmol) as a yellow semisolid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.30 – 7.28 (m, 2H), 7.18 – 7.16 (m, 1H), 6.13 (s, 1H), 2.96 (t, *J* = 7.8 Hz, 2H), 2.75 (t, *J* = 7.7 Hz, 2H), 2.63 (q, *J* = 7.6 Hz, 2H), 1.29 (t, *J* = 7.6 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 135.1, 134.3, 132.7, 130.7, 129.5, 127.8, 122.9, 117.6, 117.0, 99.5, 29.6, 21.7, 21.0, 13.8. IR (neat): 3415, 2926, 1699, 1521, 1263 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{14}H_{14}BrN$ $(M)^+$ 275.0310, found: 275.0306.



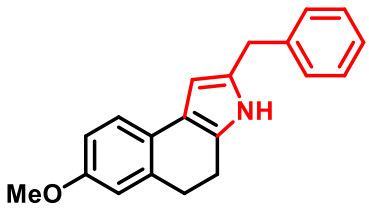
*2-benzyl-7-bromo-4,5-dihydro-3H-benzo[e]indole (**164h**):*

Prepared according to general procedure D and D', using (S)-(−)-2-Amino-3-phenyl-1-propanol (53 mg, 0.35 mmol)/(151 mg, 1 mmol) to afford 2-benzyl-7-bromo-4,5-dihydro-3*H*-benzo[*e*]indole **164h** (59 mg, 50%) using (0.35 mmol) and (152 mg, 45%) using (1 mmol) as a yellow semisolid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.35 – 7.30 (m, 2H), 7.29 – 7.21 (m, 5H), 7.14 (d, *J* = 7.8 Hz, 1H), 6.18 (d, J = 2.3 Hz, *1*H), 3.96 (s, 2H), 2.92 (t, *J* = 7.8 Hz, 2H), 2.70 (t, *J* = 7.8 Hz, 2H).^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 139.3, 135.0, 132.5, 130.7, 130.7, 129.5, 128.8, 128.8, 128.7, 126.7, 122.9, 117.7, 117.1, 101.8, 34.4, 29.5, 21.7. IR (neat): 3411, 2919, 1195, 1140 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{19}H_{17}BrN$ $(M+H)^+$ 338.0544, found: 338.0519.



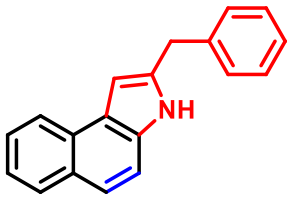
*2-benzyl-7-methoxy-4,5-dihydro-3H-benzo[e]indole (**164i**):*

Prepared according to general procedure D and D', using (S)-(−)-2-Amino-3-phenyl-1-propanol (53 mg, 0.35 mmol)/(151 mg, 1 mmol) to afford 2-benzyl-7-methoxy-4,5-dihydro-3*H*-benzo[*e*]indole **164i** (46 mg, 46%) using (0.35 mmol) and (146 mg, 50%) using (1 mmol) as a yellow semisolid after silica gel column chromatography (EtOAc:*n*-hexane =10:90). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.27–7.21 (m, 7H), 6.73 (s, 1H), 6.17 (d, *J* = 2.3 Hz, 1H), 3.96 (s, 2H), 3.78 (s, 3H), 2.94 (t, *J* = 7.7 Hz, 2H), 2.70 (t, *J* = 7.7 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 156.8, 139.6, 134.5, 130.1,



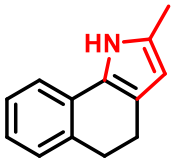
128.9, 128.7, 127.3, 126.5, 122.2, 118.2, 114.4, 111.3, 101.6, 55.4, 34.4, 30.1, 21.8. IR (neat): 3407, 2919, 1523, 1246 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{20}H_{19}NO$ $(M)^+$ 289.1467, found: 289.1455.

*2-benzyl-3H-benzo[e]indole (**165a**):*



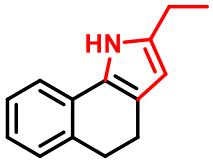
Prepared according to general procedure F, using 2-benzyl-4,5-dihydro-3*H*-benzo[*e*]indole **164d** (39 mg, 0.15 mmol) to afford 2-benzyl-3*H*-benzo[*e*]indole **165a** (9 mg, 24 % yield) White solid after silica gel column chromatography (EtOAc:*n*-hexane = 10:80). Melting point: 123−125 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.2 Hz, 1H), 8.08 (s, 1H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.53 (m, 2H), 7.42 – 7.33 (m, 4H), 7.30 (d, *J* = 7.0 Hz, 3H), 6.88 (d, *J* = 1.3 Hz, 1H), 4.23 (s, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 138.9, 136.0, 132.5, 129.2, 129.0, 128.9, 128.6, 128.0, 126.9, 125.7, 123.5, 123.3, 123.1, 122.2, 112.5, 100.6, 34.9. IR (neat): 3400, 2918, 2850, 1735, 1300, 1182 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{19}H_{15}N$ $(M)^+$ 257.1204, found: 257.1200.

*2-methyl-4,5-dihydro-1H-benzo[g]indole (**166a**):*[120]



Prepared according to general procedures E and E', using 2-aminopropan-1-ol (26 mg, 0.35 mmol)/(75 mg, 1 mmol) to afford 2-methyl-4,5-dihydro-1*H*-benzo[*g*]indole **166a** (30 mg, 47%) using (0.35 mmol) and (86 mg, 47%) using (1 mmol) as purple solid after silica gel column chromatography (EtOAc:*n*-hexane = 20:80). Melting point: 69−71 °C. (lit[21] = 70–72 °C). ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.21 – 7.16 (m, 2H), 7.09 (d, *J* = 6.7 Hz, 1H), 7.03 (td, *J* = 7.4, 1.3 Hz, 1H), 5.83 (d, *J* = 1.5 Hz, 1H), 2.93 (t, *J* = 7.6 Hz, 2H), 2.71 (t, *J* = 7.6 Hz, 2H), 2.34 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 134.5, 129.6, 128.8, 128.4, 126.6, 126.5, 124.5, 121.0, 117.7, 106.4, 30.2, 22.0, 13.4. IR (neat): 3308, 2927, 1651, 1509, 1290 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{13}H_{13}N$ $(M)^+$ 183.1048, found: 183.1044.

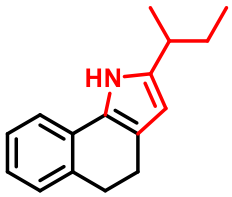
*2-ethyl-4,5-dihydro-1H-benzo[g]indole (**166b**):*[108e]



Prepared according to general procedure E and E', using 2-amino-1-butanol (31 mg, 0.35 mmol)/(89 mg, 1 mmol) to afford 2-ethyl-4,5-dihydro-1*H*-benzo[*g*]indole **166b** (36 mg, 52%) using (0.35 mmol) and (99 mg, 50%) using (1 mmol) as a pale brown oil after silica gel column chromatography

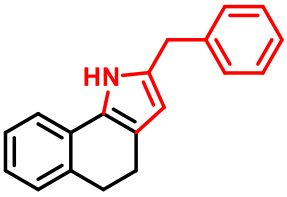
(EtOAc:*n*-hexane = 20:80). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.19 (t, *J* = 8.3 Hz, 2H), 7.11 (d, *J* = 7.4 Hz, 1H), 7.04 (td, *J* = 7.4, 1.3 Hz, 1H), 5.88 (s, 1H), 2.95 (t, *J* = 7.6 Hz, 2H), 2.72 (m, 4H), 1.32 (td, *J* = 7.6, 1.3 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 135.4, 134.5, 129.6, 128.3, 126.5, 126.4, 124.5, 120.7, 117.7, 104.7, 30.2, 22.0, 21.3, 13.8. IR (neat): 3504, 2929, 1698, 1512, 1268 cm^{-1}**.** HRMS (ESI-TOF): m/z calculated for $C_{14}H_{15}N$ $(M)^+$ 197.1204, found: 197.1200.

*2-(sec-butyl)-4,5-dihydro-1H-benzo[g]indole (**166c**):*



Prepared according to general procedure E and E', using 2-amino-3-methylpentan-1-ol (41 mg, 0.35 mmol)/(117 mg, 1 mmol) to afford 2-(*sec*-butyl)-4,5-dihydro-1*H*-benzo[*g*]indole **166c** (38 mg, 49%) using (0.35 mmol) and (102 mg, 45%) using (1 mmol) as a yellow semisolid after silica gel column chromatography (EtOAc:*n*-hexane = 20:80). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.19 (t, *J* = 7.2 Hz, 2H), 7.13 (d, *J* = 7.1 Hz, 1H), 7.06 – 7.00 (m, 1H), 5.86 (d, *J* = 2.3 Hz, 1H), 2.95 (t, *J* = 7.6 Hz, 2H), 2.74 (m, 3H), 1.76 – 1.56 (m, 2H), 1.31 (d, *J* = 6.9 Hz, 3H), 0.97 (t, *J* = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 139.0, 134.5, 129.7, 128.3, 126.5, 126.1, 124.4, 120.5, 117.7, 104.0, 34.7, 30.4, 30.2, 22.1, 20.3, 12.0. IR (neat): 3329, 2928, 1653, 1511, 1267 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{16}H_{19}N$ $(M)^+$ 225.1517, found: 225.1513.

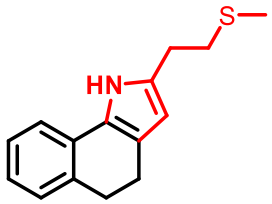
*2-benzyl-4,5-dihydro-1H-benzo[g]indole (**166d**):*[108e]



Prepared according to general procedure E and E', using (S)-(−)-2-Amino-3-phenyl-1-propanol (53 mg, 0.35 mmol)/(151 mg, 1 mmol) to afford 2-benzyl-4,5-dihydro-1*H*-benzo[*g*]indole **166d** (40 mg, 44%) using (0.35 mmol) and (130 mg, 50%) using (1 mmol) as a pale brown oil after silica gel column chromatography (EtOAc: *n*-hexane = 20:80). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.38 – 7.34 (m, 2H), 7.30 – 7.26 (m, 3H), 7.20 – 7.13 (m, 2H), 7.04 – 7.00 (m, 2H), 5.90 (d, *J* = 2.2 Hz, 1H), 4.03 (s, 2H), 2.94 (t, *J* = 7.6 Hz, 2H), 2.73 (t, *J* = 7.7 Hz, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 139.4, 134.6, 131.7, 129.5, 128.8, 128.8, 128.4, 127.3, 126.7, 126.5, 124.7, 120.7, 117.9, 107.0, 34.5, 30.1, 22.0. IR (neat): 3312, 2926, 1694, 1454 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{19}H_{17}N$ $(M)^+$ 259.1361, found: 259.1354.

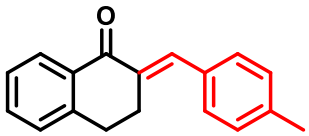
*2-(2-(methylthio)ethyl)-4,5-dihydro-1H-benzo[g]indole (**166e**):*

Prepared according to general procedure E and E', using (S)-(-)-methioninol (47 mg, 0.35 mmol)/(135 mg, 1 mmol) to afford 2-(2-(methylthio)ethyl)-4,5-dihydro-1*H*-benzo[*g*]indole **166e** (39 mg, 46%) using (0.35 mmol) and (102 mg, 42%) using (1 mmol) as a pink solid after silica gel column chromatography (EtOAc:*n*-hexane = 20:80). Melting point: 66−68 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.18 (t, *J* = 7.0, 1.3 H, 2H), 7.15 – 7.12 (m, 1H), 7.03 (td, *J* = 7.4, 1.3 Hz, 1H), 5.88 (d, *J* = 2.2 Hz, 1H), 2.97 – 2.91 (m, 4H), 2.81 (t, *J* = 7.3 Hz, 2H), 2.71 (t, *J* = 7.6 Hz, 2H), 2.17 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 134.6, 132.0, 129.5, 128.3, 127.0, 126.5, 124.7, 120.5, 118.0, 106.0, 34.7, 30.1, 27.8, 21.9, 15.7. IR (neat): 3269, 2924, 1608, 1507, 1256 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{15}H_{18}NS$ $(M+H)^+$ 244.1160, found: 244.1146.



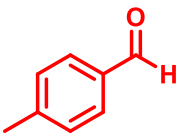
*(E)-2-(4-methylbenzylidene)-3,4-dihydronaphthalen-1(2H)-one (**167**):*[115]

Prepared according to procedure G, using tetralone **159** (300 mg, 2.05 mmol, 1.0 equiv.), aldehyde **160b** (296 mg, 2.46 mmol, 1.2 equiv.), NaOH (164 mg, 41.0 mmol, 2.0 equiv.) to provide **167a** (475 mg, 93% isolated yield) as a yellow solid after silica gel column chromatography (EtOAc:*n*-hexane = 20:80). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.87 (s, 1H), 7.49 (td, *J* = 7.5, 1.2 Hz, 1H), 7.38 – 7.34 (m, 3H), 7.25 (m, 3H), 3.14 (td, *J* = 6.5, 1.5 Hz, 2H), 2.95 (t, *J* = 6.6 2H), 2.40 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 188.0, 143.3, 138.9, 136.9, 134.8, 133.6, 133.3, 133.0, 130.1, 129.3, 128.3, 128.2, 127.1, 28.9, 27.3, 21.5. The data for this compound **167** are in agreement with the reported compound.



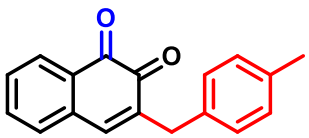
*4-methylbenzaldehyde (**160b**):*[116]

Prepared according to procedure A, 4-methylbenzyl alcohol **140b** (43 mg, 0.35 mmol, 1.0 equiv.), NaOH (42 mg, 1.05 mmol, 3 equiv.) to provide **160b** (8.5 mg, 20% isolated yield) as a yellow liquid after silica gel column chromatography (EtOAc/n-hexane = 10:80). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.95 (s, 1H), 7.76 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 2H), 2.43 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 192.1, 145.6, 134.2, 129.9, 129.8, 21.9. The data for this compound **2aa** are in agreement with the reported compound.



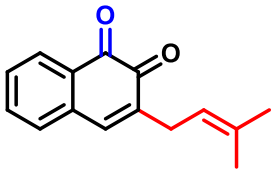
*3-(4-methylbenzyl)naphthalene-1,2-dione (**90b**):*[113]

Prepared according to procedure H, using 3-(4-methylbenzyl)naphthalen-2-ol **162a** (62 mg, 0.25 mmol, 1.0 equiv.), CuI (2.47 mg, 0.025 mmol) to provide **90b** (47 mg, 72% isolated yield) as a yellow solid after silica gel column chromatography (EtOAc:*n*-hexane = 10:80). Melting point: 92−94°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.1 Hz, 1H), 7.56 (td, *J* = 7.6, 1.4 Hz, 1H), 7.40 (td, *J* = 7.6, 1.1 Hz, 1H), 7.19 (d, *J* = 7.4 Hz, 1H), 7.14 (s, 4H), 6.97 (s, 1H), 3.73 (d, *J* = 1.1 Hz, 2H), 2.34 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) 181.0, 179.4, 141.7, 140.4, 136.5, 136.0, 135.4, 134.7, 130.7, 130.1, 130.1, 129.6, 129.6, 129.4, 34.9, 21.2. IR (neat): 2918, 2360, 1733, 1698, 1664, 1257 cm^{-1}. HRMS (ESI-TOF): m/z calculated for $C_{18}H_{15}O_2$ $(M+H)^+$ 263.1072, found: 263.1073.



*3-(3-methylbut-2-en-1-yl)naphthalene-1,2-dione (**90c**):*[113]

Prepared according to procedure H, using 3-(3-methylbut-2-en-1-yl)naphthalen-2-ol **162o** (53 mg, 0.25 mmol, 1.0 equiv.), CuI (2.47 mg, 0.025 mmol) to provide **90c** (35 mg, 62% isolated yield) as a yellow solid after silica gel column chromatography (EtOAc:*n*-hexane = 10:80). Melting point: 116−118°C. The data for this compound **90c** are in agreement with the reported compound. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.3 Hz, 1H), 7.59 (td, *J* = 7.6, 1.3 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.27 (d, *J* = 7.6 Hz, 1H), 7.11 (s, 1H), 5.24 – 5.19 (m, 1H), 3.13 (d, *J* = 7.4 Hz, 2H), 1.78 (s, 3H), 1.68 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 181.4, 179.6, 140.6, 139.8, 134.0, 135.7, 130.7, 130.1, 129.9, 129.4, 119.2, 27.7, 26.0, 18.0. IR (neat): 2920, 2361, 1733, 1694 cm^{-1}.



5.9. Appendix IV: Copies of ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra of representative compounds

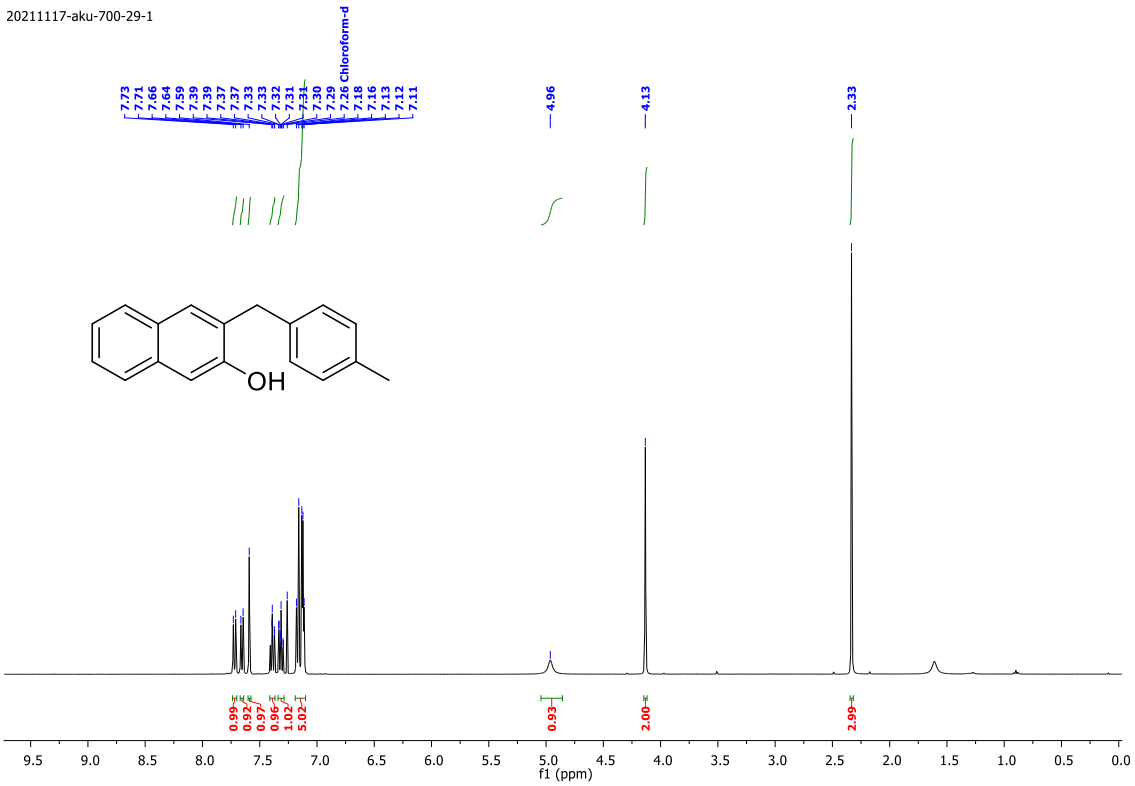


Figure 5.9.1. ^{1}H NMR (400 MHz, $CDCl_3$) of **162a**

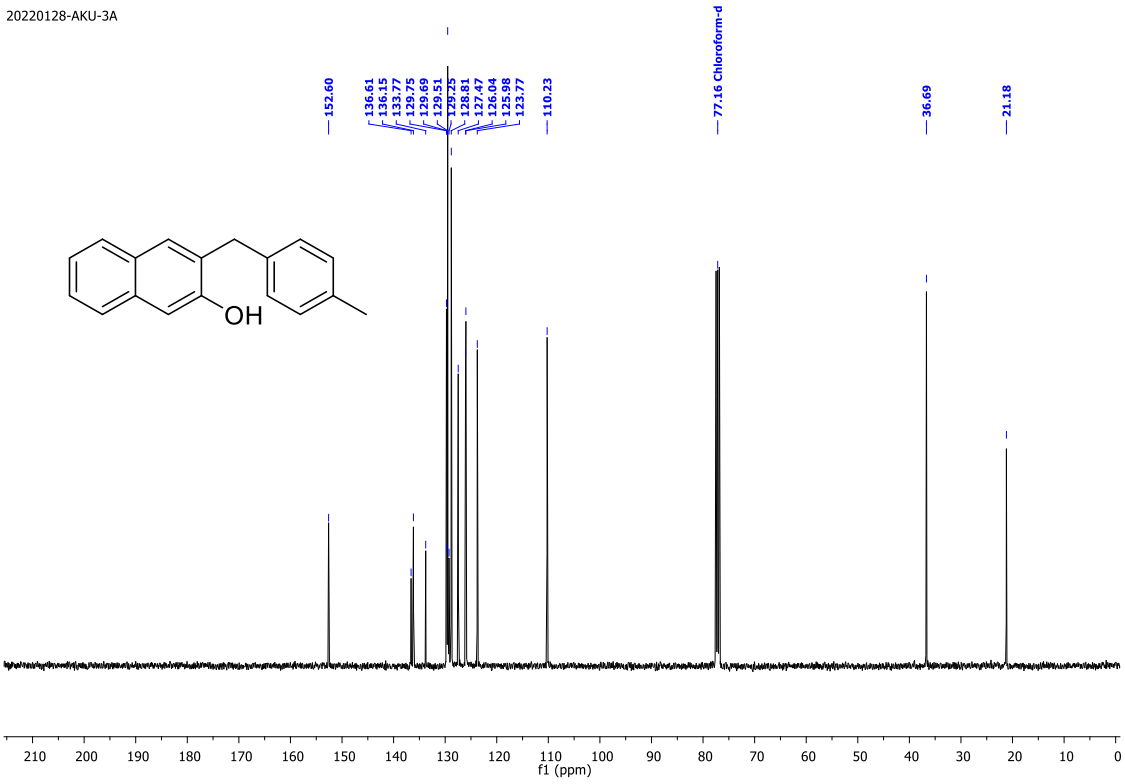


Figure 5.9.2. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) of **162a**

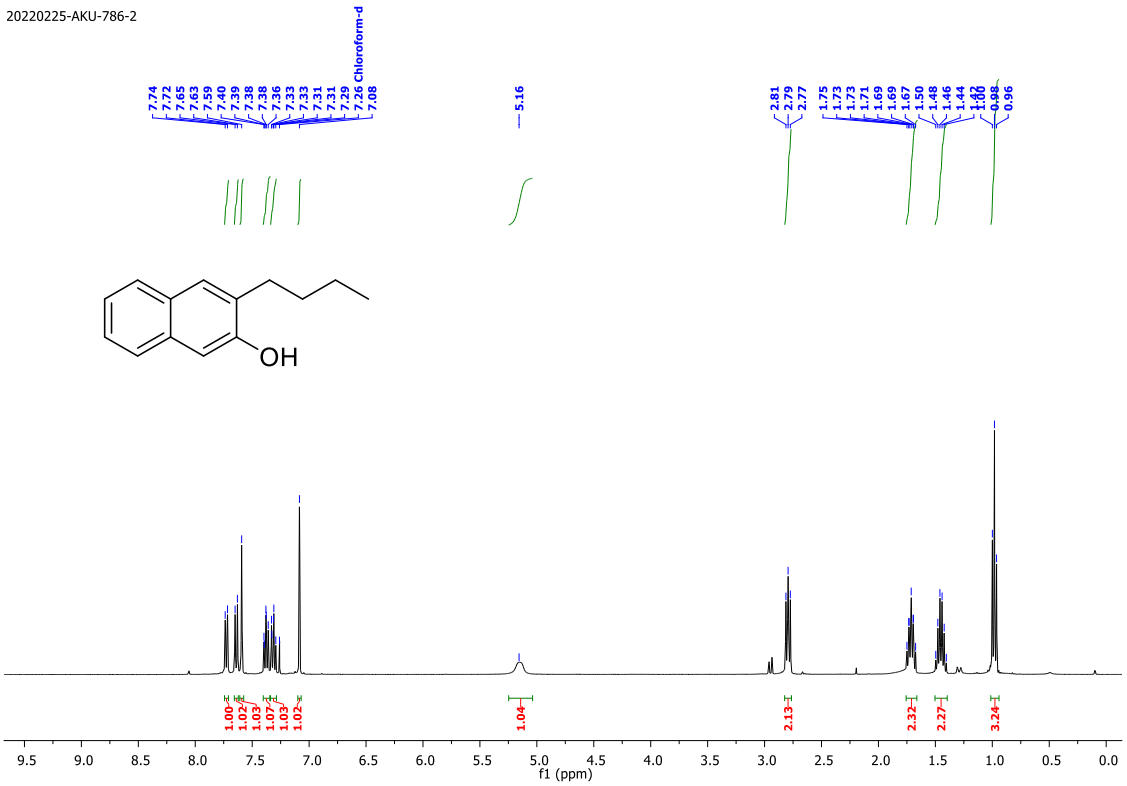


Figure 5.9.3. ^{1}H NMR (400 MHz, $CDCl_3$) of **162m**

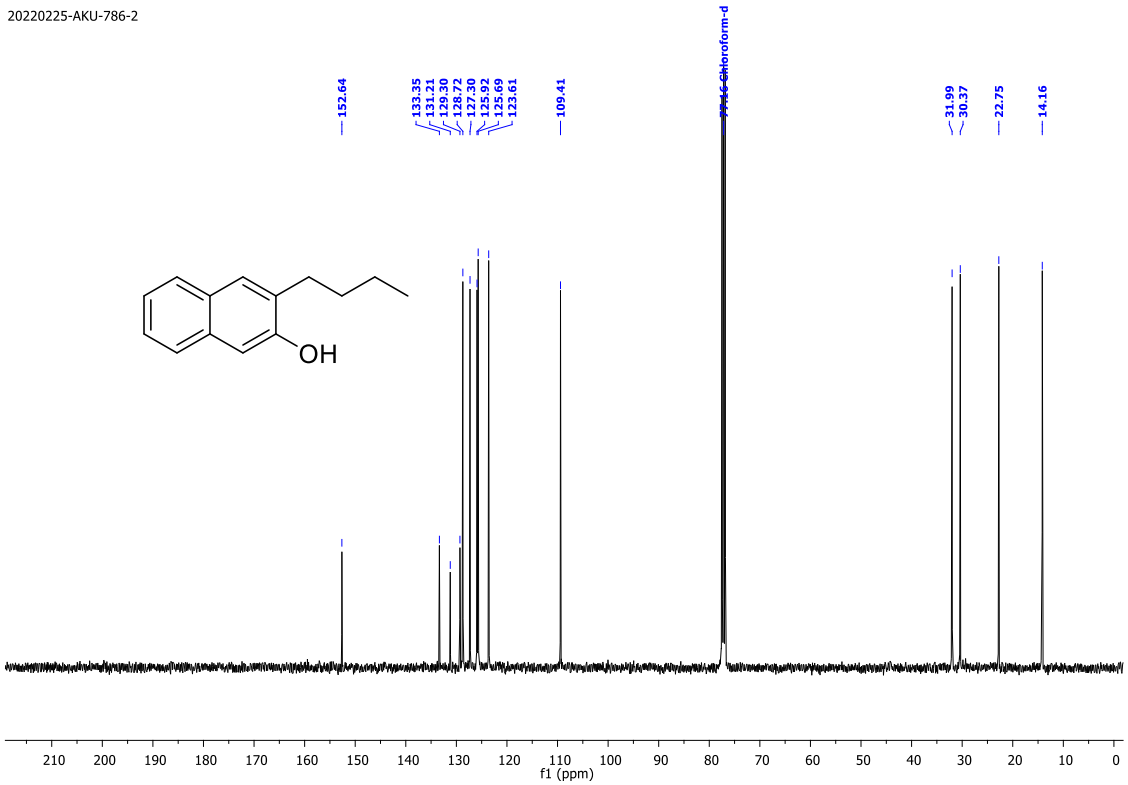


Figure 5.9.4. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) of **162m**

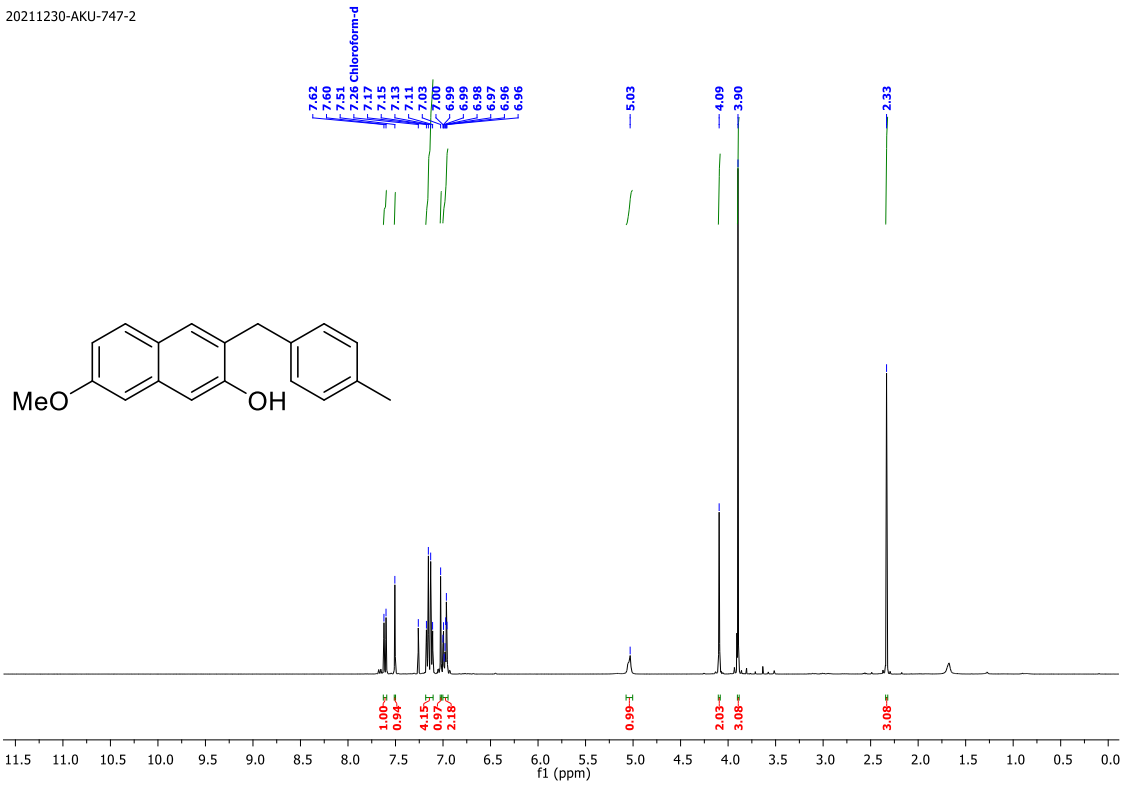


Figure 5.9.5. ^{1}H NMR (400 MHz, $CDCl_3$) of **162t**

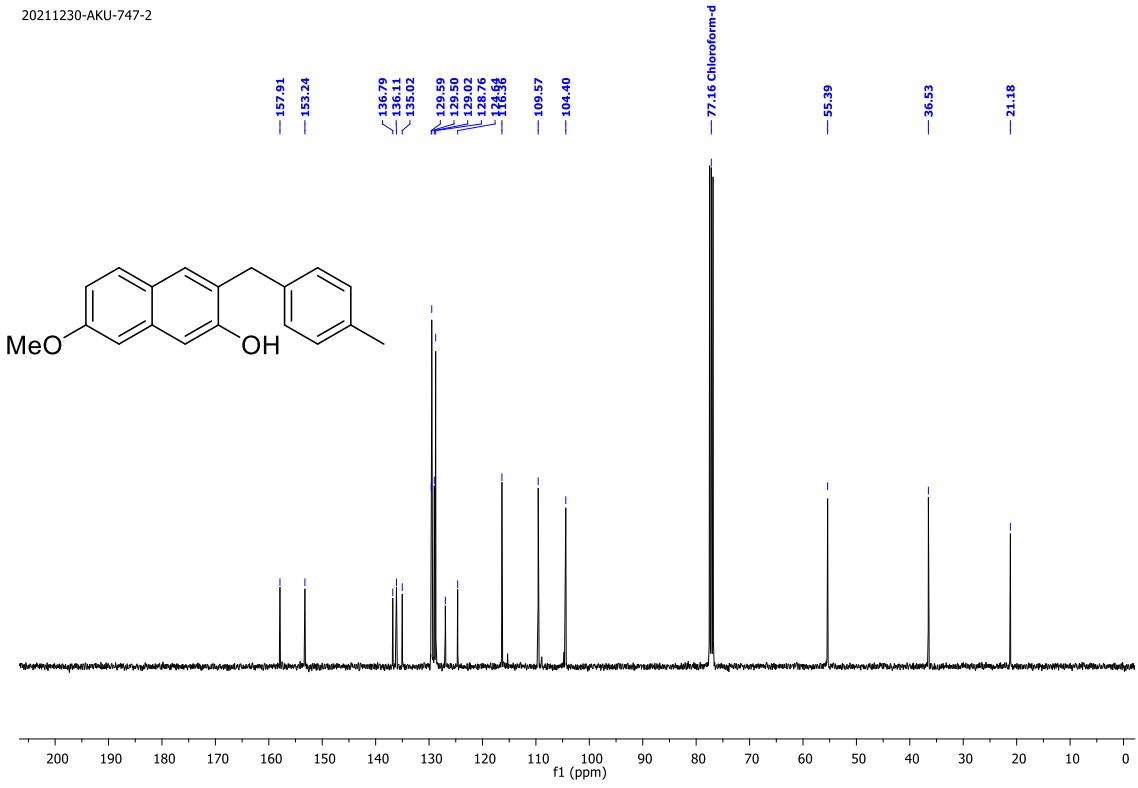


Figure 5.9.6. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) of **162t**

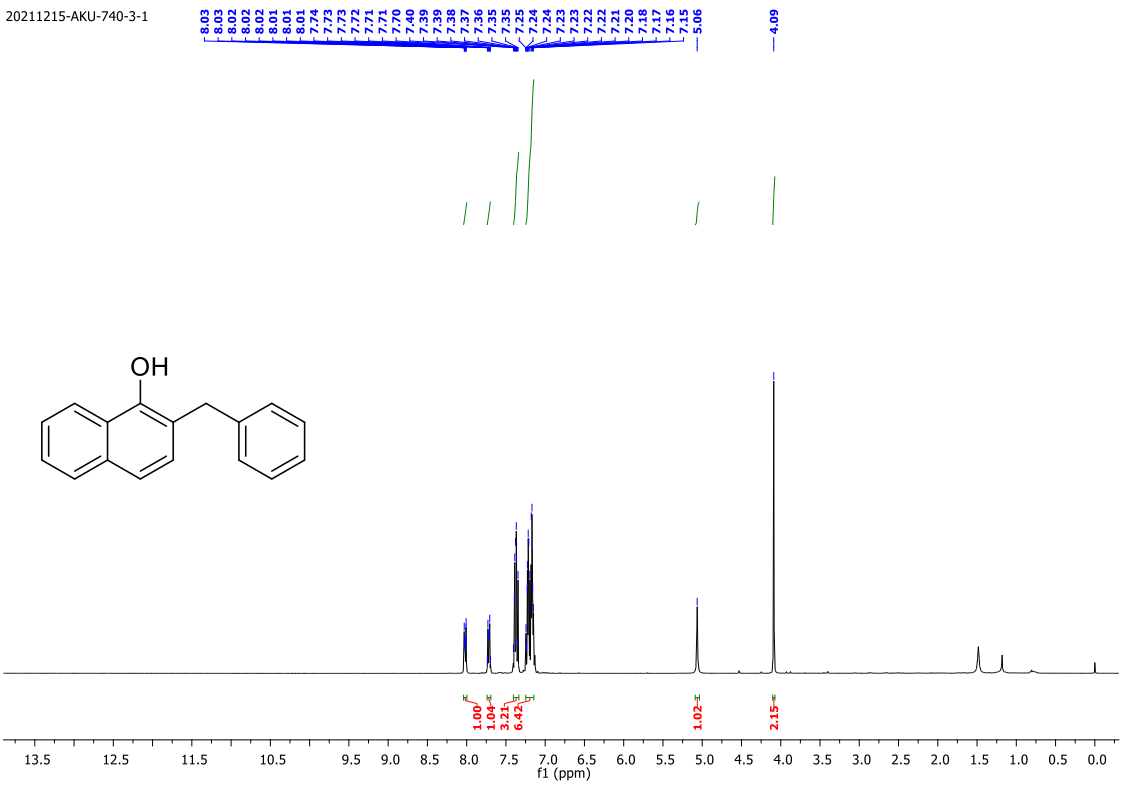


Figure 5.9.7. ^{1}H NMR (400 MHz, $CDCl_3$) of **117b**

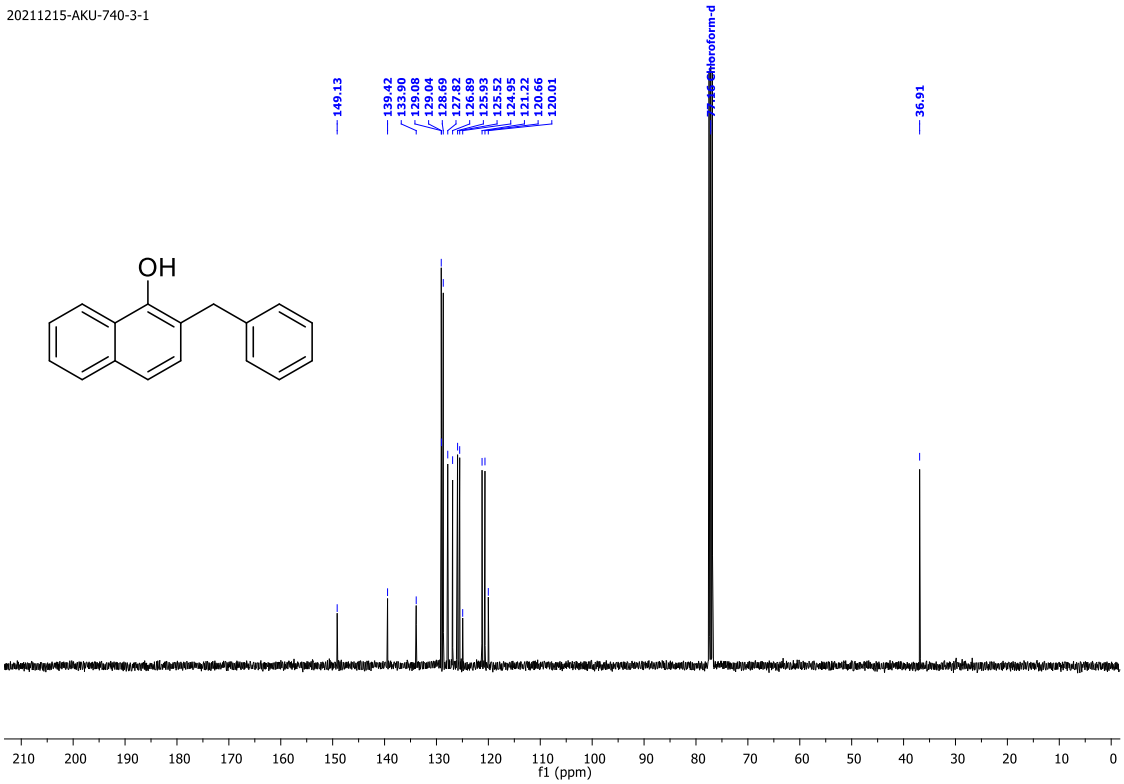


Figure 5.9.8. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) of **117b**

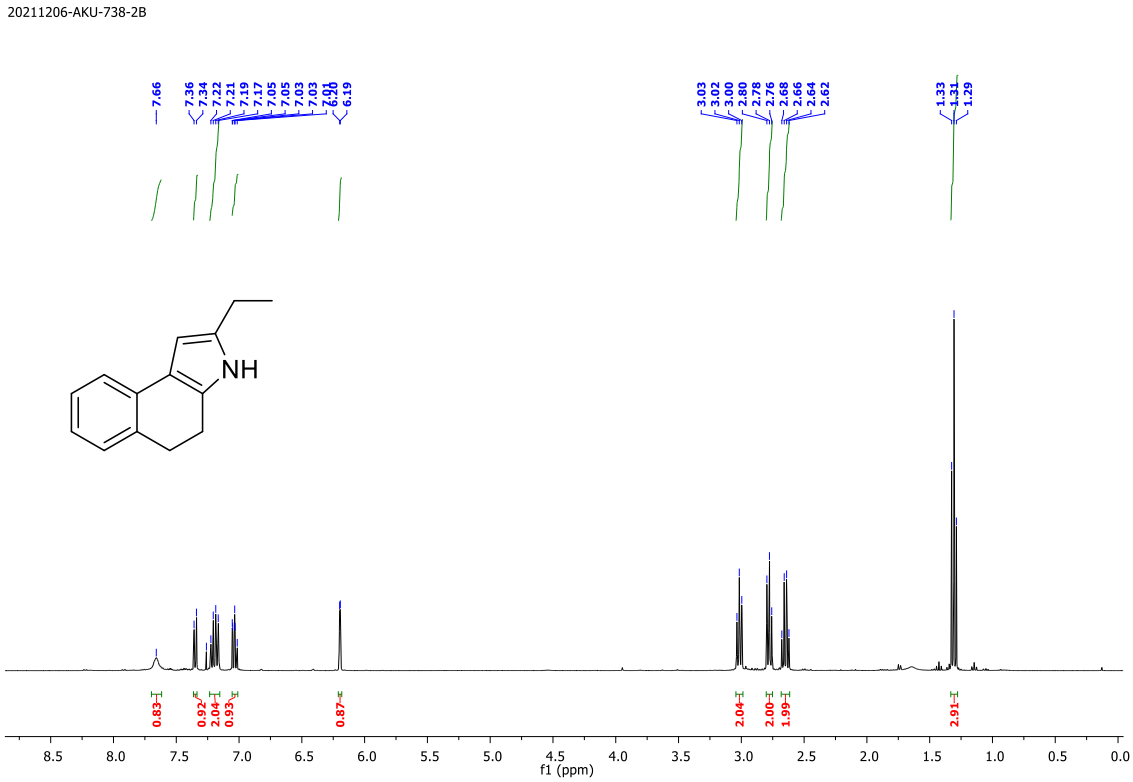


Figure 5.9.9. ^{1}H NMR (400 MHz, $CDCl_3$) of **164b**

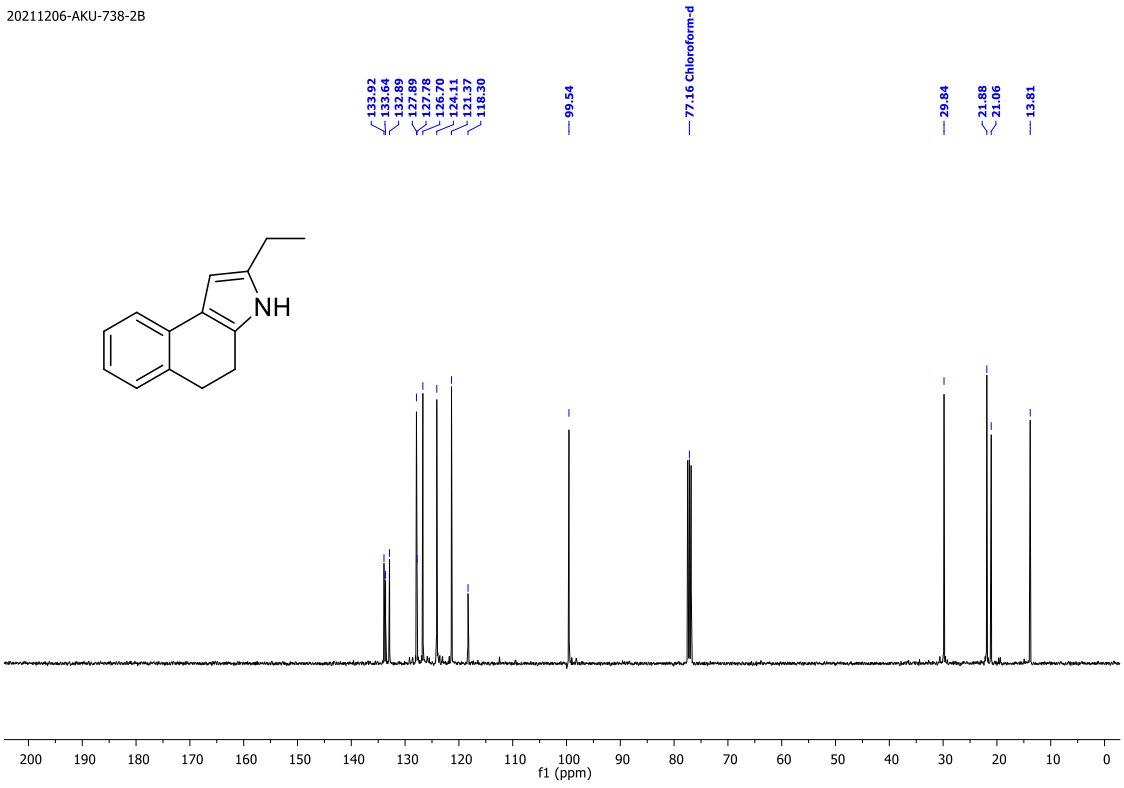


Figure 5.9.10. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) of **164b**

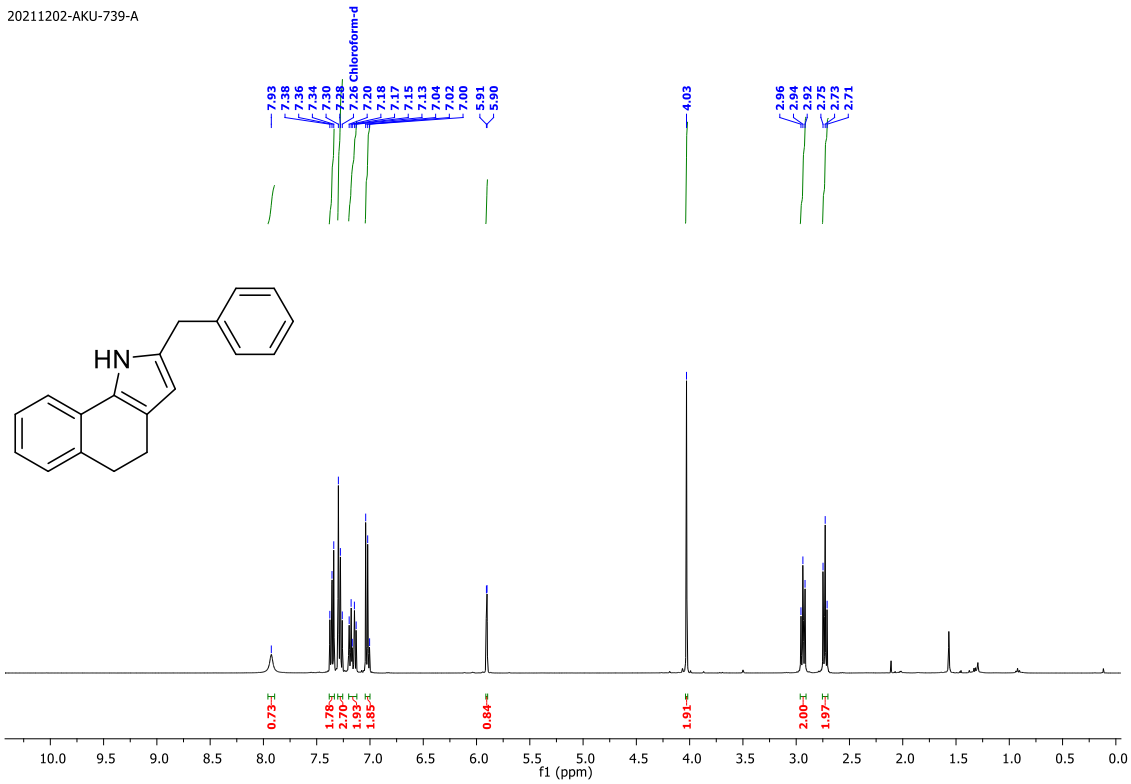


Figure 5.9.11. ^{1}H NMR (400 MHz, $CDCl_3$) of **166d**

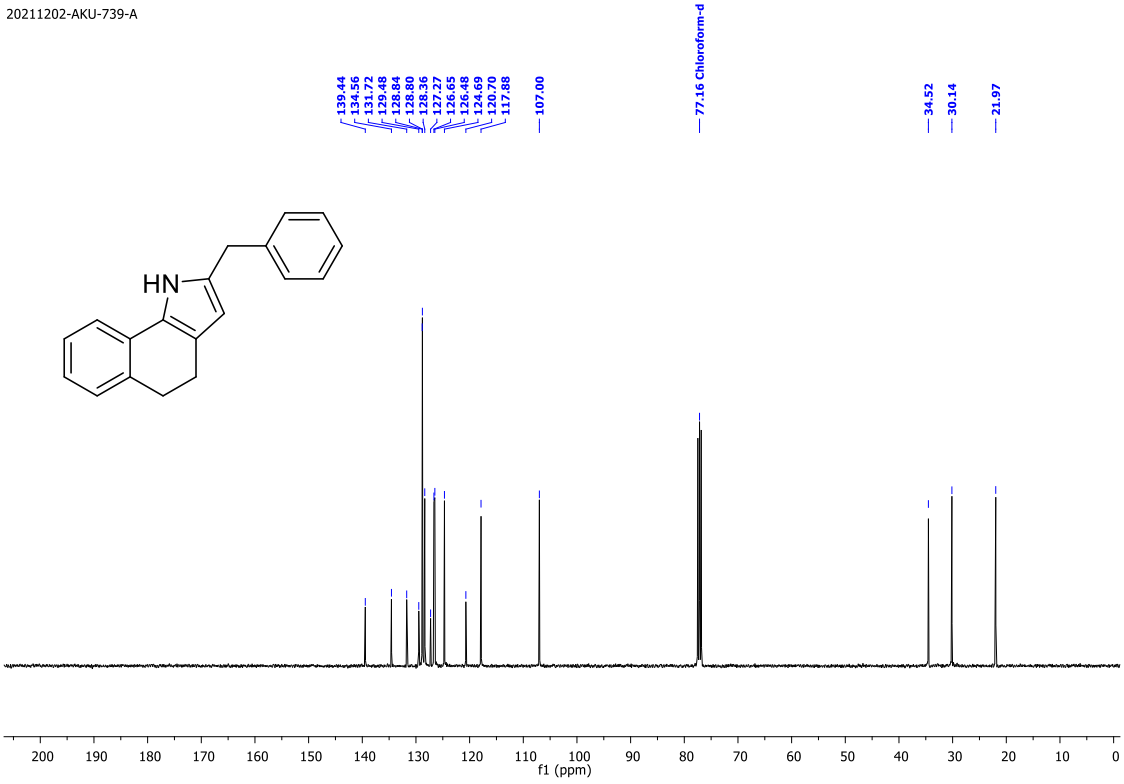


Figure 5.9.12. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) of **166d**

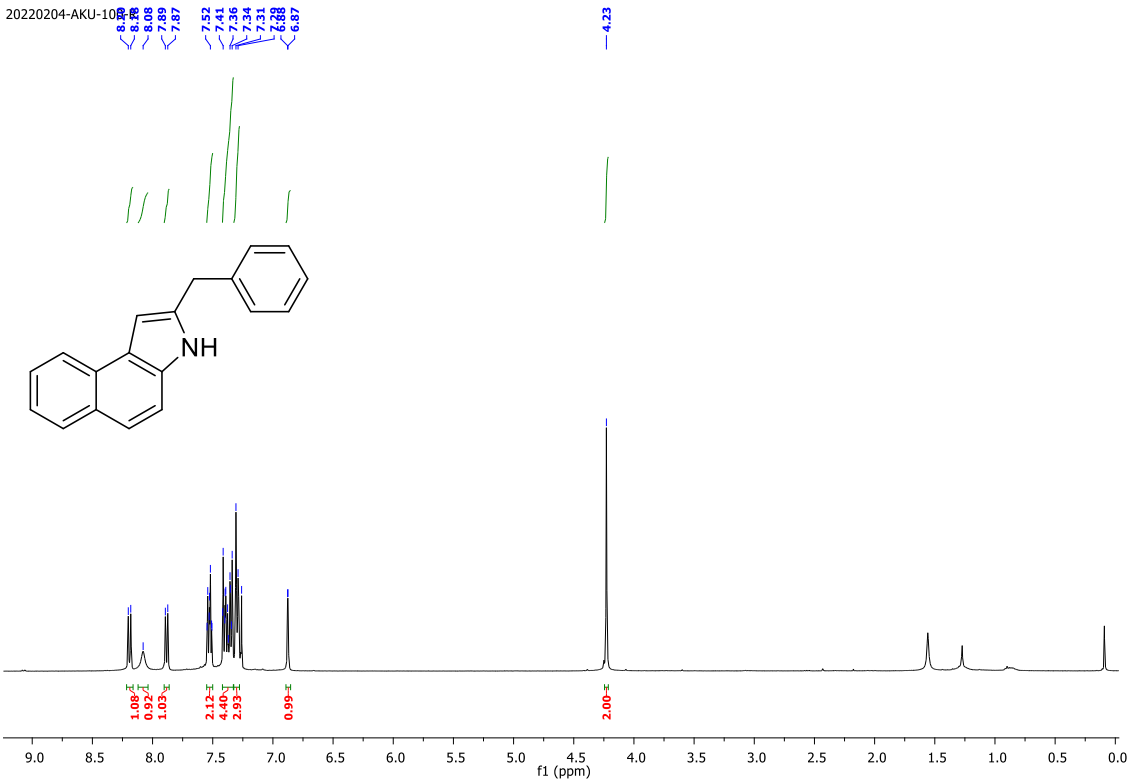


Figure 5.9.13. ^{1}H NMR (400 MHz, $CDCl_3$) of **165a**

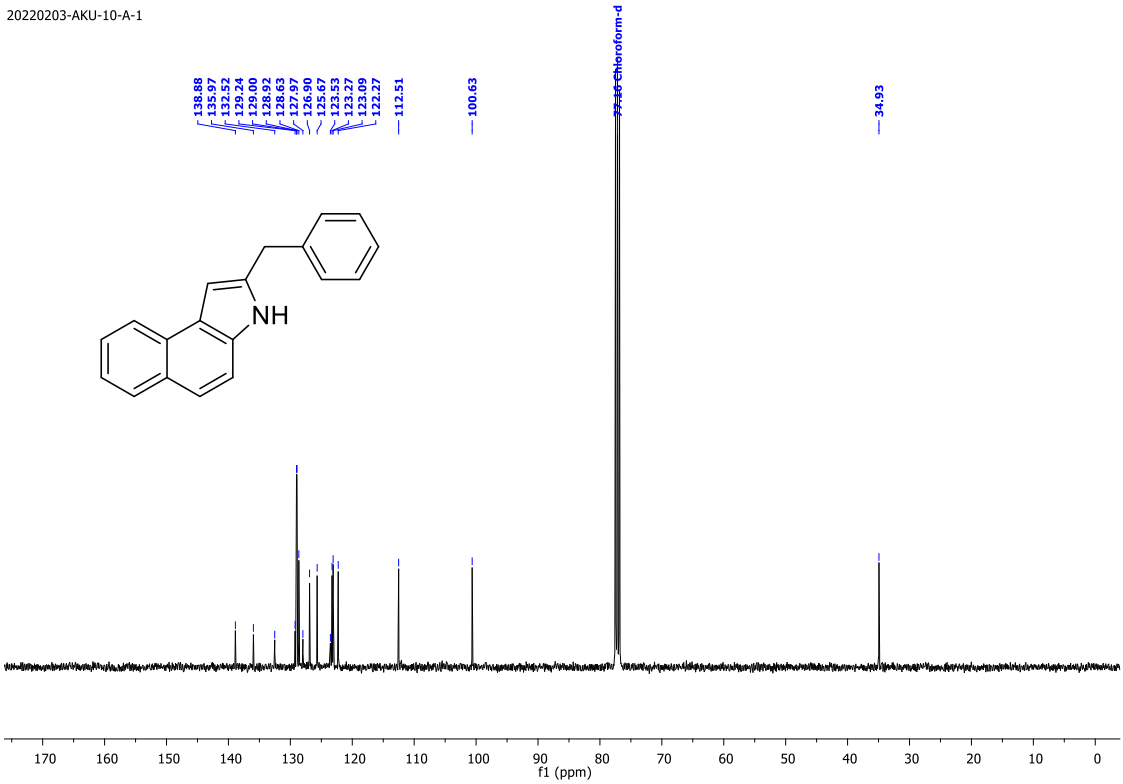


Figure 5.9.14. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) of **165a**

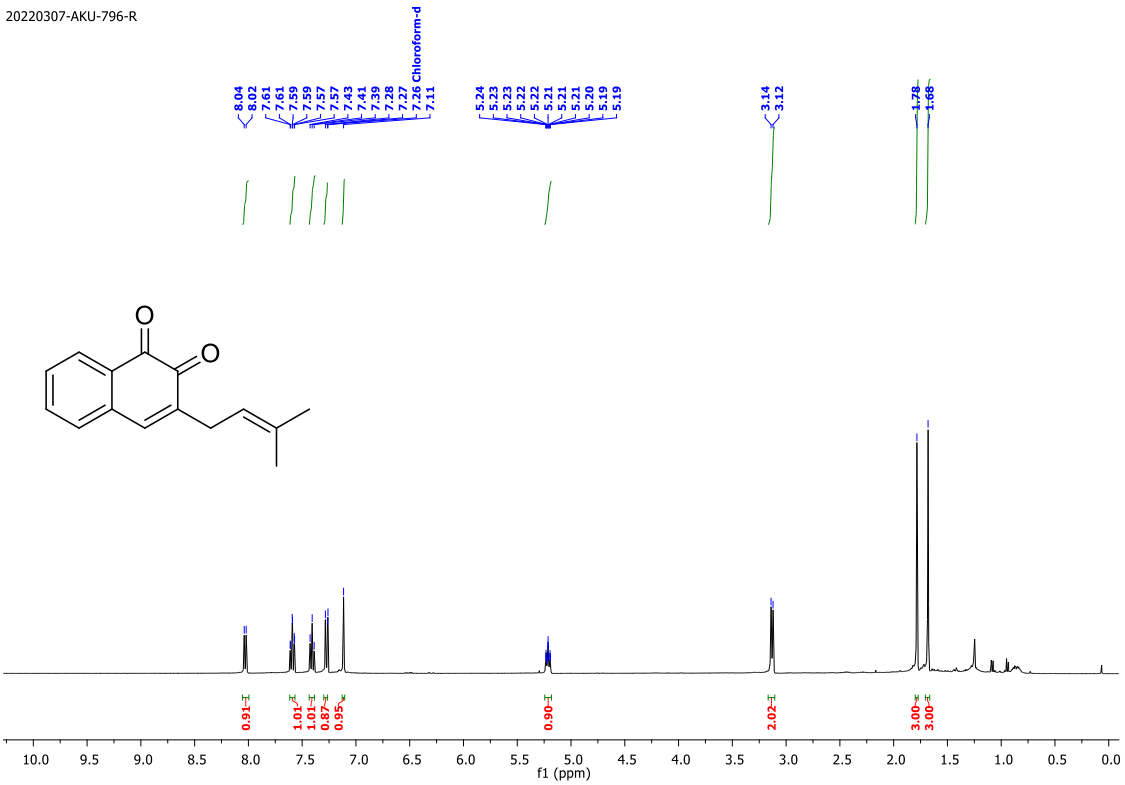


Figure 5.9.15. ^{1}H NMR (400 MHz, $CDCl_3$) of **90c**

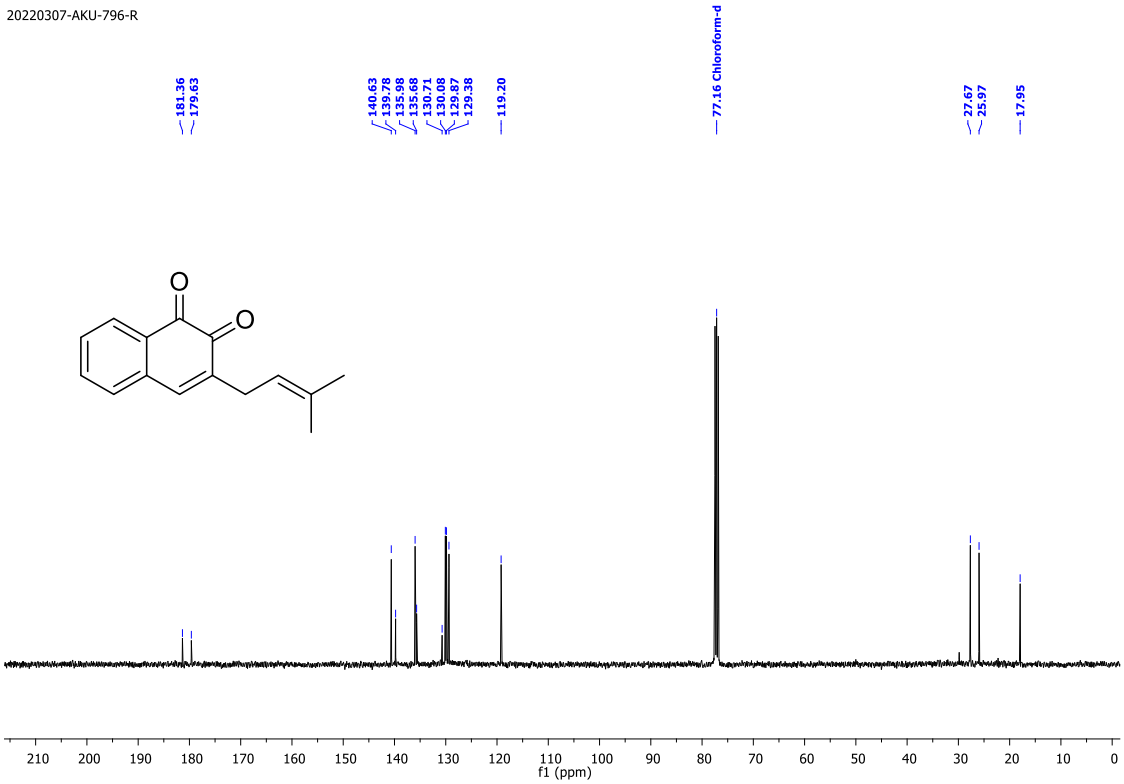


Figure 5.9.16. $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) of **90c**

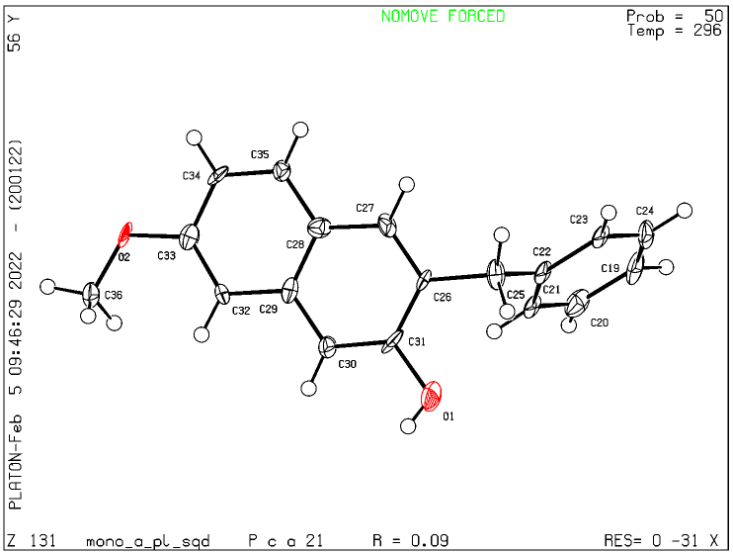


Figure 5.9.17. X-ray structure of product **162s** showing thermal ellipsoids at the 50% probability level**.**

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Transition-Metal-Free Alkylative Aromatization of Tetralone Using Alcohol/Amino Alcohol towards the Synthesis of Bioactive Naphthol and Benzo[e/g]indole Derivatives

Author: Akash S. Ubale, Gokul S. Londhe, Moseen A. Shaikh, et al
Publication: The Journal of Organic Chemistry
Publisher: American Chemical Society
Date: Jun 1, 2022

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CONCLUSION

The work presented in this thesis is related to organic synthesis and the development of novel methods for peroxidation, rearrangement reactions, and carbon-carbon (C-C), carbon-oxygen (C-O), and carbon-nitrogen (C-N) bond formation to synthesize various heterocyclic compounds. The thesis covers both batch and continuous flow techniques and aims to provide access to a diverse range of bioactive compounds, including commercial drugs and natural products. The key points presented in the thesis include: (a) Methods for peroxidation and rearrangement reactions: The thesis discussed various methods for performing peroxidation and rearrangement reactions to create heterocyclic scaffolds. These methods likely involve the introduction of peroxide groups into specific positions of molecules, followed by rearrangements to form complex heterocyclic structures.; (b) C-O bond formation *via* sp3-C-H peroxidation: One of the highlighted reactions involves the formation of carbon-oxygen (C-O) bonds through the peroxidation of sp3-hybridized carbon-hydrogen (C-H) bonds. This transformation likely involves the insertion of an oxygen atom from a peroxide source into a C-H bond, resulting in the creation of a C-O bond.; (c) Synthesis of heterocyclic compounds: This thesis developed the novel rearrangement of these peroxides to synthesize various heterocyclic bioactive compounds. Some examples of the synthesized compounds include (*Z*)-6-benzylidene-6*H*-benzo[*c*]chromene, dioxole-2-carboxamide, quinazolinone, and oxazoloquinazolinone. These compounds may have potential applications in the field of medicine and drug discovery due to their heterocyclic nature.; (d) C-C and C-N bond formation: This thesis also described the sequential transition-metal-free alkylative aromatization of tetralone using alcohol or amino alcohol as reactants. This transformation likely leads to the formation of carbon-carbon (C-C) and carbon-nitrogen (C-N) bonds, resulting in the synthesis of benzo[e/g]indole derivatives.

Overall, the thesis presented a comprehensive exploration of various methods for peroxidation, rearrangement reactions, and carbon-carbon (C-C), carbon-oxygen (C-O), and carbon-nitrogen (C-N) bond formation to synthesize diverse heterocyclic compounds. The combination of batch and continuous flow techniques showcases the versatility and potential applications of these synthetic approaches in the creation of bioactive molecules with various pharmaceutical and industrial uses.

Chapter 2: Manganese-Catalyzed Synthesis of Quaternary Peroxides: Application in Catalytic Deperoxidation and Rearrangement Reactions

This chapter described the novel class of quaternary peroxides through the use of a Mn-2,2'-bipyridine complex. The presence of the ligand was found to be crucial for achieving high yields of these peroxides, as evidenced by a decrease in yield in its absence. Among various nitrogen donor ligands tested, 2,2'-bipyridine emerged as the most effective ligand, leading to excellent yields of C-H peroxylated products. This catalytic method was successfully applied to the vicinal bisperoxidation of arylidene-9*H*-fluorene and arylideneindolin-2-one derivatives, with high selectivity over oxidative cleavage of the C=C bond, which typically forms ketone and aldehyde, all under mild reaction conditions. Importantly, the C-H peroxidation reaction could be scaled up to gram quantities without difficulty. This study also introduced a noteworthy aspect by reporting the reduction of a -O-O- bond, a type of bond reduction that had not been previously explored. This reduction induced reversibility in the reaction. Additionally, a $Sn(OTf)_2$-catalyzed skeletal rearrangement of the quaternary peroxides was discovered. This rearrangement involved an intramolecular aryl migration on an electron-deficient oxygen atom, leading to the formation of (*Z*)-6-benzylidene-6*H*-benzo[*c*]chromene derivatives. We have investigated the mechanistic aspects of the reactions in depth and proposed mechanisms for peroxidation, bisperoxidation, molecular rearrangement of peroxides, and deperoxidation reactions.

Overall, this study presents the synthesis and application of a novel class of quaternary peroxides using an Mn-2,2'-bipyridine complex. The research highlights the importance of the ligand in the transformation, introduces unique bond reduction processes, and explores intricate rearrangement reactions, all supported by detailed mechanistic investigations.

Chapter 3: Peroxidation and Skeletal Rearrangement for the Synthesis of Dioxole-2-carboxamide Derivatives under Continuous-Flow Condition

This chapter described the scalable and safer method for the peroxidation of bioactive 2-naphthols and benzofuranones derivatives. The innovation in this work was the utilization of a continuous flow setup for the peroxidation process, which offers advantages in terms of scalability and safety compared to traditional batch methods. Here, we have successfully carried out the peroxidation of benzofuranone derivatives and converted the resulting peroxides into *N*-substituted-2-phenylbenzo[*d*][1,3]dioxole-2-carboxamide derivatives. This transformation exhibited high efficiency, with yields reaching up to 95%. These final derivatives are potentially

bioactive, implying their potential use in various biological applications. Moreover, the synthesized peroxide has been successfully converted into the bioactive 3-hydroxy-3-phenylbenzofuran-2(3H)-one and 1,2-naphthoquinone. To explain the observed reactions, we have proposed a plausible mechanism based on both experimental findings and information available in the existing scientific literature.

Overall, this study presents a novel approach to the peroxidation of 2-naphthols and benzofuranones derivatives using continuous flow, which offers benefits in terms of scalability and safety. The resulting peroxides were efficiently transformed into potentially bioactive derivatives, and a proposed reaction mechanism helps explain the observed experimental results and reaction pathways.

Chapter 4: Sequential Oxidative-Fragmentation and Skeletal Rearrangement of Peroxides for the Synthesis of Quinazolinone Derivatives

This chapter described the chemical reaction involving peroxyoxindole that undergoes treatment under basic conditions, resulting in the formation of an isocyanate intermediate. This intermediate then plays a crucial role in facilitating a novel oxidative-skeletal rearrangement. This rearrangement is facilitated by the presence of a primary amine or amino alcohol. The goal of this reaction is to synthesize exo-olefinic-substituted quinazolinone or oxazoloquinazolinone compounds. The versatility of this reaction is highlighted by the fact that it works well with a broad range of substrates. Different primary amine nucleophiles can be employed in the reaction, resulting in excellent yields of the desired products. This reaction takes place at room temperature, further enhancing its practical utility. Interestingly, when secondary amines are introduced into the reaction mixture, the oxidative fragmentation process generates a diverse array of unsymmetrically substituted functionalized urea compounds. Additionally, the reaction is extended to cases involving amino alcohols as double nucleophilic scaffolds. In this scenario, the reaction proceeds through a sequential series of steps. First, there is an oxidative fragmentation, followed by nucleophilic addition. Subsequently, an intramolecular nucleophilic attack occurs on a tertiary alcohol moiety. These steps collectively lead to the formation of various tricyclic quinazolinone derivatives. These derivatives are obtained as a mixture of diastereomers, demonstrating the complexity and versatility of the reaction in creating complex molecular designs.

Overall, this chapter highlights a unique and efficient chemical transformation that allows for the synthesis of diverse quinazolinone and oxazoloquinazolinone derivatives through oxidative

rearrangements and nucleophilic reactions under basic conditions. The reaction's ability to work with various substrates and generate complex molecular structures underscores its potential significance in the field of organic synthesis. The formation of the isocyanate as a key intermediate that accelerates oxidative-skeletal rearrangement has been confirmed by trapping experiments and spectroscopic evidence.

Chapter 5: Transition-Metal-Free Alkylative Aromatization of Tetralone Using Alcohol/Amino Alcohol towards the Synthesis of Bioactive Naphthol and Benzo[*e/g*]indole Derivatives

This chapter described the synthetic method involving the transition metal-free oxidation-condensation-isomerization-aromatization process for the synthesis of bioactive naphthol and benzo[e/g]indole derivatives. This method is notable for its sequential, regioselectivity, and use of relatively inexpensive and readily available reagents. The synthesis involves the utilization of benchtop NaOH and KO*t*Bu bases, along with environmentally friendly alcohols as alkylating reagents. One of the significant advantages of this method is that it avoids the use of transition metal catalysts, which can sometimes be expensive and challenging to handle. Additionally, the absence of transition metals could reduce potential issues related to toxicity and metal contamination in the final products. The method's regioselectivity implies that the reaction prefers to occur at specific positions on the reactant molecules, leading to the desired product formation. Furthermore, the use of environmentally friendly alcohols as alkylating reagents is a step towards greener synthesis, minimizing the use of hazardous and environmentally damaging reagents. The fact that the process generates water and hydrogen peroxide as by-products suggests that the reaction has some degree of atom efficiency and that the generated waste products are relatively safe.

Overall, this synthesis method appears to be advantageous from both a practical and environmental standpoint, offering a way to generate valuable bioactive naphthol and benzo[e/g]indole derivatives with reduced reliance on expensive or toxic reagents and transition metals.

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(1) **Ubale, A. S**.; Chaudhari, M. B.; Shaikh, M. A.; Gnanaprakasam, B. Manganese-Catalyzed Synthesis of Quaternary Peroxides: Application in Catalytic Deperoxidation and Rearrangement Reactions. *J. Org. Chem.* **2020**, *85, 16*, 10488–10503.

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(8) Shaikh, M. A.; **Ubale, A. S**.; Gnanaprakasam, B. Heterogenous Amberlyst-A26 mediated Corey-Chaykovasky cyclopropanation under continuous flow. **2023** (Manuscript submitted to JOC-ACS).

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Manganese-Catalyzed Synthesis of Quaternary Peroxides: Application in Catalytic Deperoxidation and Rearrangement Reactions

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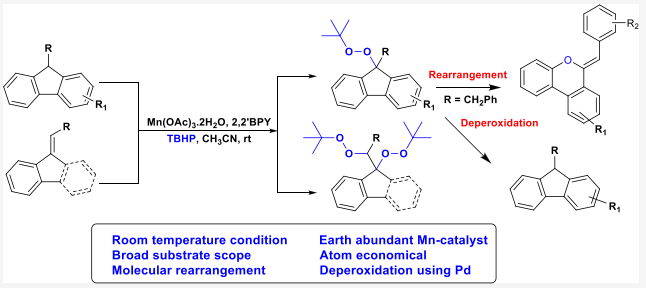
ABSTRACT: Highly efficient, selective, and direct C−H peroxidation of 9-substituted fluorenes has been achieved using a Mn−2,2′-bipyridine catalyst via radical−radical cross-coupling. Moreover, this method effectively promotes the vicinal bisperoxidation of sterically hindered various substituted arylidene-9*H*-fluorene/arylideneindolin-2-one derivatives to afford highly substituted bisperoxides with high selectivity over the oxidative cleavage of C═C bond that usually forms the ketone of an aldehyde. Furthermore, a new approach for the synthesis of (*Z*)-6-benzylidene-6*H*-benzo[*c*]chromene has been achieved via an acid-catalyzed skeletal rearrangement of these peroxides. For the first time, unlike O−O bond cleavage, reductive C−O bond cleavage in peroxides using the Pd catalyst and H_2 is described, which enables the reversible reaction to afford exclusively deperoxidized products. A detailed mechanism for peroxidation, molecular rearrangement, and deperoxidation has been proposed with preliminary experimental evidences.



INTRODUCTION

The design of a new catalytic system for the selective oxidative C−O bond formation is a formidable and long-standing goal in synthetic chemistry.[1] Organic peroxides are privileged scaffolds, and the existence of a reactive O−O bond makes them versatile intermediates in radical chemistry and many chemical syntheses. For instance, peroxides are used as precursors for the radical polymerization initiation in industrial production.[2] Moreover, the derivatives of heterocyclic peroxides function as intriguing precursors for the skeletal rearrangement reactions.[4a−e] On the other hand, several organic peroxides show promising medicinal properties by controlling the oxidative stress levels inside the cells and thus grabbed a significant attraction from across the scientific community. In the past decades, structurally discrete peroxides were found to exhibit anticancer, antimalarial, anthelmintic, antiviral, and antifungal properties which make them exciting pharmacophores in biology (Figure 1).[3a−e] Recently, Woerpel and co-workers discovered that the substituted 1,2-dioxlone derivatives show potent anticancer properties.[3e]

Metal-mediated peroxidation of organic moieties can be accomplished by using peroxy donors such as hydrogen peroxide or alkyl hydroperoxides, and the overall reaction proceeds via "shunt" and "rebound" catalysis. The peroxidation of an unactivated C−H bond and bisperoxidation of styrene derivatives are prominent transformations in metal-catalyzed chemical reactions. The pioneering example on peroxidation of α-substituted carbonyl compounds using *tert*-butyl hydroperoxide (TBHP) and CuCl was demonstrated by Kharasch and Sosnovsky.[5]

Interestingly, Murahashi and co-workers reported the peroxidation of amide and carbamate derivatives using TBHP and ruthenium catalysts.[6] An elegant method for peroxidation of dicarbonyl compounds was developed by Terent'ev and co-workers using $Cu(ClO_4)_2{\cdot}6H_2O$ and TBHP.[7] Afterward, the direct C−H peroxidation of C3-substituted-2-oxindole derivatives was reported by Liu and Stoltz group independently using a catalytic amount of cobalt and copper.[4a,8] Subsequently, our group has reported the C−H peroxidation of carbonyl-containing class of compounds such as C3-substituted-2-oxindole, coumarin, and barbituric acid derivatives using homogeneous as well as heterogeneous iron catalysts.[3b] Recently, the direct C−H peroxidation of barbituric acid derivatives using a copper catalyst or metal-free conditions was reported by Terent'ev and co-workers.[9] Furthermore, the use of stoichiometric or catalytic reagents to obtain organic peroxides has also been documented in the literature.[10]

Besides, while performing the peroxidation of styrene derivatives, Feringa and co-workers observed the bisperox-

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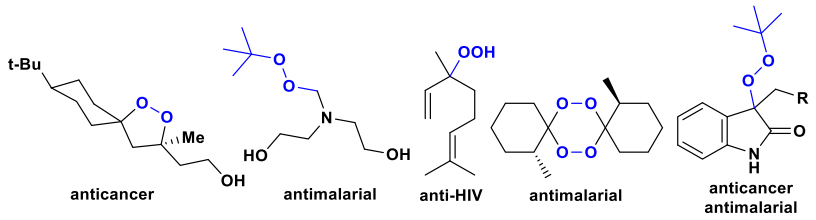
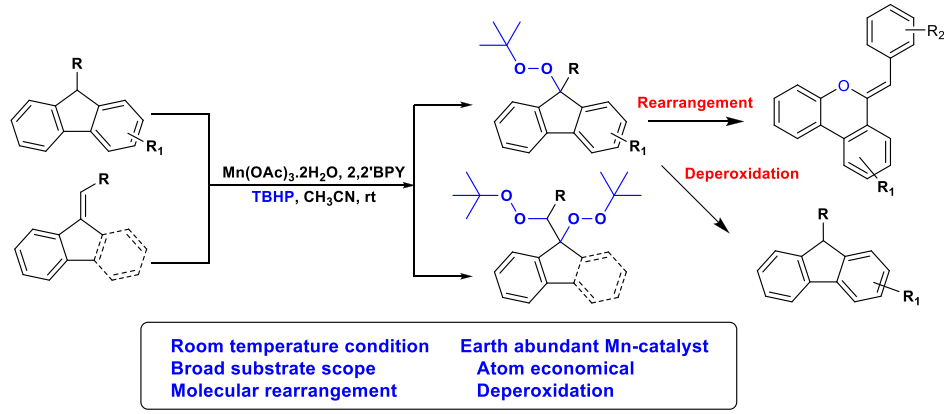


Figure 1. Representative bioactive compounds bearing peroxy functionality.

Scheme 1. Present Finding for C−H Peroxidation and Bisperoxidation



idation using the dinuclear nickel complex.[11] Later, Corey and co-workers also observed the bisperoxidation of styrene in the presence of $Pd(OAc)_2$.[12] Recently, to overcome the limitations of previously reported bisperoxidation, Terent'ev and co-workers have reported the bisperoxidation of styrene using a simple manganese catalyst with good yield.[13]

Fluorene derivatives have been attracted by chemists in the last few decades as they are useful key chemical components for poly(alkylfluorene)s because of their chemical, physical, and photoelectric properties as well as for the radical initiator and additives for several chemical transformations.[14] Hence, the C−H peroxidation of substituted fluorenes generates quaternary peroxides, which may be useful in chemical and therapeutic applications. However, to date, to the best of our knowledge, there is no report for the peroxidation of a noncarbonyl class of compounds such as 9-substituted fluorenes and vicinal bisperoxidation of arylidene-9*H*-fluorene derivatives using manganese catalysts. Furthermore, metal-catalyzed deperoxidation and molecular rearrangements using 9-substituted fluorene peroxides were not reported in the literature.

Herein, we report a mild and efficient protocol for Mn−2,2′-bipyridine-catalyzed direct C−H peroxidation of 9-substituted fluorenes, C3-substituted 2-oxindoles, and vicinal bisperoxidation of olefin derivatives at room temperature (Scheme 1). The present protocol comprises the following aspects: (i) use of earth-abundant manganese catalysts and readily available 2,2′-bipyridine ligands; (ii) rapid and room-temperature reaction conditions; (iii) wide substrate scope; (iv) single catalytic system for peroxidation and bisperoxidation; and (v) peroxidation in continuous flow. In addition, we have also reported the deperoxidation and acid-catalyzed rearrangement of the synthesized peroxides.

RESULTS AND DISCUSSION

We commenced our studies by screening the variety of ligands and solvents (Table 1). At the outset, the control reaction of compound **1** and TBHP in the absence of any catalyst was performed at room temperature, which showed no reaction (Table 1, entry 1). The decisive role of 5 mol % of $Mn(OAc)_3 \cdot 2H_2O$ on C−H peroxidation afforded product **2a** in 47% yield (Table 1, entry 2). Furthermore, excess of TBHP (4 equiv) is required for this transformation, which might be due to the high reactivity of the metal catalyst with peroxide, results in decomposition of TBHP, while the use of 1, 2, and 3 equiv of TBHP in this reaction resulted in 20, 40, and 70% yields, respectively, of product **2a**. To improve the yield, we screened a variety of ligands for this transformation and found that ligand **c** is efficient to form product **2a** in better yield (Table 1, entries 3−6). The role of a bipyridine ligand is important in this transformation because of the formation of the active and stable bipyridine-based Mn complex which might facilitate the selective radical formation via association and dissociation pathways. Next, varieties of solvents were screened to improve the yield of the peroxidation reaction (Table 1, entries 9−13). To our delight, when the reaction was performed with a 70% aqueous solution of TBHP, it provided a yield that was close to the yield for entry 5 (Table 1, entry 14). From our studies, acetonitrile is found to be the best solvent to provide **2a** in 85% yield after 4 h (Table 1, entry 5). In most of the cases, a trace of fluoren-9-one 3 was observed. Interestingly, $Co(OAc)_2$ also effectively catalyzes this reaction to afford product **2a** in 83% yield. Other metal salts such as $Cu(OAc)_2$ and $Ni(OAc)_2 \cdot 4H_2O$ were not effective for this transformation (Table 1, entries 16, 17).

Next, this optimized condition was applied to generalize the substrate scope for the C−H peroxidation reaction. Initially, the C−H peroxidation of substrates having substituents on benzyl groups was tested, and the results are summarized in Scheme 2. The electron-neutral 9-benzyl-9*H*-fluorene on

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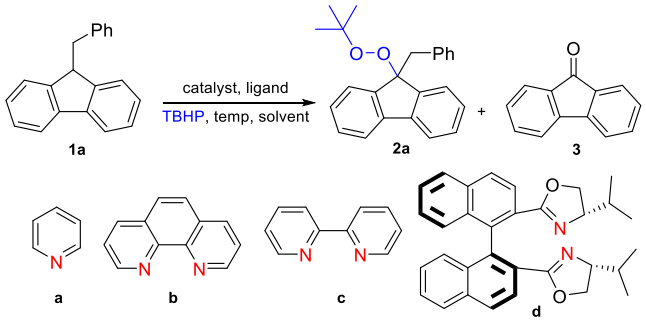
Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	ligand	solvent	yield of **2a**/**3** [%]
1			ACN	no reaction
2	$Mn(OAc)_3{\cdot}2H_2O$		ACN	47/trace
3	$Mn(OAc)_3{\cdot}2H_2O$	**a**	ACN	30/trace
4	$Mn(OAc)_3{\cdot}2H_2O$	**b**	ACN	81/5
5	$Mn(OAc)_3{\cdot}2H_2O$	**c**	ACN	85/7
6	$Mn(OAc)_3{\cdot}2H_2O$	**d**	ACN	19/trace
7	Jacobsen cat.		ACN	83/trace
8	$Mn(OAc)_3{\cdot}2H_2O$	**c**	DCM	62/trace
9	$Mn(OAc)_3{\cdot}2H_2O$	**c**	EtOH	57/trace
10	$Mn(OAc)_3{\cdot}2H_2O$	**c**	*t*-BuOH	64/trace
11	$Mn(OAc)_3{\cdot}2H_2O$	**c**	H_2O	no reaction
12	$Mn(OAc)_3{\cdot}2H_2O$	**c**	EtOAc	70/trace
13	$Mn(OAc)_3{\cdot}2H_2O$	**c**	THF	30/trace
14[b]	$Mn(OAc)_3{\cdot}2H_2O$	**c**	ACN	82/7
15	$Co(OAc)_2{\cdot}4H_2O$	**c**	ACN	83/-
16	$Cu(OAc)_2{\cdot}H_2O$	**c**	ACN	20/30
17	$Ni(OAc)_2{\cdot}4H_2O$	**c**	ACN	

[a]Reaction conditions: Mn catalyst (5 mol %, 0.0195 mmol), ligand (5 mol %, 0.0195 mmol), compound **1** (0.39 mmol), TBHP in decane (4 equiv), and solvent (2 mL) were stirred at room temperature for 4 h. [b]Aq TBHP (4 equiv) is used.

treatment with standard reaction conditions afforded peroxylated product **2a** in 85% isolated yield. The electron-donating group, such as 3-Me, 2-Me, 4-OMe, 3-OMe, 2-OMe, and 3-OPh, afforded low to excellent yield of product **2b**–**h** (Scheme 2). Subsequently, the benzyl moiety bearing electron-withdrawing functionalities such as 3-Cl, 3-Br, 4-F, and 3-CF_3 on fluorene provided moderate to good yield of the corresponding products **2i**–**l** (Scheme 2). Next, the substrate scope is extended to C–H peroxidation of substrates having substituents on fluorene as well as on benzyl group. To our delight, the reaction of 9-benzyl-2-bromo-9*H*-fluorene under optimized conditions afforded the desired product **2m** in 76% yield.

Accordingly, the other substrates bearing electronically active groups afforded expected products **2n**–**q** in good to very good yield (Scheme 2). To our delight, the aliphatic moiety on the 9-position of fluorene also reacted well to afford product **2r**–**u** in moderate to good yield (Scheme 2). Moreover, the reaction of 2-((9*H*-fluoren-9-yl)methyl)-thiophene and 9-phenyl-9*H*-fluorene with TBHP afforded **2v** and **2w** in 79 and 88% isolated yields, respectively.

To our delight, the reaction preceded smoothly even at gram scale to afford **2a** in 63% yield (Scheme 3). To extend the substrate scope for the direct C–H peroxidation, C3-substituted 2-oxindole derivatives were treated with standard reaction conditions. For instance, the reaction of 3-methyl-2-oxindole afforded 91% yield of the product **5a**. To our delight, the electron neutral, electron-donating, and electron-withdrawing substituents afforded good to excellent yield **5b-e** (Scheme 4).

The metal salts react vigorously with peroxides and lead to the exothermic reaction. Sometimes, such exothermic reactions turn out to be a runaway reaction on large scale. Therefore, in order to minimize the explosive hazards of peroxides, the C–H peroxidation reaction was performed under continuous flow (Figure 2). Thus, in one pump, 5 mL of the mixture of 0.1 M solution of 9-benzyl-9*H*-fluorene + $Mn(OAc)_3{\cdot}2H_2O$ (5 mol %) + 2,2′-bipyridine (5 mol %) in dichloromethane (DCM) and in other pump, 5 mL of 0.4 M solution of TBHP–decane in DCM were flown through the coil reactor with a flow rate of 0.2 mL/min to provide the peroxylated product **2a** in 72% yield with a residence time of 12.5 min (Figure 2). Compound **1a** was not completely soluble in acetonitrile; hence, to get complete solubility, we have used DCM as a solvent for continuous-flow experiment.

To prove the existence of a radical pathway in peroxidation reaction, the reaction was performed with the addition of radical quenchers. Accordingly, the reaction of 9-benzyl-9*H*-fluorene in the presence of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) or 1,1-diphenylethylene or α-methyl styrene or molecular oxygen was performed separately, which afforded 80, 68, 65, and 85% yields of product **2a**, respectively (Scheme 5). From these experiments, a decrease in the yield of product **2a** signifies the radical nature of the reaction.

To shed light on the mechanistic aspects of the reaction, we have performed the deuterium labeling experiments. For instance, two parallel reactions were carried out with the deuterium-labeled compound **1a′** and the unlabeled compound **1a** under standard reaction conditions. A primary kinetic isotope effect k_H/k_D = 1.3 was observed, indicating that the breaking of the sp^3-C–H bond is involved in the rate-determining step (Scheme 6).

On the basis of preliminary experimental investigation and literature report,[13] a possible mechanism for Mn-catalyzed C–H peroxidation is proposed in Scheme 7. Initially, manganese(III) acetate dihydrate reacts with 2,2′-bipyridine ligand to form complex **A**. Then, complex **A** will react with TBHP to afford oxidized Mn(IV) intermediate **B** and *tert*-butoxy radical **D**. Simultaneously, intermediate **B** reacts with another mole of TBHP to generate intermediate **C**, which undergoes homolytic cleavage to generate the *tert*-butylperoxy radical **E**. On the other hand, the previously generated *tert*-butoxy radical **D** abstracts a hydrogen atom from compound **1** to generate the fluorene radical species **F**. The radical **E** combines with radical species **F** to afford the desired peroxylated product **2**.

After attaining the fruitful results with 9-substituted fluorene, we have turned our focus on vicinal bisperoxidation of arylidene-9*H*-fluorenes (Scheme 8). For instance, the reaction of 9-benzylidene-9*H*-fluorene with 4 equiv of TBHP and 5 mol % of $Mn(OAc)_3{\cdot}2H_2O$ at room temperature provided bisperoxylated compound **7a** in 74% isolated yield. To extend the substrate scope, the reaction of other halogen-substituted arylidene fluorenes under standard reaction conditions afforded products **7b**–**e** in very good to excellent yield (Scheme 8). Likewise, the bisperoxidation of arylidene-indolin-2-one derivatives also proceeded smoothly in the presence of Mn catalyst. The reaction of 3-arylidene-indolin-2-one with 4 equiv of TBHP and 5 mol % of Mn–2,2′-bipyridine complex afforded vicinal bisperoxylated compounds **9a**–**e** in good to very good yield at room temperature (Scheme 9). The

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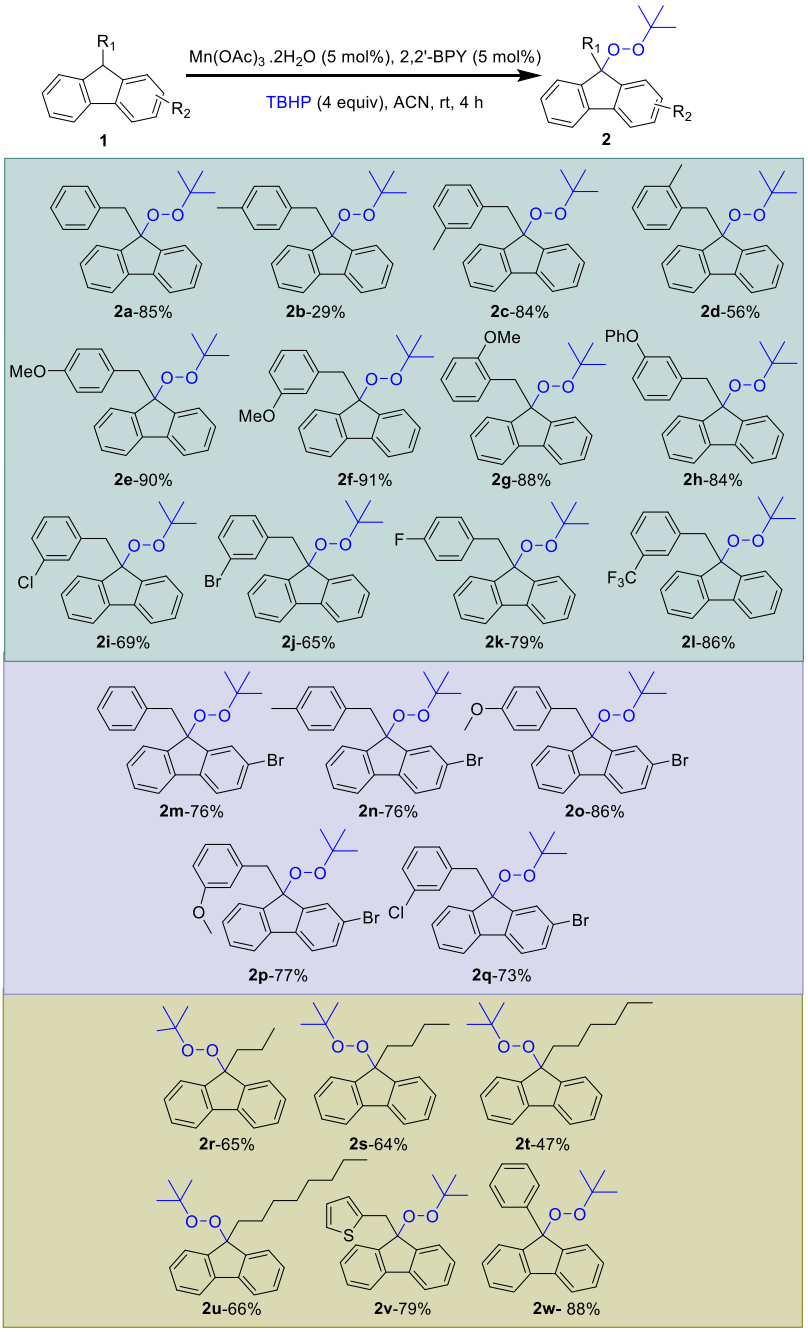
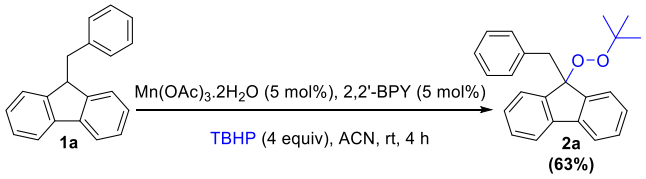
Scheme 2. Substrate Scope for C−H Peroxidation of 9-Substituted Fluorenes[a]



[a]Reaction conditions: $Mn(OAc)_3{\cdot}2H_2O$ (5 mol %, 0.019 mmol), 2,2′-bipyridine (5 mol %, 0.019 mmol), compound **1** (0.39 mmol), TBHP (4 equiv), and acetonitrile (2 mL) were stirred at room temperature for 4 h. The mentioned yields are isolated yields.

Scheme 3. Gram-Scale Reaction[a]



[a]Reaction conditions: $Mn(OAc)_3{\cdot}2H_2O$ (5 mol %, 0.30 mmol), 2,2′-bipyridine (5 mol %, 0.30 mmol), compound **1** (6.01 mmol, 1 equiv), TBHP (4 equiv), and acetonitrile (10 mL) were stirred at room temperature for 4 h.

structure and stereochemistry of compound **9e** was confirmed using single-crystal X-ray diffraction (Figure S4). Moreover, the stereochemistry of all the other bisperoxides **7** and **9** was relatively assigned based on the crystal structure of **9e**.

The mechanistic steps are similar to that of Scheme 7. However, in the case of bisperoxidation, the *tert*-butyl peroxy radical **E** combines with olefin functionality of the reactant **6** to generate a monoperoxide radical species **G** (Scheme 10). Subsequently, the intermediate **G** undergoes a recombination process with another in situ generated *tert*-butyl peroxy radical **E** or from the Mn(IV) complex **C** to afford the bisperoxylated compound **7** (Scheme 10).

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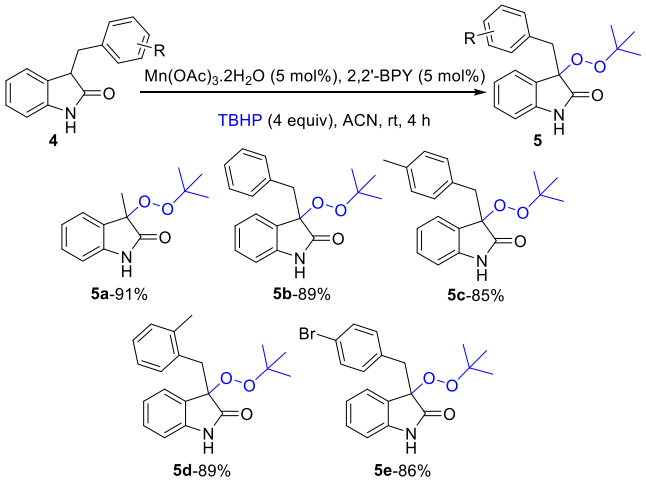
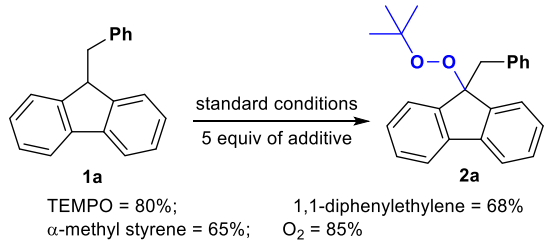
Scheme 4. Substrate Scope for C−H Peroxidation of C3-Substituted-2-oxindoles[a]



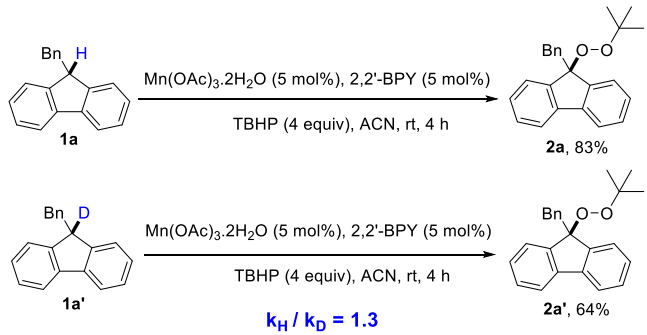
[a]Reaction conditions: $Mn(OAc)_3{\cdot}2H_2O$ (5 mol %, 0.0125 mmol), 2,2′-bipyridine (5 mol %, 0.0125 mmol), compound **4** (0.25 mmol), TBHP (4 equiv), and acetonitrile (2 mL) were stirred at room temperature for 4 h. The mentioned yields are isolated yields.

Scheme 5. Radical Quenching Experiments[a]



[a]Reaction conditions: 9-benzyl-9*H*-fluorene (0.25 mmol), TEMPO (1.25 mmol), or 1,1-diphenylethylene (1.25 mmol) or *α*-methylstyrene (1.25 mmol) or an oxygen balloon in 2 mL acetonitrile was stirred at room temperature for 4 h.

Scheme 6. Deuterium Labeling Studies



The rearrangement reactions on electron-deficient oxygen have been widely studied for the peroxides.[15] The typical example includes the Baeyer−Villiger and Criegee rearrangement of peroxides. To this context, we envisioned a Lewis acid catalyzed rearrangement of peroxides. Interestingly, the reaction of **2a** with $Sn(OTf)_2$ afforded a distinct rearrangement of peroxide. The use of Sn catalyst afforded (*Z*)-6-benzylidene-6*H*-benzo[*c*]chromene **10a** in 20% yield along with 9-benzylidene-9*H*-fluorene **6a** in 47% yield (Scheme 11). Other Lewis acids such as 10 mol % of each $FeCl_3$, $Cu(OTf)_2$, $Sc(OTf)_3$, $In(OTf)_3$, and $AuCl_3$ were not effective for the rearrangement to produce the rearrangement product **10a**. The use of 10 mol % $BF_3{\cdot}OEt_2$ afforded less conversion of peroxide with the rearrangement product **10a**. Electron-withdrawing group on the aryl ring increases the yield of the rearrangement products. Thus, bromo-substituted peroxides **2j**, **2m**, and **2q** were subjected for the rearrangement reaction using $Sn(OTf)_2$ as a catalyst, which afforded **10b−d** in 25, 31, and 42% along with the 9-benzylidene-9*H*-fluorene (**6**) derivatives as a minor quantities (Scheme 11). To the best of our knowledge, there is no literature precedence for such rearrangements of 9-substituted-9-(*tert*-butylperoxy)-9*H*-fluorenes (Scheme 11).

Interestingly, based on our experimental results and previous literature reports, the possible reaction mechanism for the formation of rearranged product **6** and elimination product **10** is shown Scheme 12.[4b] To begin with, tin(II)-trifluoromethanesulfonate coordinates with the peroxy (O−O) bond of **2** to produce complex **H**. In situ generation of triflate anions participates in the deprotonation of **H**, facilitating the generation of isobutylene gas (confirmed by gas chromatography−mass spectrometry, see the Supporting Information, Figure S3) to afford Sn-chelated complex **J**. Further, the protonation of **J** by in situ generated TfOH produces SnOTf-chelated complex **K**. Subsequently, **K** confers the synthesis of **10** and **6** via pathway "a" and "b". In pathway "a", ring expansion takes place with the elimination of Sn(OH)OTf to afford carbocation **L**. This carbocation **L** is stabilized by the abstraction of a proton by triflate anions to afford the desired product **10**. However, in the case of pathway "b", **6** may be obtained by the removal of the Sn(OOH)OTf group.

Additionally, the synthesized quaternary peroxides can be employed as valuable precursors for functional group transformations. In literature,[8] the reduction of peroxide group

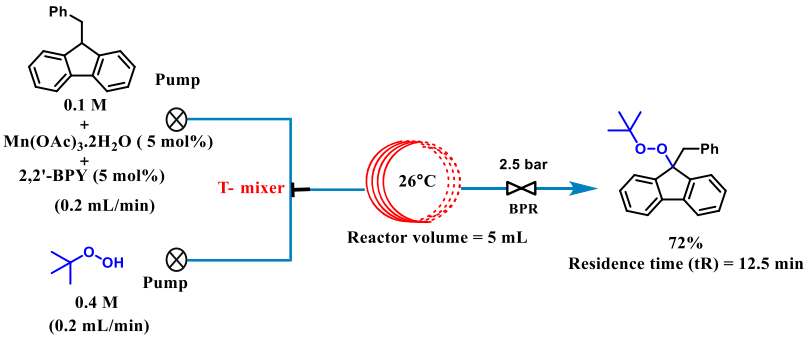


Figure 2. Continuous-flow setup for C−H peroxidation of 9-benzyl-9*H*-fluorene.

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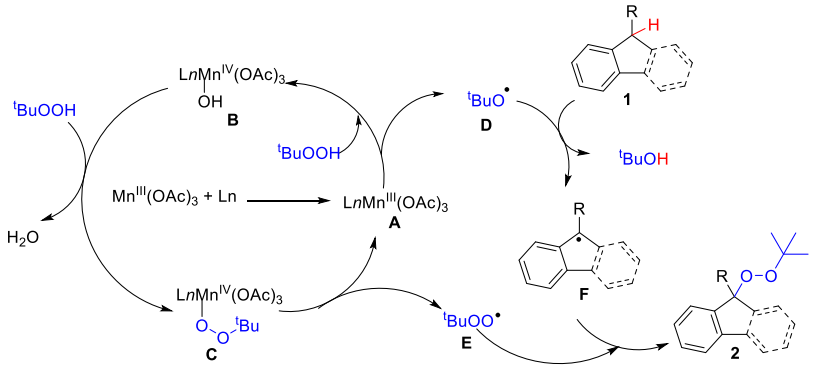
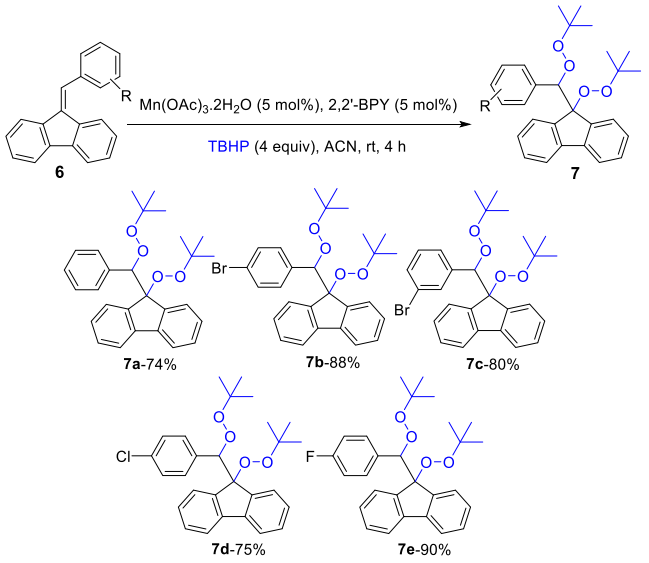
Scheme 7. Plausible Mechanism for the Mn-Catalyzed C−H Peroxidation

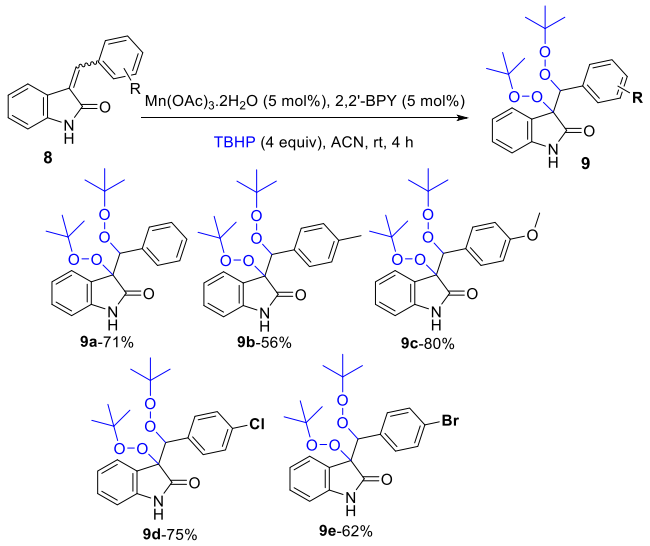


Scheme 8. Synthesis of Vicinal Bis(*tert*-butyl)peroxides from Arylidene-9*H*-fluorene[a]



[a]Reaction conditions: $Mn(OAc)_3{\cdot}2H_2O$ (5 mol %, 0.0125 mmol), ligand (5 mol %, 0.0125 mmol), compound **6** (0.25 mmol, 1 equiv), TBHP (4 equiv), and acetonitrile (2 mL) were stirred at room temperature for 4 h. The mentioned yields are isolated yields.

Scheme 9. Vicinal Bisperoxidation of 3-Arylidene-indolin-2-one[a]



[a]Reaction conditions: $Mn(OAc)_3{\cdot}2H_2O$ (5 mol %, 0.0125 mmol), 2,2′-bipyridine (5 mol %, 0.0125 mmol), compound **8** (0.25 mmol, 1 equiv), TBHP (4 equiv), and solvent (2 mL) were stirred at room temperature for 4 h. The mentioned yields are isolated yields.

using H_2, Pd/C was successfully employed for obtaining a hydroxyl moiety; however, in contrast, we have observed the complete removal of the peroxy group in high yield. To show the generality, a variety of substrates were successfully employed for the Pd/C-mediated removal of peroxide to afford the reversible deperoxidation products **1a−f** in high yield (Scheme 13).

To gain the mechanistic insights, a control experiment was performed in the absence of molecular H_2 which results in no reaction (Scheme 14a). In the presence of molecular H_2, complete conversion was observed after 8 h (Scheme 14b). However, the reaction was analyzed after 2 h, which indicated the presence of the hydroxylated fluorene **O** (Scheme 14c). Later, the hydroxyl compound **O** was prepared separately, and reduction of **O** in the presence of Pd/C and molecular H_2 provided product **1a** in 96% yield (Scheme 14e). However, in the absence of molecular H_2, there was no reaction (Scheme 14d). This experiment proves that the compound **O** serves as an intermediate in this reduction reaction. Finally, the hydrogenation of alkene **6a** was carried out in the presence of Pd/C and H_2, which afforded 97% of **1a** (Scheme 14f).

However, the possibility of alkene as an intermediate is ruled out because we observed the deperoxidation of 9-(*tert*-butylperoxy)-9-phenyl-9*H*-fluorene where the formation of an alkene intermediate is not at all possible (Scheme 13, entry **1f**).

On the basis of our experimental observations and the literature report,[16,17] we proposed a plausible mechanism for deperoxidation (Scheme 15). Initially, peroxide will coordinate with H_2 and Pd/C to form intermediate **N**. The removal of *tert*-butanol will be commenced by hydrogenolysis to afford intermediate **O**. The reduction of **O** to **1** proceeds through the insertion of Pd across the C−O bond of alcohol to form an intermediate **P**. Finally, in the presence of molecular hydrogen, the intermediate **P** may undergo hydrogenation to afford the desired product **1**.

CONCLUSIONS

In summary, a new class of quaternary peroxides have been synthesized using the Mn−2,2′-bipyridine complex. The decrease in yield was observed in the absence of ligand and signifies the decisive role of the ligand in this transformation.

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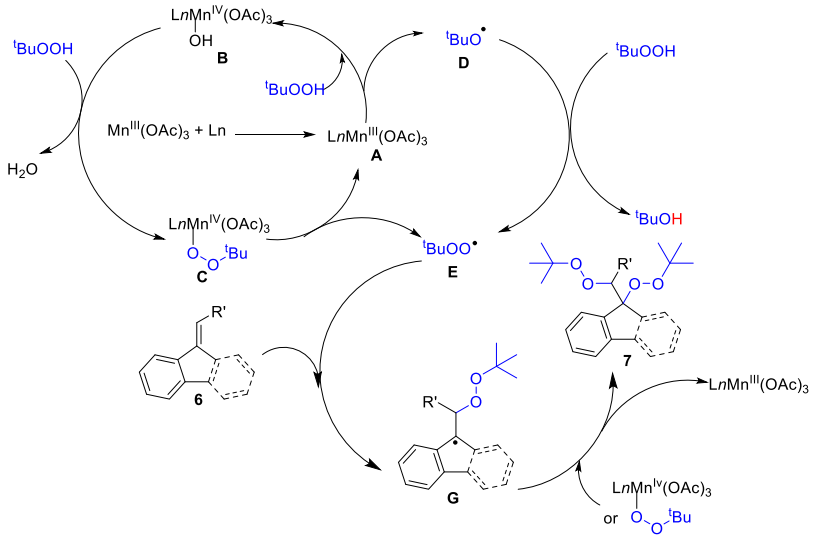
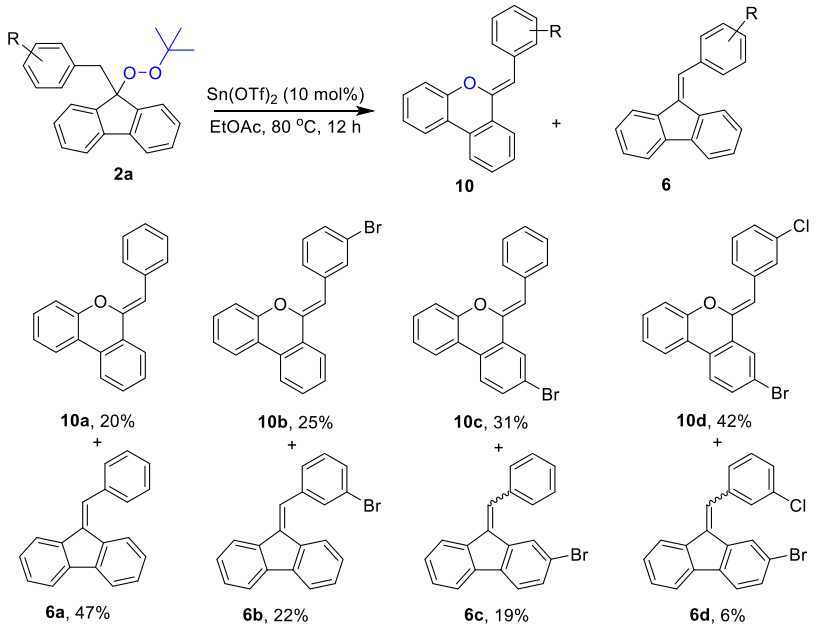
Scheme 10. Plausible Mechanism for the Mn-Catalyzed C=C Bisperoxidation



Scheme 11. Sn-Catalyzed Rearrangement of Quaternary Peroxides[a]



[a]Reaction conditions: Compound **2** (0.25 mmol) and $Sn(OTf)_2$ (10 mol %) in 2 mL ethyl acetate were heated at 80 °C for 12 h in a sealed tube. The mentioned yields are isolated yields.

Among the series of nitrogen donor ligands, 2,2′-bipyridine was found to be the best ligand to afford the C−H peroxylated product in excellent yield. This catalytic method was applicable to vicinal bisperoxidation of arylidene-9*H*-fluorene/arylideneindolin-2-one derivatives under mild reaction conditions. Advantageously, this C−H peroxidation reaction can be achieved on a gram scale without any difficulties. In contrast to the reduction of the −O−O− bond, for the first time, we reported a −C−O−bond reduction that led to the reversibility of the reaction. The $Sn(OTf)_2$-catalyzed skeletal rearrangement of the quaternary peroxide provided the new type of ring expansion route via intramolecular aryl migration on electron-deficient oxygen to form (*Z*)-6-benzylidene-6*H*-benzo[*c*]-chromene derivatives. A detailed investigation on the mechanism has been studied, and a possible mechanism was proposed for the peroxidation, bisperoxidation, and molecular rearrangement of peroxides and deperoxidation reactions.

EXPERIMENTAL SECTION

General Information and Data Collection. Manganese(III) acetate dihydrate (97%) and TBHP (5.0−6.0 M) in decane solution were purchased from Sigma-Aldrich. Starting materials **1**, **4**, **6**, and **8** were prepared by the reported method.[18−21] All the solvents used were of dry grade. The column chromatographic separations were performed over 100−200 mesh size silica gel. Visualization was accomplished with UV light, phosphomolybdic acid, and cerium ammonium molybdate stain, followed by heating. ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, using a Bruker or JEOL spectrometer. Abbreviations used in the NMR follow-up experiments: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; and m, multiple. High-resolution mass spectra were recorded using Waters-Synapt G2 with electrospray ionization (ESI). Fourier

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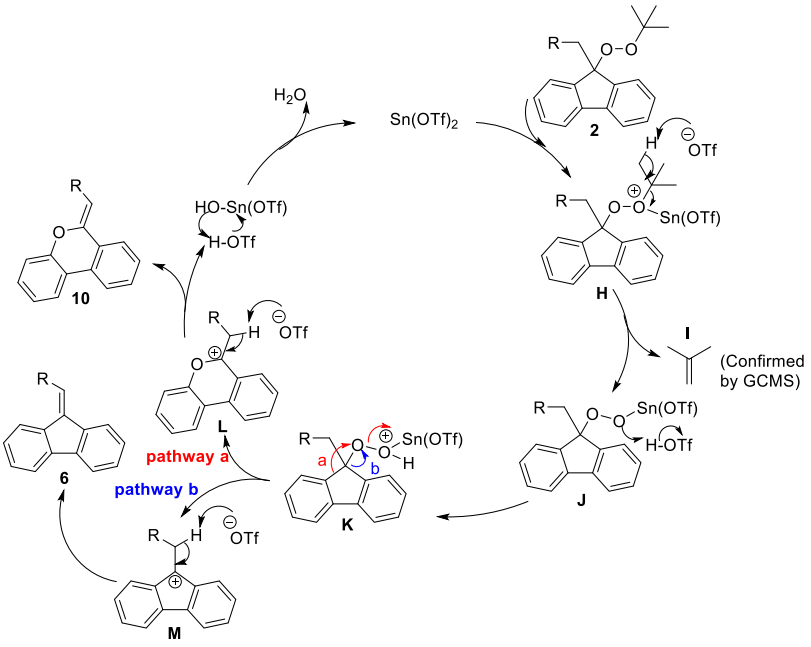
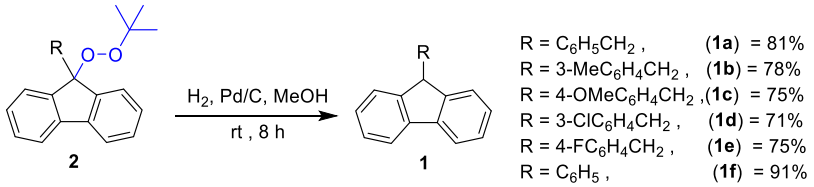
Scheme 12. Plausible Pathway for the Formation of 6 and 10 via Rearrangement



Scheme 13. Pd/C-Catalyzed Deperoxidation of Peroxyfluorenes[a]



[a]Reaction conditions: Peroxide **2** (0.15 mmol, 1 equiv) and Pd/C (10 wt %, 10 mol %) in MeOH (2 mL) were stirred under a hydrogen balloon at room temperature for 8 h. The mentioned yields are isolated yields.

transform infrared (FTIR) spectra were obtained with a Bruker Alpha-E FTIR spectrometer. Continuous-flow reactions were performed using the Vapourtec R-series. "The reaction of a metal salt with organic peroxides may lead to an explosive reaction, but we have not faced any issue even at the gram scale, be cautious while handling." Although we have not encountered any difficulty or accident while handling TBHP, for safety purpose after the completion of the reaction, one can quench the unreacted peroxide with a suitable quencher.

(A) General Experimental Procedure for C−H Peroxidation of 9-Substituted-9*H*-fluorene. In a 20 mL resealable vial were added $Mn(OAc)_3{\cdot}2H_2O$ (0.019 mmol, 5 mg, 5 mol %) and 2,2′-bipyridine (0.019 mmol, 3 mg, 5 mol %) in acetonitrile (2 mL). The solution was stirred at room temperature for 20−30 min to obtain a deep-brown color, and then 9-substituted-9*H*-fluorene compound (0.39 mmol, 1 equiv) was added. Finally 5.0−6.0 M TBHP in decane solution (1.56 mmol, 140 mg, 4 equiv) was added without maintaining any special conditions such as an inert atmosphere, and further, the tube was sealed with a rubber septum. The reaction mixture was kept at room temperature under stirring for 4 h. After completion of the reaction, a volatile component was evaporated under vacuum. The residue was directly purified by silica gel column chromatography (EtOAc/*n*-hexane = 1:99).

Note: Although we have not encountered any difficulty or accident while handling TBHP, but for safety purpose, after the completion of the reaction, one can quench the unreacted peroxide with a suitable quencher.

(B) General Experimental Procedure for C−H Peroxidation of C3-Substituted-2-oxindoles. In a 20 mL resealable vial were added $Mn(OAc)_3{\cdot}2H_2O$ (0.0125 mmol, 3 mg, 5 mol %) and 2,2′-bipyridine (0.0125 mmol, 2 mg, 5 mol %) in acetonitrile (2 mL). The solution was stirred at room temperature for 20−30 min to obtain a deep-brown color, and then C3-substituted-2-oxindole compound (0.25 mmol, 1 equiv) was added. Finally, 5.0−6.0 M TBHP in decane solution (1.0 mmol, 90 mg, 4 equiv) was added without maintaining any special conditions such as an inert atmosphere, and further, the tube was sealed with a rubber septum. The reaction mixture was kept at room temperature under stirring for 4 h. After completion of the reaction, a volatile component was evaporated under vacuum. The residue was directly purified by silica gel column chromatography (EtOAc/*n*-hexane = 20:80).

(C) Experimental Procedure for Gram-Scale C−H Peroxidation of 9-Benzyl-9*H*-fluorene (1a). In a 50 mL round-bottom flask were added $Mn(OAc)_3{\cdot}2H_2O$ (0.30 mmol, 81 mg, 5 mol %) and 2,2′-bipyridine (0.30 mmol, 47 mg, 5 mol %) in acetonitrile (20 mL). The solution was stirred at room temperature for 20−30 min to obtain a deep-brown color, and then 9-benzyl-9*H*-fluorene compound (6 mmol, 1.536 g, 1 equiv) was added. Finally, 5.0−6.0 M TBHP in decane solution (24 mmol, 2.160 g, 4 equiv) was added without maintaining any special conditions such as an inert atmosphere, and further, the tube was sealed with a rubber septum. The reaction mixture was kept at room temperature for 4 h. After completion of the reaction, a volatile component was evaporated under vacuum. The residue was directly purified by silica gel column chromatography (EtOAc/*n*-hexane = 1:99) and afforded (1.300 g, 63%) peroxide **2a** as a white semisolid.

(D) General Experimental Procedure for Bisperoxidation of 9-Arylidene-9*H*-fluorene and Arylideneindolin-2-one Compounds. In a 20 mL resealable vial were added $Mn(OAc)_3{\cdot}2H_2O$ (0.0125 mmol, 3 mg, 5 mol %) and 2,2′-bipyridine (0.0125 mmol, 2

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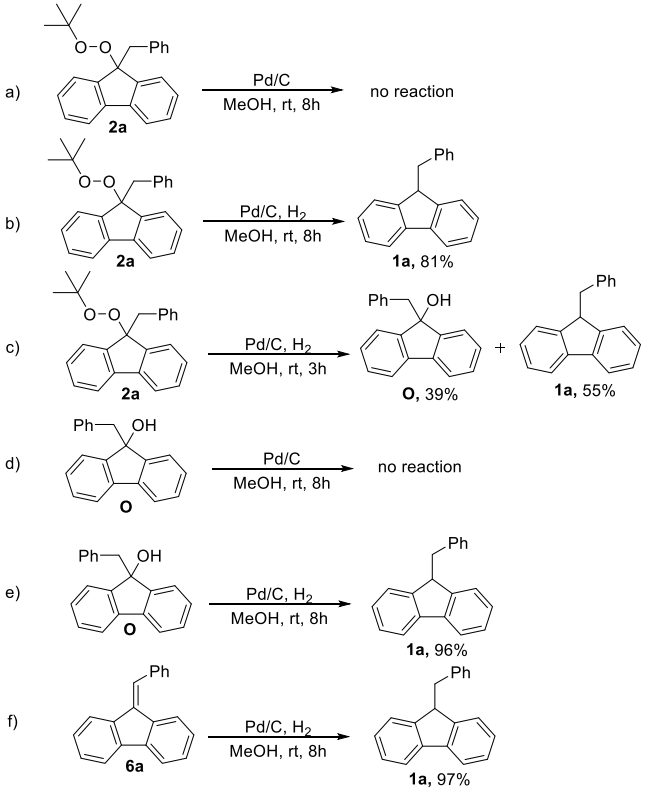
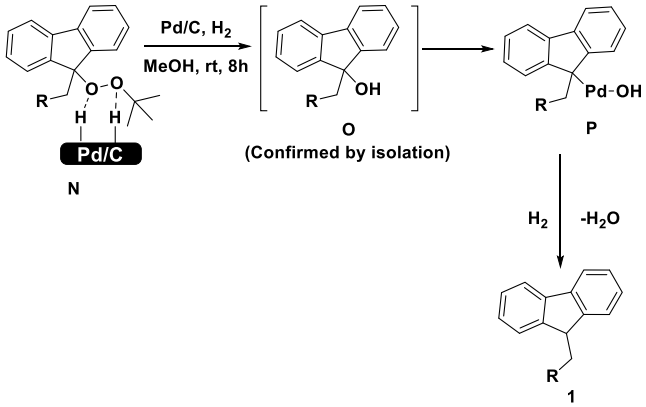
Scheme 14. Experimental Investigation for the Deperoxidation Pathway



Scheme 15. Reaction Mechanism for the Deperoxidation of Fluorene Peroxides



mg, 5 mol %) in acetonitrile (2 mL). The solution was stirred at room temperature for 20−30 min to obtain a deep-brown color, and then arylidene-9*H*-fluorene or arylideneindolin-2-one compound (0.25 mmol, 1 equiv) was added. Finally, 5.0−6.0 M TBHP in decane solution (1.0 mmol, 90 mg, 4 equiv) was added without maintaining any special conditions such as an inert atmosphere, and further, the tube was sealed with a rubber septum. The reaction mixture was kept at room temperature under stirring for 4 h. After completion of the reaction, a volatile component was evaporated under vacuum. The residue was directly purified by silica gel column chromatography [for 9-arylidene-9*H*-fluorene compound peroxidation (EtOAc/*n*-hexane = 1:99) and for arylideneindolin-2-one compound peroxidation (EtOAc/*n*-hexane = 10:90)].

(E) General Experimental Procedure for C−H Peroxidation of 9-Substituted-9*H*-fluorene under Continuous Flow. 9-Benzyl-9*H*-fluorene (0.1 M, 0.5 mmol, 128 mg, in 5 mL of DCM) was added to $Mn(OAc)_3{\cdot}2H_2O$ (0.0125 mmol, 3 mg, 5 mol %) and 2,2′-bipyridine (0.0125 mmol, 2 mg, 5 mol %) in a 30 mL vial; simultaneously, 0.4 M TBHP (2 mmol, 180 mg in 5 mL of DCM) was taken in another 30 mL vial. Both the above prepared solutions were flown through a 5 mL SS coil reactor with a flow rate of 0.2 mL/min each at room temperature at 2.3 bar pressure. The reaction mixture was collected continuously after 12.5 min, an organic layer was concentrated under reduced pressure, and the residue was subjected to column chromatography purification using EtOAc/*n*-hexane (1:99) to afford the corresponding peroxyfluorene **2a** in 72% yield.

(F) Procedure for the Synthesis of Deuterated Benzyl Alcohol.[22] The deuterated benzyl alcohol was prepared by using the procedure of Gunanathan et al. In a typical procedure, benzyl alcohol (2 mmol), Ru−MACHO (0.004 mmol), and KO^{t}Bu (0.001 mmol) were charged in a 20 mL resealable vial, which was equipped with a rubber septum and a N_2 balloon. D_2O (1.6 mL) was added using a syringe. The reaction mixture was purged with N_2, and the tube was sealed with a cap using a crimper. The reaction mixture was heated at 60 °C in an oil bath for 12 h. After completion of the reaction, the reaction mixture was extracted with DCM. The combined organic layer was washed with brine solution. The removal of the solvent under reduced pressure provided pure deuterated benzyl alcohol for further reaction. The ^{1}H NMR data are similar to the previous report and showed 87% deuterium incorporation (Figure S1).

(G) Procedure for the Synthesis of Deuterated 9-Benzyl-9*H*-fluorene. In a 20 mL resealable tube were added [Ru(*p*-cymene)Cl_2] (3 mol %), KO^{t}Bu (1.5 equiv), 9-benzyl-9*H*-fluorene (1 equiv), and deuterated benzyl alcohol (1.5 equiv), and the vial was purged with N_2 and sealed with a cap using a crimper. The reaction mixture was heated at 140 °C for 30 h. The reaction mixture was cooled, and the volatile component was evaporated under vacuum and directly purified by using column chromatography (EtOAc/*n*-hexane = 1:99) to afford the 54.34% deuterium incorporation. This pure product was used for a further similar reaction for kinetic study.

(H) Procedure for the Parallel Reaction: Peroxidation of Isotope-Labeled 9-Benzyl-9*H*-fluorene (1a′) and without Labeled 9-Benzyl-9*H*-fluorene (1a). In a 20 mL resealable vial were added $Mn(OAc)_3{\cdot}2H_2O$ (0.0125 mmol, 3 mg, 5 mol %) and 2,2′-bipyridine (0.0125 mmol, 2 mg, 5 mol %) in acetonitrile (2 mL). The solution was stirred at room temperature for 20−30 min to obtain the deep-brown color. Later, compound (**1a′**) or (**1a**) (0.19 mmol, 50 mg, 1 equiv) was added, and finally, 5.0−6.0 M TBHP in decane solution (0.78 mmol, 70 mg 4 equiv) was added without maintaining any special conditions such as an inert atmosphere. Further, the tube was sealed with a rubber septum, and the reaction mixture was kept at room temperature for 4 h. After that, a volatile component was evaporated under vacuum. The residue was directly purified by silica gel column chromatography (EtOAc/*n*-hexane = 1:99) to afford **2a′** (41 mg, 64%) or **2a** (56 mg, 83%) as a white solid.

(I) Radical Quenching Experiment. In a 20 mL resealable vial were added $Mn(OAc)_3{\cdot}2H_2O$ (0.0125 mmol, 3 mg, 5 mol %) and 2,2′-bipyridine (0.0125 mmol, 2 mg, 5 mol %) in acetonitrile (2 mL) and stirred at room temperature for 20−30 min. To the deep-brown solution were added 9-benzyl-9*H*-fluorene (64 mg, 0.25 mmol, 1 equiv), 5.0−6.0 M TBHP in decane solution (1.0 mmol, 90 mg, 4 equiv), and finally TEMPO (5 equiv) or 1,1-diphenylethylene (5 equiv) or α-methylstyrene (5 equiv) or molecular oxygen, and the resulting solution was stirred at room temperature for 4 h. The volatile component was evaporated under vacuum. The residue was directly purified by silica gel column chromatography (EtOAc/*n*-hexane = 1:99) to afford 80, 68, 65, and 85% yields of product **2a**, respectively.

(J) General Experimental Procedure for the Rearrangement Reaction of Peroxides.[4b] In a 20 mL resealable vial (equipped with a rubber septum and N_2 balloon) were added $Sn(OTf)_2$ (0.025 mmol, 10 mg, 10 mol %) and peroxy compound (0.25 mmol, 1 equiv) in the presence of ethyl acetate (2 mL). The tube was purged with N_2 and sealed with a cap using a crimper. The reaction mixture was heated at 80 °C in an oil bath for 12 h. After completion of the reaction, a volatile component was evaporated under vacuum. The residue was

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directly purified by silica gel chromatography (EtOAc/*n*-hexane = 1:99).

(K) General Experimental Procedure for Reductive Deperoxidation of Peroxyfluorenes. A solution of peroxyfluorenes **2** (0.15 mmol, 1 equiv) and Pd/C (10 wt %, 10 mol %, 16 mg) in MeOH (2 mL) was stirred under the atmosphere of hydrogen using a hydrogen balloon at room temperature for 8 h. After completion of the reaction, the mixture was filtered over Celite and evaporated with methanol under vacuum. Finally, the resulting residue was purified by using silica gel column chromatography (*n*-hexane) to afford 9-substituted-9*H*-fluorene.

(L) Experimental Evidence for the Formation of Hydroxy Intermediates by Isolation. A solution of 9-benzyl-9-(*tert*-butylperoxy)-9*H*-fluorene **2a** (0.15 mmol, 1 equiv) and Pd/C (10 wt %, 10 mol %, 16 mg) in MeOH (2 mL) was stirred under the atmosphere of hydrogen using a hydrogen balloon at room temperature for 3 h. The mixture was filtered over Celite and evaporated with methanol under vacuum. Finally, the resulting residue was purified by using silica gel column chromatography (EtOAc/*n*-hexane = 5:95) to afford product 9-benzyl-9*H*-fluorene **1a** (21 mg, 55% isolated yield) as a white solid and intermediate 9-benzyl-9*H*-fluoren-9-ol **O** (15 mg, 39% isolated yield) as a white solid.

(M) Experimental Procedure for the Reduction of 9-Benzyl-9*H*-fluoren-9-ol. A solution of 9-benzyl-9*H*-fluoren-9-ol (**O**) (0.15 mmol, 1 equiv) and Pd/C (10 wt %, 10 mol %, 16 mg) in MeOH (2 mL) was stirred under the atmosphere of hydrogen using a hydrogen balloon at room temperature for 8 h. After completion of the reaction, the mixture was filtered over Celite and evaporated with methanol under vacuum. Finally, the resulting residue was purified by using silica gel column chromatography (*n*-hexane) to afford 9-benzyl-9*H*-fluorene (37 mg, 96% isolated yield) as a white solid.

(N) Experimental Procedure for the Reduction of 9-Benzylidene-9*H*-fluorene. A solution of 9-benzylidene-9*H*-fluorene **6a** (0.15 mmol, 1 equiv) and Pd/C (10 wt %, 10 mol %, 16 mg) in MeOH (2 mL) was stirred under the atmosphere of hydrogen using a hydrogen balloon at room temperature for 8 h. After completion of the reaction, the mixture was filtered over Celite and evaporated with methanol under vacuum. Finally, the resulting residue was purified by using silica gel column chromatography (*n*-hexane) to afford 9-benzyl-9*H*-fluorene (37 mg, 97% isolated yield) as a white solid.

(O) Analytical Data for the Product. *9-Benzyl-9-(tert-butylperoxy)-9H-fluorene (**2a**).* Prepared according to general procedure A using 9-benzyl-9*H*-fluorene (100 mg, 0.39 mmol) to afford peroxyfluorene **2a** (114 mg, 0.33 mmol, 85% yield) as a white semisolid after purification by silica gel column chromatography (EtOAc/*n*-hexane = 1:99). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53 (m, 2H), 7.34−7.30 (m, 4H), 7.22−7.18 (m, 2H), 7.14−7.04 (m, 3H), 7.00−6.97 (m, 2H), 3.46 (s, 2H), 1.14 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 145.1, 140.4, 136.5, 131.1, 128.9, 127.5, 126.9, 126.3, 125.9, 119.7, 90.8, 79.7, 42.3, 26.7. FTIR (neat): 1017, 1194, 2929, 3438 cm^{-1}. HRMS (ESI-TOF) *m*/*z*: [M − OO^{t}Bu]$^+$ calcd for $C_{20}H_{15}$, 255.1168; found, 255.1174.

*9-(tert-Butylperoxy)-9-(4-methylbenzyl)-9H-fluorene (**2b**).* Prepared according to general procedure A using 9-(4-methylbenzyl)-9*H*-fluorene (105 mg, 0.39 mmol) to afford peroxyfluorene **2b** (41 mg, 0.11 mmol, 29% yield) as a yellow semisolid after purification by silica gel column chromatography (EtOAc/*n*-hexane = 1:99). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (m, 2H), 7.34−7.30 (m, 4H), 7.22 (td, *J* = 7.2, 1.1 Hz, 2H), 6.94−6.88 (m, 4H), 3.43 (s, 2H), 2.26 (s, 3H), 1.15 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 145.2, 140.4, 135.7, 133.3, 130.9, 128.8, 128.2, 126.9, 125.9, 119.7, 90.8, 79.6, 41.8, 26.7, 21.1. FTIR (neat): 830, 1195, 2917 cm^{-1}. HRMS (ESI-TOF) *m*/*z*: [M − OO^{t}Bu]$^+$ calcd for $C_{21}H_{17}$, 269.1325; found, 269.1334.

*9-(tert-Butylperoxy)-9-(3-methylbenzyl)-9H-fluorene (**2c**).* Prepared according to general procedure A using 9-(3-methylbenzyl)-9*H*-fluorene (105 mg, 0.39 mmol) to afford peroxyfluorene **2c** (117 mg, 0.32 mmol, 84% yield) as a yellow solid after purification by silica gel column chromatography (EtOAc/*n*-hexane = 1:99). Melting point: 72−74 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (m, 2H), 7.70 (m, 5H), 7.61−7.57 (m, 2H), 7.41−7.32 (m, 2H), 7.18 (d, *J* = 7.4 Hz, 1H), 3.80 (s, 2H) 2.60 (s, 3H), 1.54 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 145.3, 140.4, 136.8, 136.3, 132.1, 128.8, 128.1, 127.3, 127.0, 126.9, 125.9, 119.7, 90.8, 79.6, 42.2, 26.7, 21.4. FTIR (neat): 771, 1060, 1199, 2913, 3462 cm^{-1}. HRMS (ESI-TOF) *m*/*z*: [M − OO^{t}Bu]$^+$ calcd for $C_{21}H1_7$, 269.1325; found, 269.1335.

*9-(tert-Butylperoxy)-9-(2-methylbenzyl)-9H-fluorene (**2d**).* Prepared according to general procedure A using 9-(2-methylbenzyl)-9*H*-fluorene (105 mg, 0.39 mmol) to afford peroxyfluorene **2d** (78 mg, 0.21 mmol, 56% yield) as a yellow after purification by silica gel column chromatography (EtOAc/*n*-hexane = 1:99). Melting point: 69−71 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, *J* = 7.5 Hz, 2H), 7.47−7.43 (m, 1H), 7.36 (td, *J* = 7.4, 1.2 Hz, 2H), 7.20−7.14 (m, 4H), 7.09−7.06 (m, 3H), 3.32 (s, 2H), 1.79 (s, 3H), 1.12 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 145.9, 139.9, 137.9, 135.5, 132.2, 129.9, 128.8, 127.0, 126.7, 125.5, 125.3, 119.7, 90.5, 79.6, 38.8, 26.8, 19.9. FTIR (neat): 1060, 1188, 2972, 3446 cm^{-1}. HRMS (ESI-TOF) *m*/*z*: [M − OO^{t}Bu]$^+$ calcd for $C_{21}H_{17}$, 269.1325; found, 269.1335.

*9-(tert-Butylperoxy)-9-(4-methoxybenzyl)-9H-fluorene (**2e**).* Prepared according to general procedure A using 9-(4-methoxybenzyl)-9*H*-fluorene (112 mg, 0.39 mmol) to afford peroxyfluorene **2e** (131 mg, 0.35 mmol, 90% yield) as a yellow semisolid after purification by silica gel column chromatography (EtOAc/*n*-hexane = 1:99). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55−7.51 (m, 2H), 7.31 (d, *J* = 7.2 Hz, 4H), 7.23−7.19 (m, 2H), 6.94−6.90 (m, 2H), 6.68−6.64 (m, 2H), 3.74 (s, 3H), 3.39 (s, 2H), 1.14 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 158.1, 145.2, 140.4, 132.0, 128.8, 128.6, 126.9, 125.9, 119.7, 112.9, 90.9, 79.6, 55.2, 41.4, 26.7. FTIR (neat): 1036, 1189, 2968 cm^{-1}. HRMS (ESI-TOF) *m*/*z*: [M − OO^{t}Bu]$^+$ calcd for $C_{21}H_{17}$, 285.1274; found, 285.1283.

*9-(tert-Butylperoxy)-9-(3-methoxybenzyl)-9H-fluorene (**2f**).* Prepared according to general procedure A using 9-(3-methoxybenzyl)-9*H*-fluorene (112 mg, 0.39 mmol) to afford peroxyfluorene **2f** (133 mg, 0.35 mmol, 91% yield) as a yellow semisolid after purification by silica gel column chromatography (EtOAc/*n*-hexane = 1:99). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 7.4 Hz, 2H), 7.40 (d, *J* = 7.4 Hz, 2H), 7.34 (td, *J* = 7.6, 1.2 Hz, 2H), 7.24 (td, *J* = 7.4,1.2 Hz, 2H), 7.08 (t, *J* = 7.8 Hz, 1H), 6.71−6.69 (m, 1H), 6.61−6.58 (m, 2H), 3.64 (s, 3H), 3.50 (s, 2H), 1.19 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 158.8, 145.0, 140.4, 137.9, 128.9, 128.3, 126.9, 125.9, 123.6, 119.7, 115.8, 112.7, 90.8, 79.7, 55.1, 42.2, 26.7. FTIR (neat): 874, 1190, 2927 cm^{-1}. HRMS (ESI-TOF) *m*/*z*: [M + Na]$^+$ calcd for $C_{25}H_{26}O_3Na$, 397.1779; found, 397.1777.

*9-(tert-Butylperoxy)-9-(2-methoxybenzyl)-9H-fluorene (**2g**).* Prepared according to general procedure A using 9-(2-methoxybenzyl)-9*H*-fluorene (112 mg, 0.39 mmol) to afford peroxyfluorene **2g** (129 mg, 0.34 mmol, 88% yield) as a yellow semisolid after purification by silica gel column chromatography (EtOAc/*n*-hexane = 1:99). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54−7.51 (m, 2H), 7.32−7.27 (m, 4H), 7.17 (td, *J* = 7.5, 1.1 Hz, 2H), 7.10 (dd, *J* = 11.9, 4.6 Hz, 2H), 6.73 (td, *J* = 7.5, 1.1 Hz, 1H), 6.65−6.63 (m, 1H), 3.54 (s, 2H), 3.42 (s, 3H), 1.13 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 157.9, 145.7, 140.3, 132.2, 128.6, 127.6, 126.6, 125.7, 125.0, 119.7, 119.4, 110.1, 90.9, 79.5, 54.7, 34.4, 26.7. FTIR (neat): 868, 1174, 2916, 3340 cm^{-1}. HRMS (ESI-TOF) *m*/*z*: [M − OO^{t}Bu]$^+$ calcd for $C_{21}H_{17}$, 285.1274; found, 285.1279.

*9-(tert-Butylperoxy)-9-(3-phenoxybenzyl)-9H-fluorene (**2h**).* Prepared according to general procedure A using 9-(3-phenoxybenzyl)-9*H*-fluorene (136 mg, 0.39 mmol) to afford peroxyfluorene **2h** (143 mg, 0.32 mmol, 84% yield) as a yellow semisolid after purification by silica gel column chromatography (EtOAc/*n*-hexane = 1:99). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55−7.52 (m, 2H), 7.37−7.31 (m, 4H), 7.31−7.25 (m, 3H), 7.20 (td, *J* = 7.5, 1.1 Hz, 2H), 7.05 (m, 1H), 6.81−6.78 (m, 3H), 6.69−6.67 (m, 2H), 3.46 (s, 2H), 1.11 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 157.6, 156.2, 144.9, 140.4, 138.4, 129.7, 129.0, 128.7, 127.1, 126.2, 125.8, 122.8, 121.9, 119.8, 118.5, 117.6, 90.8, 79.8, 42.0, 26.7. FTIR (neat): 858, 1186, 1249, 2977 cm^{-1}. HRMS (ESI-TOF) *m*/*z*: [M]$^+$ calcd for $C_{30}H_{28}O_3$, 436.2038; found, 436.2029.

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*9-(tert-Butylperoxy)-9-(3-chlorobenzyl)-9H-fluorene (**2i**).* Prepared according to general procedure A using 9-(3-chlorobenzyl)-9*H*-fluorene (113 mg, 0.39 mmol) to afford peroxyfluorene **2i** (102 mg, 0.26 mmol, 69% yield) as a yellow semisolid after purification by silica gel column chromatography (EtOAc/*n*-hexane = 1:99). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (dd, J = 6.7, 0.8 Hz, 2H), 7.34 (td, J = 7.4, 1.3 Hz, 2H), 7.29−7.27 (m, 2H), 7.21 (td, J = 7.4, 1.1 Hz, 2H), 7.14−7.11 (m, 2H), 7.05−7.01 (m, 1H), 6.85−6.83 (m, 1H), 3.41 (s, 2H), 1.15 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 144.8, 140.4, 138.6, 133.3, 131.2, 129.2, 129.1, 128.6, 127.1, 126.5, 125.9, 119.8, 90.5, 80.0, 41.7, 26.7. FTIR (neat): 883, 1060, 1201, 2986, 3443 cm^{-1}. HRMS (ESI-TOF) m/z: [M − OO^{t}Bu]$^+$ calcd for $C_{20}H_{14}Cl$, 289.0779; found, 289.0783.

*9-(3-Bromobenzyl)-9-(tert-butylperoxy)-9H-fluorene (**2j**).* Prepared according to general procedure A using 9-(3-bromobenzyl)-9*H*-fluorene (131 mg, 0.39 mmol) to afford peroxyfluorene **2j** (108 mg, 0.25 mmol, 65% yield) as a white solid after purification by silica gel column chromatography (EtOAc/*n*-hexane = 1:99). Melting point: 85−87 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, J = 7.5 Hz, 2H), 7.34 (td, J = 7.4, 1.2 Hz, 2H), 7.28 (m, 4H), 7.22 (t, J = 7.4 Hz, 2H), 6.98 (t, J = 7.7 Hz, 1H), 6.89 (d, J = 7.6 Hz, 1H), 3.41 (s, 2H), 1.17 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 144.7, 140.3, 138.9, 134.2, 129.7, 129.4, 129.1, 129.0, 127.1, 125.9, 121.6, 119.8, 90.4, 80.0, 41.7, 26.7. FTIR (neat): 1056, 1209, 2983 cm^{-1}. HRMS (ESI-TOF) m/z: [M − OO^{t}Bu]$^+$ calcd for $C_{20}H_{14}Br$, 333.0273; found, 333.0273.

*9-(tert-Butylperoxy)-9-(4-fluorobenzyl)-9H-fluorene (**2k**).* Prepared according to general procedure A using 9-(4-fluorobenzyl)-9*H*-fluorene (107 mg, 0.39 mmol) to afford peroxyfluorene **2k** (112 mg, 0.30 mmol, 79% yield) as a yellow solid after purification by silica gel column chromatography (EtOAc/*n*-hexane = 1:99). Melting point: 64−66 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, J = 7.4 Hz, 2H), 7.35−7.30 (m, 4H), 7.23−7.19 (m, 2H), 6.93 (dd, J = 8.5, 5.7 Hz, 2H), 6.78 (t, J = 8.8 Hz, 2H), 3.43 (s, 2H), 1.14 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 161.7 (d, J = 242 Hz), 144.9, 140.4, 132.4 (d, J = 7.8 Hz), 132.1 (d, J = 3.2 Hz), 129.0, 127.0, 125.8, 119.8, 114.2 (d, J = 21.0 Hz), 90.7, 79.8, 41.4, 26.7. FTIR (neat): 877, 1222, 2893 cm^{-1}. HRMS (ESI-TOF) m/z: [M − OO^{t}Bu]$^+$ calcd for $C_{20}H_{14}F$, 273.1074; found, 273.1083.

*9-(tert-Butylperoxy)-9-(3-(trifluoromethyl)benzyl)-9H-fluorene (**2l**).* Prepared according to general procedure A using 9-(3-(trifluoromethyl)benzyl)-9*H*-fluorene (126 mg, 0.39 mmol) to afford peroxyfluorene **2l** (139 mg, 0.33 mmol, 86% yield) as a yellow semisolid after purification by silica gel column chromatography (EtOAc/*n*-hexane = 1:99). Melting point: 73−75 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, J = 7.5 Hz, 2H), 7.36 (m, 2H), 7.30 (td, J = 7.4, 1.3 Hz, 2H), 7.23 (m, 2H), 7.17 (m, 3H), 7.07 (d, J = 7.7 Hz, 1H), 3.45 (s, 2H), 1.13 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 114.6, 140.3, 137.4, 134.4, 129.8 (q, J = 32.6 Hz), 129.2, 128.0 (q, J = 3.6), 127.8, 127.1, 125.8, 124.4 (q, J = 271.6 Hz), 123.2 (q, J = 3.2 Hz), 119.9, 90.4, 80.0, 42.0, 26.7. FTIR (neat): 885, 1174, 2947, 3412 cm^{-1}. HRMS (ESI-TOF) m/z: [M − OO^{t}Bu]$^+$ calcd for $C_{21}H_{14}F_3$, 323.1042; found, 323.1042.

*9-Benzyl-2-bromo-9-(tert-butylperoxy)-9H-fluorene (**2m**).* Prepared according to general procedure A using 9-benzyl-2-bromo-9*H*-fluorene (130 mg, 0.39 mmol) to afford peroxyfluorene **2m** (125 mg, 0.29 mmol, 76% yield) as a yellow solid after purification by silica gel column chromatography (EtOAc/*n*-hexane = 1:99). Melting point: 65−67 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, J = 7.5 Hz, 1H), 7.45−7.43 (m, 2H), 7.39−7.36 (m, 1H), 7.34−7.30 (m, 1H), 7.25−7.20 (m, 2H), 7.16−7.09 (m, 3H), 6.97 (m, 2H), δ 3.43 (d, J = 13.4 Hz, 1H), 3.36 (d, J = 13.6 Hz, 1H), 1.13 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 147.4, 144.8, 139.4, 139.3, 135.9, 131.9, 131.1, 129.2, 129.1, 127.6, 127.4, 126.6, 125.8, 121.0, 120.7, 119.8, 90.6, 80.0, 42.3, 26.8. FTIR (neat): 1070, 1188, 1263, 2979, 3425 cm^{-1}. HRMS (ESI-TOF) m/z: [M − OO^{t}Bu]$^+$ calcd for $C_{20}H_{14}Br$, 333.0273; found, 333.0271.

*2-Bromo-9-(tert-butylperoxy)-9-(4-methylbenzyl)-9H-fluorene (**2n**).* Prepared according to general procedure A using 2-bromo-9-(4-methylbenzyl)-9*H*-fluorene (136 mg, 0.39 mmol) to afford peroxyfluorene **2n** (130 mg, 0.29 mmol, 76% yield) as a yellow solid after purification by silica gel column chromatography (EtOAc/*n*-hexane = 1:99). Melting point: 73−75 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51−7.49 (m, 1H), 7.47 (m, 1H), 7.45−7.43 (m, 1H), 7.39−7.37 (m, 1H), 7.34−6.30 (m, 2H), 7.24−7.22 (m, 2H), 6.94−6.84 (m, 4H), 3.41 (d, J = 13.6 Hz, 1H), 3.32 (d, J = 13.6 Hz, 1H), 2.26 (s, 3H), 1.13 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 147.5, 144.8, 139.4, 139.3, 136.0, 132.7, 131.8, 130.9, 129.1, 129.1, 128.3, 127.3, 125.8, 121.1, 120.7, 119.8, 90.6, 79.9, 41.9, 26.7, 21.2. FTIR (neat): 1070, 1188, 1263, 2979, 3425 cm^{-1}. HRMS (ESI-TOF) m/z: [M − OO^{t}Bu]$^+$ calcd for $C_{21}H_{16}Br$, 347.0430; found, 347.0441.

*2-Bromo-9-(tert-butylperoxy)-9-(4-methoxybenzyl)-9H-fluorene (**2o**).* Prepared according to general procedure A using 2-bromo-9-(4-methoxybenzyl)-9*H*-fluorene (142 mg, 0.39 mmol) to afford peroxyfluorene **2o** (152 mg, 0.33 mmol, 86% yield) as a yellow solid after purification by silica gel column chromatography (EtOAc/*n*-hexane = 1:99). Melting point: 69−71 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50−7.47 (m, 2H), 7.44 (dd, J = 7.9, 1.8 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.34−7.30 (m, 1H), 7.25−7.22 (m, 2H), 6.91−6.88 (m, 2H), 6.71−6.65 (m, 2H), 3.74 (s, 3H), 3.39 (d, J = 13.8 Hz, 1H), 3.30 (d, J = 13.8 Hz, 1H), 1.15 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 158.3, 147.5, 144.8, 139.4, 139.3, 132.0, 131.8, 129.1, 127.9, 127.3, 125.8, 121.1, 120.7, 119.8, 113.0, 90.7, 79.9, 55.2, 41.4, 26.7. FTIR (neat): 1045, 1184, 1245, 2968, 3471 cm^{-1}. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{25}H_{25}BrO_3Na$, 475.0884; found, 475.0867.

*2-Bromo-9-(tert-butylperoxy)-9-(3-methoxybenzyl)-9H-fluorene (**2p**).* Prepared according to general procedure A using 2-bromo-9-(3-methoxybenzyl)-9*H*-fluorene (142 mg, 0.39 mmol) to afford peroxyfluorene **2p** (137 mg, 0.30 mmol, 77% yield) as a yellow solid after purification by silica gel column chromatography (EtOAc/*n*-hexane = 1:99). Melting point: 74−75 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52−7.48 (m, 2H), 7.44 (dd, J = 8.0, 1.8 Hz, 1H), 7.39−7.27 (m, 3H), 7.25−7.21 (m, 1H), 7.04−6.96 (m, 1H), 6.68 (ddd, J = 8.2, 2.6, 0.9 Hz, 1H), 6.56−6.50 (m, 2H), 3.65 (s, 3H), 3.43 (d, J = 14.0 Hz, 1H), 3.36 (d, J = 13.5 Hz, 1H), 1.15 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 158.9, 147.3, 144.5, 139.4, 139.3, 137.3, 131.9, 129.2, 128.5, 127.4, 125.8, 123.6, 121.1, 120.7, 119.9, 115.8, 113.0, 90.6, 80.0, 55.2, 42.3, 26.7. FTIR (neat): 1045, 1184, 2968, 3471 cm^{-1}. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{25}H_{25}BrO_3Na$, 475.0884; found, 475.0872.

*2-Bromo-9-(tert-butylperoxy)-9-(3-chlorobenzyl)-9H-fluorene (**2q**).* Prepared according to general procedure A using 2-bromo-9-(3-chlorobenzyl)-9*H*-fluorene (144 mg, 0.39 mmol) to afford peroxyfluorene **2q** (130 mg, 0.28 mmol, 73% yield) as a yellow solid after purification by silica gel column chromatography (EtOAc/*n*-hexane = 1:99). Melting point: 85−87 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, J = 7.52 Hz, 1H), 7.47−7.39 (m, 3H), 7.34 (td, J = 7.3, 1.3, 1H), 7.25−7.11 (m, 4H), 7.07 (t, J = 7.8 Hz, 1H), 6.84 (d, J = 7.5 Hz, 1H), 3.43 (d, J = 13.7 Hz, 1H), 3.30 (d, J = 13.7 Hz, 1H), 1.17 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 147.1, 144.3, 139.3, 139.2, 138.0, 133.4, 132.1, 131.2, 129.4, 129.2, 129.1, 128.8, 127.5, 126.8, 125.8, 121.2, 120.8, 120.0, 90.2, 80.2, 41.8, 26.7. FTIR (neat): 1067, 1197, 2961 cm^{-1}. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{24}H_{22}BrClO_2Na$, 479.0389; found, 479.0375.

*9-(tert-Butylperoxy)-9-propyl-9H-fluorene (**2r**).* Prepared according to general procedure A using 9-propyl-9*H*-fluorene (81 mg, 0.39 mmol) to afford peroxyfluorene **2r** (75 mg, 0.25 mmol, 65% yield) as a white semisolid after purification by silica gel column chromatography (EtOAc/*n*-hexane = 1:99). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (m, 2H), 7.54 (m, 2H), 7.37 (td, J = 7.5, 1.2 Hz, 2H), 7.29 (td, J = 7.4, 1.1 Hz, 2H), 2.31−2.27 (m, 2H), 1.12 (s, 9H), 0.92−0.86 (m, 2H), 0.78 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 145.8, 140.8, 128.8, 127.3, 125.0, 119.8, 91.2, 79.3, 38.1, 26.7, 17.3, 14.5. FTIR (neat): 884, 1198, 3427 cm^{-1}. HRMS (ESI-TOF) m/z: [M − OO^{t}Bu]$^+$ calcd for $C_{16}H_{15}$, 207.1168; found, 207.1170.

*9-Butyl-9-(tert-butylperoxy)-9H-fluorene (**2s**).* Prepared according to general procedure A using 9-butyl-9*H*-fluorene (87 mg, 0.39 mmol) to afford peroxyfluorene **2s** (78 mg, 0.25 mmol, 64% yield) as a yellow semisolid after purification by silica gel column

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chromatography (EtOAc/*n*-hexane = 1:99). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64−7.62 (m, 2H), 7.56−7.54 (m, 2H), 7.37 (td, J = 7.5, 1.2 Hz, 2H), 7.29 (td, J = 7.4, 1.1 Hz, 2H), 2.33−2.29 (m, 2H), 1.23−1.16 (m, 2H), 1.11 (s, 9H), 0.87−0.79 (m, 2H), 0.76 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 145.7, 140.8, 128.8, 127.3, 125.0, 119.8, 91.2, 79.3, 35.5, 26.7, 25.9, 23.1, 14.0. FTIR (neat): 758, 1197, 2858, 3487 cm^{-1}. HRMS (ESI-TOF) m/z: [M − OO^{t}Bu]$^+$ calcd for $C_{17}H_{17}$, 221.1325; found, 221.1326.

*9-(tert-Butylperoxy)-9-hexyl-9H-fluorene (**2t**).* Prepared according to general procedure A using 9-hexyl-9*H*-fluorene (98 mg, 0.39 mmol) to afford peroxyfluorene **2t** (62 mg, 0.18 mmol, 47% yield) as a white semisolid after purification by silica gel column chromatography (EtOAc/*n*-hexane = 1:99). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, J = 7.4 Hz, 2H), 7.56 (d, J = 7.3 Hz, 2H), 7.39 (td, J = 7.5, 1.2 Hz, 2H), 7.30 (td, J = 7.4, 1.2 Hz, 2H), 2.33−2.28 (m, 2H), 1.22−1.12 (m, 6H), 1.12 (s, 9H), 0.89−0.80 (m, 5H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 145.7, 140.8, 128.8, 127.3, 125.0, 119.8, 91.3, 79.3, 35.7, 31.6, 29.7, 26.7, 23.7, 22.7, 14.1. FTIR (neat): 757, 1196, 2958, 3464 cm^{-1}. HRMS (ESI-TOF) m/z: [M − OO^{t}Bu]$^+$ calcd for $C_{19}H_{21}$, 249.1638; found, 249.1639.

*9-(tert-Butylperoxy)-9-octyl-9H-fluorene (**2u**).* Prepared according to general procedure A using 9-octyl-9*H*-fluorene (109 mg, 0.39 mmol) to afford peroxyfluorene **2u** (94 mg, 0.25 mmol, 66% yield) as a faint yellow semisolid after purification by silica gel column chromatography (EtOAc/*n*-hexane = 1:99). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, J = 7.5 Hz, 2H), 7.55 (dd, J = 7.4, 0.4 Hz, 2H), 7.37 (t, J = 7.4 Hz, 2H), 7.29 (t, J = 7.4 Hz, 2H), 2.32−2.28 (m, 2H), 1.39−1.15 (m, 10H), 1.15 (s, 9H), 0.87−0.81 (m, 5H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 145.7, 140.8, 128.8, 127.3, 125.0, 119.8, 91.3, 79.3, 35.7, 31.9, 30.0, 29.4, 29.3, 26.7, 23.7, 22.7, 14.2. FTIR (neat): 758, 1196, 2924, 3473 cm^{-1}. HRMS (ESI-TOF) m/z: [M − OO^{t}Bu]$^+$ calcd for $C_{21}H_{25}$, 277.1951; found, 277.1949.

*2-((9-(tert-Butylperoxy)-9H-fluoren-9-yl)methyl)thiophene (**2v**).* Prepared according to general procedure A using 2-((9*H*-fluoren-9-yl)methyl)thiophene (102 mg, 0.39 mmol) to afford peroxyfluorene **2v** (108 mg, 0.30 mmol, 79% yield) as a greenish semisolid after purification by silica gel column chromatography (EtOAc/*n*-hexane = 1:99). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, J = 7.5 Hz, 2H), 7.39 (d, J = 7.5 Hz, 2H), 7.35 (td, J = 7.5, 1.2 Hz, 2H), 7.23 (td, J = 7.5, 1.1 Hz, 2H), 7.03 (dd, J = 5.1, 1.2 Hz, 1H), 6.76 (m, 1H), 6.55 (dd, J = 3.4, 0.9 Hz, 1H), 3.73 (s, 2H), 1.16 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 144.6, 140.7, 138.3, 129.2, 127.5, 127.2, 126.0, 125.7, 124.5, 119.8, 90.2, 79.9, 36.5, 26.7. FTIR (neat): 855, 1200, 1655, 2962 cm^{-1}. HRMS (ESI-TOF) m/z: [M − OO^{t}Bu]$^+$ calcd for $C_{18}H_{13}S$, 261.0733; found, 261.0740.

*9-(tert-Butylperoxy)-9-phenyl-9H-fluorene (**2w**).* Prepared according to general procedure A using 9-phenyl-9*H*-fluorene (95 mg, 0.39 mmol) to afford peroxyfluorene 2w (114 mg, 0.34 mmol, 88% yield) as a white solid after purification by silica gel column chromatography (EtOAc/*n*-hexane = 1:99). Melting point: 91−93 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 7.5 Hz, 2H), 7.42−7.36 (m, 6H), 7.31−7.21 (m, 5H), 1.08 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 146.8, 141.6, 140.9, 129.1, 128.2, 127.6, 127.5, 126.8, 126.4, 119.9, 92.3, 79.9, 26.6. FTIR (neat): 883, 1210, 2929, 3428 cm^{-1}. HRMS (ESI-TOF) m/z: [M − OO^{t}Bu]$^+$ calcd for $C_{19}H_{13}$, 241.1012; found, 241.1013.

*3-(tert-Butylperoxy)-3-methylindolin-2-one (**5a**).*[3b] Prepared according to general procedure B using 3-methylindolin-2-one (37 mg, 0.25 mmol) to afford peroxyoxindole **5a** (54 mg, 0.22 mmol, 91% isolated yield) as a white solid after purification by silica gel column chromatography (EtOAc/*n*-hexane = 20:80). The data for this compound are in agreement with the reported compound.

*3-Benzyl-3-(tert-butylperoxy)indolin-2-one (**5b**).*[3b] Prepared according to general procedure B using 3-benzylindolin-2-one (56 mg, 0.25 mmol) to afford peroxyoxindole **5b** (69 mg, 0.22 mmol, 89% isolated yield) as a white solid after purification by silica gel column chromatography (EtOAc/*n*-hexane = 20:80). The data for this compound are in agreement with the reported compound.

*3-(tert-Butylperoxy)-3-(4-methylbenzyl)indolin-2-one (**5c**).*[3b] Prepared according to general procedure B using 3-(4-methylbenzyl)-indolin-2-one (59 mg, 0.25 mmol) to afford peroxyoxindole **2h** (69 mg, 0.21 mmol, 85% yield) as a yellow solid after purification by silica gel column chromatography (EtOAc/*n*-hexane = 20:80). The data for this compound are in agreement with the reported compound.

*3-(tert-butylperoxy)-3-(2-methylbenzyl)indolin-2-one (**5d**).*[3b] Prepared according to general procedure B using 3-(2-methylbenzyl)-indolin-2-one (59 mg, 0.25 mmol) to afford peroxyoxindole **5d** (72 mg, 0.22 mmol, 89% yield) as a yellow solid after purification by silica gel column chromatography (EtOAc/*n*-hexane = 20:80). The data for this compound are in agreement with the reported compound.

*3-(4-Bromobenzyl)-3-(tert-butylperoxy)indolin-2-one (**5e**).*[3b] Prepared according to general procedure B using 3-(4-bromobenzyl)-indolin-2-one (75 mg, 0.25 mmol) to afford peroxyoxindole **5e** (78 mg, 0.20 mmol, 86% yield) as a light yellow solid after purification by silica gel column chromatography (EtOAc/*n*-hexane = 20:80). The data for this compound are in agreement with the reported compound.

*9-(tert-Butylperoxy)-9-((tert-butylperoxy)(phenyl)methyl)-9H-fluorene (**7a**).* Prepared according to general procedure D using 9-benzylidene-9*H*-fluorene (63.58 mg, 0.25 mmol) to afford bisperoxyfluorene & 9*H*-fluoren-9-one (**7a**) (80 mg, 74% yield) as a yellow solid after purification by silica gel column chromatography (EtOAc/*n*-hexane = 1:99). A minor quantity of **3** has been observed as an inseparable mixture with **7a**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 7.3 Hz, 1H), 7.67 (d, J = 7.4 Hz, 1H), 7.52 (d, J = 7.3 Hz, 2H), 7.49 (td, J = 7.3, 1.1 Hz, 2H), 7.43 (t, J = 6.76 Hz, 2H), 7.36−7.25 (m, 6H), 7.22 (td, J = 7.4, 1.2 Hz, 1H), 7.15 (t, J = 7.4 Hz, 1H), 7.03−6.99 (m, 1H), 6.94 (t, J = 7.5 Hz, 2H), 6.87 (d, J = 7.9 Hz, 2H), 5.81 (s, 1H), 1.23 (s, 9H), 1.14 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 194.1, 144.6, 143.3, 142.3, 141.4, 140.9, 137.0, 134.8, 134.3, 129.2, 129.2, 129.0, 128.6, 127.6, 127.2, 126.9, 126.7, 126.7, 126.5, 124.5, 120.5, 119.5, 119.3, 92.8, 86.7, 80.7, 79.9, 26.7, 26.7. FTIR (neat): 732, 1017, 1192 cm^{-1}. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{28}H_{32}O_4Na$, 455.2198; found, 455.2198.

*9-((4-Bromophenyl)(tert-butylperoxy)methyl)-9-(tert-butylperoxy)-9H-fluorene (**7b**).* Prepared according to general procedure D using 9-(4-bromobenzylidene)-9*H*-fluorene (83 mg, 0.25 mmol) to afford bisperoxyfluorene **7b** (112 mg, 0.21 mmol, 88% yield) as a yellow solid after purification by silica gel column chromatography (EtOAc/*n*-hexane = 1:99). Melting point: 116−118 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (dd, J = 7.4, 0.5 Hz, 1H), 7.34−7.28 (m, 2H), 7.23 (td, J = 7.5, 1.1 Hz, 1H), 7.19−7.11 (m, 3H),7.04 (t, J = 7.4 Hz, 1H), 6.96 (d, J = 8.2 Hz, 2H), 6.64 (d, J = 8.0 Hz, 2H), 5.68 (s, 1H), 1.10 (s, 9H), 1.02 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 142.8, 141.9, 141.4, 140.9, 136.3, 130.2, 129.9, 129.4, 129.2, 127.5, 127.0, 126.7, 126.6, 121.3, 119.7, 119.5, 92.4, 85.9, 80.8, 80.1, 26.7, 26.7. FTIR (neat): 737, 1010, 1363, 1195 cm^{-1}. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{28}H_{31}BrO_4Na$, 533.1303; found, 533.1299.

*9-((3-Bromophenyl)(tert-butylperoxy)methyl)-9-(tert-butylperoxy)-9H-fluorene (**7c**).* Prepared according to general procedure D using 9-(3-bromobenzylidene)-9*H*-fluorene (83 mg, 0.25 mmol) to afford bisperoxyfluorene **7c** (101 mg, 0.19 mmol, 80% yield) as a yellow semisolid after purification by silica gel column chromatography (EtOAc/*n*-hexane = 1:99). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (m, 1H), 7.48−7.46 (m, 1H), 7.42−7.38 (m, 1H), 7.36 (td, J = 7.5, 1.2 Hz, 2H), 7.30 (dd, J = 7.4, 1.2 Hz, 1H), 7.28−7.24 (m, 1H), 7.20−7.16 (m, 2H), 7.12 (m, 1H), 6.88−6.83 (m, 2H), 5.81 (s, 1H), 1.22 (s, 9H), 1.18 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 142.6, 142.1, 141.3, 140.9, 139.6, 131.8, 130.2, 129.4, 129.3, 128.3, 127.4, 127.1, 127.0, 126.7, 120.9, 119.6, 119.5, 92.4, 85.8, 80.9, 80.2, 26.7, 26.6. FTIR (neat): 876, 1193, 2974 cm^{-1}. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for $C_{28}H_{31}BrO_4Na$, 533.1303; found, 533.1295.

*9-(tert-Butylperoxy)-9-((tert-butylperoxy)(4-chlorophenyl)-methyl)-9H-fluorene (**7d**).* Prepared according to general procedure D using 9-(4-chlorobenzylidene)-9*H*-fluorene (77 mg, 0.26 mmol) to afford bisperoxyfluorene **7d** (92 mg, 0.19 mmol, 75% yield) as a yellow solid after purification by silica gel column chromatography (EtOAc/*n*-hexane = 1:99). Melting point: 105−107 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 7.4 Hz, 1H), 7.45 (m, 2H), 7.39 (m, 1H), 7.35 (m, 1H), 7.32−7.28 (m, 1H), 7.27−7.23 (m, 1H), 7.17

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(td, J = 7.5, 1.1 Hz, 1H), 6.98−6.92 (m, 2H), 6.83−6.80 (m, 2H), 5.82 (s, 1H), 1.24 (s, 9H), 1.16 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 142.9, 141.9, 141.4, 140.9, 135.7, 134.8, 132.9, 129.8, 129.4, 129.2, 127.5, 127.0, 126.7, 126.6, 119.7, 119.5, 92.5, 85.9, 80.8, 80.1, 26.7, 26.6. FTIR (neat): 873, 1015, 1194, 3406 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{28}H_{31}ClO_4Na$, 489.1809; found, 489.1812.

*9-(tert-Butylperoxy)-9-((tert-butylperoxy)(4-fluorophenyl)-methyl)-9H-fluorene (**7e**).* Prepared according to general procedure D using 9-(4-fluorobenzylidene)-9*H*-fluorene (100 mg, 0.36 mmol) to afford bisperoxyfluorene **7e** (148 mg, 0.32 mmol, 90% yield) as a yellow solid after purification by silica gel column chromatography (EtOAc/*n*-hexane = 1:99). Melting point: 104−106 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.76−7.73 (m, 1H), 7.48−7.43 (m, 2H), 7.35 (dd, J = 15.2, 7.5 Hz, 2H), 7.29 (m, 1H), 7.23 (t, J = 7.4 Hz, 1H), 7.16 (t, J = 7.4 Hz, 1H), 6.86−6.82 (m, 2H), 6.64 (td, J = 8.7, 1.3 Hz, 2H), 5.83 (d, J = 1.8 Hz, 1H), 1.25 (d, J = 1.5 Hz, 9H), 1.16 (d, J = 1.4 Hz, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 162.1 (d, J = 243.24 Hz), 143.1, 142.0, 141.0, 140.0, 134.8, 132.8 (d, J = 3.0 Hz), 130.0 (d, J = 8.1 Hz), 129.3, 129.1, 127.5, 127.0, 126.6, 126.5, 119.5 (d, J = 17.6 Hz), 113.6 (d, J = 21.09 Hz), 92.7, 86.0, 80.8, 80.0, 26.7, 26.7. FTIR (neat): 733, 1195, 2973 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{28}H_{31}FO_4Na$, 473.2103; found, 473.2112.

*3-(tert-Butylperoxy)-3-((tert-butylperoxy)(phenyl)methyl)indolin-2-one (**9a** & **9a′**).* Prepared according to general procedure D using (*E*/*Z*)-3-benzylideneindolin-2-one (55.31 mg, 0.25 mmol) to afford bisperoxyoxindole diastereomers **9a** & **9a′** having a ratio of 1:3 with an overall yield of 71% (71 mg, 0.17 mmol) as a yellow solid after purification by silica gel column chromatography (EtOAc/*n*-hexane = 10:90). Selected signal for the major isomer: ^1H NMR (400 MHz, $CDCl_3$): δ 7.69−7.66 (m, 1H), 7.36 (s, 1H), 7.23−7.19 (m, 1H), 7.09−7.05 (m, 4H), 6.98−6.96 (m, 2H), 6.53 (d, J = 7.7 Hz, 1H), 5.46 (s, 1H), 1.33 (s, 9H), 1.17 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 173.5, 141.5, 134.6, 129.9, 128.3, 128.1, 127.6, 127.4, 124.9, 122.3, 109.3, 88.5, 86.5, 81.5, 80.9, 26.7, 26.5. FTIR (neat): 1055, 1194, 1732, 1471, 2972, 3628 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{30}NO_5$, 400.2124; found, 400.2130.

*3-(tert-Butylperoxy)-3-((tert-butylperoxy)(p-tolyl)methyl)indolin-2-one (**9b** & **9b′**).* Prepared according to general procedure D using (*E*/*Z*)-3-(4-methylbenzylidene)indolin-2-one (58.77 mg, 0.25 mmol) to afford bisperoxyoxindole diastereomers **9b** & **9b′** having a ratio of 1:3 with an overall yield of 56% (58 mg, 0.14 mmol) as a yellow solid after purification by silica gel column chromatography (EtOAc/*n*-hexane = 10:90). Selected signal for the major isomer: ^1H NMR (400 MHz, $CDCl_3$): δ 7.67 (dd, J = 6.9, 0.5 Hz, 1H), 7.56 (m, 1H), 7.22−7.18 (m, 2H), 7.07 (td, J = 7.6, 1.0 Hz, 1H), 6.85 (s, 3H), 6.55 (d, J = 7.6 Hz, 1H), 5.43 (s, 1H), 2.19 (s, 3H), 1.32 (s, 9H), 1.16 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 173.9, 141.7, 138.0, 132.8, 131.5, 129.8, 128.4, 128.2, 125.0, 122.2, 109.5, 88.6, 86.4, 81.4, 80.8, 26.6, 26.5, 21.3. FTIR (neat): 1020, 1121, 1472, 1733 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{24}H_{31}NO_5Na$, 436.2102; found, 436.2103.

*3-(tert-Butylperoxy)-3-((tert-butylperoxy)(4-methoxyphenyl)-methyl)indolin-2-one (**9c** & **9c′**).* Prepared according to general procedure D using (*E*/*Z*)-3-(4-methoxybenzylidene)indolin-2-one (62.77 mg, 0.25 mmol) to afford bisperoxyoxindole diastereomers having a ratio of 1:3 **9c** & **9c′** with an overall yield of 80% (85 mg, 0.19 mmol) as an orange solid after purification by silica gel column chromatography (EtOAc/*n*-hexane = 10:90). Selected signal for the major isomer: ^1H NMR (400 MHz, $CDCl_3$): δ 7.84 (m, 1H), 7.68 (d, J = 7.2 Hz, 1H), 7.31−7.20 (m, 2H), 6.92−6.85 (m, 3H), 6.58 (d, J = 7.9 Hz, 2H), 5.43 (s, 1H), 3.65 (s, 3H), 1.34 (s, 9H), 1.17 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 174.2, 159.5, 141.8, 129.8, 129.5, 128.0, 126.6, 125.0, 122.1, 113.1, 109.6, 88.6, 86.1, 81.4, 80.8, 55.0, 26.6, 26.5. FTIR (neat): 874, 1052, 1196, 1472, 1733, cm^{-1}. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{24}H_{31}NO_6Na$, 452.2048; found, 452.2052.

*3-(tert-Butylperoxy)-3-((tert-butylperoxy)(4-chlorophenyl)-methyl)indolin-2-one (**9d** & **9d′**).* Prepared according to general procedure D using (*E*/*Z*)-3-(4-chlorobenzylidene)indolin-2-one (63.92 mg, 0.25 mmol) to afford bisperoxyoxindole as diastereomers **9d** & **9d′** in the ratio 1:3 with an overall yield of 75% (81 mg, 0.18 mmol) as a yellow solid. These diastereomers were separated by column purification and afforded syn-bisperoxyoxindole **9d′** (30 mg, 0.069 mmol, 28% yield) (melting point: 146−147 °C) and anti-bisperoxyoxindole **9d** (51 mg, 0.11 mmol, 47% yield) as a yellow solid (melting point: 132−134 °C) after purification by silica gel column chromatography (EtOAc/*n*-hexane = 10:90). Data for compound **9d**: ^1H NMR (400 MHz, $CDCl_3$): δ 7.63 (dt, J = 6.4, 3.2 Hz, 1H), 7.53 (s, 1H), 7.21 (td, J = 7.7, 1.3 Hz, 1H), 7.07 (td, 1H), 7.05−7.02 (m, 2H), 6.93−6.90 (m, 2H), 6.57 (d, J = 7.7 Hz, 1H), 5.43 (s, 1H), 1.31 (s, 9H), 1.15 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 173.6, 141.5, 134.2, 133.2, 130.1, 129.7, 127.9, 127.9, 124.5, 122.4, 109.7, 88.2, 85.7, 81.7, 81.0, 26.6, 26.5. FTIR (neat): 1020, 1196, 1472, 1733 cm^{-1}. HRMS (ESI) m/z: calcd for $C_{23}H_{28}ClNO_5Na$, 456.1553; found, 456.1541. Data for compound **9d′**: ^1H NMR (400 MHz, $CDCl_3$): δ 7.36−7.30 (m, 4H), 7.23 (td, J = 7.7, 1.2 Hz, 1H), 6.82−6.82 (m, 2H), 6.43 (d, J = 7.4 Hz, 1H), 5.56 (s, 1H), 1.11 (s, 9H), 1.04 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 175.7, 142.4, 134.5, 134.1, 130.0, 129.7, 127.7, 127.0, 124.6, 121.6, 109.8, 84.7, 83.7, 81.6, 81.1, 26.6, 26.4. FTIR (neat): 1020, 1196, 1472, 1733 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{23}H_{28}ClNO_5Na$, 456.1553; found, 456.1556.

*3-((4-Bromophenyl)(tert-butylperoxy)methyl)-3-(tert-butylperoxy)indolin-2-one (**9e**).* Prepared according to general procedure D using (*E*/*Z*)-3-(4-bromobenzylidene)indolin-2-one (75.03 mg, 0.25 mmol) to afford bisperoxyoxindole as diastereomers **9e** & **9e′** in the ratio 1:3 with an overall yield of 62% (74 mg, 0.15 mmol) as a yellow solid. This diastereomers was separated by column purification and afforded syn-bisperoxyoxindole **9e′** (15 mg, 0.031 mmol, 13%) (melting point: 146−147 °C) and anti-bisperoxyoxindole **9e** (59 mg, 0.12 mmol, 49% yield) as a yellow solid (melting point: 138−139 °C) after purification by silica gel column chromatography (EtOAc/*n*-hexane = 10:90). Data for compound **9e**: ^1H NMR (400 MHz, $CDCl_3$): δ 7.63 (dd, J = 7.4, 0.5 Hz, 1H), 7.42 (s, 1H), 7.23−7.17 (m, 3H), 7.07 (td, J = 7.6, 0.9 Hz, 1H), 6.87−6.84 (m, 2H), 6.57 (d, J = 7.7 Hz, 1H), 5.41 (s, 1H), 1.31 (s, 9H), 1.15 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 173.5, 141.5, 133.8, 130.8, 130.1, 130.0, 127.9, 124.5, 122.6, 122.4, 109.7, 88.1, 85.8, 81.7, 81.0, 26.6, 26.5. FTIR (neat): 1121, 1194, 1473, 1622, 1753, 2914, 3566 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{23}H_{28}BrNO_5Na$, 500.1048; found, 500.1050. Data for compound **9e′**: ^1H NMR (400 MHz, $CDCl_3$): δ 8.43 (m, 1H), 7.52−7.49 (m, 2H), 7.27−7.21 (m, 3H), 6.85 (m, 2H), 6.44 (d, J = 7.4 Hz, 1H), 5.54 (s, 1H), 1.11 (s, 9H), 1.04 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 175.7, 142.4, 135.0, 130.7, 130.0, 126.9, 124.6, 122.4, 121.6, 109.8, 84.6, 83.7, 81.6, 81.1, 26.6, 26.4. FTIR (neat): 1121, 1194, 1473, 1622, 1753, 2914, 3566 cm^{-1}. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{23}H_{28}BrNO_5Na$, 500.1048; found, 500.1044.

*(Z)-6-Benzylidene-6H-benzo[c]chromene (**10a**).*[23] Prepared according to general procedure J using 9-benzyl-9-(*tert*-butylperoxy)-9*H*-fluorene (86 mg, 0.25 mmol) to afford (*Z*)-6-benzylidene-6*H*-benzo[*c*]chromene **10a** (14 mg, 0.051 mmol, 20% yield) as a yellow solid and 9-benzylidene-9*H*-fluorene **6a** (30 mg, 0.118 mmol, 47% yield) as a white solid after purification by silica gel column chromatography (EtOAc/*n*-hexane = 1:99). Spectroscopic data match with the previously reported compound.[23] Data for compound **10a**: ^1H NMR (400 MHz, $CDCl_3$): δ 7.86−7.83 (m, 3H), 7.81 (dd, J = 7.8, 1.4 Hz, 1H), 7.77−7.74 (m, 1H), 7.39−7.27 (m, 5H), 7.22 (t, J = 7.4 Hz, 1H), 7.18 (dd, J = 8.1, 1.1 Hz, 1H), 7.12−7.07 (td, J = 7.4, 1.1 Hz, 1H), 6.27 (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 152.0, 147.8, 135.8, 129.8, 129.4, 128.8, 128.7, 128.5, 128.2, 127.9, 126.3, 124.0, 122.9, 122.6, 121.9, 119.6, 116.7, 103.6. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{15}O$, 271.1123; found, 271.1120.

Data for 9-benzylidene-9*H*-fluorene (**6a**):[20] ^1H NMR (400 MHz, $CDCl_3$): δ 7.82−7.78 (m, 1H), 7.74−7.71 (m, 3H), 7.57 (dd, J = 14.7, 7.7 Hz, 3H), 7.49−7.45 (m, 2H), 7.42−7.29 (m, 4H), (td, J = 7.7, 1.0 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 141.5, 139.4, 137.2, 136.4, 135.9, 131.9, 131.1, 128.9, 128.6, 127.2, 126.9, 126.8,

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125.8, 124.5, 120.4, 120.0, 120.0, 119.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{16}$, 255.1173; found, 255.1174.

*(Z)-6-(3-Bromobenzylidene)-6H-benzo[c]chromene (**10b**).* Prepared according to general procedure J using 9-(3-bromobenzyl)-9-(*tert*-butylperoxy)-9*H*-fluorene (106 mg, 0.25 mmol) to afford (*Z*)-6-(3-Bromobenzylidene)-6*H*-benzo[*c*]chromene **10b**. (22 mg, 0.063 mmol, 25% yield) as a yellow solid (melting point: 112−113 °C) and 9-(3-bromobenzylidene)-9*H*-fluorene **6b** (18 mg, 0.054 mmol, 22% yield) as a yellow solid after purification by silica gel column chromatography (EtOAc/*n*-hexane = 1:99). Data for compound **10b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.86 (dd, J = 16.0, 7.8 Hz, 2H), 7.74 (dd, J = 12.2, 7.8 Hz, 2H), 7.45 (t, J = 7.5 Hz, 1H), 7.35−7.30 (m, 3H), 7.23 (d, J = 7.9 Hz, 1H), 7.19 (d, J = 7.5 Hz, 1H), 7.14 (t, J = 7.5 Hz, 1H), 6.21 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 151.6, 148.9, 137.9, 131.4, 129.9, 129.9, 129.8, 128.9, 128.9, 128.3, 127.3, 124.0, 123.1, 122.6, 122.6, 122.0, 119.4, 116.7, 101.9. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{29}BrNO_5$, 349.0228; found, 349.0231. Data for 9-(3-bromobenzylidene)-9*H*-fluorene (**6b**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, J = 7.5 Hz, 1H), 7.66 (d, J = 7.5 Hz, 2H), 7.51 (dd, J = 13.9, 8.1 Hz, 4H), 7.39 (d, J = 8.4 Hz, 2H), 7.36−7.43 (m, 1H), 7.20−7.26 (m, 2H), 7.06−7.02 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 141.5, 139.4, 139.3, 137.1, 136.4, 135.9, 131.8, 131.1, 128.9, 128.6, 127.2, 126.9, 125.8, 124.4, 122.2, 120.4, 120.0, 119.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{14}Br$, 333.0278; found, 333.0289.

*(Z)-6-Benzylidene-8-bromo-6H-benzo[c]chromene (**10c**).* Prepared according to general procedure J using 9-benzyl-2-bromo-9-(*tert*-butylperoxy)-9*H*-fluorene (106 mg, 0.25 mmol) to afford (*Z*)-6-benzylidene-8-bromo-6*H*-benzo[*c*]chromene **10c** (27 mg, 0.077 mmol, 31% yield) as a yellow solid and (*E*/*Z*)-9-benzylidene-2-bromo-9*H*-fluorene **6c** & **6c′** (16 mg, 0.048 mmol, 19% yield) as a yellow solid after purification by silica gel column chromatography (EtOAc/*n*-hexane = 1:99). Data for compound **10c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (m, 3H), 7.71−7.68 (m, 1H), 7.62 (d, J = 8.5 Hz, 1H), 7.45 (dd, J = 8.5, 1.8 Hz, 1H), 7.40 (t, J = 7.7 Hz, 2H), 7.30−7.23 (m, 2H), 7.13 (d, J = 7.7 Hz, 1H), 7.06 (t, J = 7.5 Hz, 1H), 6.17 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 151.8, 146.3, 135.3, 132.2, 130.2, 129.7, 129.0, 128.5, 127.2, 126.6, 126.6, 123.5, 123.0, 122.7, 122.4, 118.8, 116.8, 104.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{14}BrO$, 349.0228; found, 349.0211. Data for (*E*/*Z*)-9-benzylidene-2-bromo-9*H*-fluorene (**6c**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, J = 1.2 Hz, 1H), 7.71−7.69 (m, 1H), 7.65−7.64 (m, 2H), 7.60 (dd, J = 6.9, 2.4 Hz, 2H), 7.57 (s, 1H), 7.54−7.45 (m, 7H), 7.43−7.35 (m, 8H), 7.31 (td, J = 6.3, 1.0 Hz, 2H), 7.26 (t, J = 7.5 Hz, 1H), 7.04 (t, J = 7.6 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 141.5, 140.4, 140.1, 139.3, 138.4, 138.3, 138.0, 136.4, 136.4, 136.3, 135.6, 135.5, 131.3, 131.0, 129.3, 129.3, 128.8, 128.8, 128.8, 128.7, 128.6, 128.6, 128.5, 128.4, 127.5, 127.4, 127.1, 124.5, 123.7, 121.0, 121.0, 120.9, 120.5, 120.4, 119.9, 119.7. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{14}Br$, 333.0279; found, 333.0244.

*(Z)-8-Bromo-6-(3-chlorobenzylidene)-6H-benzo[c]chromene (**10d**).* Prepared according to general procedure J using 2-bromo-9-(*tert*-butylperoxy)-9-(3-chlorobenzyl)-9*H*-fluorene (114 mg, 0.25 mmol) to afford (*Z*)-8-bromo-6-(3-chlorobenzylidene)-6*H*-benzo[*c*]-chromene **10d** (39 mg, 0.101 mmol, 42% yield) as a pale yellow solid (melting point: 113−115 °C) and (*E*/*Z*)-2-bromo-9-(3-chlorobenzylidene)-9*H*-fluorene **6d** & **6d′** (6 mg, 0.016 mmol, 6% yield) as a yellow solid after purification by silica gel column chromatography (EtOAc/*n*-hexane = 1:99). Data for compound **10d**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.77 (d, J = 1.4 Hz, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.63 (d, J = 8.5 Hz, 1H), 7.58 (d, J = 7.7 Hz, 1H), 7.46 (dd, J = 8.5, 1.6 Hz, 1H), 7.31−7.24 (m, 2H), 7.18 (d, J = 7.8 Hz, 1H), 7.12−7.05 (m, 2H), 6.08 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 151.4, 147.3, 137.1, 134.3, 132.6, 130.3, 129.6, 129.1, 128.6, 127.3, 127.0, 126.7, 126.4, 123.6, 123.3, 122.7, 122.5, 118.6, 116.8, 103.2. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{13}BrClO$, 382.9838; found, 382.9841. Data for (*E*/*Z*)-2-bromo-9-(3-chlorobenzylidene)-9*H*-fluorene (**6d**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, J = 1.4 Hz, 1H), 7.72 (d, J = 7.1 Hz, 1H), 7.64 (d, J = 7.5 Hz, 2H), 7.60 (d, J = 1.4 Hz, 1H), 7.57 (s, 1H), 7.52−7.43 (m, 7H), 7.42−7.34 (m, 8H), 7.30 (t, J = 7.5 Hz, 2H), 7.09 (t, J = 7.6 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 141.2, 140.6, 140.3, 139.0, 138.5, 138.3, 138.2, 138.1, 138.1, 136.6, 136.6, 136.1, 134.8, 134.7, 131.7, 131.4, 130.0, 129.2, 129.2, 128.9, 128.6, 128.5, 127.6, 127.5, 127.5, 127.3, 126.7, 126.6, 124.5, 123.8, 121.2, 121.1, 121.0, 120.6, 120.5, 120.0, 119.8. HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{20}H_{13}BrCl$, 366.9889; found, 366.9896.

*9-Benzyl-9H-fluorene (**1a**).*[18] Prepared according to general procedure K using 9-benzyl-9-(*tert*-butylperoxy)-9*H*-fluorene **2a** (51.6 mg, 0.15 mmol) to afford 9-benzyl-9*H*-fluorene **1a** (31 mg, 0.121 mmol, 81% yield) as a white solid after purification by silica gel column chromatography (*n*-hexane). The data for this compound are in agreement with the reported compound.

*9-(3-Methylbenzyl)-9H-fluorene (**1b**).* Prepared according to general procedure K using 9-(*tert*-butylperoxy)-9-(3-methylbenzyl)-9*H*-fluorene **2c** (53.7 mg, 0.15 mmol) to afford 9-(3-methylbenzyl)-9*H*-fluorene **1b** (31 mg, 0.114 mmol, 78% yield) as a white solid after purification by silica gel column chromatography (*n*-hexane). The data for this compound are in agreement with the reported compound **1b**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, J = 7.6 Hz, 2H), 7.34 (t, J = 7.4 Hz, 2H), 7.21 (td, J = 7.3, 0.9 Hz, 3H), 7.15 (d, J = 7.5 Hz, 2H), 7.06 (m, 3H), 4.22 (t, J = 7.7 Hz, 1H), 3.06 (d, J = 7.7 Hz, 2H), 2.37 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 147.0, 140.9, 139.9, 138.0, 130.4, 128.3, 127.3, 127.2, 126.7, 126.6, 119.9, 48.8, 40.2, 21.6. HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{21}H_{18}Na$, 293.1306; found, 293.1314.

*9-(4-Methoxybenzyl)-9H-fluorene (**1c**).*[18] Prepared according to general procedure K using 9-(*tert*-butylperoxy)-9-(4-methoxybenzyl)-9*H*-fluorene **2e** (56.1 mg, 0.15 mmol) to afford 9-(4-methoxybenzyl)-9*H*-fluorene **1c** (32 mg, 0.111 mmol, 75% yield) as a white solid after purification by silica gel column chromatography (*n*-hexane). The data for this compound are in agreement with the reported compound.

*9-(3-Chlorobenzyl)-9H-fluorene (**1d**).*[18] Prepared according to general procedure K using 9-(*tert*-butylperoxy)-9-(3-chlorobenzyl)-9*H*-fluorene **2i** (56.2 mg, 0.15 mmol) to afford 9-(3-chlorobenzyl)-9*H*-fluorene **1d** (30 mg, 0.103 mmol, 71% yield) as a white solid after purification by silica gel column chromatography (*n*-hexane). The data for this compound are in agreement with the reported compound.

*9-(4-Fluorobenzyl)-9H-fluorene (**1e**).*[18] Prepared according to general procedure K using 9-(*tert*-butylperoxy)-9-(4-fluorobenzyl)-9*H*-fluorene **2k** (54.3 mg, 0.15 mmol) to afford 9-(4-fluorobenzyl)-9*H*-fluorene **1e** (31 mg, 0.113 mmol, 75% yield) as a white solid after purification by silica gel column chromatography (*n*-hexane). The data for this compound are in agreement with reported compound.

*9-Phenyl-9H-fluorene (**1f**).*[24] Prepared according to general procedure K using 9-(*tert*-butylperoxy)-9-phenyl-9*H*-fluorene **2w** (49.5 mg, 0.15 mmol) to afford 9-phenyl-9*H*-fluorene **1f** (33 mg, 0.136 mmol, 91% yield) as a white solid after purification by silica gel column chromatography (*n*-hexane). The data for this compound are in agreement with reported compound.

*9-Benzyl-9H-fluoren-9-ol (**O**).*[18b] Prepared according to general procedure L using 9-benzyl-9-(tert-butylperoxy)-9*H*-fluorene **2a** (52 mg, 0.15 mmol) to afford 9-benzyl-9*H*-fluoren-9-ol **O** (15 mg, 0.055 mmol, 38% yield) as a white solid after purification by silica gel column chromatography (EtOAc/*n*-hexane = 5:95) (melting point: 138−140 °C). The data for this compound are in agreement with the reported compound. ^{1}H NMR (400 MHz, $CDCl_3$) 7.54 (d, J = 7.4 Hz, 2H), 7.35−7.22 (m, 6H), 7.18−7.10 (m, 3H), 6.98 (dd, J = 7.5, 2.0 2H), 3.30 (s, 2H), 2.17 (br s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 148.3, 139.4, 136.4, 130.9, 129.0, 127.7, 127.6, 126.6, 124.4, 120.0, 82.4, 45.9. HRMS (ESI-TOF) m/z: $(M + H- H_2O)^+$ calcd for $C_{20}H_{15}$, 255.1168; found, 255.1179.

■ ASSOCIATED CONTENT

Supporting Information

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Copies of ^{1}H and ^{13}C NMR spectra for compounds and mechanistic studies and crystallographic data (PDF)
Crystallographic data for compound **9e** (CIF)

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Notes

The authors declare no competing financial interest.

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Peroxidation and Skeletal Rearrangement for the Synthesis of Dioxole-2-Carboxamide Derivatives under Continuous-Flow Conditions

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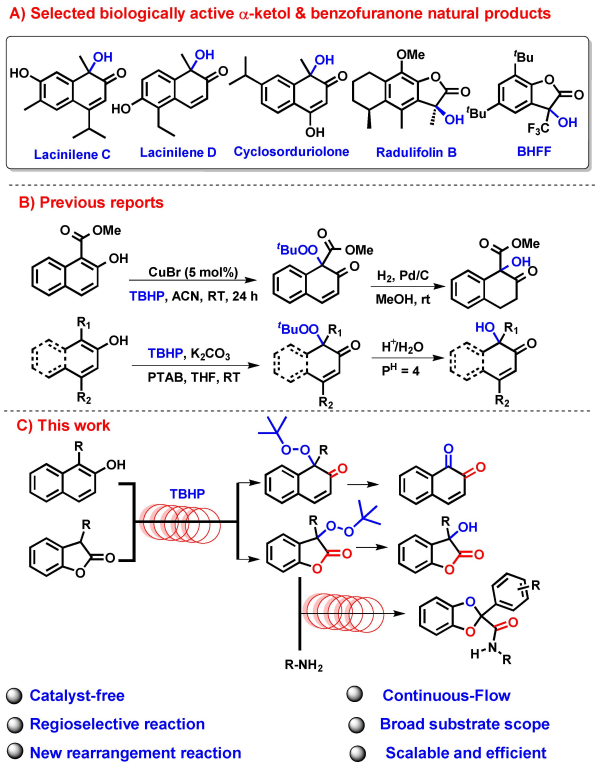
Abstract: Herein, we report peroxidative dearomatization of 2-naphthol and C–H peroxidation of 3-arylbenzofuran-2-ones with 66–94% yield under catalyst-free conditions using continuous flow module. Besides, an approach for the synthesis of *N*-substituted-2-phenylbenzo[*d*][*1,3*]dioxole-2-carboxamide has been achieved via the skeletal rearrangement of peroxybenzofuranone using amines in the absence of catalyst under continuous flow. The mechanistic study suggests that this peroxidation reaction proceeds via free radical formation under thermolytic conditions.

Keywords: Continuous Flow; Peroxidation; Rearrangement reaction; Catalyst-free reaction; Dearomatization



Scheme 1. State of the art for the peroxidation of 1-substituted-naphthol.

Peroxides (R–O–O–R) are the ubiquitous functional group that acts as a source of hydroxyl functionality due to the existence of reactive (O–O) bond (ΔH°_{298} = 158–194 kJ mol^{-1}).[1] Organic peroxide represents a predominant unit in innumerable natural products and bioactive compounds.[2a,b] Likewise, naphthalen-2(1*H*)-ones[3] and 3-hydroxy-3-substituted-benzofuran-2(3*H*)-one[4] are essential structural motifs in natural products and biologically important molecules, including anti-cancer radulifolin B,[4a,b] BHFF acts as the positive allosteric modulator of $GABA_B$ receptors and displays potential therapeutic action against alcoholism.[4b,c] (Scheme 1A). Oxidative-dearomatization can be a reaction of enormous synthetic importance in natural product synthesis.[5] In this context, quaternary hydroxyl motifs have been achieved by concomitant peroxidative dearomatization of naphthol and peroxide reduction. Interestingly, extensive literature reports are available on oxidative-alkylation for the dearomatization of various aromatic compounds via metal and metal-free approaches.[5,6] However, very limited noteworthy reports on the dearomatization of naphthols are documented. The Krohn group reported the oxidation of naphthols to such ketols catalyzed by zirconium and TBHP.[7] This can also be achieved by using

oxaziridines[8a] and chiral iodine complexes.[8b] The conversion of naphthols to α-ketols were reported by the Sarkar group using phenyl selenyl bromide in open-air conditions.[9] Later, Dhineshkumar et al. described the synthesis of quaternary peroxides from 2-naphthol derivatives using a copper catalyst.[10]

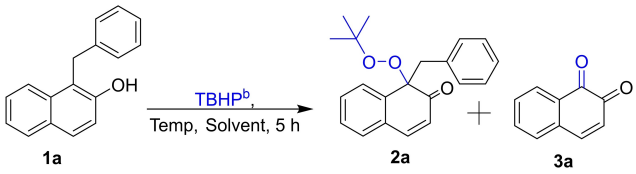
Subsequently, the Sarkar group reported metal-free conditions for peroxidation of 2-naphthol using the reagent system of TBHP, K_2CO_3 and phenyl trimethyl ammonium tribromide (PTAB)[11] (Scheme 1B). Nevertheless, there are no reports on the peroxidation of 3-aryl-benzofuran-2(3*H*)-one.

In synthetic chemistry, the rearrangement of organic peroxides is the key step in many well-known processes such as the Baeyer–Villiger (BV),[12a] Criegee,[12b] Hock reactions,[12c] Kornblum–DeLaMare rearrangement,[12d] and Dakin reaction.[12e] Based on these rearrangements, the skeletal rearrangement of the peroxides to access biologically important intermediates is an attractive paradigm for constructing heterocyclic scaffolds. For instance, Stoltz and co-workers reported a Cu-catalyzed C–H peroxidation of 2-oxindole and subsequent base-mediated skeletal fragmentation.[13a] Subsequently, our group reported that peroxyoxindole, under the basic condition, forms isocyanate as a key intermediate, which accelerates novel oxidative-skeletal rearrangement using primary amine or amino alcohol for the synthesis of exo-olefinic-quinazolinone or oxazoloquinazolinone.[13b] The rearrangement reactions of C3-substituted 2-oxindole peroxide were also described using Brønsted and Lewis acid catalyst.[13c–e] Other research groups have reported a few other rearrangements using different heterocyclic peroxides.[14] Although several peroxidation reactions have been achieved using metal[15] towards the skeletal rearrangement reaction, very limited metal-free conditions[16a–c] for peroxidation of 3-substituted indolin-2-ones,[16d] and 3,4-dihydro-1,4-benzoxazin-2-ones[16e] have been accounted recently. In addition, a transition metal catalyst[10] and stoichiometric reagents[11] have been used for the peroxidation of 2-naphthols. Some of the transition-metal residues are difficult to separate from desired products and are unsuitable for pharmaceuticals. The prolonged heating of peroxides under batch conditions can lead to unwanted reactions and also be associated with safety hazards. Hence, we chose to develop a continuous flow protocol that enables green principles using controlled addition of reagents to enhance safety and easy scalability, increase heat transfer, and reduce the reaction time. The advantages of continuous flow inspired us to develop a catalyst-free, safer and scalable route for the peroxidation of 2-naphthols and 3-arylbenzofuran-2-ones, and its rearrangements for synthesis of heterocycles.

In this work, we have developed the catalyst-free and scalable peroxidation of 2-naphthols and 3-arylbenzofuran-2-ones using continuous flow conditions (Scheme 1C). Additionally, a novel approach to synthesize *N*-substituted-2-phenylbenzo[*d*][*1,3*]dioxole-2-carboxamide has been presented via the skeletal rearrangement of peroxybenzofuranone in the absence of a catalyst under continuous flow conditions (Scheme 1C). The current work includes the following features: (i) catalyst-free peroxidation and step-economy; (ii) oxidative fragmentation and skeletal rearrangement of peroxides in one step; (iii) demonstrated broad substrate scope with high yields.

To establish a catalyst-free peroxidation of naphthol and 3-arylbenzofuran-2(3*H*)-one, initial optimization was performed with 1-benzylnaphthalen-2-ol **1a** and TBHP in decane under batch condition. A control experiment with **1a** and TBHP (5–6 M, 4 equiv.) in decane at room temperature in acetonitrile (ACN) resulted in a trace amount of the desired product **2a** (Table 1, entry 1). Next, we performed this reaction at 60 °C and provided 30% of **2a** (Table 1, entry 2). After that, we increased the temperature, resulting in a slight increase in yield (Table 1, entry 3). Also, 70% TBHP in water (4 equiv.) at 80 °C and with TBHP 5–6 M in decane (4 equiv.) gives slightly similar yields (Table 1, entry 4). Notably, 88% of **2a** was observed when the reaction was performed at 100 °C (Table 1, entry 5). The yield was decreased by reducing the reaction period from 5 h to 2 h (Table 1, entry 6). Other

Table 1. Optimization of reaction conditions for the peroxidation of 1-benzylnaphthalene-2-ol under batch conditions.[a]



Entry	Solvent	Temp °C	Yield [%] **2a**/**3a**
1	ACN	rt	trace/ND
2	ACN	60	30/ND
3	ACN	80	48/ND
4[c]	ACN	80	45/ND
5	ACN	100	88/trace
6[d]	ACN	100	50/trace
7	DCE	80	85/trace
8	THF	80	10/ND
9	EtOAc	80	58/ND
10	EtOH	80	40/ND

[a] Reaction conditions: compound **1a** (0.25 mmol), TBHP (4 equiv.) and solvent (2 mL) was stirred in a preheated oil bath (see table) for 5 h.
[b] 5–6 M in decane.
[c] 70% in water.
[d] Reaction performed for 2 h.
ND = not detected.
The mentioned yields are isolated yields.

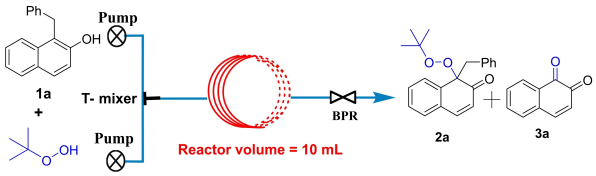
solvents for this reaction failed to improve the yield (Table 1, entries 7–10).

In order to perform the scalability and to avoid safety hazards, we optimized the reaction condition under continuous flow. Initially, solutions of **1a** (0.1 M) and TBHP (0.4 M in ACN) were passed through a coil reactor with 0.1 mL/min flow rate each at room temperature and 0.2 mL/min flow rate each at 80 °C resulted in a trace amount of product **2a** (Table 2, entries 1, 2). When solutions of **1a** (0.1 M) and (0.4 M) TBHP were passed through a coil reactor with the flow rate 0.1 mL/min each at 80 °C afforded **2a** in 41% yield (Table 2, entry 3) after 2 runs with the residence time (t_R) of 50 min for each run. With increased reaction temperature, a slight increase in yield of **2a** was observed, i.e., 47% and 75% yields of **2a**, after 2 and 3 runs, respectively (Table 2, entries 4 and 5).

This reaction was also studied at different concentrations of 0.05 M **1a** and 0.2 M TBHP with different residence time (t_R) afforded 15%, 45%, and 73% yields of **2a**, respectively (Table 2, entries 6, 7, and 8). This reaction with 0.2 M **1a** and 0.8 M TBHP with different residence time (t_R) furnished 30%, 48%, and 78% yield respectively (Table 2, entries 9, 10, and 11). Finally, we have kept the concentration of **1a** constant and varied the molar concentration of TBHP, and the results have shown in Table 2 (entries 12, 13, and 14). This optimization result indicated that solutions of **1a** (0.1 M) and TBHP (0.6 M) were passed through a coil reactor at 0.1 mL/min. each at 100 °C afforded product **2a** in 93% (Table 2, entry 14) with $t_R = 50$ min. for each run.

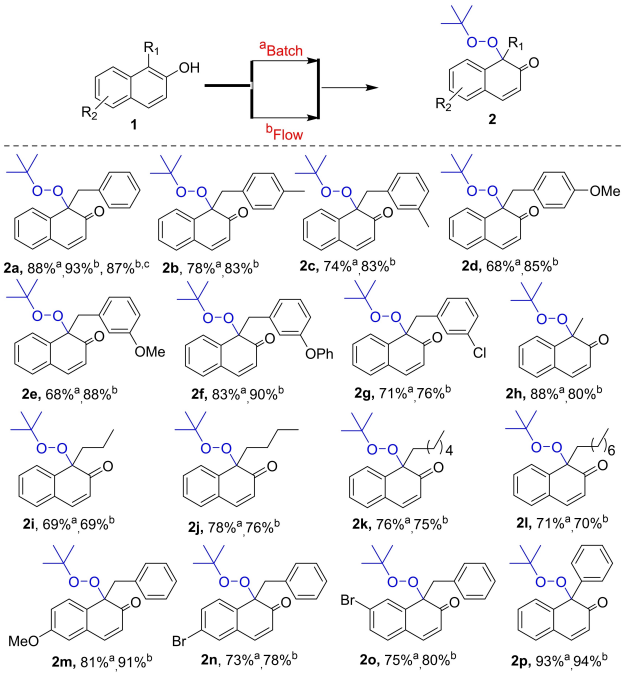
With optimized conditions in hand, the substrate scope for flow was applied to generalize the peroxidation of substituted naphthols (Scheme 2). The benzyl groups bearing electron-donating groups such as 4-Me, 3-Me, 4-OMe, 3-OMe, and 3-OPh afforded good to excellent yields of the products **2b–2f** (Scheme 2). The electron-withdrawing substituent such as 3-Cl on the benzyl group provided a moderate yield of the corresponding product **2g** (Scheme 2). To our delight, the aliphatic moiety on the 1-position of naphthol also reacted well to afford products **2h–2l** in moderate to good yields (Scheme 2). When 1-benzyl-

Table 2. Continuous flow optimization of peroxidation of 1-benzyl naphthalene-2-ol.[a]



Entry	Conc. (M) **1a**	TBHP	Flow rate in mL/min each	Temp °C	t_R(min)/number of runs	Yield **2a**/**3a** in (%)
1	0.1	0.4	0.1	rt	50/1	trace/ND
2	0.1	0.4	0.2	80	50/1	trace/ND
3	0.1	0.4	0.1	80	100/2	41/ND
4	0.1	0.4	0.1	100	100/2	47/trace
5	0.1	0.4	0.1	100	150/3	75/trace
6	0.05	0.2	0.1	100	50/1	15/ND
7	0.05	0.2	0.1	100	100/2	45/trace
8	0.05	0.2	0.1	100	150/3	73/trace
9	0.2	0.8	0.1	100	50/1	30/ND
10	0.2	0.8	0.1	100	100/2	48/trace
11	0.2	0.8	0.1	100	150/3	78/trace
12	0.1	0.5	0.1	100	100/2	58/trace
13	0.1	0.6	0.1	100	100/2	70/trace
14	0.1	0.6	0.1	100	150/3	93/trace

[a] Reaction conditions: A 0.05–0.2 M (see table) solution of **1a** and 0.2–0.6 M (see table) TBHP were flown through the 10 mL stainless steel (SS) tubular reactor (Vapourtec R-series) at a specified temperature. All solutions of **1a** and TBHP (5–6 M in decane) were prepared from 5 mL ACN.
t_R = residence time.
ND = Not detected.
The mentioned yields are isolated yields.



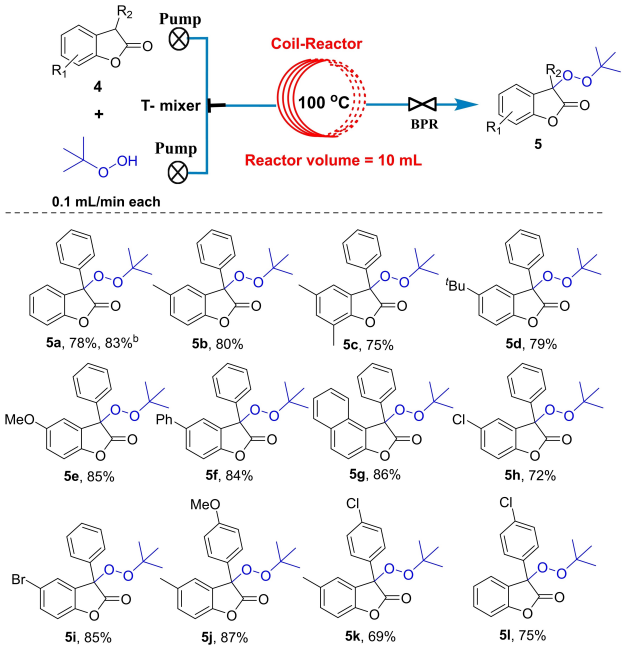
Scheme 2. Substrate scope for the dearomative peroxidation of 1-substituted-2-naphthols under batch and continuous flow conditions. Reaction conditions: [a]Method A (batch): compound **1a** (0.25 mmol), TBHP (4 equiv.) 5–6 M in decane and ACN (2 mL) were stirred in a preheated oil bath at 100 °C for 5 hrs. [b]Method B (continuous flow): 0.1 M solution of **1** and 0.6 M TBHP were flown through the 10 mL SS tubular reactor (Vapourtec R-series) three times run at 100 °C. All solutions of **1** and TBHP (5–6 M in decane) were prepared from 5 mL ACN. t_R = residence time. [c]Gram scale and isolated yields.

6-methoxynaphthalen-2-ol (**1m**), 1-benzyl-6-bromonaphthalen-2-ol (**1n**), 1-benzyl-7-bromonaphthalen-2-ol (**1o**) were subjected to continuous flow peroxidation, furnished products **2m**–**2o** in good to excellent yields (Scheme 2). Gratifyingly, the reaction of 1-phenylnaphthalen-2-ol afforded **2p** in 94% yield. The structure of product **2p** was supported by single-crystal XRD (see SI, Fig. S2). To our delight, a gram-scale reaction was also performed using the flow method to afford 87% (1.4 gm) of product **2a**.

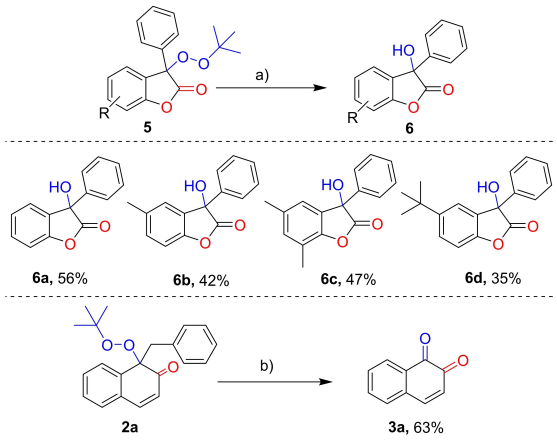
The continuous flow peroxidation was also investigated with 3-substituted benzofuran-2(3*H*)-ones **4** (Scheme 3). By using standard reaction conditions, the reaction of 0.1 M solution of **4a** and 0.6 M TBHP has flown through the 10 mL SS tubular reactor to afford the product **5a** in 78% yield. The electron-rich 5-substituted-3-phenylbenzofuran-2(3*H*)-one afforded **5b**–**5e** in 80%, 75%, 79%, and 85% yields, respectively (Scheme 3). Further, 3,5-diphenylbenzofuran-2(3*H*)-one **4f** and 1-phenylnaphtho[2,1-*b*]furan-2(1*H*)-one **4g** afforded the product **5f** in 84% and **5g** in 86% yields respectively. (Scheme 3). The electron-withdrawing group of 5-substituted-3-phenylbenzofuran-2(3*H*)-one afforded **5h** and **5i** in 72% to 85% yields. The 3-(4-methoxy-phenyl)-5-methylbenzofuran-2(3*H*)-one **4j**, 3-(4-chlorophenyl)-5-methylbenzofuran-2(3*H*)-one **4k** and 3-(4-chlorophenyl)benzofuran-2(3*H*)-one **4l** afforded products **5j**, **5k**, and **5l** in 87%, 69%, and 75% yields respectively.

Afterward, the application of peroxybenzofuranone and peroxynaphthols derivatives has been investigated to synthesize bioactive 3-hydroxy-5-substituted-3-phenylbenzofuran-2(3*H*)-one and 1,2-naphthoquinone by an oxidation and reduction reaction. Therefore, the reduction of peroxybenzofuranone derivatives **5** has been performed using 10 mol% of CuI and afforded **6a**–**6d** in moderate yields (Scheme 4). Unreacted starting material was recovered from these reactions. Moreover, oxidative cleavage has been performed using **2a** in the presence of catalytic CuBr to afford **3a** in 63% yield (Scheme 4). The synthesized 1,2-naphthoquinone (**3a**) and 3-hydroxy-3-phenylbenzofuran-2(3*H*)-one (**6a**) can be used as a valuable precursor in the synthesis of various bioactive molecules.[3,4]

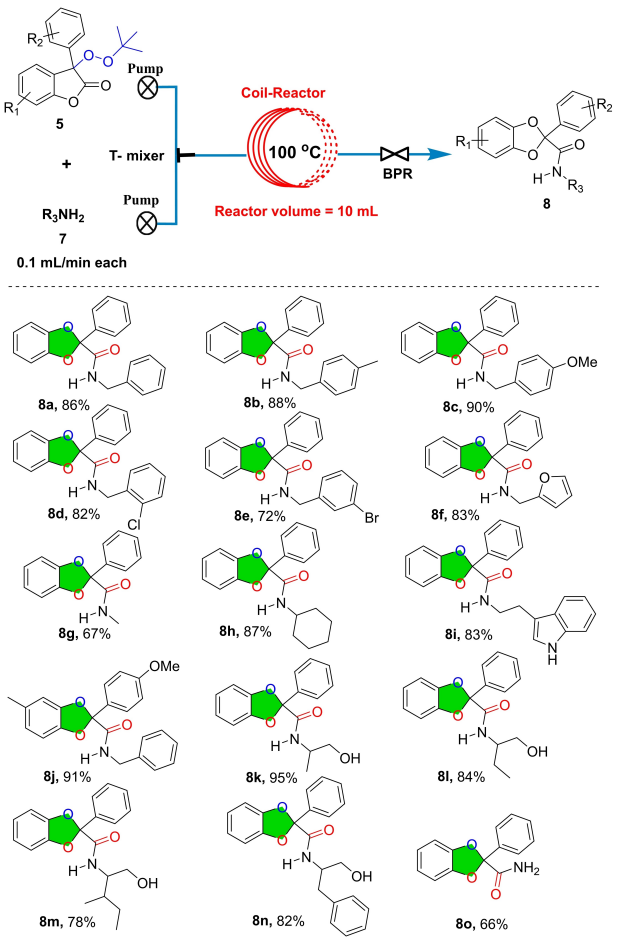
Next, we have envisioned catalyst-free molecular reconstruction of the peroxides **5** towards *N*-substituted-2-phenylbenzo[*d*][1,3]dioxole-2-carboxamide derivatives in a continuous flow approach. Accordingly, compound **5** (0.1 M, 5 mL of ACN) in a 30 mL vial was combined in a T-piece with a stream of amines (0.2 M, 5 mL of ACN) in another 30 mL vial. The prepared solutions were flown through a 10 mL SS coil reactor with a flow rate of 0.1 mL/min each for three-run at 100 °C at 3–4 bar pressure afforded *N*-benzyl-2-phenylbenzo[*d*][1,3]dioxole-2-carboxamide **8a** in 86% isolated yield. Other amines also reacted well for this reaction to obtain **8b**–**8j** in good to excellent yields (Scheme 5). Similarly, *N*-(1-hydroxy-substituted)-2-phenylbenzo[*d*][1,3]dioxole-2 carboxamide derivative and 2-phenylbenzo[*d*][1,3]dioxole-2-carboxamide (**8k**–**8o**) were also successfully synthe-



Scheme 3. Substrate scope for the peroxidation of 3-aryl benzofuran-2(3*H*)-ones under continuous flow. Reaction conditions: Method B (continuous flow): 0.1 M solution of **4** and 0.6 M TBHP were flown through the 10 mL SS tubular reactor (Vapourtec R-series) thrice at 100 °C. All solutions of **4** and TBHP (5–6 M in decane) were prepared from 5 mL ACN. [b]Gram scale and isolated yields.



Scheme 4. Synthesis of 3-hydroxy-5-substituted-3-phenylbenzofuran-2(3*H*)-one and 1,2-naphthoquinone. Reaction conditions: a) peroxides **5** (0.25 mmol, 1 equiv.), CuI (10 mol%), THF, 65 °C, 30 h; b) CuBr (10 mol%), DCE, 65 °C, 12 h; The mentioned yields are isolated yields.



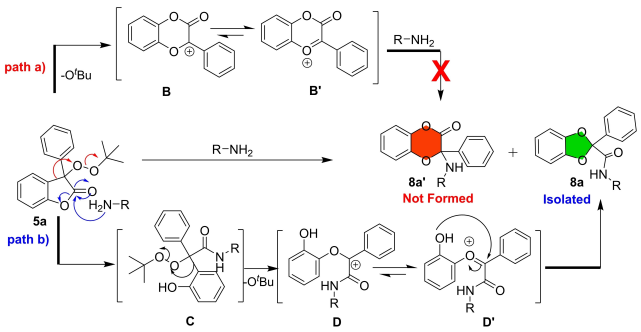
Scheme 5. Skeletal rearrangements and substrate scope towards *N*-substituted-2-phenylbenzo[*d*][1,3]dioxole-2-carboxamide. Reaction conditions: compound **5** (0.1 M, 5 mL of ACN) in a 30 mL vial was combined in a T-piece with a stream of amines (0.2 M, 5 mL of ACN) in another 30 mL vial. All solutions of **5**/**7** were prepared from 5 mL ACN. The prepared solutions were flown through a 10 mL SS coil reactor with a flow rate of 0.1 mL/min each for three runs at 100 °C and 3–4 bar pressure. The mentioned yields are isolated yields.

sized under catalyst-free rearrangement of the respective peroxides (Scheme 5).

To understand the reaction pathway, a series of control experiments were performed to elucidate the mechanism of this peroxidation of naphthol and benzofuran. When 2.0 equiv. of radical scavengers such as TEMPO or BHT were added to the reaction, and the yield of **2a** and **5a** decreased significantly, which proves the reaction follows a radical path. This reaction involves a radical process, and BHT can capture the peroxy radical intermediate to give product **9a** (see SI, I.1.). On the basis of literature precedent and control experiments, we have proposed a plausible mechanism for the peroxidation of 2-naphthols and benzofuranones (see SI, (J)). Initially, when TBHP was heated, the (O–O) bond of the TBHP was fragmented, and *tert*-butoxyl radical and hydroxyl radical were formed in the system (see SI, (J)). Then, *tert*-butoxyl or hydroxyl radicals react with TBHP to form *tert*-butylperoxy radicals via hydrogen abstraction (see SI, (J)). Simultaneously, the hydrogen atom from 2-naphthols, mainly from hydroxy group **1a** or adjacent to the carbonyl group of benzofuranones **4a**, is abstracted by the *tert*-butoxyl or hydroxyl radical to form radical intermediate **A** or **A′** (see SI, (J)). Finally, radical **A** or **A′** is trapped by the *tert*-butylperoxy radical to afford desired products **2a** and **5a** (see SI, (J)). Similarly, a control experiment was conducted in the presence of radical quencher TEMPO for the rearrangement reaction to understand the reaction pathway. When 2.0 equiv. of radical quencher such as TEMPO was added to the reaction, giving a yield of **8a** that was close to the yield of the reaction in the absence of a radical quencher (see SI, I.2.). This proves the reaction does not follow a radical path.

There are two possible ways of rearrangement **5a** to form the products **8a** and **8a′** (Scheme 6). In pathway (a), we envision the migration of the aryl group towards the oxygen that would lead to 3-(substituted-amino)-3-phenylbenzo[*b*][1,4]dioxin-2(3*H*)-one product **8a′** *via* intermediate **B**/**B′** (Scheme 6, pathway a). But pathway (a) is ruled out since **8a′** is not formed. However, in the pathway (b), peroxybenzofuranone **5a** undergoes 4-oxa-Grob type fragmentation[17] in the presence of amines. In pathway b, the fragmentation of the C2–C3 bond of benzofuranone moiety by amine attack generates the intermediate **C** (Scheme 6, pathway b). The in situ generated intermediate **C** was highly unstable and could not be isolated. Then, the intermediate **C** immediately undergoes migration of the aryl group to the oxygen to afford the desired product **8a** via the intermediate **D**/**D′** (Scheme 6, pathway b).

In summary, we described scalable and safer peroxidation of bioactive 2-naphthols and benzofuranones derivatives using continuous flow. The peroxides derived from benzofuranone derivatives were trans-



Scheme 6. A plausible mechanism for the *N*-substituted-2-phenylbenzo[*d*][*1,3*]dioxole-2-carboxamide.

formed into various potentially bio-active *N*-substituted-2-phenylbenzo[*d*][*1,3*]dioxole-2-carboxamide derivatives up to 94% yield. Based on the experimental results and previous literature studies, a plausible mechanism was proposed for peroxidation and rearrangement reactions.

Experimental Section

General experimental procedure for dearomative peroxidation of 1-substituted-2-naphthols under batch conditions: In a 20 mL re-sealable vial was added 1-substituted-2-naphthols compound **1** (0.25 mmol, 1 equiv.) and 5.0–6.0 M *tert*-butyl hydroperoxide (TBHP) in decane solution (1.00 mmol, 181 µL, 4 equiv.) without maintaining any special conditions like inert atmosphere. The tube was sealed with a cap using a crimper. The reaction mixture was stirred at 100 °C for 5 h in a preheated oil bath. After completion of the reaction, a volatile component was evaporated using a vacuum. The residue was directly purified by silica gel column chromatography (EtOAc:*n*-hexane = 5:95).

General experimental procedure for dearomative peroxidation of 1-substituted-2-naphthols under continuous flow: The 1-substituted-2-naphthols compound **1** (0.50 mmol, 1 equiv.) in a 30 mL vial, and simultaneously 5.0–6.0 M *tert*-butyl hydroperoxide (TBHP) in decane solution (3.00 mmol, 545 µL, 6 equiv.) was taken in another 30 mL vial. All solutions of **1** and TBHP (5–6 M in decane) were prepared from 5 mL ACN. The prepared solutions were flown through a 10 mL SS coil reactor with a flow rate of 0.1 mL/min each at 100 °C temperature with 3–4 bar pressure. The reaction mixture was continuously collected after 50 min. The same reaction mixture was subjected to the next run with a residence time of 50 min for each cycle. After running three cycles, the volatile component was evaporated using a vacuum, and the residue was directly purified by silica gel column chromatography (EtOAc: *n*-hexane = 5:95).

General experimental procedure for C-H peroxidation of 3-aryl benzofuran-2(3*H*)-ones under continuous flow: The 3-aryl benzofuran-2(3*H*)-ones compound **4** (0.50 mmol, 1 equiv.) in a 30 mL vial, and simultaneously 5.0–6.0 M *tert*-butyl hydroperoxide (TBHP) in decane solution (3.00 mmol, 545 µL, 6 equiv.) was taken in another 30 mL vial. All solutions of **4** and TBHP (5–6 M in decane) were prepared from 5 mL ACN. The prepared solutions were flown through a 10 mL SS coil reactor with a flow rate of 0.1 mL/min each at 100 °C temperature with 3–4 bar pressure. The reaction mixture was continuously collected after 50 min. Then, the same reaction mixture was subjected to the next run with a residence time of 50 min for each cycle. After running three cycles, the volatile component was evaporated using a vacuum, and the residue was directly purified by silica gel column chromatography (EtOAc:*n*-hexane = 5:95).

General experimental procedure for the rearrangement reaction: The compound 3-(*tert*-butylperoxy)-3-arylbenzofuran-2(3*H*)-one **5** (0.1 M, 5 mL of ACN) in a 30 mL vial was combined in a T-piece with a stream of amines (0.2 M, 5 mL of ACN) in a 30 mL another vial. All solutions of **5**/**7** were prepared from 5 mL ACN. The prepared solutions were flown through a 10 mL SS coil reactor with a flow rate of 0.1 mL/min each at 100 °C at 3–4 bar pressure. The reaction mixture was continuously collected after 50 min. Later, the same reaction mixture was subjected to the next run with a residence time of 50 min for each cycle. After running three cycles, the volatile component was evaporated using a vacuum, and the residue was directly purified by silica gel column chromatography (EtOAc: *n*-hexane = 30:70-50:50).

The X-ray crystal structure: Crystallographic data are deposited with the Cambridge Crystallographic Data Centre (CCDC) under the following accession numbers: **2p** (2252438), **5g** (2203780), **8a** (2252449) and **8d** (2252424). The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/data_request/cif

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Sequential Oxidative Fragmentation and Skeletal Rearrangement of Peroxides for the Synthesis of Quinazolinone Derivatives

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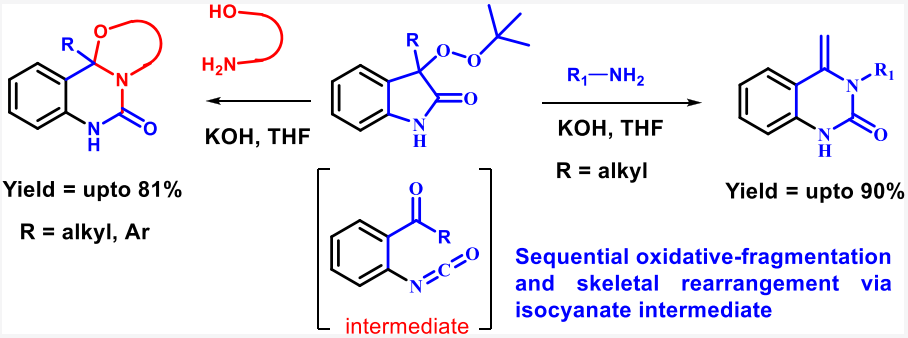

ABSTRACT: For the first time, the sequential reaction of peroxyoxindole that involves base-promoted oxidative fragmentation to isocyanate formation and primary amine or amino alcohol accelerated skeletal rearrangement to synthesize exo-olefinic-substituted quinazolinone or oxazoloquinazolinone is reported. The advantages of this new reaction include a broad substrate scope and transition-metal-free and room-temperature conditions. The formation of the isocyanate as a key intermediate that accelerates oxidative skeletal rearrangement has been confirmed by trapping experiments and spectroscopic evidence.

INTRODUCTION

Heterocycles are the most essential and important chemical entity in pharmaceuticals and agricultural applications.[1] A large number of alkaloids contain diverse heterocycles in the scaffold. Peroxide-functionalized heterocycles emerge as a vital intermediate in diverse oxidative transformations.[2] Moreover, the incorporation of peroxide functionality on the oxindole or substituted-2-oxindole derivatives makes them fascinating precursors for structurally distinct rearrangement reactions.[3] In general, peroxides are known to perform Baeyer−Villiger oxidation,[4] and the Hock process[5] to produce phenol from cumene hydroperoxide involving the migration of an aryl/alkyl group to an electron-deficient oxygen atom has been broadly studied under an acid source. Synthetically, the Kornblum−DeLaMare rearrangement[6] is an important rearrangement in organic peroxide for the production of ketones and alcohols under basic conditions (Scheme 1A).[6] On the basis of these rearrangements, the skeletal rearrangement of the peroxides to access biologically important intermediates is an attractive paradigm in organic synthesis. Recently, pioneering work on direct C−H peroxidation of 2-oxindole by a Cu catalyst and subsequent base-mediated fragmentation has been reported by Stoltz and co-workers (Scheme 1B).[7a] Subsequently, our group reported the rearrangement of C3-substituted 2-oxindole peroxide using a Lewis acid as well as a Brønsted acid (Scheme 1C).[7b−d] A few other rearrangements have also been reported by other research groups by using different heterocyclic peroxides.[7e−g]

Nitrogen-containing heterocyclic compounds such as C4-substituted quinazolinone[8] and quinazolinediones[9] exhibit a wide range of biological properties such as Na^+/Ca^{2+} exchange inhibitor,[10] anti-inflammatory,[11] anticancer,[12] antimalarial,[13] antidiabetic,[14] and antihypertensive[15] activities (Figure 1). Hence, it has a central role in drug development, medicinal chemistry, and corresponding drug-target relationships superintended for specific biological activity and drug action. In the literature, few pioneering methods have been reported for the synthesis of 4-methylene-3,4-dihydroquinazolin-2-ones.[16a,b] Gimeno et al. reported the Au(I)-complex-catalyzed synthesis of 4-methylene-3,4-dihydroquinazolin-2-ones from 1-(*o*-alkynylaryl) urea.[16c−e] Afterward, Barba and co-workers described the synthesis of 3-substituted 2-quinazolinones from the reaction of 2-aminoacetophenone and an electrogenerated cyanomethyl anion from acetonitrile reduction at a graphite electrode.[16f] Recently, to overcome the use of expensive catalysts or ligands,

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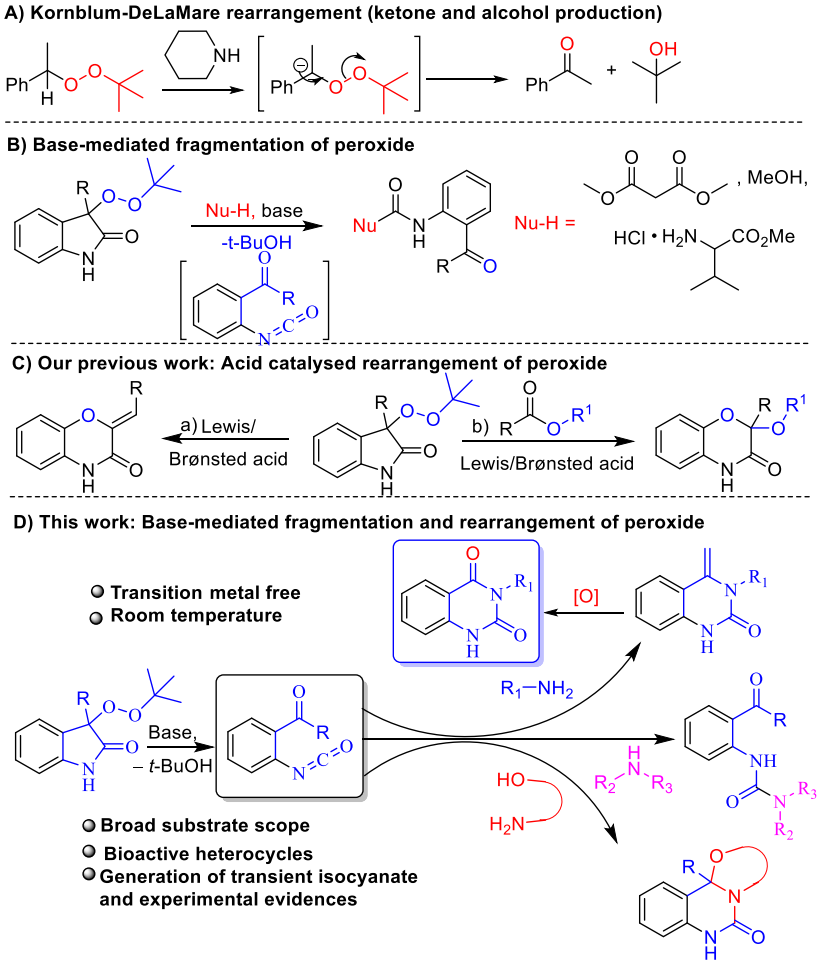
Scheme 1. State of the Art in a Rearrangement of Peroxide



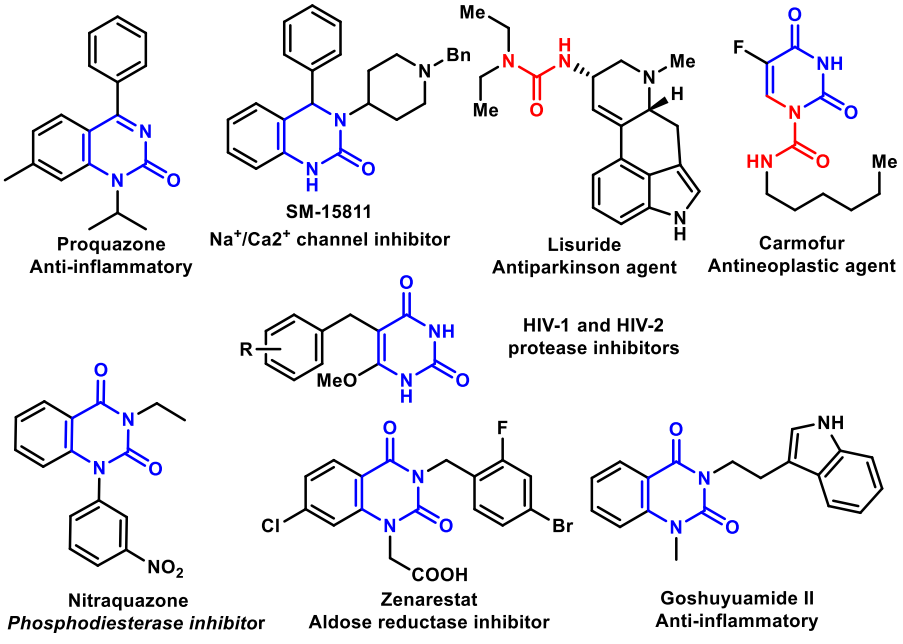


Figure 1. Pharmacologically active quinazolinone framework.

Ma and co-workers reported a variant protocol for the synthesis of 4-alkenylquinazolinons and 4-alkenylquinazolinthione by using catalytic amounts of NaOH under reflux.[17] Although there are pros and cons of the reported method for the quinazolinone derivatives, designing an attractive and newer approach for these heterocycles is an evergrowing paradigm in chemical synthesis.

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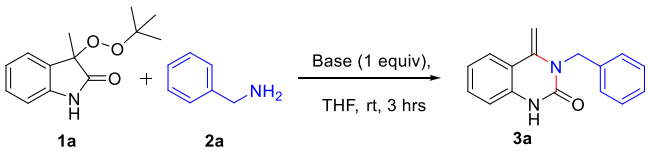
From the literature, it is evident that no peroxide rearrangement has been used for the construction of the quinazolinone derivatives. As a part of our research on the rearrangement of peroxides toward the synthesis of heterocycles (Scheme 1C),[7b−d] herein we report the transition-metal-free oxidative fragmentation of peroxyoxindole derivatives to synthesize bioactive quinazolinone derivatives in the presence of various amine nucleophiles. The present work includes the following features: (i) first report on quinazolinone using a peroxide via oxidative fragmentation and skeletal rearrangement; (ii) transition-metal-free and room-temperature reaction conditions; and (iii) efficient, broad substrate scope and high yield.

RESULTS AND DISCUSSION

To establish a base-mediated oxidative fragment and skeletal rearrangement to 4-methylene-3-substituted quinazolinone, initial optimization was performed with peroxides **1a** and **2a**. Control experiments **1a** and **2a** in the absence of base at room temperature or 60 °C in THF solvent did not produce the desired product **3a** (Table 1, entries 1 and 2). Hence, base has a

Table 1. Optimization of Reaction Conditions[a]



entry	base	solvent	yield (%) of **3a**
1		THF	no reaction
2[b]		THF	no reaction
3	Na_2CO_3	THF	25
4	K_2CO_3	THF	no reaction
5	Cs_2CO_3	THF	74
6	NaOH	THF	77
7	KOH	THF	87
8	*t*-BuOK	THF	75
9	*t*-BuOLi	THF	82
10[c]	KOH	THF	27
11[d]	KOH	THF	55
12	KOH	DCM	67
13	KOH	EtOH	78
14	KOH	*t*-BuOH	55
15	KOH	H_2O	no reaction
16	KOH	EtOAc	76
17	KOH	ACN	80

[a]Reaction conditions: base (0.35 mmol), compound **1a** (0.35 mmol), compound **2a** (0.42 mmol), and solvent (2 mL) were stirred at room temperature for 3 h. [b]At 60 °C. [c]0.2 equiv of base used. [d]0.5 equiv of base used. The mentioned yields are isolated yields.

decisive role in the oxidative fragmentation of the peroxide. When this reaction was performed in the presence of Na_2CO_3, product **3a** was obtained in 25% yield (Table 1, entry 3). Next, K_2CO_3 failed to give **3a** (Table 1, entry 4). Interestingly, the reaction works well in the presence of Cs_2CO_3 and provided product **3a** in 74% yield. Furthermore, we screened a variety of bases for this reaction. Notably, the addition of NaOH results in a slight improvement in the yield of product **3a** to 77% yield (Table 1, entry 6). An excellent yield was obtained for **3a** in the case of KOH as a base (Table 1, entry 7). Other bases such as KO*t*Bu and LiO*t*Bu are also efficient to form the product **3a** in 75 and 82% yields, respectively (Table 1, entries 8 and 9). From our survey of bases, KOH is found to be the best base for this transformation. Furthermore, by decreasing the KOH quantity, a decrease in yield was observed (Table 1, entries 10 and 11). Next, varieties of solvents were tested to enhance the product yield of **3a**, but no improvement was detected (Table 1, entries 12−17). In the case of water, there was no detection of desired product **3a**. From this experimental study, THF is established to be the best solvent for this conversion to provide **3a** in 87% yield after 3 h (Table 1, entry 7). Product **3a** was characterized by spectroscopic techniques and single-crystal XRD (Figure 2).

Next, we started our studies to generalize the substrate scope for quinazolinone derivatives. Initially, electron-rich benzyl amines such as 2-Me, 4-Me, 4-OMe, 3,4-OMe, 2,3,4-OMe, and 4-Ph afforded a 64−90% yield of products **3b−3g** (Scheme 2). Afterward, in the presence of an electron-withdrawing substituent such as 4-F, 3-Br, or 4-CF_3 on benzyl amines, moderate to good yields of corresponding products **3h−3j** were provided (Scheme 2). Gratifyingly, heteroaryl amines were well tolerated under optimized experimental conditions. 2-Picolylamine, tryptamine, and furfuryl amine were successfully converted to **3k**, **3l**, and **3m** in 58, 61, and 67% yields, respectively. Furthermore, the scope of the reaction was analyzed with primary aliphatic amines. When cyclopropyl, methyl, ethyl, hexyl, and octyl amines were used under standard optimized conditions, products **3n−3r** were isolated in moderate to good yields (Scheme 2). Additionally, propargylamine and allylamine provided corresponding products **3s** and **3t** in 65 and 61% yields, respectively. Notably, 3-methoxyphenethylamine provided quinazolinone product **3u** in 65% yield. Similarly, the reaction of 3-butyl-3-(*tert*-butylperoxy)-indolin-2-one **1c** with **2a** afforded product **3v** as an exclusive E isomer in 21% yield. Furthermore, the reaction of peroxide **1d** with 4-methoxybenzylamine **2d** afforded **3w** as an E/Z mixture in 50% yield. A reaction of peroxide **1b** with **2d** led to product **3x** in 63% yield. Furthermore, this reaction with primaquine bisphosphate amine afforded the respective product **3y** in 45% yield. However, the reaction of **1a** with aniline, 4-methoxy aniline, or tryptophan led to a complicated reaction mixture that could not be separated by column chromatography. Remarkably, the reaction of **1a′** with amines preceded instinctively to give the desired derivatives of the 4-methylene-3-substituted quinazolinone in 58−85% yields (Scheme 3). To our delight, a gram-scale reaction was also successfully performed with **1a** (1.0 g, 4.25 mmol) and **2a** under optimized conditions to afford a 65% yield of product **3a**.

In contrast to primary amines, the reaction of peroxyoxindole with secondary amine-based nucleophiles generates a variety of urea derivatives (Scheme 4). Thus, the reaction of **1a** and secondary amine having different substitutions such as −N(Me)$_2$, −N(iPr)$_2$, and −N(iBu)$_2$ under the above standard reaction condition by using KOH (1 equiv) for 2 h afforded urea derivatives **6a−6c** in moderate to good yields (Scheme 4). Moreover, pyrrolidine and morpholine afforded 80 and 71% yields of products **6d** and **6e**, respectively.

Next, we have extended this concept to the molecular reconstruction of the peroxyoxindole by using amino alcohols. For instance, the reaction of peroxyoxindole **1a** with 1.5 equiv of KOH and ethanolamine **8a** at room temperature afforded tricyclic compound **9a** in 81% isolated yield. To outspread the substrate scope, this reaction was performed with other amino alcohols to afford products **9b−9g** in moderate to good yields (Scheme 5).

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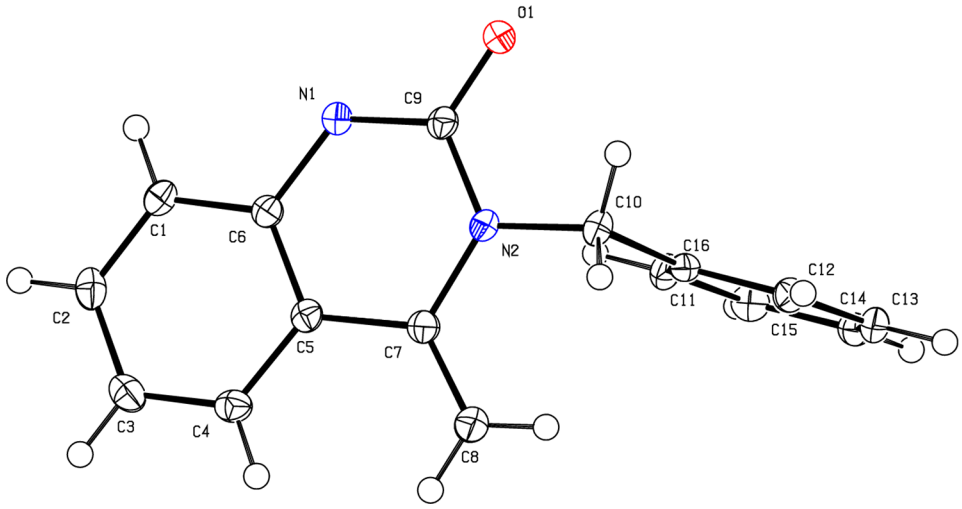

Figure 2. ORTEP crystal structure of **3a** showing thermal ellipsoids at the 50% probability level.

Likewise, the formation of other tricyclic compounds from peroxyoxindole derivatives also progressed well in the presence of chiral amino alcohols to afford as a diastereomeric mixture [**9h** (*de* = 97%):**9h′** (*de* = 90%, dr = 3.4:1), [**9i** (*de* = 94%):**9i′** (*de* = 95%, dr = 2.4:1), and [(**9j** (*de* 94%):**9j′** (*de* = 84%, dr = 1.3:1] in good yields. The stereochemistry and structure of compound **9h** was confirmed using single-crystal XRD (Figure 3). Moreover, the stereochemistry of all of the other tricyclic compounds (**9h, 9h′, 9i, 9i′**, and **9j, 9j′**) was comparatively dispensed on the basis of the crystal structure of **9h**.

To understand the reaction pathway for the formation of 4-methylene-3-substituted quinazolinone, we have performed several experiments using peroxyoxindole (Scheme 6). The reaction of *N*-methylated peroxyoxindole **1aa** has been proven to be chemically inactive under optimized reaction conditions (Scheme 6,(i)). This experiment suggests that the abstraction of proton from oxindole nitrogen was a crucial step for this transformation. To identify the intermediate in this reaction, a trapping experiment was performed with other nucleophiles. Hence, we reacted peroxyoxindole **1a** with alcohol **2aa**, which gave carbamate **6g** in 53% yield (Scheme 6,(ii)). This reaction confirmed the generation of isocyanate intermediate **B**, and this in-situ-generated isocyanate intermediate was trapped by alcohol **2aa**. From this experimental observation, we hypothesized that after deprotonation at oxindole nitrogen, an isocyanate intermediate was formed. Furthermore, in the absence of an external nucleophile, peroxyoxindole **1a** undergoes intramolecular cyclization to afford 4-hydroxyquinolinone **7a** (Scheme 6,(iii)).[7a]

On the basis of experimental observations and literature precedents,[7a] we have proposed the two possible pathways shown in Scheme 7. In pathway (a), we envision the complete elimination of *t*-BuOOH from peroxyoxindole **1a** that would lead to *N*-alkylated product **4a** *via* intermediate **A** (Scheme 7, pathway a). But pathway (a) failed to deliver product **4a**. However, in pathway (b), peroxyoxindole **1a** is followed by Kornblum−DeLaMare rearrangement,[6] similar to 4-oxa-Grob fragmentation,[18] and Stoltz's group reported oxidative fragmentation.[7a] Pathway (b) allowed the fragmentation of the C2−C3 bond and elimination of *tert*-butyl alcohol to the simultaneous formation of ketone, and isocyanate is an intermediate (**B**) generated in situ (Scheme 7, pathway (b)). The **B** intermediate was highly unstable even in the absence of amine and was not able to be isolated from the reaction, which immediately gave cyclized product **3a**. To confirm the isocyanate as the intermediate, we have performed the reaction of 2-amino acetophenone and benzylisocyanate in the presence or absence of KOH, resulting in product **3a** (Scheme 6, entry (vi)). Furthermore, this intermediate (**B**) was also confirmed by a trapping experiment with different secondary amine/oxygen-based nucleophiles (Schemes 4 and 6, entry (ii)). The isocyanate formation in the reaction was also confirmed by the in situ analysis of IR and HRMS (SI Figures S3 and S1). In the case of product **9**, intermediate **B** undergoes a reaction with a primary amine/amino alcohol to obtain urea derivative **C**/**C′**. Furthermore, intermediate **C** containing a nitrogen atom is highly unstable (not able to isolate from the reaction mixture), undergoing a rapid intramolecular reaction with ketone to form the **D**/**D′** hemiaminol intermediate. Interestingly, intermediate **C′** was isolated from the reaction of peroxide **1a** and 3-amino-1-propanol and performed the cyclization in the presence of KOH to give product **9a** (Scheme 6, entry (v)). Finally, the dehydration of **D** afforded product **3a**. Afterward, iminium cation **E** formed upon dehydration of **D′** to facilitate another intramolecular addition reaction (i.e., oxygen attack over the iminium cation to generate **9a** (Scheme 7).

Next, the application of a 4-methylene-3-substituted quinazolinone derivative has been investigated for the synthesis of 3-substituted quinazoline-2,4-diones by an oxidation reaction. This oxidation has been performed using **3a** and **3p** with $CuCl_2$ and TBHP.[19] After the reaction was complete, corresponding products **10a** and **10b** were isolated in 78 and 69% yields (Scheme 8). Moreover, the synthesized quinazoline-2,4-diones can be employed as valuable precursors in the synthesis of various bioactive molecules.[9]

CONCLUSIONS

We have developed a novel transition-metal-free sequential oxidative fragmentation and rearrangement of peroxyoxindole for the synthesis of 4-methylene-3-substituted quinazolinone derivatives in the presence of a varieties of amine and hydroxyl nucleophiles. This reaction was easily achieved by inexpensive benchtop KOH base under ambient condition and synthesized a large number of quinazolinone derivatives in good to excellent yields. A plausible mechanism has been proposed on the basis of the experimental results, and previous literature studies involved

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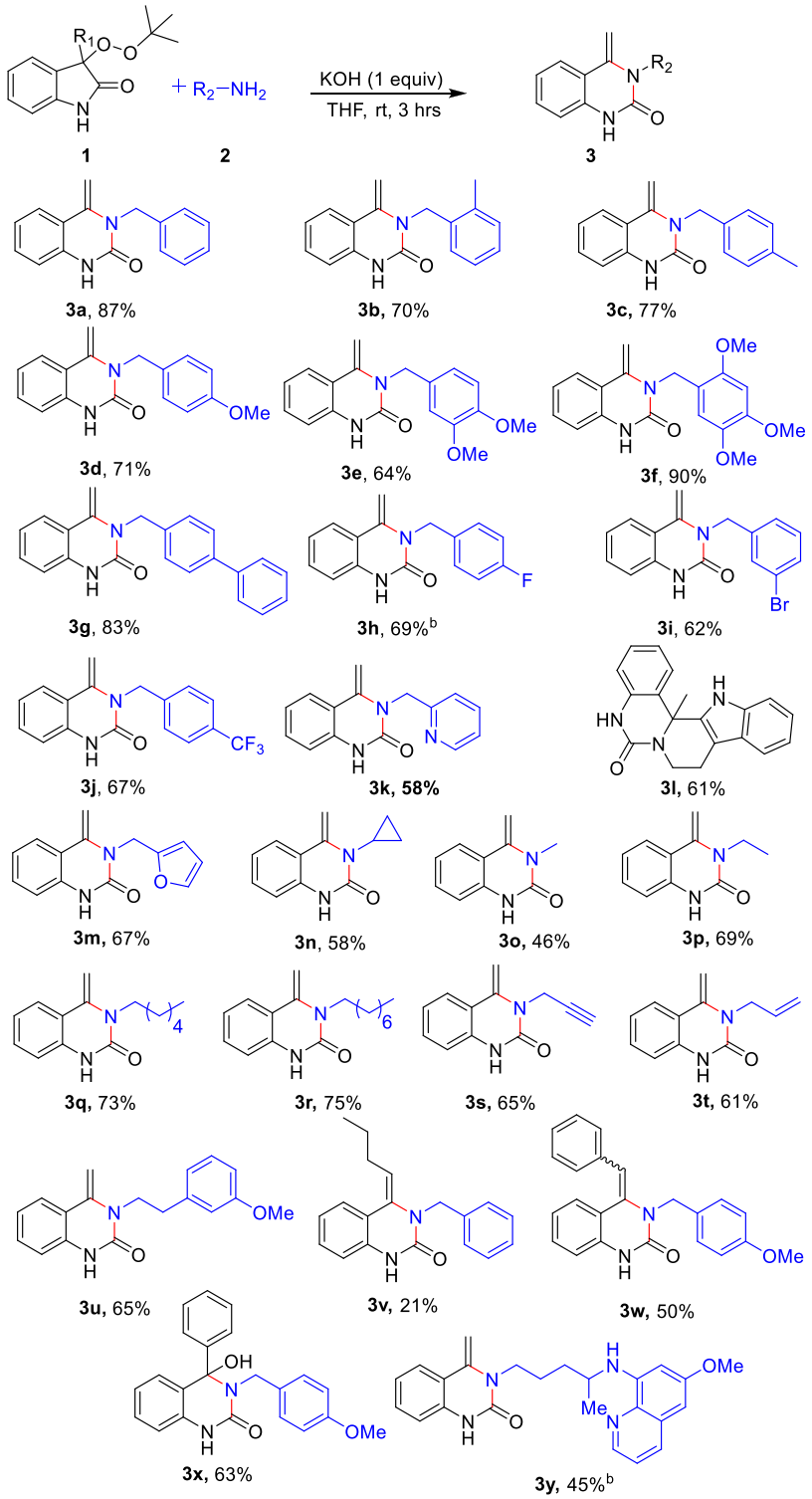
Scheme 2. Substrate Scope for Quinazolinone Derivatives[a]



[a]Reaction conditions: KOH (19 mg, 0.35 mmol, 1 equiv), peroxy compound **1** (0.35 mmol, 1 equiv), and amines **2** (0.42 mmol, 1.2 equiv) in THF (2 mL) were stirred at room temperature for 3 h. [b]2 equiv of base was used. The mentioned yields are isolated yields. For product **3v**, 3-butyl-3-(*tert*-butylperoxy)indolin-2-one has been used. For product **3w**, 3-benzyl-3-(*tert*-butylperoxy)indolin-2-one has been used. For **3x**, 3-phenyl-3-(*tert*-butylperoxy)indolin-2-one has been used.

the fragmentation of peroxyoxindole via deprotanation to form isocyanate as the key step in the formation of quinazolinone derivatives.

EXPERIMENTAL SECTION

General Information and Data Collection. The amines, 2-oxindole, amino alcohols, KOH, cupric chloride, and *tert*-butyl hydroperoxide (TBHP) 5.0−6.0 M in decane solution were purchased from Sigma-Aldrich. All of the solvents used in the reactions were dry

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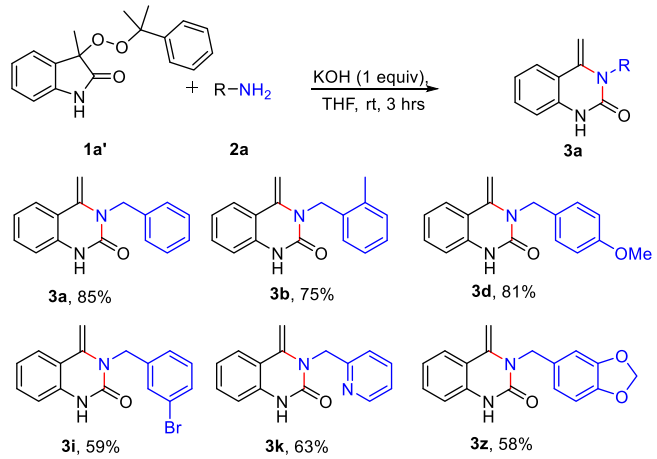
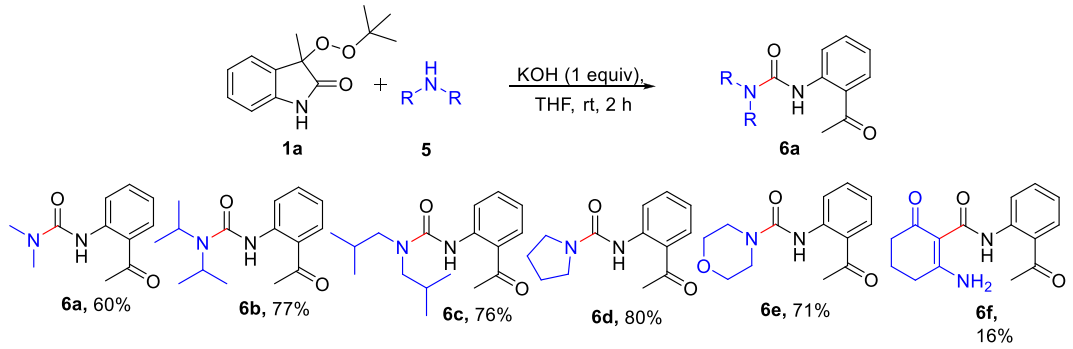
Scheme 3. Substrate Scope for Quinazolinone Derivatives[a]



[a]Reaction conditions: KOH (19 mg, 0.35 mmol, 1 equiv), peroxy compound **1a′** (0.35 mmol, 1 equiv), and amine **2a** (0.42 mmol, 1.2 equiv) in THF (2 mL) were stirred at room temperature for 3 h. The mentioned yields are isolated yields.

Scheme 4. Synthesis of Urea Derivatives[a]



[a]Reaction conditions: KOH (0.35 mmol), compound **1** (0.35 mmol), compound **5** (0.42 mmol), and THF (2 mL) were stirred at room temperature for 2 h. The mentioned yields are isolated yields.

grade. The column chromatographic separation separations were achieved over 100−200 mesh size silica gel. Visualization completed with UV light, PMA, and CAM staining go along with the heating method. By using a Bruker or JEOL spectrometer, the ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. The following information was used in NMR follow-up experiments: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad; ddd, doublet of doublets of doublets. High-resolution mass spectra were recorded via a Waters Synapt G2 applying electrospray ionization (ESI). Infrared (ATR) spectra were obtained with a Bruker Alpha-E infrared spectrometer. HPLC analysis was performed using an Agilent 1200 infinity series HPLC system with a diode array detector. Diastereomeric excess values were determined by HPLC analysis on a Chiralpak IA (4.6 mm × 250 mm) column in comparison with authentic racemic material using *n*-heptane and isopropanol as eluents. Data were analyzed using Agilent OpenLAB software. The melting point was measured using the BUCHI M-560 melting-point instrument. All melting points were measured in an open glass capillary tube. Single-crystal diffraction analysis data were collected at 100 K with a Bruker Kappa Apex III CCD Duo diffractometer (operated at 1500 W power: 50 kV, 30 mA) using graphite monochromatic Mo Kα radiation and Cu Kα radiation. More information on crystal structures can also be obtained from the Cambridge Crystallographic Data Centre (CCDC) via deposition numbers 2053446 (**3a**) and 2053447 (**9h**).

*(A) General Experimental Procedure for the Synthesis 4-Methylene-3-Substituted Quinazolinone Derivatives (**3**).* In a 20 mL resealable vial, KOH (19 mg, 0.35 mmol, 1 equiv), peroxy compound (0.35 mmol, 1 equiv), and amine (0.42 mmol, 1.2 equiv) were added to THF (2 mL). Then the tube was sealed with a rubber septum, and the reaction mixture was kept at room temperature with stirring for 3 h. After the completion of the reaction, water was added, and the resulting mixture was extracted with ethyl acetate two times using 10 mL of solvent each time. The organic layers were combined and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by using column chromatography (EtOAc:*n*-hexane = 30:70 to 70:30).

*(B) Experimental Procedure for the Gram-Scale Synthesis of **3a**.* In a 20 mL resealable vial, KOH (238 mg, 4.25 mmol, 1 equiv), compound **1a** (1000 mg, 4.25 mmol, 1 equiv), and benzyl amine **2a** (546 mg, 5.1 mmol, 1.2 equiv) were added to THF (10 mL). Then the tube was sealed with a rubber septum, and the reaction mixture was kept at room temperature with stirring for 3 h. After the completion of the reaction, water was added, and the resulting mixture was extracted with ethyl acetate two times using 20 mL of solvent each time. The organic layers were combined and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by using column chromatography (EtOAc:*n*-hexane = 30:70) to afford 3-benzyl-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one **3a** (694 mg, 65%) as a white solid.

(C) General Experimental Procedure for the Synthesis of Urea Derivatives. In a 20 mL resealable vial, KOH (19 mg, 0.35 mmol, 1 equiv), compound **1a** (0.35 mmol, 1 equiv), and amine **5a** (0.42 mmol, 1.2 equiv) were added to THF (2 mL). Then the tube was sealed with a rubber septum, and the reaction mixture was kept at room temperature with stirring for 2 h. After the completion of the reaction, water was added, and the resulting mixture was extracted with ethyl acetate two

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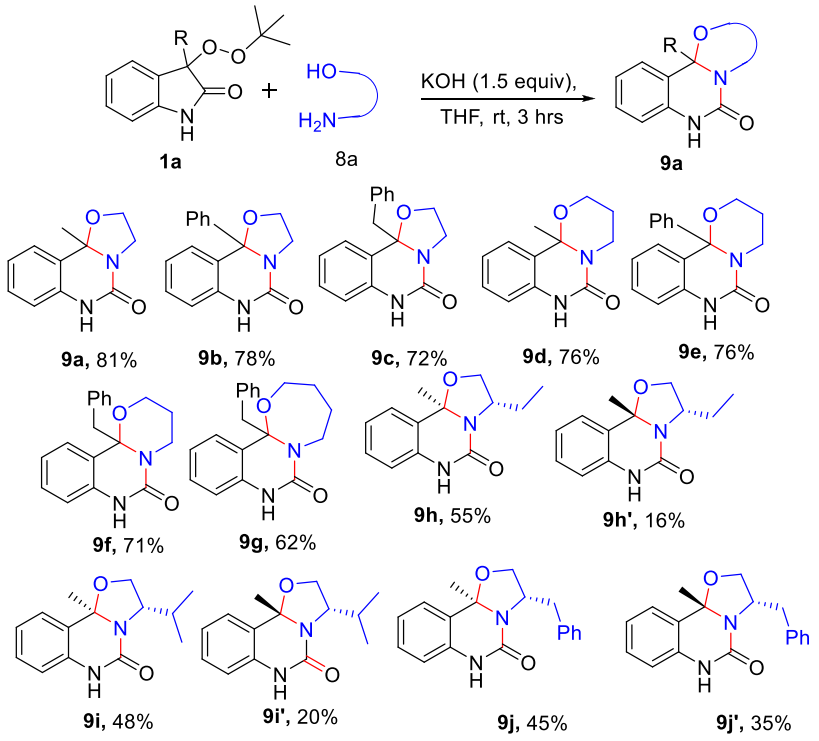
Scheme 5. Synthesis of a Polyheterocycle Scaffold[a]



[a]Reaction conditions: KOH (1.5 eq, 0.525 mmol), compound **1** (0.35 mmol), compound **8** (1.2 eq 0.42 mmol), and solvent (2 mL) were stirred at room temperature for 3 h. The mentioned yields are isolated yields.

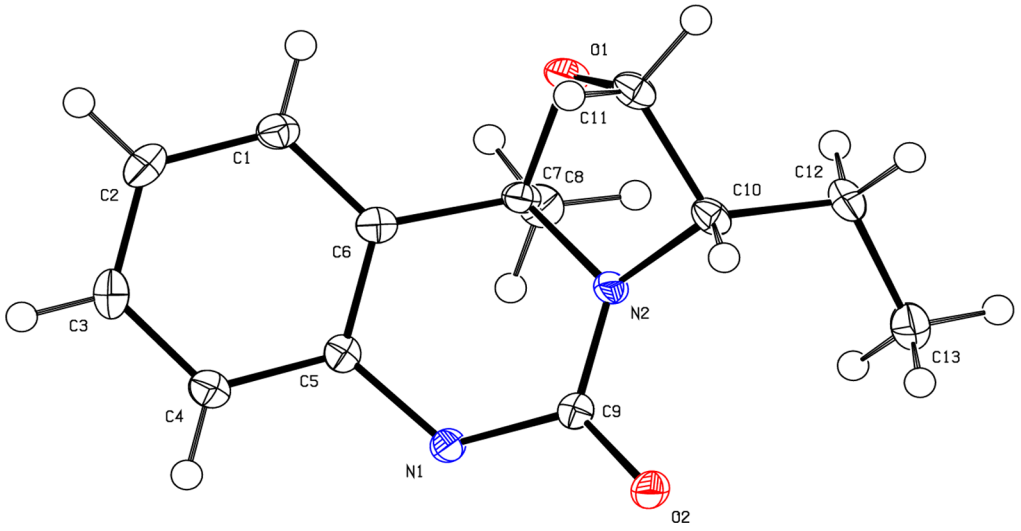


Figure 3. ORTEP crystal structure of **9h** showing thermal ellipsoids at the 50% probability level.

times using 10 mL of solvent each time. The organic layers were combined and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by using column chromatography (EtOAc:*n*-hexane = 20:80 to 50:50).

*(D) Experimental Procedure for the Synthesis Carbamates (**6g**).* In a 20 mL resealable vial, KOH (19 mg, 0.35 mmol, 1 equiv), compound **1a** (82 mg, 0.35 mmol, 1 equiv), and 2-methoxybenzyl alcohol **2aa** (58 mg, 0.42 mmol, 1.2 equiv) were added to THF (2 mL). Then the tube was sealed with a rubber septum, and the reaction mixture was kept at room temperature with stirring for 3 h. After the completion of the reaction, water was added, and the resulting mixture was extracted with ethyl acetate two times using 10 mL of solvent each time. The organic layers were combined and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by using column chromatography (EtOAc:*n*-hexane = 10:90).

*(E) Experimental Procedure for the Synthesis of 1-(2-Acetylphenyl)-3-(3-hydroxypropyl)urea (**6i**).* In a 20 mL resealable vial, KOH (29.5 mg, 0.52 mmol, 1.5 equiv), peroxy compound **1a** (0.35 mmol, 1 equiv), and 3-aminopropan-1-ol (0.42 mmol, 1.2 equiv) were added to THF (2 mL). Then the tube was sealed with a rubber septum, and the reaction mixture was kept at room temperature with stirring for 20−30 min. Water was added to the reaction mixture, and the resulting mixture was extracted with ethyl acetate two times using 10 mL of solvent each time. The organic layers were combined and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by using column chromatography (EtOAc:*n*-hexane = 30:70 to 70:30).

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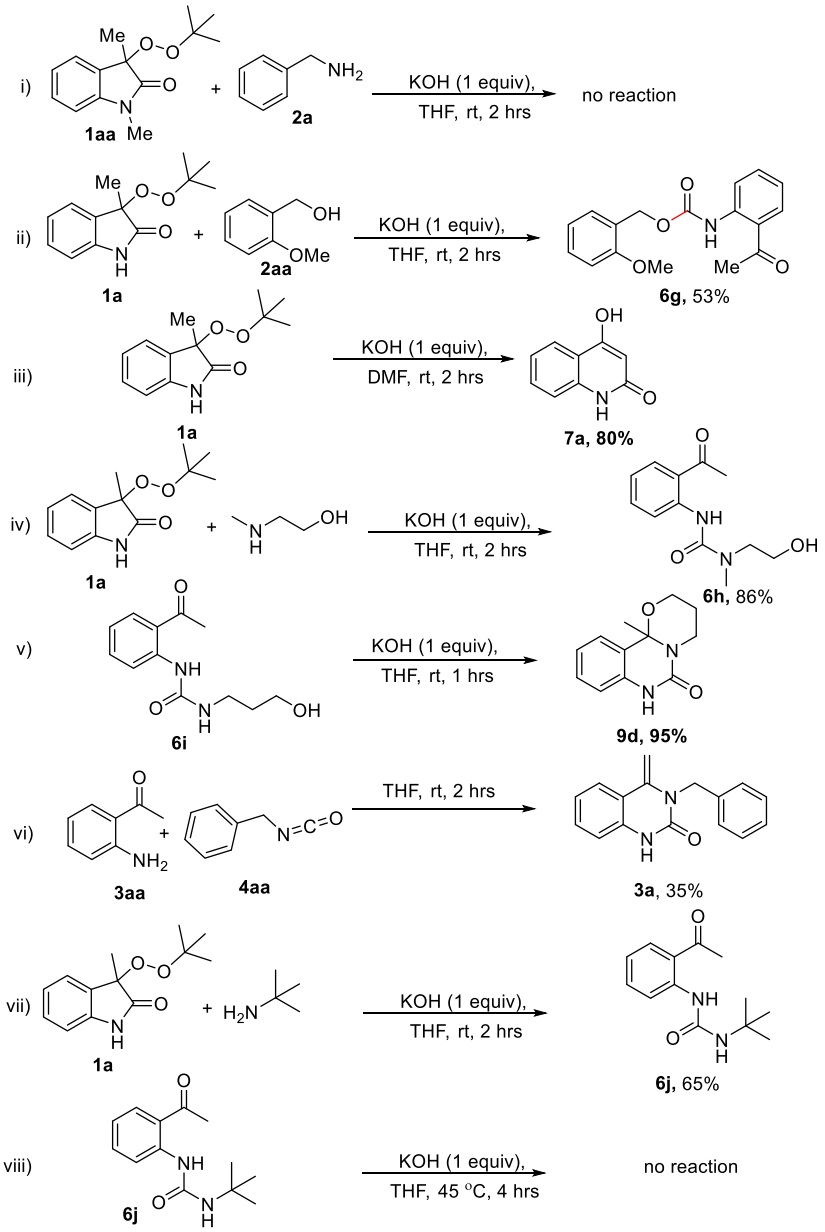
Scheme 6. Experiments for Mechanistic Studies



*(F) Experimental Procedure for the Synthesis 4-Hydroxyquinolin-2(1H)-one (**7a**).* Compound 7**a** was prepared according to the reported procedure by the Stoltz group.[7a] In a 20 mL resealable vial, KOH (19 mg, 0.35 mmol, 1 equiv) and compound **1a** (82 mg, 0.35 mmol, 1 equiv) were added to DMF (2 mL). Then the tube was sealed with a rubber septum, and the reaction mixture was kept at room temperature with stirring for 2 h. After the completion of the reaction, the resulting mixture was filtered through a plug of Celite and the filtrate was concentrated under reduced pressure. Finally, the residue was purified by using column chromatography (DCM:MeOH = 90:10).

*(G) General Experimental Procedure for the Synthesis of a Polyheterocycle Scaffold (**9**).* In a 20 mL resealable vial, KOH (29.5 mg, 0.52 mmol, 1.5 equiv), peroxy compound (0.35 mmol, 1 equiv), and amino alcohols (0.42 mmol, 1.2 equiv) were added to THF (2 mL). Then the tube was sealed with a rubber septum, and the reaction mixture was kept at room temperature with stirring for 3 h. After the completion of the reaction, water was added, and the resulting mixture was extracted with ethyl acetate two times using 10 mL of solvent each time. The organic layers were combined and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by using column chromatography (EtOAc:*n*-hexane = 30:70 to 70:30).

*(H) Experimental Procedure for the Oxidation of the 4-Methylene-3-Substituted Quinazolinone Derivative (**10**).* In a 50 mL round-bottomed flask, compound **3a** (0.25 mmol, 1 equiv), $CuCl_2$ (5 mol %), 2,2′-bipyridine (5 mol %), and 5.0−6.0 M *tert*-butyl hydroperoxide (TBHP) in decane solution (0.50 mmol, 2 equiv) were added to acetonitrile (2 mL). Then the round-bottomed flask was sealed using a rubber septum without maintaining any special conditions such as an inert atmosphere. The reaction mixture was kept at room temperature for 12 h. After the completion of the reaction, a volatile component was evaporated under vacuum. The residue was directly purified by silica gel chromatography (EtOAc:*n*-hexane = 30:70).

(I) Experimental Procedure for the Detection of the Isocyanate Intermediate Using HRMS Analysis. In a 20 mL resealable vial, compound **1b** (104 mg, 0.35 mmol, 1 equiv) and KOH (20 mg, 0.35 mmol, 1 equiv) were added at 0 °C in dry THF (2 mL). Then the tube was sealed with a rubber septum, and the reaction was performed under a nitrogen atmosphere. After 5 min, the reaction mixture was subjected to HRMS analysis. The presence of m/z = 224.0716 corresponds to isocyanate intermediate **B** (SI, Figure S1).

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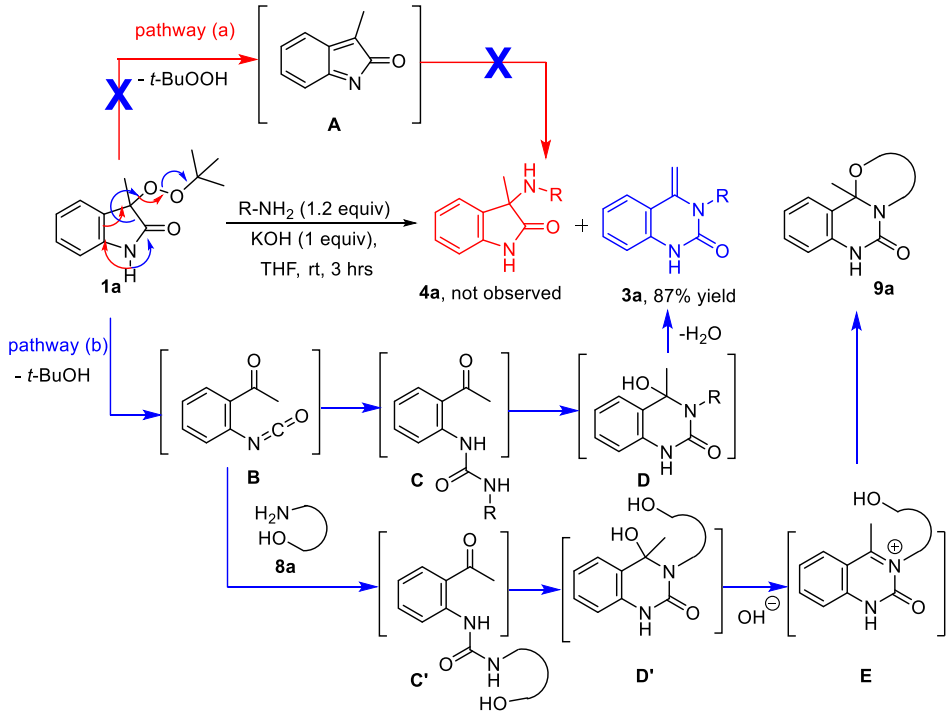
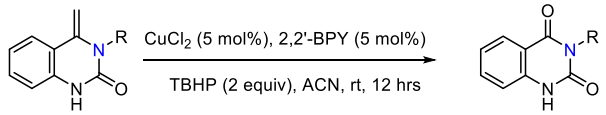
Scheme 7. Plausible Mechanism for Products 3a and 9a



Scheme 8. Oxidation of 4-Methylene-3-Substituted Quinazolinone Derivative[a]



R = $C_6H_5CH_2$, **3a**
R = CH_2CH_3 , **3p**

R = $C_6H_5CH_2$, (**10a**) =78%
R = CH_2CH_3, (**10b**) =69%

[a]Reaction conditions: compound **3a**/**3p** (0.25 mmol, 1 equiv), $CuCl_2$ (5 mol %), 2,2′-bipyridine (5 mol %), and TBHP (2 equiv) in 2 mL of acetonitrile were stirred at room temperature for 12 h.

(J) Experimental Procedure for the Observation of the Isocyanate Intermediate Using IR Analysis. In a 20 mL resealable vial, compound **1b** (104 mg, 0.35 mmol, 1 equiv) and KOH (20 mg, 0.35 mmol, 1 equiv) were added at 0 °C to dry THF (2 mL). Then the tube was sealed with a rubber septum, and the reaction was performed under a nitrogen atmosphere. After 5 min, the IR spectrum was recorded for the reaction mixture (Figure S3). Then 4-methoxybenzylamine **2d** (48 mg, 0.35 mmol, 1 equiv) was added to the reaction mixture, and the IR spectrum was recorded after 10 min (Figure S4). The IR spectra indicate the disappearance of the isocyanate peak. Interestingly, after 2 h the complete disappearance of the isocyanate peak was noticed (Figure S5).

*(K) Analytical Data for the Product. 3-Benzyl-4-methylene-3,4-dihydroquinazolin-2(1H)-one (**3a**).* Prepared according to general procedure A, using benzylamine (45 mg, 0.42 mmol) to afford 3-benzyl-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one (**3a**) (76 mg, 87% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP = 198−201 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.28 (s, 1H), 7.61 (d, J = 7.9 Hz, 1H), 7.35−7.20 (m, 6H), 6.99−6.91 (m, 2H), 5.00 (s, 2H), 4.81 (d, J = 2.3 Hz, 1H), 4.12 (d, J = 2.3 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 150.1, 139.7, 137.0, 135.6, 130.1, 128.4, 126.7, 126.3, 123.9, 122.1, 115.9, 114.6, 85.2, 45.8. IR (neat): 1453, 1685, 2919, 3207 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{16}H_{15}N_2O$ $(M + H)^+$ 251.1184, found 251.1184. Crystals of compound **3a** were grown using dichloromethane and petroleum ether (2:1) as a solvent by slow evaporation. A needle-shaped single crystal was mounted on a loop by applying a small amount of paraffin oil. Crystal data for compound **3a**: $C_{16}H_{15}N_2O$, M = 249.28, monoclinic, space group $P21/n$ with a = 10.4745(5) Å, b = 5.5284(2) Å, c = 21.446(1) Å, α = 90°, β = 101.990(1)°, γ = 90°, V = 1214.79(9) Å^3, T = 296(2) K, R1 = 0.0490, wR2 = 0.1282 on observed data, z = 4, D_{calcd} = 1.363 g cm^{-3}, $F(000)$ = 524, absorption coefficient = 0.127 mm^{-1}, λ = 0.71073 Å, 3014 reflections collected on a Bruker APEX-II CCD single-crystal diffractometer, and 2362 observed reflections ($I \geq 2\sigma(I)$). The largest difference peak and hole are 0.875 and −0.267 eÅ^{-3}, respectively

*3-(2-Methylbenzyl)-4-methylene-3,4-dihydroquinazolin-2(1H)-one (**3b**).* Prepared according to general procedure A, using 2-methylbenzylamine (51 mg, 0.42 mmol) to afford 3-(2-methylbenzyl)-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one (**3b**) (65 mg, 70% yield) as a yellow solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP = 249−252 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.23 (s, 1H), 7.56 (d, J = 7.4 Hz, 1H), 7.25−7.20 (m, 1H), 7.16−7.12 (m, 1H), 7.09−7.01 (m, 2H), 6.94−6.86 (m, 3H), 4.88 (s, 2H), 4.73 (d, J = 2.4 Hz, 1H), 3.87 (d, J = 2.4 Hz, 1H), 2.29 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 149.9, 139.9, 135.6, 134.7, 133.8, 130.0, 126.3, 125.7, 124.1, 123.8, 122.0, 115.9, 114.6, 84.8, 44.3, 18.6. IR (neat): 1502, 1694, 2919, 3358 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{17}H_{17}N_2O$ $(M + H)^+$ 265.1341, found 265.1349.

*3-(4-Methylbenzyl)-4-methylene-3,4-dihydroquinazolin-2(1H)-one (**3c**).* Prepared according to general procedure A, using 4-methylbenzylamine (59 mg, 0.42 mmol) to afford 3-(4-methylbenzyl)-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one (**3c**) (71 mg, 77% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP = 183−186 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.51 (d, J = 7.9 Hz, 1H), 7.24−7.19 (m, 3H), 7.13 (d, J = 8.0 Hz, 2H), 6.98 (t, J = 7.7 Hz, 1H), 6.77 (d, J = 7.9 Hz, 1H), 5.08 (s, 2H), 4.78 (d, J = 2.6 Hz, 1H), 4.24 (d, J = 2.6 Hz, 1H), 2.32 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 140.2, 136.7, 134.9, 133.5, 130.2, 129.4, 126.5, 124.1, 122.9, 117.1, 114.7, 86.5, 47.1, 21.2. IR (neat): 1508, 1630, 1979, 2921, 3204 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{17}H_{17}N_2O$ $(M + H)^+$ 265.1341, found 265.1339.

*3-(4-Methoxybenzyl)-4-methylene-3,4-dihydroquinazolin-2(1H)-one (**3d**).* Prepared according to general procedure A, using 4-

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methoxybenzylamine (58 mg, 0.42 mmol) to afford 3-(4-methoxybenzyl)-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one (**3d**) (70 mg, 71% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP = 175−185 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 7.51 (d, J = 7.9 Hz, 1H), 7.24−7.21 (m, 3H), 7.00−6.95 (m, 1H), 6.89−6.84 (m, 2H), 6.80 (d, J = 8.0 Hz, 1H), 5.06 (s, 2H), 4.79 (d, J = 2.6 Hz, 1H), 4.26 (d, J = 2.6 Hz, 1H), 3.78 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.8, 151.8, 140.2, 135.0, 130.2, 128.7, 127.9, 124.0, 122.8, 117.1, 114.9, 114.2, 86.2, 55.4, 46.7. IR (neat): 1464, 1521, 1696, 2917, 3131 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{17}H_{17}N_2O_2$ $(M + H)^+$ 281.1290, found 281.1297.

*3-(3,4-Dimethoxybenzyl)-4-methylene-3,4-dihydroquinazolin-2(1H)-one (**3e**).* Prepared according to general procedure A, using 3,4-dimethoxybenzylamine (70 mg, 0.42 mmol) to afford 3-(3,4-dimethoxybenzyl)-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one (**3e**) (70 mg, 64% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP = 209−211 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (s, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.25−7.22 (m, 1H), 7.01−6.96 (m, 1H), 6.89−6.79 (m, 4H), 5.06 (s, 2H), 4.80 (d, J = 2.6 Hz, 1H), 4.29 (d, J = 2.6 Hz, 1H), 3.85 (d, J = 2.7 Hz, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 151.8, 151.8, 149.3, 148.2, 140.3, 135.0, 130.2, 129.2, 124.0, 122.9, 118.8, 117.0, 114.8, 111.2, 110.0, 86.3, 56.0, 47.2. IR (neat): 1513, 1632, 1679, 2954, 3441 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{18}H_{19}N_2O_3$ $(M + H)^+$ 311.1395, found 311.1388.

*4-Methylene-3-(2,4,5-trimethoxybenzyl)-3,4-dihydroquinazolin-2(1H)-one (**3f**).* Prepared according to general procedure A, using 3,4,5-trimethoxybenzylamine (83 mg, 0.42 mmol) to afford 4-methylene-3-(2,4,5-trimethoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one (**3f**) (107 mg, 90% yield) as a yellow solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP = 225−227 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.53 (d, J = 7.9 Hz, 1H), 7.27−7.21 (m, 1H), 7.02−6.97 (m, 1H), 6.83−6.77 (m, 1H), 6.51 (s, 2H), 5.03 (s, 2H), 4.81 (d, J = 2.6 Hz, 1H), 4.28 (d, J = 2.7 Hz, 1H), 3.81 (s, 9H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 153.6, 151.7, 140.4, 137.0, 134.9, 132.5, 130.3, 124.1, 123.0, 117.0, 114.8, 103.4, 86.7, 61.0, 56.2, 47.8. IR (neat): 1460, 1519, 1651, 2925, 3273 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{19}H_{20}N_2O_4$ $(M + H)^+$ 341.1501, found 341.1505.

*3-([1,1′-Biphenyl]-4-ylmethyl)-4-methylene-3,4-dihydroquinazolin-2(1H)-one (**3g**).* Prepared according to general procedure A, using 4-phenylbenzylamine (77 mg, 0.42 mmol) to afford 3-([1,1′-biphenyl]-4-ylmethyl)-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one (**3g**) (95 mg, 83% yield) as a faint yellow solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP = 228−231 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.30 (s, 1H), 7.62 (t, J = 7.2 Hz, 5H), 7.45 (t, J = 7.6 Hz, 2H), 7.38−7.26 (m, 4H), 6.96 (dd, J = 14.1, 7.7 Hz, 2H), 5.05 (s, 2H), 4.85 (d, J = 2.0 Hz, 1H), 4.18 (d, J = 2.1 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 150.1, 139.9, 139.7, 138.7, 136.3, 135.6, 130.2, 128.9, 127.3, 127.0, 126.8, 126.5, 123.9, 122.1, 115.9, 114.6, 85.3, 45.5. IR (neat): 1514, 1696, 1743 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{22}H_{19}N_2O$ $(M + H)^+$ 327.1497, found 327.1490.

*3-(4-Fluorobenzyl)-4-methylene-3,4-dihydroquinazolin-2(1H)-one (**3h**).* Prepared according to general procedure A, using 4-fluorobenzylamine (53 mg, 0.42 mmol) to afford 3-(4-fluorobenzyl)-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one (**3h**) (65 mg, 69% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP = 180−183 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.29 (dd, J = 8.3, 5.2 Hz, 2H), 7.24 (*t*, J = 7.7 Hz, 1H), 7.05−6.97 (m, 3H), 6.83−6.79 (m, 1H), 5.09 (s, 2H), 4.79 (d, J = 2.8 Hz, 1H), 4.20 (d, J = 2.8 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.4, (d, J = 243.5 Hz), 151.9 (d, J = 6.5 Hz), 140.2, 135.0, 132.3 (d, J = 2.5 Hz), 130.3, 128.2 (d, J = 7.9 Hz), 124.0, 122.9, 116.9, 115.7, 115.5, 115.0 (d, J = 1.3 Hz), 86.2, 46.7. IR (neat): 1507, 1678, 2921 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{16}H_{14}FN_2O$ $(M + H)^+$ 269.1090, found 269.1084.

*3-(3-Bromobenzyl)-4-methylene-3,4-dihydroquinazolin-2(1H)-one (**3i**).* Prepared according to general procedure A, using 3-bromobenzylamine (78 mg, 0.42 mmol) to afford 3-(3-bromobenzyl)-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one (**3i**) (71 mg, 62% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP = 196−198 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H), 7.52 (d, J = 7.7 Hz, 1H), 7.45 (s, 1H), 7.38 (dt, J = 7.5, 1.6 Hz, 1H), 7.28−7.167 (m, 4H), 7.03−6.99 (m, 1H), 6.80 (dd, J = 8.0, 0.9 Hz, 1H), 5.08 (s, 2H), 4.80 (d, J = 2.8 Hz, 1H), 4.17 (d, J = 2.9 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 151.6, 140.2, 139.1, 134.9, 130.4, 130.4, 130.3, 129.6, 125.2, 124.1, 123.0, 123.0, 116.9, 114.9, 86.5, 46.9. IR (neat): 1521, 1695, 2847, 3260 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{16}H_{14}BrN_2O$ $(M + H)^+$ 329.0289, found 329.0294.

*4-Methylene-3-(4-(trifluoromethyl)benzyl)-3,4-dihydroquinazolin-2(1H)-one (**3j**).* Prepared according to general procedure A, using 4-(trifluoromethyl)benzylamine (74 mg, 0.42 mmol) to afford 4-methylene-3-(4-(trifluoromethyl)benzyl)-3,4-dihydroquinazolin-2(1*H*)-one (**3j**) (75 mg, 67% yield) as a yellow solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP = 180−182 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.61 (d, J = 8.2 Hz, 2H), 7.54 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 2H), 7.28−7.24 (m, 1H), 7.03 (t, J = 7.4 Hz, 1H), 6.85 (d, J = 7.9 Hz, 1H), 5.20 (s, 2H), 4.82 (d, J = 2.8 Hz, 1H), 4.15 (d, J = 2.8 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.0, 140.9, 140.2, 134.9, 130.4, 129.5 (q, J = 32.0 Hz), 127.9 (q, J = 42.6 Hz), 125.7 (q, J = 3.4 Hz), 124.2 (q, J = 271.5 Hz), 124.0, 123.1, 116.7, 115.1, 86.3, 47.0. IR (neat): 1325, 1496, 1680, 2923 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{17}H_{14}F_3N_2O$ $(M + H)^+$ 319.1058, found 319.1050.

*4-Methylene-3-(pyridin-2-ylmethyl)-3,4-dihydroquinazolin-2(1H)-one (**3k**).* Prepared according to general procedure A, using 2-picolylamine (45 mg, 0.42 mmol) to afford 4-methylene-3-(pyridin-2-ylmethyl)-3,4-dihydroquinazolin-2(1*H*)-one (**3k**) (51 mg, 58% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP = 173−176 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.58 (ddd, J = 4.9, 1.7, 0.9 Hz, 1H), 7.62 (td, J = 7.7, 1.8 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.29−7.22 (m, 2H), 7.17 (dd, J = 6.9, 5.4 Hz, 1H), 6.99 (t, J = 7.7 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 5.24 (s, 2H), 4.78 (d, J = 2.8 Hz, 1H), 4.25 (d, J = 2.8 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.0, 151.6, 149.4, 140.2, 137.0, 134.9, 130.3, 124.0, 123.0, 122.2, 120.7, 117.0, 114.9, 86.7, 49.5. IR (neat): 1439, 1676, 2922, 3213 cm^{-1}. HRMS (ESI-TOF)m/z calculated for $C_{15}H_{14}N_3O$ $(M + H)^+$ 252.1137, found 252.1138.

*14b-Methyl-8,9,14,14b-tetrahydroindolo[2′,3′:3,4]pyrido[1,2-c]-quinazolin-6(5H)-one (**3l**).* Prepared according to general procedure A, using tryptamine (67 mg, 0.42 mmol) to afford 14b-methyl-8,9,14,14b-tetrahydroindolo[2′,3′:3,4]pyrido[1,2-*c*]quinazolin-6(5*H*)-one (**3l**) (65 mg, 61% yield) as a yellow solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 50:50). MP = 175−178 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.45−7.41 (m, 2H), 7.25−7.21 (m, 3H), 7.16 (t, J = 7.4 Hz, 1H), 7.00 (t, J = 7.6 Hz, 1H), 6.80 (dd, J = 7.7, 3.4 Hz, 1H), 4.82−4.75 (m, 1H), 3.26 (ddd, J = 12.9, 10.9, 4.7 Hz, 1H), 2.93−2.79 (m, 2H), 1.85 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 154.6, 136.2, 136.0, 134.3, 128.7, 126.9, 125.3, 123.9, 122.6, 122.5, 120.1, 118.8, 114.7, 111.1, 110.7, 58.8, 38.6, 26.8, 21.1. IR (neat): 1520, 1657, 2900 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{19}H_{18}N_3O$ $(M + H)^+$ 304.1450, found 304.1457.

*3-(Furan-2-ylmethyl)-4-methylene-3,4-dihydroquinazolin-2(1H)-one (**3m**).* Prepared according to general procedure A, using furfurylamine (41 mg, 0.42 mmol) to afford 3-(furan-2-ylmethyl)-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one (**3m**) (57 mg, 67% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP = 180−183 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (s, 1H), 7.52 (d, J = 8.0 Hz, 1H), 7.36−7.30 (m, 1H), 7.22 (t, J = 7.2 Hz, 1H), 6.97 (t, J = 7.6 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 6.33 (d, J = 1.7 Hz, 2H), 5.07 (s, 2H), 4.84 (d, J = 2.7 Hz, 1H), 4.49 (d, J = 2.7 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 151.7, 150.3, 141.7, 140.2, 134.9, 130.1, 123.8, 122.7, 116.9, 115.0, 110.4, 108.0, 85.4, 40.5. IR (neat): 1520, 1696, 3612 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{14}H_{13}N_2O_2$ $(M + H)^+$ 241.0977, found 241.0981.

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*3-Cyclopropyl-4-methylene-3,4-dihydroquinazolin-2(1H)-one (**3n**).* Prepared according to general procedure A, using cyclopropylamine (24 mg, 0.42 mmol) to afford 3-cyclopropyl-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one (**3n**) (40 mg, 58% yield) as a black solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP = 145−147 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.21 (s, 1H), 7.50 (d, J = 7.3 Hz, 1H), 7.25−7.20 (m, 1H), 7.00−6.95 (m, 1H), 6.86−6.83 (m, 1H), 4.89 (d, J = 1.6 Hz, 1H), 4.72 (d, J = 1.6 Hz, 1H), 2.66−2.60 (m, 1H), 1.16−1.09 (m, 2H), 0.79−0.74 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 153.0, 141.8, 135.2, 129.8, 123.9, 122.6, 118.2, 114.7, 88.4, 26.1, 10.3. IR (neat): 1415, 1517, 1683, 2922, 3214, cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{12}H_{13}N_2O$ (M + H)$^+$ 201.1028, found 201.1033.

*3-Methyl-4-methylene-3,4-dihydroquinazolin-2(1H)-one (**3o**).* Prepared according to general procedure A, using methylamine (13 mg, 0.42 mmol) to afford 3-methyl-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one (**3o**) (28 mg, 46% yield) as a yellow solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP = 155−157 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (s, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.26 (t, J = 7.6 Hz, 1H), 7.00 (t, J = 7.3 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 4.82 (d, J = 2.3 Hz, 1H), 4.26 (d, J = 2.3 Hz, 1H), 3.29 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 151.5, 141.8, 135.0, 130.2, 123.9, 122.7, 116.8, 114.9, 84.3, 30.6. IR (neat): 1454, 1559, 1637, 2924, 3344 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{10}H_{11}N_2O$ (M + H)$^+$ 175.0871, found 175.0878.

*3-Ethyl-4-methylene-3,4-dihydroquinazolin-2(1H)-one (**3p**).* Prepared according to general procedure A, using ethylamine (19 mg, 0.42 mmol) to afford 3-ethyl-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one (**3p**) (45 mg, 69% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP = 159−162 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (s, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.27−7.22 (m, 1H), 7.01−6.95 (m, 1H), 6.81 (d, J = 8.0 Hz, 1H), 4.83 (d, J = 2.5 Hz, 1H), 4.32 (d, J = 2.5 Hz, 1H), 3.93 (q, J = 7.1 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 151.2, 140.1, 135.3, 130.1, 124.0, 122.6, 117.1, 114.8, 84.0, 38.4, 11.3. IR (neat): 1441, 1495, 1654, 2924, 3204 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{11}H_{13}N_2O$ (M + H)$^+$ 189.1028, found 189.1030.

*3-Hexyl-4-methylene-3,4-dihydroquinazolin-2(1H)-one (**3q**).* Prepared according to general procedure A, using hexylamine (43 mg, 0.42 mmol) to afford 3-hexyl-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one (**3q**) (63 mg, 73% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP = 108−110 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.26−7.22 (m, 1H), 7.00−6.96 (m, 1H), 6.84 (dd, J = 8.1, 0.9 Hz, 1H), 4.82 (d, J = 2.4 Hz, 1H), 4.28 (d, J = 2.5 Hz, 1H), 3.85 (t, J = 7.7 Hz, 2H), 1.74−1.67 (m, 2H), 1.43−1.31 (m, 6H), 0.90 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 151.6, 140.3, 135.4, 130.0, 123.9, 122.5, 117.0, 114.9, 84.0, 43.4, 31.7, 26.8, 25.6, 22.7, 14.2. IR (neat): 1424, 1497, 1629, 1684, 2929, 3202 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{15}H_{21}N_2O$ (M + H)$^+$ 245.1654, found 245.1651.

*4-Methylene-3-octyl-3,4-dihydroquinazolin-2(1H)-one (**3r**).* Prepared according to general procedure A, using octylamine (54 mg, 0.42 mmol) to afford 4-methylene-3-octyl-3,4-dihydroquinazolin-2(1*H*)-one (**3r**) (71 mg, 75% yield) as a yellow solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP = 108−110 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.19 (s, 1H), 7.54 (dd, J = 8.1, 1.1 Hz, 1H), 7.25−7.20 (m, 1H), 7.00−6.95 (m, 1H), 6.83 (dd, J = 7.9, 0.8 Hz, 1H), 4.82 (d, J = 2.5 Hz, 1H), 4.28 (d, J = 2.5 Hz, 1H), 3.87−3.80 (m, 2H), 1.74−1.66 (m, 2H), 1.33−1.25 (m, 10H), 0.86 (t, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 151.4, 140.3, 135.3, 130.0, 123.9, 122.5, 117.0, 114.8, 84.1, 43.5, 31.9, 29.4, 29.4, 27.1, 25.6, 22.7, 14.2. IR (neat): 1433, 1679, 2921, 3204 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{17}H_{25}N_2O$ (M + H)$^+$ 273.1967, found 273.1971.

*4-Methylene-3-(prop-2-yn-1-yl)-3,4-dihydroquinazolin-2(1H)-one (**3s**).* Prepared according to general procedure A, using propargylamine (23.13 mg, 0.42 mmol) to afford 4-methylene-3-(prop-2-yn-1-yl)-3,4-dihydroquinazolin-2(1*H*)-one (**3s**) (45 mg, 65% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP = 170−172 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.28−7.25 (m, 1H), 7.02 (t, J = 7.7 Hz, 1H), 6.79 (d, J = 7.9 Hz, 1H), 4.96 (d, J = 3.0 Hz, 1H), 4.65 (d, J = 2.4 Hz, 2H), 4.54 (d, J = 3.0 Hz, 1H), 2.24 (t, J = 2.4 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 150.4, 139.6, 134.6, 130.3, 124.1, 123.1, 117.0, 114.8, 86.1, 78.1, 77.1, 71.7, 33.2. IR (neat): 1462, 1521, 1686, 3284 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{12}H_{11}N_2O$ (M + H)$^+$ 199.0871, found 199.0873.

*3-Allyl-4-methylene-3,4-dihydroquinazolin-2(1H)-one (**3t**).* Prepared according to general procedure A, using allylamine (28 mg, 0.42 mmol) to afford 3-allyl-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one (**3t**) (42 mg, 61% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP = 127−130 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (s, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.26−7.22 (m, 1H), 6.99 (dd, J = 7.9, 7.4 Hz, 1H), 6.84 (d, J = 7.8 Hz, 1H), 5.93−5.84 (m, 1H), 5.30−5.21 (m, 2H), 4.83 (d, J = 2.5 Hz, 1H), 4.52−4.51 (m, 2H), 4.32 (d, J = 2.3 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 151.5, 140.4, 135.1, 132.0, 130.1, 123.9, 122.7, 117.0, 116.7, 115.0, 85.5, 46.1. IR (neat): 1496, 1654, 2923, 3242 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{12}H_{13}N_2O$ (M + H)$^+$ 201.1028, found 201.1027.

*3-(3-Methoxyphenethyl)-4-methylene-3,4-dihydroquinazolin-2(1H)-one (**3u**).* Prepared according to general procedure A, using 3-methoxyphenethylamine (52.92 mg, 0.42 mmol) to afford 3-(3-methoxyphenethyl)-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one (**3u**) (67 mg, 65% yield) as a yellow solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP = 128−130 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.58 (d, J = 7.3 Hz, 1H), 7.28−7.22 (m, 2H), 7.03−6.99 (m, 1H), 6.93−6.85 (m, 2H), 6.78 (dd, J = 8.2, 1.7 Hz, 2H), 4.90 (d, J = 2.6 Hz, 1H), 4.43 (d, J = 2.7 Hz, 1H), 4.10−4.04 (m, 2H), 3.80 (s, 3H), 3.01−2.97 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.9, 150.9, 140.6, 140.2, 135.1, 130.2, 129.7, 124.1, 122.8, 121.2, 117.0, 114.7, 114.6, 112.0, 84.6, 55.3, 44.9, 32.0. IR (neat): 1517, 1680, 2927, 3616 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{18}H_{19}N_2O_2$ (M + H)$^+$ 295.1446, found 295.1456.

*(E)-3-Benzyl-4-butylidene-3,4-dihydroquinazolin-2(1H)-one (**3v**).* Prepared according to general procedure A, using benzylamine (45 mg, 0.42 mmol) to afford (*E*)-3-benzyl-4-butylidene-3,4-dihydroquinazolin-2(1*H*)-one (**3v**) (22 mg, 21% yield) as a yellow solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP = 122−124 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.39 (d, J = 7.9 Hz, 1H), 7.31−7.28 (m, 4H), 7.24−7.21 (m, 2H), 7.01−6.97 (m, 1H), 6.79 (dd, J = 7.9, 0.8 Hz, 1H), 5.04 (s, 2H), 4.99 (t, J = 7.1 Hz, 1H), 2.28 (q, J = 7.2 Hz, 2H), 1.38−1.29 (m, 2H), 0.80 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 153.5, 137.5, 136.8, 133.0, 129.1, 128.6, 127.1, 126.9, 126.6, 121.7, 118.4, 114.1, 112.7, 48.2, 30.6, 23.9, 13.7. IR (neat): 1448, 1500, 1669, 2922, 3211 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{19}H_{21}N_2O$ (M + H)$^+$ 293.1654, found 293.1660.

*(E/Z)-4-Benzylidene-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1H)-one (**3w**).* Prepared according to general procedure A, using 4-methoxybenzylamine (58 mg, 0.42 mmol) to afford (*E*/*Z*)-4-benzylidene-3-(4-methoxybenzyl)-3,4-dihydroquinazolin-2(1*H*)-one (**3w**) (62 mg, 50% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP = 236−238 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.21 (s, 1H), 7.49 (d, J = 7.4 Hz, 1H), 7.39−7.35 (m, 4H), 7.29−7.27 (m, 3H), 7.24−7.20 (m, 3H), 7.14−7.10 (m, 3H), 7.04−7.00 (m, 2H), 6.89−6.83 (m, 5H), 6.77 (t, J = 7.2 Hz, 2H), 6.67−6.62 (m, 3H), 6.31 (s, 1H), 6.08 (s, 1H), 5.13 (s, 2H), 4.70 (s, 2H), 3.79 (s, 3H), 3.70 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.7, 154.4, 152.9, 137.3, 136.6, 136.2, 135.3, 134.3, 134.1, 129.9, 129.8, 129.4, 129.2, 128.9, 128.8, 128.8, 128.6, 128.5, 128.4, 127.9, 127.2, 126.7, 123.0, 122.8, 121.8, 121.6, 117.0, 114.4, 114.4, 114.2, 113.8, 113.6, 111.8, 109.7, 55.4, 55.2, 49.5, 47.4. IR (neat): 1454, 1509, 1678, 2918 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{23}H_{21}N_2O_2$ (M + H)$^+$ 357.1603, found 357.1604.

*4-Hydroxy-3-(4-methoxybenzyl)-4-phenyl-3,4-dihydroquinazolin-2(1H)-one (**3x**).* Prepared according to general procedure A, using 4-methoxybenzylamine (48 mg, 0.35 mmol) to afford 4-hydroxy-3-(4-

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methoxybenzyl)-4-phenyl-3,4-dihydroquinazolin-2(1*H*)-one (**3x**) (80 mg, 63% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 70:30). MP = 140−143 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.78 (s, 1H), 7.40−7.38 (m, 1H), 7.28 (t, J = 7.5 Hz, 2H), 7.23−7.19 (m, 2H), 7.16−7.11 (m, 1H), 7.08 (d, J = 8.6 Hz, 2H), 6.97 (d, J = 7.7 Hz, 1H), 6.86−6.79 (m, 2H), 6.70 (d, J = 8.7 Hz, 2H), 4.30 (d, J = 15.1 Hz, 1H), 4.12 (d, J = 15.0 Hz, 1H), 3.67 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6) δ 157.5, 152.0, 145.6, 134.8, 132.0, 128.9, 128.6, 128.0, 127.7, 127.5, 125.8, 124.9, 120.9, 113.3, 112.8, 87.6, 54.9, 45.2. IR (neat): 1456, 1540, 1607, 1656, 2922, 2853 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{22}H_{20}N_2O_3Na$ (M + Na)$^+$ 383.1372, found 383.1382.

3-(4-((6-Methoxyquinolin-8-yl)amino)pentyl)-4-methylene-3,4-dihydroquinazolin-2(1H)-one (**3y**). Prepared according to general procedure A, using primaquine (109 mg, 0.42 mmol) to afford 3-(4-((6-methoxyquinolin-8-yl)amino)pentyl)-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one (**3y**) (64 mg, 45% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 60:40). MP = 90−93 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 1H), 8.50 (dd, J = 4.2, 1.6 Hz, 1H), 7.90 (dd, J = 8.3, 1.6 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.29−7.25 (m, 1H), 7.21−7.17 (m, 1H), 6.95−6.91 (m, 1H), 6.79 (d, J = 7.9 Hz, 1H), 6.31 (q, J = 2.5 Hz, 2H), 6.03 (s, 1H), 4.76 (d, J = 2.5 Hz, 1H), 4.24 (d, J = 2.6 Hz, 1H), 3.86 (s, 3H), 3.73−3.60 (m, 2H), 1.92−1.81 (m, 4H), 1.72−1.67 (m, 1H), 1.30 (d, J = 6.3 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.5, 151.5, 145.1, 144.3, 140.1, 135.5, 135.2, 134.8, 130.1, 130.0, 123.9, 122.6, 121.9, 116.9, 114.8, 96.8, 91.7, 84.4, 55.3, 48.0, 43.2, 34.0, 22.4, 20.6. IR (neat): 1453, 1519, 1661, 2956 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{24}H_{27}N_4O_2$ (M + H)$^+$ 403.2134, found 403.2134.

3-(Benzo[d][1,3]dioxol-5-ylmethyl)-4-methylene-3,4-dihydroquinazolin-2(1H)-one (**3z**). Prepared according to general procedure A, using piperonylamine (64 mg, 0.42 mmol) to afford 3-(benzo[*d*][1,3]-dioxol-5-ylmethyl)-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one (**3z**) (60 mg, 58% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP = 173−175 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.25 (s, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.31−7.25 (m, 1H), 6.98−6.91 (m, 2H), 6.83 (dd, J = 9.0, 4.7 Hz, 2H), 6.74 (dd, J = 8.0, 1.4 Hz, 1H), 5.97 (s, 2H), 4.90 (s, 2H), 4.82 (d, J = 2.3 Hz, 1H), 4.17 (d, J = 2.4 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 150.1, 147.4, 146.0, 139.6, 135.5, 130.9, 130.1, 123.9, 122.1, 119.6, 116.0, 114.6, 108.2, 107.0, 100.8, 85.3, 45.5. IR (neat): 1440, 1546, 1626, 1681, 3062 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{17}H_{15}N_2O_3$ (M + H)$^+$ 295.1083, found 295.1093.

3-(2-Acetylphenyl)-1,1-dimethylurea (**6a**). Prepared according to general procedure C, using dimethylamine (19 mg, 0.42 mmol) to afford 3-(2-acetylphenyl)-1,1-dimethylurea (**6a**) (43 mg, 60% yield) as a yellow solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 20:80). MP = 85−88 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.40 (s, 1H), 8.63 (dd, J = 8.6, 0.9 Hz, 1H), 7.84 (dd, J = 8.0, 1.5 Hz, 1H), 7.49 (ddd, J = 8.6, 7.3, 1.5 Hz, 1H), 6.98−6.94 (m, 1H), 3.07 (s, 6H), 2.63 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 203.0, 155.8, 143.4, 135.2, 131.7, 120.9, 120.3, 119.7, 36.4, 28.5. IR (neat): 1524, 1738, 2921, 3616 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{11}H_{15}N_2O_2$ (M + H)$^+$ 207.1134, found 207.1141.

3-(2-Acetylphenyl)-1,1-diisopropylurea (**6b**). Prepared according to general procedure C, using diisopropylamine (25 mg, 0.42 mmol) to afford 3-(2-acetylphenyl)-1,1-diisopropylurea (**6b**) (71 mg, 77% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 20:80). MP = 199−102 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.15 (s, 1H), 8.48 (dd, J = 8.6, 1.0 Hz, 1H), 7.83 (dd, J = 8.1, 1.6 Hz, 1H), 7.47 (ddd, J = 8.7, 7.2, 1.6 Hz, 1H), 6.96−6.92 (m, 1H), 3.98−3.88 (m, 2H), 2.64 (s, 3H), 1.38 (s, 6H), 1.37 (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 202.9, 154.5, 143.7, 135.0, 131.7, 121.2, 120.5, 120.0, 46.5, 28.5, 21.2. IR (neat): 1309, 1521, 1645, 1734, 3264 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{15}H_{23}N_2O_2$ (M + H)$^+$ 263.1759, found 263.1759.

3-(2-Acetylphenyl)-1,1-diisobutylurea (**6c**). Prepared according to general procedure C, using diisobutylamine (54 mg, 0.42 mmol) to afford 3-(2-acetylphenyl)-1,1-diisobutylurea (**6c**) (78 mg, 76% yield) as a red liquid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 20:80). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.39 (s, 1H), 8.68 (dd, J = 8.6, 0.8 Hz, 1H), 7.82 (dd, J = 8.0, 1.4 Hz, 1H), 7.48−7.44 (m, 1H), 6.95−6.91 (m, 1H), 3.23 (s, 2H), 3.21 (s, 2H), 2.62 (s, 3H), 2.13−2.02 (m, 2H), 0.94 (s, 6H), 0.93 (s, 6H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 202.7, 155.5, 143.4, 135.1, 131.6, 120.8, 120.1, 119.7, 55.9, 28.4, 27.7, 20.2. IR (neat): 1240, 1449, 1527, 1647, 1735 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{17}H_{27}N_2O_2$ (M + H)$^+$ 291.2072, found 291.2072.

N-(2-Acetylphenyl)pyrrolidine-1-carboxamide (**6d**). Prepared according to general procedure C, using pyrrolidine (30 mg, 0.42 mmol) to afford *N*-(2-acetylphenyl)pyrrolidine-1-carboxamide (**6d**) (65 mg, 80% yield) as a yellow solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 20:80). MP = 96−98 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.24 (s, 1H), 8.68 (dd, J = 8.6, 1.0 Hz, 1H), 7.82 (dd, J = 8.1, 1.5 Hz, 1H), 7.48 (ddd, J = 8.7, 7.3, 1.5 Hz, 1H), 6.94 (ddd, J = 8.3, 7.2, 1.2 Hz, 1H), 3.53−3.50 (m, 4H), 2.62 (s, 3H), 1.95 (s, 4H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 202.9, 154.1, 143.4, 135.2, 131.7, 120.6, 120.1, 119.6, 45.8, 28.5. IR (neat): 1525, 1648, 1735, 2930, 3615 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{13}H_{17}N_2O_2$ (M + H)$^+$ 233.1290, found 233.1297.

N-(2-Acetylphenyl)morpholine-4-carboxamide (**6e**). Prepared according to general procedure C, using morpholine (37 mg, 0.42 mmol) to afford *N*-(2-acetylphenyl)morpholine-4-carboxamide (**6e**) (62 mg, 71% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 20:80). MP = 133−135 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.52 (s, 1H), 8.58 (dd, J = 8.6, 0.8 Hz, 1H), 7.84 (dd, J = 8.0, 1.4 Hz, 1H), 7.50 (ddd, J = 8.7, 7.4, 1.5 Hz, 1H), 7.00−6.96 (m, 1H), 3.73 (t, J = 4.64 Hz, 4H), 3.56 (t, J = 5.12 Hz, 4H), 2.63 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 203.3, 154.9, 143.0, 135.3, 131.8, 120.9, 120.7, 119.8, 66.6, 44.0, 28.5. IR (neat): 1243, 1528, 1644, 1734, 2922 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{13}H_{17}N_2O_3$ (M + H)$^+$ 249.1239, found 249.1248.

N-(2-Acetylphenyl)-2-amino-6-oxocyclohex-1-ene-1-carboxamide (**6f**). Prepared according to general procedure C, using 3-amino-2-cyclohexen-1-one (47 mg, 0.42 mmol) to afford *N*-(2-acetylphenyl)-2-amino-6-oxocyclohex-1-ene-1-carboxamide (**6f**) (15 mg, 16% yield) as a yellow solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 20:80). MP = 120−123 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (dd, J = 8.6, 0.8 Hz, 1H), 8.01 (dd, J = 8.5, 0.7 Hz, 1H), 7.77 (ddd, J = 8.3, 6.8, 1.3 Hz, 1H), 7.56 (ddd, J = 8.3, 6.8, 1.3 Hz, 1H), 3.27 (t, J = 6.04 Hz 1H), 3.05 (s, 3H), 2.80 (t, J = 6.36 Hz, 2H), 2.24−2.16 (m, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 200.8, 162.2, 150.1, 148.0, 131.6, 129.3, 127.8, 126.5, 125.6, 125.5, 41.2, 34.9, 21.4, 16.2. IR (neat): 1524, 1695, 1739, 3616 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{15}H_{17}N_2O_3$ (M + H)$^+$ 273.1239, found 273.1237.

2-Methoxybenzyl (2-Acetylphenyl)carbamate (**6g**). Prepared according to general procedure D, using 2-methoxybenzyl alcohol (58 mg, 0.42 mmol) to afford 2-methoxybenzyl (2-acetylphenyl)-carbamate (**6g**) (51 mg, 53% yield) as a faint green solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 10:90). MP = 108−110 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.22 (s, 1H), 8.52 (dd, J = 8.6, 0.9 Hz, 1H), 7.86 (dd, J = 8.0, 1.5 Hz, 1H), 7.54 (ddd, J = 8.6, 7.4, 1.4 Hz, 1H), 7.41 (dd, J = 7.5, 1.6 Hz, 1H), 7.31 (td, J = 8.1, 1.7 Hz, 1H), 7.06 (ddd, J = 8.3, 7.3, 1.2 Hz, 1H), 6.96 (td, J = 7.5, 0.9 Hz, 1H), 6.90 (d, J = 8.2 Hz, 1H), 5.28 (s, 2H), 3.86 (s, 3H), 2.64 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 202.3, 157.5, 154.0, 141.5, 135.1, 131.7, 129.6, 129.5, 124.6, 121.6, 121.4, 120.5, 119.4, 110.5, 62.4, 55.5, 28.6. IR (neat): 1522, 1650, 1732, 3615 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{17}H_{17}NO_4Na$ (M + Na)$^+$ 322.1055, found 322.1060.

3-(2-Acetylphenyl)-1-(2-hydroxyethyl)-1-methylurea (**6h**). Prepared according to general procedure C, using 2-(methylamino)-ethanol (31 mg, 0.42 mmol) to afford 3-(2-acetylphenyl)-1-(2-hydroxyethyl)-1-methylurea (**6h**) (71 mg, 86% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP = 112−115 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.46 (s, 1H), 8.58 (dd, J = 8.6, 1.1 Hz, 1H), 7.87−7.84 (m, 1H), 7.53−7.48 (m, 1H), 7.02−6.98 (m, 1H), 3.83 (s, 3H), 3.60−3.57 (m, 2H), 3.18−3.17 (m, 10H), 2.66−2.65 (m, 3H), 1.82 (s, 1H). ^{13}C{^{1}H} NMR

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(100 MHz, $CDCl_3$) δ 203.2, 157.1, 143.0, 135.3, 131.8, 121.2, 120.8, 120.0, 61.8, 52.1, 35.9, 28.6. IR (neat): 1203, 1452, 1644, 2923 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{12}H_{16}N_2O_3Na$ $(M + Na)^+$ 259.1059, found 259.1059.

*1-(2-Acetylphenyl)-3-(3-hydroxypropyl)urea (**6i**).* Prepared according to general procedure E, using 3-aminopropan-1-ol (32 mg, 0.42 mmol) to afford 1-(2-acetylphenyl)-3-(3-hydroxypropyl)urea (**6i**) (25 mg, 31% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP = 111−113 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 10.34 (s, 1H), 8.12 (dd, J = 8.0, 1.3 Hz, 1H), 7.61 (m, 1H), 7.25−7.21 (m, 1H), 7.12 (d, J = 8.1 Hz, 1H), 4.19 (m, 4H), 2.06 (m, 2H), 2.02 (s, 3H), 1.82 (bs, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 192.6, 171.3, 162.5, 152.1, 138.7, 135.2, 128.5, 123.5, 115.1, 114.6, 62.5, 38.3, 27.2, 21.0. IR (neat): 1243, 1660, 1715, 1733, 2921 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{12}H_{17}N_2O_3$ $(M + H)^+$ 237.1239, found 237.1240.

*1-(2-Acetylphenyl)-3-(tert-butyl)urea (**6j**).* Prepared according to general procedure C, using *tert*-butylamine (31 mg, 0.42 mmol) to afford 1-(2-acetylphenyl)-3-(*tert*-butyl)urea (**6j**) (53 mg, 65% yield) as a yellow liquid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). ^1H NMR (400 MHz, $CDCl_3$) δ 10.95 (s, 1H), 8.52 (d, J = 8.7 Hz, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.47 (t, J = 7.9 Hz, 1H), 6.95 (t, J = 7.6 Hz, 1H), 2.63 (s, 3H), 1.39 (s, 9H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 203.0, 154.2, 143.4, 135.1, 131.7, 120.7, 120.2, 120.1, 119.9, 51.1, 29.3. IR (neat): 1014, 1539, 1649, 1715, 3350 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{13}H_{18}N_2O_2Na$ $(M + Na)^+$ 257.1265, found 257.1247.

*4-Hydroxyquinolin-2(1H)-one (**7a**).*[7a,20] Prepared according to general procedure F, using 3-(*tert*-butylperoxy)-3-methylindolin-2-one (82 mg, 0.35 mmol) to afford 4-hydroxyquinolin-2(1*H*)-one (**7a**) (45 mg, 80% yield) as a white solid after purification using silica gel column chromatography (DCM:MeOH = 90:10). The data for this compound and for the reported compound are in agreement.

*10b-Methyl-2,3,6,10b-tetrahydro-5H-oxazolo[3,2-c]quinazolin-5-one (**9a**).* Prepared according to general procedure G, using ethanolamine (26 mg, 0.42 mmol) to afford 10b-methyl-2,3,6,10b-tetrahydro-5*H*-oxazolo[3,2-*c*]quinazolin-5-one (**9a**) (58 mg, 81% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP = 161−163 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 7.37 (d, J = 7.6 Hz, 1H), 7.25−7.22 (m, 1H), 7.04 (t, J = 7.5 Hz, 1H), 6.86−6.84 (m, 1H), 4.18−4.10 (m, 2H), 3.94 (dd, J = 14.3, 7.1 Hz, 1H), 3.66 (dt, J = 10.4, 7.0 Hz, 1H), 1.54 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.6, 134.5, 129.3, 124.5, 123.1, 122.7, 114.2, 91.9, 63.5, 43.4, 27.6. IR (neat): 1517, 1673, 3061, 3616 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{11}H_{13}N_2O_2$ $(M + H)^+$ 205.0977, found 205.0978.

*10b-Phenyl-2,3,6,10b-tetrahydro-5H-oxazolo[3,2-c]quinazolin-5-one (**9b**).* Prepared according to general procedure G, using ethanolamine (26 mg, 0.42 mmol) to afford 10b-phenyl-2,3,6,10b-tetrahydro-5*H*-oxazolo[3,2-*c*]quinazolin-5-one (**9b**) (75 mg, 78% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP = 170−173 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.51 (m, 2H), 7.38−7.30 (m, 3H), 7.30−7.27 (m, 1H), 7.19 (m, 1H), 6.97 (td, J = 7.7, 1.1 Hz, 1H), 6.82 (dd, J = 8.0, 0.7 Hz, 1H), 4.26 (ddd, J = 10.7, 8.2, 5.9 Hz, 1H), 4.08 (td, J = 8.2, 5.9 Hz, 1H), 3.95 (td, J = 8.3, 5.9 Hz, 1H) 3.36 (ddd, J = 10.7, 8.4, 5.9 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.7, 143.0, 134.0, 129.5, 128.8, 128.4, 126.6, 125.1, 122.9, 121.4, 114.4, 94.2, 62.8, 43.4. IR (neat): 1434, 1602, 1670, 2920, 3212 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{16}H_{15}N_2O_2$ $(M + H)^+$ 267.1134, found 267.1131.

*10b-Benzyl-2,3,6,10b-tetrahydro-5H-oxazolo[3,2-c]quinazolin-5-one (**9c**).* Prepared according to general procedure G, using ethanolamine (26 mg, 0.42 mmol) to afford 10b-benzyl-2,3,6,10b-tetrahydro-5*H*-oxazolo[3,2-*c*]quinazolin-5-one **9c** (71 mg, 72% yield) as a yellow solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP = 154−156 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.28 (d, J = 7.6 Hz, 1H), 7.23 (dd, J = 7.5, 1.4 Hz, 1H), 7.20−7.16 (m, 3H), 7.05−6.98 (m, 3H), 6.75−6.73 (m, 1H), 4.11−4.06 (m, 1H), 4.00 (m, 1H), 3.84 (q, J = 7.7 Hz, 1H), 3.16 (m, 1H), 3.01 3.05 (d, J = 13.5 Hz, 1H), 2.97 (d, J = 13.5 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 151.7, 135.1, 134.9, 130.7, 129.3, 128.1, 126.9, 124.8, 122.5, 122.1, 113.9, 94.1, 64.3, 47.0, 44.1. IR (neat): 1438, 1671, 2912, 3212 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{17}H_{17}N_2O_2$ $(M + H)^+$ 281.1290, found 281.1289.

*11b-Methyl-3,4,7,11b-tetrahydro-2H,6H-[1,3]oxazino[3,2-c]-quinazolin-6-one (**9d**).* Prepared according to general procedure G, using 3-aminopropan-1-ol (32 mg, 0.42 mmol) to afford 11b-methyl-3,4,7,11b-tetrahydro-2*H*,6*H*-[1,3]oxazino[3,2-*c*]quinazolin-6-one (**9d**) (58 mg, 76% yield) as a yellow solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP = 140−142 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.37 (dd, J = 7.8, 1.4 Hz, 1H), 7.24−7.20 (m, 1H), 7.02 (td, J = 7.6, 1.1 Hz, 1H), 6.72 (dd, J = 8.0, 0.8 Hz, 1H), 4.48−4.43 (m, 1H), 4.09 (td, J = 11.4, 3.6 Hz, 1H), 3.98−3.94 (m, 1H), 3.29 (td, J = 13.2, 4.0 Hz, 1H), 2.10−1.88 (m, 2H), 1.72 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.0, 134.0, 129.3, 124.9, 124.2, 122.6, 113.6, 86.3, 60.6, 35.8, 25.1, 23.0. IR (neat): 1520, 1657, 1716, 3615 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{12}H_{15}N_2O_2$ $(M + H)^+$ 219.1133, found 219.1136.

*11b-Phenyl-3,4,7,11b-tetrahydro-2H,6H-[1,3]oxazino[3,2-c]-quinazolin-6-one (**9e**).* Prepared according to general procedure G, using 3-aminopropan-1-ol (32 mg, 0.42 mmol) to afford 11*b*-phenyl-3,4,7,11*b*-tetrahydro-2*H*,6*H*-[1,3]oxazino[3,2-*c*]quinazolin-6-one (**9e**) (75 mg, 76% yield) as a faint yellow solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP = 189−192 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 9.08 (s, 1H), 7.48 (d, J = 7.5 Hz, 2H), 7.41−7.36 (m, 3H), 7.28 (t, J = 7.3 Hz, 1H), 7.13 (td, J = 7.9, 1.3 Hz, 1H), 6.94−6.89 (m, 1H), 6.77 (d, J = 7.9 Hz, 1H), 4.61 (dd, J = 13.4, 3.2 Hz, 1H), 4.09−4.01 (m, 2H), 3.04 (td, J = 13.2, 3.1 Hz, 1H), 2.17−2.03 (m, 1H), 1.50 (d, J = 13.1 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.0, 140.9, 133.5, 129.3, 129.2, 128.2, 126.2, 123.1, 122.5, 114.1, 89.9, 62.6, 37.8, 25.3. IR (neat): 1425, 1605, 1666, 2922, 3204 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{17}H_{17}N_2O_2$ $(M + H)^+$ 281.1290, found 281.1297

*11b-Benzyl-3,4,7,11b-tetrahydro-2H,6H-[1,3]oxazino[3,2-c]-quinazolin-6-one (**9f**).* Prepared according to general procedure G, using 3-aminopropan-1-ol (32 mg, 0.42 mmol) to afford 11b-benzyl-3,4,7,11b-tetrahydro-2*H*,6*H*-[1,3]oxazino[3,2-*c*]quinazolin-6-one (**9f**) (73 mg, 71% yield) as a yellow solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP = 156−158 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.23 (d, J = 6.7 Hz, 1H), 7.18−7.14 (m, 1H), 7.12 (d, J = 7.3 Hz, 1H), 7.07 (t, J = 7.2 Hz, 2H), 6.96 (t, J = 7.6 Hz, 1H), 6.76−6.69 (m, 2H), 6.52−6.46 (m, 1H), 4.53 (dd, J = 13.6, 5.9 Hz, 1H), 4.27−4.20 (m, 1H), 4.01−3.96 (m, 1H), 3.66 (d, J = 13.3 Hz, 1H), 3.38 (td, J = 13.0, 4.4 Hz, 1H), 3.00 (d, J = 13.3 Hz, 1H), 2.06−1.94 (m, 1H), 1.86−1.81 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.1, 135.1, 134.6, 130.4, 129.4, 127.9, 126.8, 125.6, 122.0, 121.5, 113.2, 89.2, 60.4, 41.8, 35.7, 24.9. IR (neat): 1437, 1664, 2920 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{18}H_{19}N_2O_2$ $(M + H)^+$ 295.1446, found 295.1452

*12b-Benzyl-2,3,4,5,8,12b-hexahydro-7H-[1,3]oxazepino[3,2-c]-quinazolin-7-one (**9g**).* Prepared according to general procedure G, using 4-amino-1-butanol (37 mg, 0.42 mmol) to afford 12b-benzyl-2,3,4,5,8,12b-hexahydro-7*H*-[1,3]oxazepino[3,2-*c*]quinazolin-7-one (**9g**) (67 mg, 62% yield) as a yellow solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP = 195−198 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.29 (dd, J = 7.7, 1.3 Hz, 1H), 7.20−7.15 (m, 1H), 7.09−6.97 (m, 4H), 6.71−6.68 (m, 2H), 6.54 (dd, J = 8.0, 0.8 Hz, 1H), 4.39 (d, J = 13.3 Hz, 1H), 3.78 (d, J = 13.8 Hz, 1H), 3.60 (td, J = 12.2, 1.3 Hz, 1H), 3.30 (t, J = 12.5 Hz, 1H), 3.18 (d, J = 13.2 Hz, 1H), 2.98 (d, J = 13.2 Hz, 1H), 1.84−1.71 (m, 2H), 1.65−1.44 (m, 2H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.8, 136.5, 134.7, 130.4, 129.4, 127.7, 126.7, 125.7, 121.8, 120.6, 113.2, 92.8, 64.6, 47.3, 40.3, 29.2, 27.3. IR (neat): 1448, 1495, 1603, 1658, 2923, 3202 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{18}H_{19}N_2O_2$ $(M + H)^+$ 309.1603, found 309.1596

*(3S,10bR)-3-Ethyl-10b-methyl-2,3,6,10b-tetrahydro-5H-oxazolo-[3,2-c]quinazolin-5-one (**9h**) and (3S,10bS)-3-Ethyl-10b-methyl-2,3,6,10b-tetrahydro-5H-oxazolo[3,2-c]quinazolin-5-one (**9h′**).* Prepared according to general procedure G, using (*S*)-(+)-2-amino-1-

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propanol (37 mg, 0.42 mmol) to afford (3*S*,10b*R*)-3-ethyl-10b-methyl-2,3,6,10b-tetrahydro-5*H*-oxazolo[3,2-*c*]quinazolin-5-one **9h** (45 mg, 55% yield) as a faint pink solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70) with MP = 185−187 °C and (3*S*,10b*S*)-3-ethyl-10b-methyl-2,3,6,10b-tetrahydro-5*H*-oxazolo-[3,2-*c*]quinazolin-5-one **9h′** (13 mg, 16% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 70:30) with MP = 184−186 °C. Diastereomers **9h** and **9h′** are present in a ratio of 3.4:1. HPLC for **9h** (CHIRALPAK IA column, *n*-heptane/isopropanol = 80/20, flow rate = 0.7 mL/min, l = 254 nm): tR = 9.62 min (major), tR= 7.23 min (minor), 97% *de*. HPLC for **9h′** (CHIRALPAK IA column, *n*-heptane/isopropanol = 80/20, flow rate = 0.7 mL/min, l = 254 nm): tR= 9.88 min (major), tR = 9.61 min (minor), 90% *de*. (3*S*,10b*R*)-3-Ethyl-10b-methyl-2,3,6,10b-tetrahydro-5*H*-oxazolo[3,2-c]quinazolin-5-one (**9h**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.35 (d, J = 7.6 Hz, 1H), 7.22 (td, J = 8.1, 1.3 Hz, 1H), 7.03 (t, J = 7.5 Hz, 1H), 6.79 (t, J = 7.1 Hz, 1H), 4.10 (td, J = 10.5, 5.5 Hz, 1H), 4.01 (dd, J = 8.4, 6.6 Hz, 1H), 3.91 (dd, J = 8.5, 4.6 Hz, 1H), 2.23−2.12 (m, 1H), 1.74−1.63 (m, 1H), 1.56 (s, 3H), 1.03 (t, J = 7.5 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.4, 134.8, 129.1, 124.0, 122.7, 114.0, 113.9, 92.4, 69.1, 59.1, 29.5, 28.0, 10.7. IR (neat): 1524, 1690, 1739, 3616 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{13}H_{17}N_2O_2$ (M + H)$^+$ 233.1290, found 233.1295. The crystals of compound **9h** were grown using dichloromethane and petroleum ether (2:1) as a solvent by slow evaporation. A needle-shaped single crystal was mounted on a loop by applying a small amount of paraffin oil. Crystal data for compound **9h**: $C_{13}H_{15}N_2O_2$, M = 231.27, orthorhombic, space group P 21 21 21 with a = 7.5792(3) Å, b = 7.7672(3) Å, c = 19.9951(7) Å, α = 90°, β = 90°, γ = 90°, V = 1177.09(8) Å^3, T = 296(2) K, R1 = 0.0306, wR2 = 0.0814 for observed data, z = 4, D_{calcd} = 1.305 g cm^{-3}, F(000) = 492, absorption coefficient = 0.725 mm^{-1}, λ = 1.54178 Å, 1999 reflections collected on a Bruker APEX-II CCD single-crystal diffractometer, and 1964 observed reflections ($I \geq 2\sigma(I)$). The largest difference peak and hole are 0.510 and −0.142 eÅ^{-3}, respectively

*(3S,10bS)-3-Ethyl-10b-methyl-2,3,6,10b-tetrahydro-5H-oxazolo-[3,2-c]quinazolin-5-one (**9h′**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.32 (dd, J = 7.6, 1.1 Hz, 1H), 7.22 (td, J = 7.8, 1.4 Hz, 1H), 7.04 (td, J = 7.5, 0.9 Hz, 1H), 6.80 (d, J = 7.9 Hz, 1H), 4.37 (dd, J = 8.8, 7.0 Hz, 1H), 4.14−4.08 (m, 1H), 3.99 (dd, J = 8.9, 2.7 Hz, 1H), 2.07−1.96 (m, 1H), 1.67−1.60 (m, 1H), 1.45 (s, 3H), 0.80 (t, J = 7.5 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 151.2, 134.8, 128.8, 125.5, 123.0, 122.8, 114.0, 92.4, 69.0, 56.4, 25.5, 24.1, 9.3. IR (neat): 1520, 1674, 3615 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{13}H_{17}N_2O_2$ (M + H)$^+$ 233.1290, found 233.1295.

*(3S,10bR)-3-Isopropyl-10b-methyl-2,3,6,10b-tetrahydro-5H-oxazolo[3,2-c]quinazolin-5-one (**9i**) and (3S,10bS)-3-Isopropyl-10b-methyl-2,3,6,10b-tetrahydro-5H-oxazolo[3,2-c]quinazolin-5-one (**9i′**).* Prepared according to general procedure G, using (*S*)-(+)-2-amino-3-methyl-1-butanol (43 mg, 0.42 mmol) to afford (3*S*,10b*R*)-3-isopropyl-10b-methyl-2,3,6,10b-tetrahydro-5*H*-oxazolo[3,2-*c*]-quinazolin-5-one (**9i**) (41 mg, 48% yield) as a gray solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70) with MP = 205−208 °C and (3*S*,10b*S*)-3-isopropyl-10b-methyl-2,3,6,10b-tetrahydro-5*H*-oxazolo[3,2-*c*]quinazolin-5-one **9i′** (17 mg, 20% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 70:30) with MP = 204−207 °C. Diastereomers **9i** and **9i′** are present in a ratio of 2.4:1. HPLC for **9i** (CHIRALPAK IA column, *n*-heptane/isopropanol = 80/20, flow rate = 0.7 mL/min, l = 254 nm): tR= 8.03 min (major), tR = 6.82 min (minor), 94% *de*. HPLC for **9i′** (CHIRALPAK IA column, *n*-heptane/isopropanol = 80/20, flow rate = 0.7 mL/min, l = 254 nm): tR = 13.63 min (major), tR = 8.12 min (minor), 95% *de*. (3*S*,10b*R*)-3-isopropyl-10b-methyl-2,3,6,10b-tetrahydro-5*H*-oxazolo[3,2-c]quinazolin-5-one (**9i**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.38−7.34 (m, 1H), 7.22 (td, J = 7.7, 1.5 Hz, 1H), 7.03 (td, J = 7.5, 1.1 Hz, 1H), 6.77 (dd, J = 8.0, 0.7 Hz, 1H), 3.98 (dd, J = 8.4, 2.9 Hz, 1H), 3.93−3.88 (m, 1H), 3.76 (dd, J = 8.4, 5.9 Hz, 1H), 2.17−2.04 (m, 1H), 1.56 (s, 3H), 1.15 (d, J = 6.9 Hz, 3H), 1.03 (d, J = 6.6 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 153.2, 135.0, 129.1, 124.3, 124.0, 122.6, 113.8, 92.5, 67.7, 64.2, 31.8, 30.0, 19.9, 19.6. IR (neat): 1524, 1693, 1739, 3616 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{14}H_{19}N_2O_2$ (M + H)$^+$ 247.1446, found 247.1444.

*(3S,10bS)-3-Isopropyl-10b-methyl-2,3,6,10b-tetrahydro-5H-oxazolo[3,2-c]quinazolin-5-one (**9i′**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 7.0 Hz, 1H), 7.23 (td, J = 7.8, 1.4 Hz, 1H), 7.05 (td, J = 7.5, 0.9 Hz, 1H), 6.98 (s, 1H), 6.76 (d, J = 8.0 Hz, 1H), 4.26−4.21 (m, 1H), 4.13−4.09 (m, 2H), 2.69−2.59 (m, 1H), 1.45 (s, 3H), 0.89 (d, J = 7.1 Hz, 3H), 0.58 (d, J = 6.9 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 150.7, 128.7, 125.6, 125.5, 123.1, 122.9, 113.7, 92.4, 64.8, 60.0, 26.2, 25.2, 19.5, 14.7.IR (neat): 1511, 1605, 1670, 3062, 3613 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{14}H_{19}N_2O_2$ (M + H)$^+$ 247.1446, found 247.1451.

*(3S,10bR)-3-Benzyl-10b-methyl-2,3,6,10b-tetrahydro-5H-oxazolo[3,2-c]quinazolin-5-one (**9j**) and (3S,10bS)-3-Benzyl-10b-methyl-2,3,6,10b-tetrahydro-5H-oxazolo[3,2-c]quinazolin-5-one (**9j′**).* Prepared according to general procedure G, using (*S*)-2-amino-3-phenylpropan-1-ol (64 mg, 0.42 mmol) to afford (3*S*,10b*R*)-3-benzyl-10b-methyl-2,3,6,10b-tetrahydro-5*H*-oxazolo[3,2-*c*]quinazolin-5-one (**9j**) (47 mg, 45% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70) with MP = 122−125 °C and (3*S*,10b*S*)-3-benzyl-10b-methyl-2,3,6,10b-tetrahydro-5*H*-oxazolo[3,2-*c*]quinazolin-5-one (**9j′**) (36 mg, 35% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 70:30) with MP = 92−95 °C. Diastereomers **9j** and **9j′** are present in a ratio of 1.3:1. HPLC for **9j** (CHIRALPAK IA column, *n*-heptane/isopropanol = 80/20, flow rate = 0.7 mL/min, l = 254 nm): tR = 11.84 min (major), tR = 4.72 min (minor), 94% *de*. HPLC for **9j′** (CHIRALPAK IA column, *n*-heptane/isopropanol = 80/20, flow rate = 0.7 mL/min, l = 254 nm): tR = 13.47 min (major), tR = 11.81 min (minor), 84% *de*. (3*S*,10b*R*)-3-Benzyl-10b-methyl-2,3,6,10b-tetrahydro-5*H*-oxazolo[3,2-c]quinazolin-5-one (**9j**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1H), 7.38−7.33 (m, 5H), 7.30−7.22 (m, 2H), 7.04 (t, J = 7.5 Hz, 1H), 6.90−6.89 (m, 1H), 4.47−4.43 (m, 1H), 4.00 (dd, J = 8.8, 5.4 Hz, 1H), 3.90 (t, J = 7.8 Hz, 1H), 3.54 (d, J = 13.2 Hz, 1H), 3.06−2.99 (m, 1H), 1.48 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 152.9, 137.6, 134.9, 129.7, 129.1, 128.7, 126.8, 124.0, 123.9, 122.6, 114.2, 92.7, 68.2, 58.7, 40.4, 29.2. IR (neat): 1524, 1685, 3617 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{18}H_{19}N_2O_2$ (M + H)$^+$ 295.1446, found 295.1444.

*(3S,10bS)-3-Benzyl-10b-methyl-2,3,6,10b-tetrahydro-5H-oxazolo[3,2-c]quinazolin-5-one (**9j′**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.01 (s, 1H), 7.34−7.17 (m, 8H), 7.02 (td, J = 7.5, 1.0 Hz, 1H), 6.91 (d, J = 8.0 Hz, 1H), 4.41−4.36 (m, 1H), 4.18 (dd, J = 8.9, 6.9 Hz, 1H), 4.03 (dd, J = 9.3, 2.4 Hz, 1H), 3.66 (dd, J = 13.2, 2.7 Hz, 1H), 2.51 (dd, J = 13.2, 10.3 Hz, 1H), 1.46 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 151.9, 138.0, 135.0, 129.4, 128.8, 128.7, 126.6, 125.5, 122.8, 122.7, 114.2, 92.6, 68.5, 56.8, 37.7, 25.6. IR (neat): 1523, 1685, 3615 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{18}H_{19}N_2O_2$ (M + H)$^+$ 295.1446, found 295.1443.

*3-Benzylquinazoline-2,4(1H,3H)-dione (**10a**).* Prepared according to general procedure H, using 3-benzyl-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one **3a** (63 mg, 0.25 mmol) to afford 3-benzylquinazoline-2,4(1*H*,3*H*)-dione **10a** (49 mg, 78% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP = 203−205 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.93 (s, 1H), 8.13 (d, J = 7.9 Hz, 1H), 7.58 (t, J = 7.7 Hz, 1H), 7.54−7.52 (m, 2H), 7.33−7.29 (m, 2H), 7.25−7.20 (m, 2H), 7.04 (d, J = 8.1 Hz, 1H), 5.27 (s, 2H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.4, 152.0, 138.6, 137.0, 135.2, 129.0, 128.7, 128.6, 127.8, 123.5, 115.0, 114.7, 44.3. IR (neat): 1459, 1645, 1735, 2922, 3282 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{15}H_{13}N_2O_2$ (M + H)$^+$ 253.0977, found 253.0968.

*3-Ethylquinazoline-2,4(1H,3H)-dione (**10b**).* Prepared according to general procedure H, using 3-ethyl-4-methylene-3,4-dihydroquinazolin-2(1*H*)-one **3p** (47 mg, 0.25 mmol) to afford 3-ethylquinazoline-2,4(1*H*,3*H*)-dione **10b** (33 mg, 69% yield) as a white solid after purification using silica gel column chromatography (EtOAc:*n*-hexane = 30:70). MP = 190−192 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.35 (s, 1H), 8.14 (d, J = 7.9 Hz, 1H), 7.61 (ddd, J = 8.2, 7.3, 1.5 Hz,

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1H), 7.25−7.21 (m, 1H), 7.14 (d, J = 8.1 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.3, 52.1, 138.7, 135.0, 128.4, 123.4, 115.1, 114.8, 36.3, 13.3. IR (neat): 1455, 1659, 1715, 2919, 3058 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{10}H_{11}N_2O_2$ $(M + H)^+$ 191.0820, found 191.0824.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00889.

Copies of ^1H and ^{13}C NMR spectra and crystallographic data (PDF).

FAIR data, including the primary NMR FID files, for compounds **3a−z**, **6a−j**, **7a**, **9a−h**, **9h′**, **9i**, **9i′**, **9j**, **9j′**, **10a**, and **10b** (ZIP)

Accession Codes

CCDC 2053446−2053447 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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Transition-Metal-Free Alkylative Aromatization of Tetralone Using Alcohol/Amino Alcohol towards the Synthesis of Bioactive Naphthol and Benzo[*e*/*g*]indole Derivatives

Akash S. Ubale, Gokul S. Londhe, Moseen A. Shaikh, and Boopathy Gnanaprakasam*

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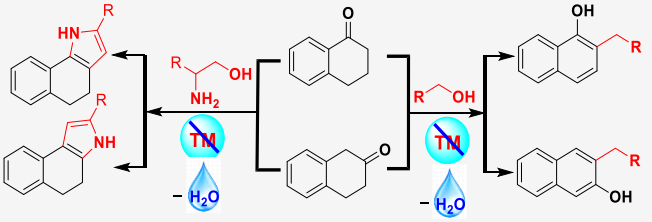
ABSTRACT: Herein, we report alkylative aromatization of tetralone for the synthesis of bioactive naphthols and benzo[*e*/*g*]indole derivatives using alcohols in the presence of NaOH via an aerobic oxidative cross-coupling protocol. This is a general and transition-metal-free method, which uses an inexpensive base, avoids inert conditions, and furnishes water and hydrogen peroxide as the byproducts. Moreover, this method demonstrated with wide substrate scope and obtained exclusive regioselectivity.



INTRODUCTION

The naphthols and benzo[*e*]indoles are important structural motifs in organic chemistry and have been found in a variety of functionalized molecules, ranging from naturally occurring bioactive compounds to pharmaceutical agents.[1,2,18] This type of compound exhibits broad therapeutic applications such as anticancer, antioxidant, and antipsoriatic agents, and 5-lipoxygenase inhibitor properties, which make them powerful pharmacophores in biology (Figure 1).[3a−e] Furthermore, functionalized naphthols are a useful precursor for the synthesis of chiral binaphthol, which serves as a chiral ligand in many asymmetric syntheses.[4] Intense application of this important subunit has resulted in a range of methods for its constructions.

The common classical approaches that are widely used in the industrial-scale synthesis of naphthol derivatives from naphthalene involve multistep reactions, sulfonation-hydrolysis, or nitration-reduction-hydrolysis at high temperature and pressure (Scheme 1A).[5] These processes suffer from high toxicity, harsh conditions, and large-scale waste generation. In 1990, Batt et al. reported the base-catalyzed condensation of 1-tetralone with an aromatic aldehyde to provide the benzylidene ketone, upon which further isomerization formed the derivative of naphthol.[6] A catalytic olefin-isomerization process was also reported for the synthesis of naphthols using benzylidene ketone in the presence of Rh and Ir-catalyst along with a strong base.[7] Catalytic dehydrogenation methods were reported for the synthesis of a variety of substituted phenols and naphthols using cyclohexanone and tetralone in the presence of Pt and Ir-catalyst (Scheme 1B(a)).[8] Recently, He et al. reported a photocatalytic dehydrogenative method for α-naphthols from 1-tetralones under ambient conditions (Scheme 1B(b)).[9] Furthermore, 2-methyl-1-tetralone and 1-naphthol were reacted to produce 2-methyl-1-naphthol from 1-tetralone via methylation and dehydrogenation proceeding by modified iron oxide and Pd-supported on activated carbon, at high temperature (Scheme 1B(c)).[10a] Later, Koltunov et al. described the dehydrogenation of tetralones and tetralin to form naphthols and naphthalene under supercritical (T = 400 °C, ρ = 0.2 g/cm3) water.[10b] Recently, the Yi research group reported Ru−H catalyzed tandem dehydrogenation-alkylation using tetralone and alcohols at 200 °C (Scheme 1B(d)).[11]

Moreover, this type of catalytic borrowing alkylation strategy was reported for the synthesis of various annulated heterocycles.[12] The Friedel−Crafts alkylation strategy was also reported for the synthesis of alkyl naphthol derivatives using naphthol and alcohols in the presence of $ZnCl_2$ and $AlCl_3$ supported on silica gel under microwave irradiation (Scheme 1B(e)).[13] At the outset, most of the modern synthesis reactions are catalyzed by a specially designed catalyst and multidentate ligands,[14] which require stoichiometric bases. These transition-metal complexes are usually expensive, less abundant in nature, and much more sensitive to air/moisture. Besides, transition-metal residues are difficult to separate from desired products that are not suitable for pharmaceuticals. Consequently, alternative efficient synthetic methods for the synthesis of naphthols and benzo[*e*/*g*]indoles that avoid expensive transition-metal catalyst are in high demand in contemporary research. In this context, various chemical transformations promoted by diverse bases under transition-metal-free conditions have been accounted in recent decades. Interestingly, NaOH has been widely used for metal-free coupling reactions of

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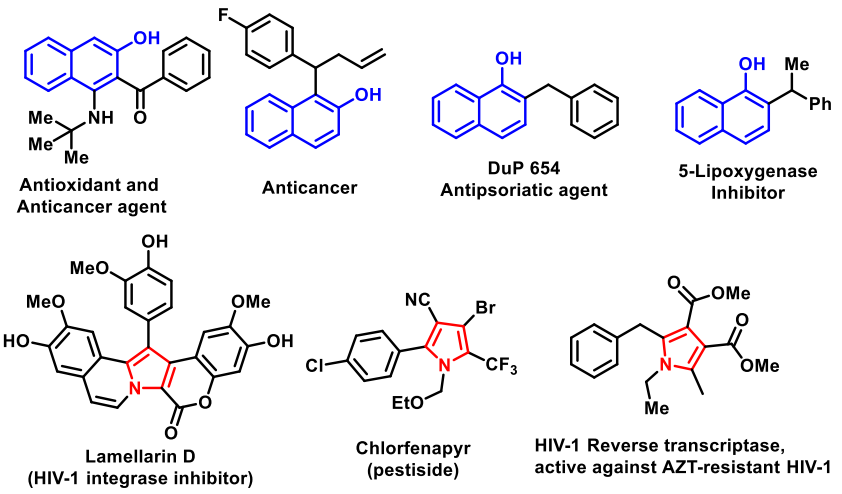
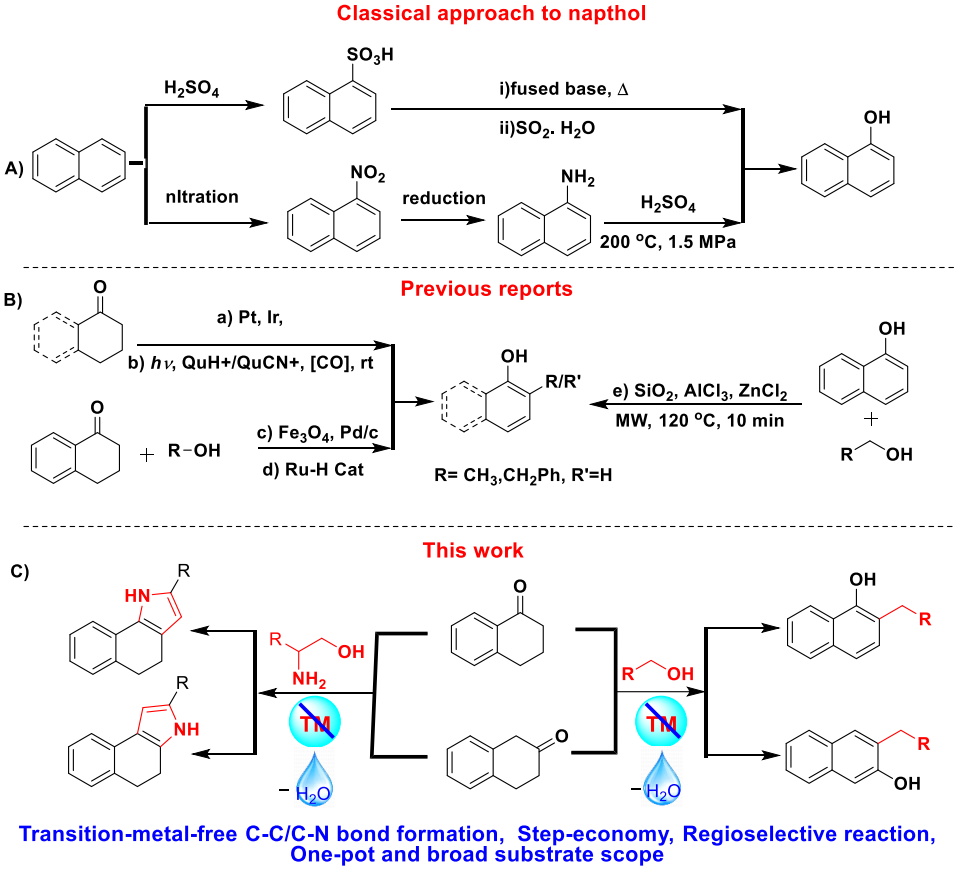


Figure 1. Naphthol and pyrrole derivatives in bioactive molecules.

Scheme 1. State of the Art for the Synthesis of Naphthol Derivatives



alcohol with ketone.[15a] Furthermore, KO*t*Bu has been widely used for single electron transfer reactions and metal-free cross-coupling reactions of aryl halides with arenes.[15b]

In this work, we report the transition-metal-free reaction of tetralones and alcohol/amino alcohol toward the synthesis of bioactive naphthol and benzo[*e*/*g*]indole derivatives promoted by the inexpensive base (Scheme 1C). The present work includes the following features: (i) sequential oxidation-condensation-isomerization-aromatization reactions in one step; (ii) transition-metal-free C−C/C−N bond formation and step-economy; (iii) demonstrated broad substrate scope with high yield.

RESULTS AND DISCUSSION

To establish a transition-metal-free alkylative aromatization, initial optimization was performed with 2-tetralone **1a** and **2a**. A control experiment **1a** and **2a** in the absence of base at 140 °C in toluene solvent did not produce the desired products **3a** and **4a** (Table 1, entry 1). Next, we have performed the reaction of **1a** and **2a** in the presence of 1 mol % $RuHCl(CO)(PPh_3)_3$ and 1 equiv of NaOH, and 34% of **3a** and **4a** was observed with a 25:1

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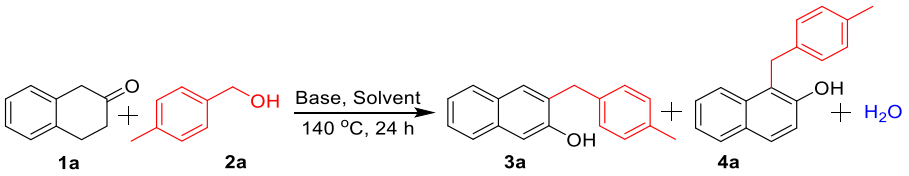
Table 1. Optimization of Reaction Conditions[a]



entry	base (equiv)	solvent	yield [%][b] (3a + 4a)	ratio[c] (3a:4a)
1	–	toluene	–	–
2[d,e]	NaOH (1)	toluene	34	25:1
3[e]	NaOH (3)	toluene	41	50:1
4[e]	NaOH (5)	toluene	47	50:1
5[f]	NaOH (3)	toluene	62	100:1
6	NaOH (3)	toluene	93	100:1
7	NaOH (2)	toluene	78	100:1
8	NaOH (1)	toluene	67	100:1
9	NaOH (0.2)	toluene	26	100:1
10[g]	NaOH (3)	toluene	82	100:1
11	KO*t*Bu (3)	toluene	70	20:1
12	KOH (3)	toluene	65	4:1
13	Cs_2CO_3 (3)	toluene	35	100:1
14	K_2CO_3 (3)	toluene	–	–
15	NaOH (3)	1.4-dioxane	86	100:1
16	NaOH (3)	xylene	81	100:1
17	NaOH (3)	DMF	trace	–
18	NaOH (3)	DMSO/H_2O	–	–
19[h]	NaOH (3)	toluene	78	100:1

[a]Reaction conditions: Compound **1a** (0.70 mmol), **2a** (0.35 mmol), and solvent (2 mL) were stirred in a preheated oil bath to 140 °C. For base equivalents, see table. [b]Isolated yields. [c]Ratios **3a**/**4a** were determined by ^{1}H NMR analysis. [d]With 1 mol % $RuHCl(CO)(PPh_3)_3$. [e]Compound (**1a**:**2a** = 0.35:0.35). [f]Compound (**1a**:**2a** = 0.52:0.35). [g]After 16 h. [h]At 120 °C.

ratio (Table 1, entry 2). In the absence of the Ru-catalyst, 41% of **3a** and **4a** was observed with a 50:1 ratio (Table 1, entry 3). Then, we increased the base equivalent, and a slight increase in yield was observed. Effects of base equivalents for this reaction are summarized in Table 1 (entry 4−10). Notably, an increase in the equivalent of **1a** (i.e., **1a**:**2a** = 0.70:0.35), 93% yield, has been observed (Table 1, entry 6). Furthermore, we screened a variety of bases such as KO*t*Bu, KOH, Cs_2CO_3, K_2CO_3 for this reaction, and the results are capitulated in Table 1 (entry 11−14). From our survey of bases, NaOH was found to be the best base for this transformation. Further, varieties of solvents were tested to enhance the product yield of **3a** and **4a**, but no improvement was detected (Table 1, entries 15−18), whereas in the case of DMSO and water, there was no detection of the desired products **3a** and **4a**. From these experimental solvent studies, toluene is established as the best solvent for this conversion. A decrease in yield was observed when the temperature of the reaction decreased (Table 1, entry 19). Moreover, hydrogen peroxide and water were the only byproducts in this transformation.

To generalize the substrate scope for 3-substituted-2-naphthol derivatives, the alkylative aromatization of 2-tetralone **1a** with **2a** provided **3a** in a 93% yield. A variety of alcohols was satisfactorily reacted with 2-tetralone **1a** to produce the corresponding 3-substituted-2-naphthol derivatives in good to excellent yield (Scheme 2). Electron-neutral benzyl alcohol afforded product **3b** in 85% yield. Electron-rich benzyl alcohol afforded 56% to 83% yields of the products **3c**−**3g** (Scheme 2). The electron-withdrawing substituents such as 4-F, 4-CF_3, 3-Cl, 2-Br on benzyl alcohol provided moderate to good yield of the corresponding products **3h**−**3k** (Scheme 2). Gratifyingly, aliphatic and heteroaryl alcohol were well tolerated under optimized experimental conditions. Aliphatic alcohols such as propan-1-ol, 1-butanol, 1-hexanol, 3-methyl-2-buten-1-ol, furfuryl alcohol, and 2-thiophenemethanol were successfully converted into **3l**−**3o**, **3p**, and **3q** in 64−82%, 67%, and 91% yield, respectively. Notably, 3-phenyl-1-propanol provided naphthol products **3r** in 78% yield. Furthermore, the substrate scope is extended to naphthol derivatives having substituents on 2-tetralone **1** as well as on benzyl alcohol. 7-Methoxy-2-tetralone, 6-methoxy-2-tetralone, and 6-bromo-2-tetralone with respective alcohols led to products **3s**−**3y** in good to excellent yield (Scheme 2). The product **3s** was characterized by spectroscopic techniques and single-crystal XRD (Figure 2). To our delight, a gram-scale reaction was performed to afford 77% of the product **3a**.

Next, alkylative aromatization of 1-tetralone **5a** is studied using alcohols (Scheme 3). For instance, the reaction of 1-tetralone **5a** and benzyl alcohol with the slightly modified standard condition (**5a**:**2** = 0.35:0.70) using *tert*-butyl alcohol as a solvent afforded product **6a** in 83% yield. Further electron-rich benzyl alcohols afforded **6b**−**6e** in 48% to 66% yield (Scheme 3). The electron-withdrawing benzyl alcohol afforded the desired products **6f**, **6g**, and **6h** in 47%, 55%, and 48% yields, respectively. Further, 2-thiophenemethanol afforded the product **6i** in 70% yield (Scheme 3). All the above reactions were also performed on a 1.0 mmol scale, and the results are summarized in Scheme 2 and Scheme 3.

Next, this concept extended toward the synthesis of benzo[*e*]indoles derivatives. For instance, the transition-metal-free reaction of 2-tetralone **1a** and 2-aminopropan-1-ol **7a** in the presence of NaOH afforded benzo[*e*]indoles derivative **8a** in

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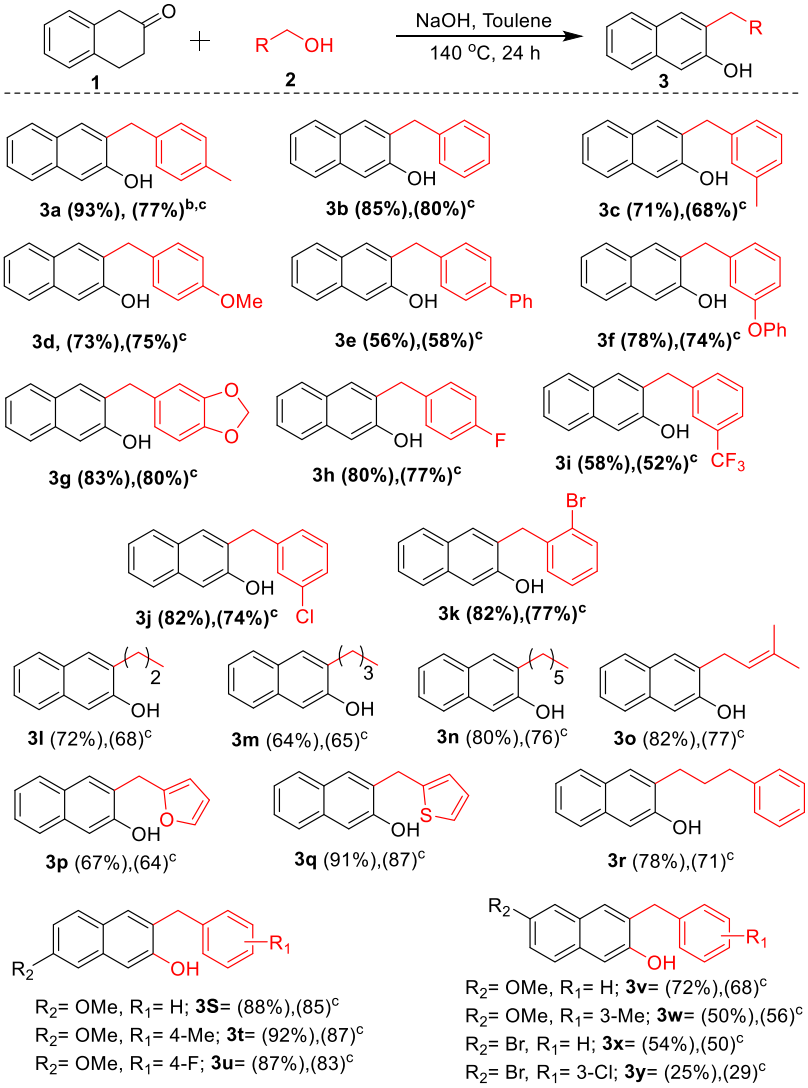
Scheme 2. Substrate Scope for 3-Substituted-2-Naphthols[a]



[a]Reaction conditions: Compound **1** (0.70 mmol), **2** (0.35 mmol), NaOH (3 equiv), and toluene (2 mL) were stirred in an preheated oil bath at 140 °C for 24 h. [b]Gram scale. [c]With 1 mmol scale. The mentioned yields are isolated yields.

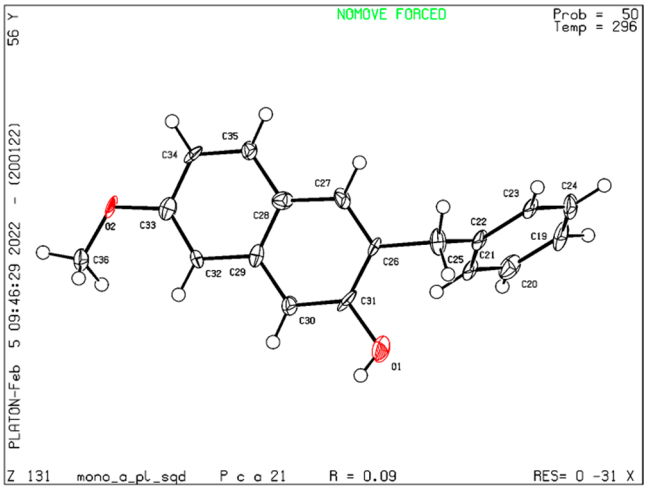


Figure 2. X-ray structure of product **3s**.

67% isolated yield. Other amino alcohols also reacted well for this reaction to obtain an **8b**−**8i** in moderate to good yields (Scheme 4). Similarly, the formation of benzo[*g*]indole derivatives from 1-tetralone **5** and amino alcohols **7** also progressed well to give the desired products **9a**−**9e** in moderate to good yields (Scheme 5). Moreover, the reaction performed in 1 mmol scale, and slightly decreasing yield has been observed (Scheme 4 and Scheme 5). Further oxidation has been performed using **8d** with DDQ, which afforded the corresponding product **10a** in 24% yield (Scheme 4). Moreover, the synthesized 2-benzyl-3*H*-benzo[*e*]indole **10a** can be used as a valuable precursor in the synthesis of various bioactive molecules.[16]

Next, the application of regioselective 3-substituted-2-naphthol derivatives has been investigated for the synthesis of crucial intermediate naphthalene-1,2-dione by an oxidation reaction. This oxidation has been performed using **3a** and **3o** with CuCl and an oxygen balloon.[17] Upon completion of the reaction, corresponding products **14a** and **14b** were isolated in 72% and 62% yields (Scheme 6). Moreover, the synthesized naphthalene-1,2-dione can be employed as valuable precursors in the synthesis of α/β-lapachone drug.[18]

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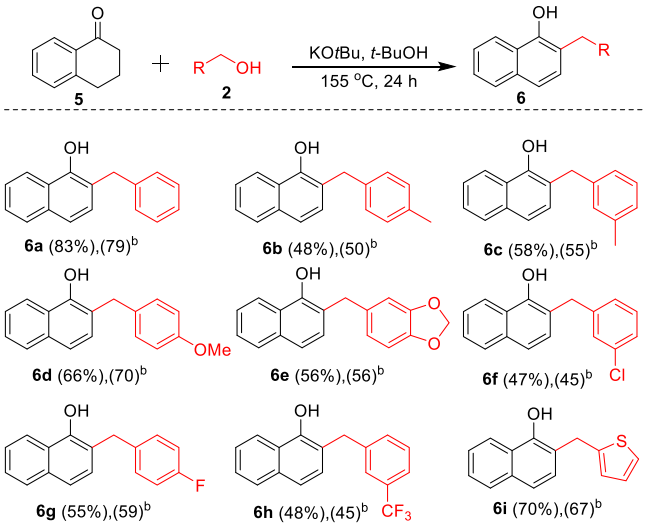
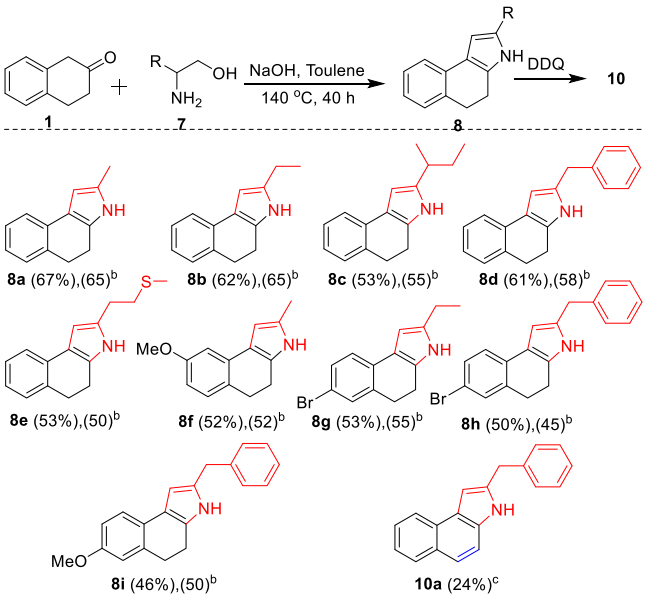
Scheme 3. Substrate Scope for 2-Substituted-1-Naphthols[a]



[a]Reaction conditions: Compound **5** (0.35 mmol), **2** (0.70 mmol), KO*t*Bu (4 equiv), and *t*-BuOH (4 mL) were stirred in a preheated oil bath at 155 °C for 24 h. [b]With 1 mmol scale. The mentioned yields are isolated yields.

Scheme 4. Benzo[*e*]indoles from 2-Tetralone[a]



[a]Reaction conditions: Compound **1** (0.70 mmol), **7** (0.35 mmol), NaOH (3 equiv), and toluene (2 mL) were stirred in an preheated oil bath at 140 °C for 40 h. [b]With 1 mmol scale. [c]DDQ (2 equiv). The mentioned yields are isolated yields.

To understand the reaction pathway, a series of control experiments were performed (Scheme 7A). In the absence of tetralone, 4-methylbenzyl alcohol **2a** afforded methylbenzaldehyde **2aa** (Scheme 7A(i)).[15a] A reaction of 2-tetralone **1a** with 4-methylbenzaldehyde **2aa** provided **3a** in 92% yield under optimized reaction conditions (Scheme 7A(ii)).[6] This experiment suggests that the oxidation of alcohol to aldehyde was a crucial step for this transformation. To identify the intermediate of this reaction, benzylidene **11a** was subjected to the standard reaction condition and afforded product **3a** in 20% yield (Scheme 7A(iii)).[7] This experiment confirmed the in situ generation of benzylidene **11a** as an intermediate during this reaction.[15c] Furthermore, we hypothesized that NaOH mediated deprotonated isomerization of benzylidene **11a** results in aromatization and forms the product **3a**. To prove the existence of a radical pathway for the oxidation of alcohol, the reaction was performed in the presence of radical quencher TEMPO, and no detection of product **3a** has been observed. The absence of a product of **3a** indicates the radical nature of the reaction (Scheme 7A(iv)). The reaction of tetralone **1a**, alcohol **2a**, and benzophenone **2b** under optimized conditions did not afford the benzhydrol, which confirms that this reaction did not proceed through Oppernauer-type oxidation (Scheme 7A(v)). On the basis of experimental observations and literature precedents,[15a−e] we have proposed the possible mechanism for the transition-metal-free reaction (Scheme 7B). Initially, there is the aerobic oxidation of alcohols in the presence of the base.[15d] First, alcohol **2a** was in equilibrium with its corresponding Na/K alkoxide **2a-1**. The alkoxide anion facilitated easy abstraction of oxygen-connected α-CH of **2a-1** by O_2 to form a carbon-centered radical **2a-2** and hydrogen peroxide radical. The combination of these two radicals generated intermediate **2a-3**, with the elimination of HOOM from **2a-3**, which afforded aldehyde **2aa**.

Next, aldehyde undergoes aldol condensation with tetralone in the presence of a base to form the intermediate **11a**. Isomerization of benzylidene **11a** generates the product **6a**.[7,15c] In the case of product **9a**, the reaction of amino alcohol **7a** and 1-tetralone **5a** affords imine as an initial intermediate **12a**. Subsequently, imine **12a** proceeds base-mediated oxidation of alcohol to form **13a**,[15d,e] which is confirmed by HRMS (see SI, Figure S1). Finally, **13a** facilitates intramolecular aldol condensation to afford **9a** (Scheme 7B).

CONCLUSION

In summary, we described regioselective transition-metal-free dehydrogenative C−C/C−N coupling for the bioactive naphthol and benzo[*e*/*g*]indole derivatives in good to excellent yields. This reaction was step-economic, regioselective, and involved inexpensive benchtop NaOH and KO*t*Bu bases. Moreover, an α/β-lapachone drug could be achieved using this protocol, which uses environmentally benign alcohol as an alkylating reagent, avoids halogenated reagents, and affords water and hydrogen peroxide as the byproducts. A plausible mechanism has been proposed on the basis of the experimental results and previous literature studies.

EXPERIMENTAL SECTION

General Information and Data Collection. The α-tetralone (**5**), β-tetralone (**1**), alcohol (**2**), amino alcohol (**7**), KO*t*Bu, and NaOH were purchased from Sigma-Aldrich or Alfa-Aesar. All the solvents used in the reactions were dry grade. The column chromatographic separation separations were achieved over 100−200 mesh size silica-gel. Visualization completed with UV light, PMA, and CAM stain go along with heating. By using a Bruker or JEOL spectrometer, the ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. Brief information used in NMR follow-up experiments: s, singlet; d, doublet; t, triplet; q, quartet; m, multiple; b, broad; ddd, doublet of doublets of doublets. High-resolution mass spectra were recorded by Waters-Synapt G2 applying electrospray ionization (ESI-TOF). Infrared (ATR) spectra were obtained with a Bruker Alpha-E infrared spectrometer. The melting point was measured using the BUCHI M-560 melting-point instrument. All melting points were measured in an open glass capillary tube. Single-crystal diffraction analysis data were collected at 100 K with a Bruker Kappa Apex IIICCD Duo

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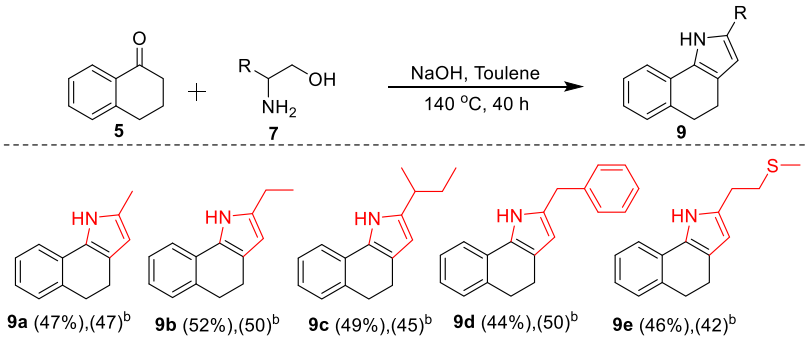
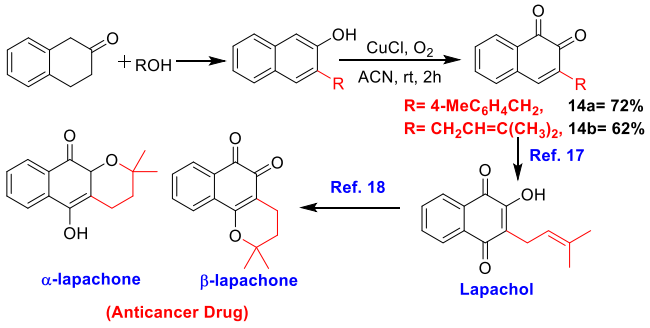
Scheme 5. Benzo[*g*]indoles from 1-Tetralone[a]



[a]Reaction conditions: Compound **5** (0.35 mmol), **7** (0.70 mmol), NaOH (3 equiv), and toluene (2 mL) were stirred in an preheated oil bath at 140 °C for 40 h. [b]With 1 mmol scale. The mentioned yields are isolated yields.

Scheme 6. Synthesis of α/β-Lapachone Drug Intermediate



diffractometer (operated at 1500 W power: 50 kV, 30 mA) using graphite monochromatic Mo Kα radiation. More information on crystal structures (**3s**) can also be obtained from the Cambridge Crystallographic Data Centre (CCDC) via deposition number 2150250.

A. General Experimental Procedure for the Synthesis of 3-Substituted-2-Naphthol Derivatives. In a 20 mL resealable vial was added NaOH (42 mg, 1.05 mmol, 3 equiv), 2-tetralone compound **1** (0.70 mmol, 2 equiv), alcohol **2** (0.35 mmol, 1 equiv) in toluene (2 mL). Further, the tube was sealed with a cap using a crimper. The reaction mixture was stirred at 140 °C for 24 h in a preheated oil bath. After completion of the reaction, aqueous HCl (1 M, 1 mL) was added and the resulting mixture was extracted with ethyl acetate two times using 10 mL of solvent each time. The organic layers were combined and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by using column chromatography (EtOAc/*n*-hexane = 10:90).

A′. General Experimental Procedure for the Synthesis of 3-Substituted-2-Naphthol Derivatives on a 1.0 mmol Scale. In a 20 mL resealable vial was added NaOH (120 mg, 3 mmol, 3 equiv), 2-tetralone compound **1** (2 mmol, 2 equiv), alcohol **2** (1 mmol, 1 equiv) in toluene (3 mL). Further, the tube was sealed with a cap using a crimper. The reaction mixture was stirred at 140 °C for 24 h in a preheated oil bath. After completion of the reaction, aqueous HCl (1 M, 2 mL) was added and the resulting mixture was extracted with ethyl acetate two times using 10 mL of solvent each time. The organic layers were combined and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by using column chromatography (EtOAc/*n*-hexane = 10:90).

B. Experimental Procedure for the Synthesis of 3a (Gram-Scale Synthesis). In a 20 mL resealable vial was added NaOH (983 mg, 24.6 mmol, 3 equiv), 2-tetralone compound **1a** (2.396 g, 16.4 mmol, 2 equiv), alcohol **2a** (1 g, 8.2 mmol, 1 equiv) in toluene (10 mL). Further, the tube was sealed with a cap using a crimper. The reaction mixture was stirred at 140 °C for 24 h in a preheated oil bath. After completion of the reaction, aqueous HCl (1 M, 5 mL) was added and the resulting mixture was extracted with ethyl acetate two times using 25 mL of solvent each time. The organic layers were combined and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by using column chromatography (EtOAc/*n*-hexane = 10:90) to furnish **3a** in 77% (1.55 g) yield.

C. General Experimental Procedure for the Synthesis of 2-Substituted-1-Naphthol Derivatives. In a 20 mL resealable vial was added KO*t*Bu (157 mg, 1.40 mmol, 4 equiv), 1-tetralone **5** (0.35 mmol, 1 equiv), alcohol **2** (0.70 mmol, 2 equiv) in *t*-BuOH (4 mL). Further, the tube was sealed with a cap using a crimper. The reaction mixture was stirred at 155 °C for 24 h in a preheated oil bath. After completion of the reaction, aqueous HCl (1 M, 1 mL) was added and the resulting mixture was extracted with ethyl acetate two times using 10 mL of solvent each time. The organic layers were combined and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by using column chromatography (EtOAc/*n*-hexane = 10:90).

C′. General Experimental Procedure for the Synthesis of 2-Substituted-1-Naphthol Derivatives on a 1.0 mmol Scale. In a 20 mL resealable vial was added KO*t*Bu (448 mg, 4 mmol, 4 equiv), 1-tetralone **5** (1 mmol, 1 equiv), alcohol **2** (2 mmol, 2 equiv) in *t*-BuOH (6 mL). Further, the tube was sealed with a cap using a crimper. The reaction mixture was stirred at 155 °C for 24 h in a preheated oil bath. After completion of the reaction, aqueous HCl (1 M, 3 mL) was added and the resulting mixture was extracted with ethyl acetate two times using 20 mL of solvent each time. The organic layers were combined and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by using column chromatography (EtOAc/*n*-hexane = 10:90).

D. General Experimental Procedure for the Synthesis of Benzo[*e*]indole Derivatives from 2-Tetralone. In a 20 mL resealable vial was added NaOH (42 mg, 1.05 mmol, 3 equiv), 2-tetralone compound **1** (0.70 mmol, 2 equiv), amino alcohol **7** (0.35 mmol, 1 equiv) in toluene (2 mL). Further, the tube was sealed with a cap using a crimper. The reaction mixture was stirred at 140 °C for 40 h in a preheated oil bath. After completion of the reaction, aqueous HCl (1 M, 1 mL) was added and the resulting mixture was extracted with ethyl acetate two times using 10 mL of solvent each time. The organic layers were combined and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by using column chromatography (EtOAc/*n*-hexane = 10:90).

D′. General Experimental Procedure for the Synthesis of Benzo[*e*]indole Derivatives from 2-Tetralone on a 1.0 mmol Scale. In a 20 mL resealable vial was added NaOH (120 mg, 3 mmol, 3 equiv), 2-tetralone compound **1** (2 mmol, 2 equiv), amino alcohol **7** (1 mmol, 1 equiv) in toluene (3 mL). Further, the tube was sealed with a cap using a crimper. The reaction mixture was stirred at 140 °C for 40 in a preheated oil bath. After completion of the reaction, aqueous HCl (1 M, 2 mL) was added and the resulting mixture was extracted with ethyl acetate two times using 10 mL of solvent each time. The organic layers were combined and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by using column chromatography (EtOAc/*n*-hexane = 10:90).

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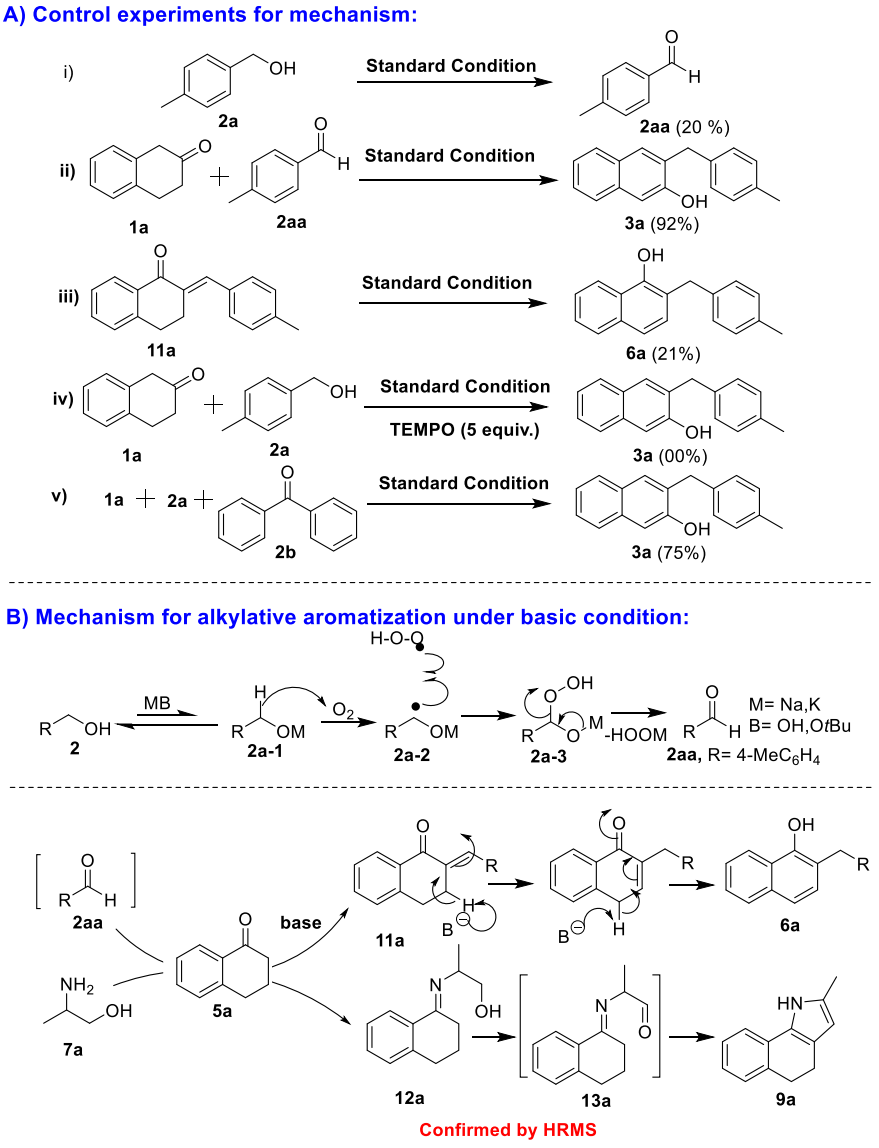
Scheme 7. Control Experiments and Plausible Mechanism for the Alkylative Aromatization



E. General Experimental Procedure for the Synthesis of Benzo[*g*]indole Derivatives from 1-Tetralone. In a 20 mL resealable vial was added NaOH (42 mg, 1.05 mmol, 3 equiv), 1-tetralone compound **5** (0.35 mmol, 1 equiv), alcohol (0.35 mmol, 1 equiv) in toluene (2 mL). Further, the tube was sealed with a cap using a crimper. The reaction mixture was stirred at 140 °C for 40 h in a preheated oil bath. After completion of the reaction, aqueous HCl (1 M, 1 mL) was added and the resulting mixture was extracted with ethyl acetate two times using 10 mL of solvent each time. The organic layers were combined and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by using column chromatography (EtOAc/*n*-hexane = 20:80).

E′. General Experimental Procedure for the Synthesis of Benzo[*g*]indole Derivatives from 1-Tetralone on a 1.0 mmol Scale. In a 20 mL resealable vial was added NaOH (120 mg, 3 mmol, 3 equiv), 1-tetralone compound **5** (1 mmol, 1 equiv), alcohol (1 mmol, 1 equiv) in toluene (3 mL). Further, the tube was sealed with a cap using a crimper. The reaction mixture was stirred at 140 °C for 40 h in a preheated oil bath. After completion of the reaction, aqueous HCl (1 M, 2 mL) was added and the resulting mixture was extracted with ethyl acetate two times using 10 mL of solvent each time. The organic layers were combined and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by using column chromatography (EtOAc/*n*-hexane = 20:80).

F. General Experimental Procedure for the Synthesis of 2-Benzyl-3*H*-benzo[*e*]indole (10a) from 2-Benzyl-4,5-dihydro-3*H*-benzo[*e*]indole (8d). The compound **8a** (39 mg, 0.15 mmol) was dissolved in 5 mL of 1,4-dioxane in a 25 mL RB flask closed with a glass stopper. DDQ (68 mg, 2.0 mmol) was added slowly. The reaction mixture was kept at room temperature with stirring for 12 h. After completion of the reaction, water was added and the resulting mixture was extracted with ethyl acetate two times using 10 mL of solvent each time. The organic layers were combined and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by using column chromatography (EtOAc/*n*-hexane = 10:90).

G. Experimental Procedure for the Synthesis of (*E*)-2-(4-Methylbenzylidene)-3,4-dihydronaphthalen-1(2*H*)-one (11a).[19] According to the reported procedure by Esguerra, K. et al.[19] A 50 mL round-bottom flask equipped with a Teflon coated stir bar was charged with the appropriate 1-tetralone (1 equiv), 4-methylbenzaldehyde (1.2 equiv), and degassed ethanol/water (9:1, 0.25 M with respect to the 1-tetralone). Sodium hydroxide (2 equiv) was then added and the reaction mixture was stirred at room temperature for 12 h. The reaction mixture was quenched by the addition of $NaHSO_4$ (10 mL, 10% by weight aqueous solution), and diluted with CH_2Cl_2 (5 mL). Then, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic fractions were dried over $MgSO_4$, and after removing the solvent under reduced pressure,

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the residue was purified by using column chromatography (EtOAc/*n*-hexane = 20:80).

H. Experimental Procedure for the Synthesis of Naphthalene-1,2-dione Derivatives (14).[22] According to the reported procedure by Ghera, E. et al.[22] A 50 mL round-bottom flask with dry oxygen was immersed in dry CH_3CN (6 mL) in a suspension of CuCl (2.47 mg, 10 mol %) for 30 min at room temperature. A solution of the corresponding naphthalen-2-ol (**3a**/**3o**) (0.25 mmol) in dry CH_3CN (3 mL) was added dropwise, and the mixture was constantly stirring with oxygen bubbling until TLC showed no further starting material (2 h). After completion of the reaction, aqueous 5% $NaHCO_3$ was added and the resulting mixture was extracted twice with chloroform using 10 mL of solvent each time. The organic layers were combined and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by using column chromatography (EtOAc/*n*-hexane = 10:90), which afforded the yellow-colored quinone.

I. Experimental Procedure for the Radical Quenching. In a 20 mL resealable vial was added NaOH (42 mg, 1.05 mmol, 3 equiv), β-tetralone compound **1** (0.70 mmol, 2 equiv), alcohol **2** (0.35 mmol, 1 equiv) in toluene (2 mL), and finally 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) (5 equiv). Further, the tube was sealed with a cap using a crimper. The reaction mixture was stirred at 140 °C for 24 h in a preheated oil bath. After completion of the reaction, aqueous HCl (1 M, 1 mL) was added and the resulting mixture was extracted with ethyl acetate two times using 10 mL of solvent each time. The organic layers were combined and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by using column chromatography (EtOAc/*n*-hexane = 10:90). From these experiments, no detection of product **3a** signifies the radical nature of the reaction.

J. Analytical Data for the Product. *3-(4-Methylbenzyl)-naphthalen-2-ol (**3a**).* Prepared according to general procedure A and A′, using 4-methylbenzyl alcohol (43 mg, 0.35 mmol)/(122 mg, 1 mmol) to afford 3-(4-methylbenzyl)naphthalen-2-ol **3a** (81 mg, 93%) using (0.35 mmol) and (191 mg, 77%) using (1 mmol) as a white solid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). Melting point: 113−115 °C. ^{1}H NMR (400 MHz, CDCl3) δ 7.72 (d, J = 8.1 Hz, 1H), 7.65 (d, J = 7.8 Hz, 1H), 7.59 (s, 1H), 7.38 (dd, J = 8.2, 1.3 Hz, 1H), 7.33−7.29 (m,1H), 7.18−7.11 (m, 5H), 4.96 (s, 1H), 4.13 (s, 2H), 2.33 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 152.6, 136.6, 136.1, 133.7, 129.7, 129.6, 129.5, 129.2, 128.8, 127.4, 126.0, 125.9, 123.7, 110.2, 36.6, 21.1. IR (neat) 1264, 1633, 3053, 3526 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{18}H_{17}O$ $(M + H)^+$ 249.1279, found 249.1284.

*3-Benzylnaphthalen-2-ol (**3b**).* Prepared according to general procedure A and A′, using benzyl alcohol (38 mg, 0.42 mmol)/ (108 mg, 1 mmol) to afford 3-benzylnaphthalen-2-ol **3b** (70 mg, 85%) using (0.35 mmol) and (187 mg, 80%) using (1 mmol) as a yellow solid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). Melting point: 80−82 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8.0 Hz, 1H), 7.68−7.62 (m, 2H), 7.43 (t, J = 7.4 Hz, 1H), 7.38−7.25 (m, 6H), 7.09 (s, 1H), 5.27 (s, 1H), 4.20 (s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 152.6, 139.9, 133.8, 129.8, 129.6, 129.2, 129.0, 128.7, 127.5, 127.5, 126.5, 126.0, 123.8, 110.1, 36.9. IR (neat) 1236, 1633, 3056, 3527 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{17}H_{15}O$ $(M + H)^+$ 235.1123, found 235.1117.

*3-(3-Methylbenzyl)naphthalen-2-ol (**3c**).* Prepared according to general procedure A and A′, using 3-methylbenzyl alcohol (43 mg, 0.35 mmol)/(122 mg, 1 mmol) to afford 3-(3-methylbenzyl)naphthalen-2-ol **3c** (62 mg, 71%) using (0.35 mmol) and (170 mg, 68%) using (1 mmol) as a yellow semisolid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 7.8 Hz, 1H), 7.67 (d, J = 8.1 Hz, 1H), 7.62 (s, 1H), 7.45−7.40 (m, 1H), 7.38−7.33 (m, 1H), 7.25−7.22 (m, 1H), 7.12−7.08 (m, 4H), 5.29 (s, 1H), 4.16 (s, 2H), 2.34 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 152.6, 139.7, 138.4, 133.7, 129.7, 129.6, 129.2, 128.6, 127.4, 127.3, 126.0, 125.9, 123.7, 110.1, 36.9, 21.5. IR (neat) 1224, 1604, 2921, 3054, 3524 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{18}H_{17}O$ $(M + H)^+$ 249.1279, found 249.1277.

*3-(4-Methoxybenzyl)naphthalen-2-ol (**3d**).* Prepared according to general procedure A and A′, using 4-methoxybenzyl alcohol (48 mg, 0.35 mmol)/(138 mg, 1 mmol) to afford 3-(4-methoxybenzyl)-naphthalen-2-ol **3d** (67 mg, 73%) using (0.35 mmol) and (197 mg, 75%) using (1 mmol) as a yellow solid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). Melting point: 98−100 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.1 Hz, 1H), 7.65 (d, J = 8.2 Hz, 1H), 7.58 (s, 1H), 7.39 (m, 1H), 7.34−7.30 (m, 1H), 7.21 (d, J = 8.6 Hz, 2H), 7.11 (s, 1H), 6.88−6.86 (m, 2H), 5.23 (s, 1H), 4.12 (s, 2H), 3.80 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 158.3, 152.6, 133.7, 131.8, 129.9, 129.6, 129.2, 127.4, 126.0, 125.9, 123.7, 114.2, 110.1, 55.4, 36.1. IR (neat) 1214, 1611, 2921, 3401 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{18}H_{17}O_2$ $(M + H)^+$ 265.1229, found 265.1237.

*3-([1,1′-Biphenyl]-4-ylmethyl)naphthalen-2-ol (**3e**).* Prepared according to general procedure A and A′, using biphenyl-4-methanol (64 mg, 0.35 mmol)/(184 mg, 1 mmol) to afford 33-([1,1′-biphenyl]-4-ylmethyl)naphthalen-2-ol **3e** (61 mg, 56%) using (0.35 mmol) and (180 mg, 58%) using (1 mmol) as a yellow solid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). Melting point: 145−147 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.1 Hz, 1H), 7.69−7.64 (m, 2H), 7.61−7.55 (m, 4H), 7.47−7.40 (m, 3H), 7.38−7.32 (m, 4H), 7.14 (s, 1H), 5.14 (s, 1H), 4.22 (s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 152.57, 141.06, 139.45, 139.06, 133.82, 129.89, 129.47, 129.37, 129.30, 128.87, 127.51, 127.47, 127.26, 127.16, 126.08, 126.04, 123.84, 110.17, 36.63. IR (neat) 1264, 1632, 3054, 3527 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{23}H_{19}O$ $(M + H)^+$ 311.1436, found 311.1442.

*3-(3-Phenoxybenzyl)naphthalen-2-ol (**3f**).* Prepared according to general procedure A and A′, using 3-phenoxybenzyl alcohol (70 mg, 0.35 mmol)/(200 mg, 1 mmol) to afford 3-(3-phenoxybenzyl)-naphthalen-2-ol **3f** (89 mg, 78%) using (0.35 mmol) and (240 mg, 74%) using (1 mmol) as a yellow solid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). Melting point: 100−102 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78−7.72 (m, 1H), 7.67−7.61 (m, 2H), 7.47−7.27 (m, 5H), 7.16−7.07 (m, 6H), 6.93−6.92 (m, 1H). 5.49 (s, 1H), 4.18 (s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 157.4, 157.2, 152.4, 142.2, 133.7, 129.8, 129.7, 129.3, 129.2, 128.6, 127.4, 126.0, 125.9, 123.9, 123.8, 123.2, 119.7, 118.9, 116.7, 109.9, 36.7. IR (neat) 1236, 1486, 3055, 3526 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{23}H_{19}O_2$ $(M + H)^+$ 327.1385, found 327.1384.

*3-(Benzo[d][1,3]dioxol-5-ylmethyl)naphthalen-2-ol (**3g**).* Prepared according to general procedure A and A′, using piperonyl alcohol (53 mg, 0.35 mmol)/(152 mg, 1 mmol) to afford 3-(benzo[*d*][1,3]dioxol-5-ylmethyl)naphthalen-2-ol **3g** (81 mg, 83%) using (0.35 mmol) and (224 mg, 80%) using (1 mmol) as a yellow solid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). Melting point: 78−80 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 8.1 Hz, 1H), 7.59 (s, 1H), 7.42 (t, J = 7.5 Hz, 1H), 7.36−7.32 (m, 1H), 7.09 (s, 1H), 6.80−6.78 (m, 3H), 5.93 (s, 2H), 5.60 (s, 1H), 4.10 (s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 152.5, 147.8, 146.1, 133.8, 133.7, 129.7, 129.5, 129.1, 127.4, 125.9, 123.7, 121.7, 110.0, 109.4, 108.3, 100.9, 36.5. IR (neat) 1244, 1491, 1633, 2916, 3664 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{18}H_{15}O_3$ $(M + H)^+$ 279.1021, found 279.1021.

*3-(4-Fluorobenzyl)naphthalen-2-ol (**3h**).* Prepared according to general procedure A and A′, using 4-fluorobenzyl alcohol (44 mg, 0.35 mmol)/(126 mg, 1 mmol) to afford 3-(4-fluorobenzyl)naphthalen-2-ol **3h** (70 mg, 80%) using (0.35 mmol) and (195 mg, 77%) using (1 mmol) as a white solid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). Melting point: 77−79 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 7.4 Hz, 1H), 7.66 (d, J = 8.2 Hz, 1H), 7.57 (s, 1H), 7.42 m, 1H), 7.37−7.32 (m, 1H), 7.25 (m, 2H), 7.10 (s, 1H), 7.03−6.98 (m, 2H), 5.05 (s, 1H), 4.14 (s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 161.7 (d, J = 244.2 Hz), 152.4, 135.7 (d, J = 2.7 Hz), 133.8, 130.4 (d, J = 7.7 Hz), 129.7, 129.5, 129.3, 127.5, 126.1 (d, J = 14.5 Hz), 123.9, 115.5, 115.3, 110.1, 36.1. IR (neat) 1222, 1508, 3054, 3649 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{18}H_{17}O_2$ $(M + H)^+$ 265.1229, found 265.1237.

*3-(3-(Trifluoromethyl)benzyl)naphthalen-2-ol (**3i**).* Prepared according to general procedure A and A′, using 3-(trifluoromethyl)benzyl alcohol (62 mg, 0.35 mmol)/(176 mg, 1 mmol) to afford 3-(3-

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(trifluoromethyl)benzyl)naphthalen-2-ol **3i** (62 mg, 58%) using (0.35 mmol) and (156 mg, 52%) using (1 mmol) as a yellow solid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). Melting point: 90−92 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.1 Hz, 1H), 7.65 (d, J = 8.1 Hz, 1H), 7.58 (m, 2H), 7.49−738 (m, 4H), 7.33 (t, J = 7.6 Hz, 1H), 7.10 (s, 1H), 5.05 (s, 1H), 4.21 (s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 152.2, 141.3, 133.8, 132.4, 130.9 (q, J = 32.0 Hz),130.0, 129.3, 129.0, 128.9, 127.6, 126.3, 126.0, 125.8 (q, J = 3.6 Hz), 124.4 (q, J = 270.5 Hz), 124.0, 123.2 (q, J = 3.8 Hz), 110.0, 36.7. IR (neat) 1122, 1358, 3056, 3528 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{18}H_{14}F_3O$ (M + H)$^+$ 303.0997, found 303.1008.

*3-(3-Chlorobenzyl)naphthalen-2-ol (**3j**).* Prepared according to general procedure A and A′, using 3-chlorobenzyl alcohol (50 mg, 0.35 mmol)/(143 mg, 1 mmol) to afford 3-(3-chlorobenzyl)naphthalen-2-ol **3j** (77 mg, 82%) using (0.35 mmol) and (200 mg, 74%) using (1 mmol) as a white solid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). Melting point: 85−87 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.1 Hz, 1H), 7.65 (d, J = 8.2 Hz, 1H), 7.58 (s, 1H), 7.41 (t, J = 7.5 Hz, 1H), 7.35−7.31 (m, 1H), 7.27 (s, 1H), 7.25−7.16 (m, 3H), 7.09 (s, 1H), 5.15 (s, 1H), 4.13 (s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 152.3, 142.3, 134.4, 133.8, 129.9, 129.8, 129.2, 129.0, 128.9, 127.5, 127.1, 126.5, 126.2, 125.9, 123.9, 110.0, 36.5. IR (neat) 1264, 1515, 3056, 3672 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{17}H_{14}ClO$ (M + H)$^+$ 269.0733, found 269.0725.

*3-(2-Bromobenzyl)naphthalen-2-ol (**3k**).* Prepared according to general procedure A and A′, using 2-bromobenzyl alcohol (65 mg, 0.35 mmol)/(187 mg, 1 mmol) to afford 3-(2-bromobenzyl)naphthalen-2-ol **3k** (90 mg, 82%) using (0.35 mmol) and (240 mg, 77%) using (1 mmol) as a yellow semisolid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71−7.62 (m, 3H), 7.48 (s, 1H), 7.43−7.39 (m, 1H), 7.34−7.30 (m, 1H), 7.25−7.21 (m, 1H), 7.15−7.11 (m, 3H), 5.31 (s, 1H), 4.28 (s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 152.5, 139.3, 133.8, 132.9, 130.8, 129.9, 129.2, 128.1, 128.1, 127.7, 127.6, 126.1, 126.0, 125.1, 123.8, 109.8, 36.7. IR (neat) 1225, 1632, 3056, 3527 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{17}H_{14}BrO$ (M + H)$^+$ 313.0228, found 313.0221.

*3-Propylnaphthalen-2-ol (**3l**).* Prepared according to general procedure A and A′, using propyl alcohol (21 mg, 0.35 mmol)/(60 mg, 1 mmol) to afford 3-propylnaphthalen-2-ol **3l** (47 mg, 72%) using (0.35 mmol) and (127 mg, 68%) using (1 mmol) as a yellow solid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). Melting point: 34−36 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.1 Hz, 1H), 7.65 (d, J = 8.2 Hz, 1H), 7.61 (s, 1H), 7.40 (m, 1H), 7.35−7.31 (m, 1H), 7.08 (s, 1H), 5.41 (s, 1H), 2.79 (t, J = 7.2 Hz, 2H), 1.85−1.73 (m, 2H), 1.05 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 152.7, 133.4, 131.1, 129.2, 128.8, 127.3, 125.9, 125.7, 123.6, 109.4, 32.7, 23.0, 14.2. IR (neat) 1221, 1454, 1633, 2928, 2959, 3528 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{13}H_{15}O$ (M + H)$^+$ 187.1123, found 187.1125.

*3-Butylnaphthalen-2-ol (**3m**).* Prepared according to general procedure A and A′, using butyl alcohol (26 mg, 0.35 mmol)/(72 mg, 1 mmol) to afford 3-butylnaphthalen-2-ol **3m** (45 mg, 64%) using (0.35 mmol) and (130 mg, 65%) using (1 mmol) as a white solid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). Melting point: 78−80 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.1 Hz, 1H), 7.64 (d, J = 8.1 Hz, 1H), 7.59 (s, 1H), 7.40−7.36 (m, 1H), 7.33−7.31 (m, 1H), 7.08 (s, 1H), 5.16 (s, 1H), 2.79 (t, J = 7.6 Hz, 2H), 1.75−1.67 (m, 2H), 1.50−1.40 (m, 2H), 0.98 (t, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 152.6, 133.4, 131.2, 129.3, 128.7, 127.3, 125.9, 125.7, 123.6, 109.4, 32.0, 30.4, 22.8, 14.2. IR (neat) 1193, 1515, 1632, 2925, 3510 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{14}H_{17}O$ (M + H)$^+$ 201.1279, found 201.1272.

*3-Hexylnaphthalen-2-ol (**3n**).* Prepared according to general procedure A and A′, using hexyl alcohol (36 mg, 0.35 mmol)/(102 mg, 1 mmol) to afford 3-hexylnaphthalen-2-ol **3n** (64 mg, 80%) using (0.35 mmol) and (174 mg, 76%) using (1 mmol) as a yellow solid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). Melting point: 78−80 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.1 Hz, 1H), 7.64 (d, J = 8.1 Hz, 1H), 7.58 (s, 1H), 7.37 (ddd, J = 8.2, 6.9, 1.3 Hz, 1H), 7.30 (ddd, J = 8.0, 6.9, 1.2 Hz, 1H), 7.09 (s, 1H), 4.96 (s, 1H), 2.77 (t, J = 7.6 Hz, 2H), 1.71 (m, 2H), 1.44−1.32 (m, 6H), 0.90 (t, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 152.6, 133.4, 131.2, 129.3, 128.7, 127.3, 125.9, 125.7, 123.6, 109.4, 31.9, 30.7, 29.8, 29.4, 22.8, 14.2. IR (neat) 1264, 1515, 2927, 3515 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{16}H_{21}O$ (M + H)$^+$ 229.1592, found 229.1610.

*3-(3-Methylbut-2-en-1-yl)naphthalen-2-ol (**3o**).* Prepared according to general procedure A and A′, using 3-methylbut-2-en-1-ol (30 mg, 0.35 mmol)/(86 mg, 1 mmol) to afford 3-(3-methylbut-2-en-1-yl)naphthalen-2-ol **3o** (61 mg, 82%) using (0.35 mmol) and (164 mg, 77%) using (1 mmol) as a yellow solid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). Melting point: 78−80 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.1 Hz, 1H), 7.66 (d, J = 8.1 Hz, 1H), 7.61 (s, 1H), 7.43−7.38 (m, 1H), 7.34 (ddd, J = 8.1, 6.9, 1.3 Hz, 1H), 7.14 (s, 1H), 5.61 (s, 1H), 5.48−5.43 (m, 1H), 3.56 (d, J = 7.1 Hz, 2H), 1.84 (s, 6H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 153.1, 135.0, 133.6, 129.6, 129.2, 128.5, 127.3, 126.1, 125.8, 123.6, 121.8, 110.0, 30.1, 26.0, 18.1. IR (neat) 1376, 1664, 2921, 3443 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{15}H_{17}O$ (M + H)$^+$ 213.1279, found 213.1270.

*3-(Furan-2-ylmethyl)naphthalen-2-ol (**3p**).* Prepared according to general procedure A and A′, using furfuryl alcohol (34 mg, 0.35 mmol)/(98 mg, 1 mmol) to afford 3-(furan-2-ylmethyl)naphthalen-2-ol **3p** (53 mg, 67%) using (0.35 mmol) and (143 mg, 64%) using (1 mmol) as a yellow semisolid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.1 Hz, 1H), 7.66 (d, J = 8.3 Hz, 1H), 7.63 (s, 1H), 7.44−7.31 (m, 3H), 7.15 (s, 1H), 6.35 (s, 1H), 6.12 (d, J = 3.1 Hz, 1H), 5.55 (s, 1H), 4.18 (s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 153.6, 152.3, 141.6, 133.9, 129.6, 129.2, 127.5, 126.9, 126.2, 126.1, 123.8, 110.6, 110.5, 106.6, 29.7. IR (neat) 1229, 1511, 1699, 3055, 3526 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{15}H_{13}O_2$ (M + H)$^+$ 225.0916, found 225.0918.

*3-(Thiophen-2-ylmethyl)naphthalen-2-ol (**3q**).* Prepared according to general procedure A and A′, using 2-thiophenemethanol (40 mg, 0.35 mmol)/(114 mg, 1 mmol) to afford 3-(thiophen-2-ylmethyl)-naphthalen-2-ol **3q** (77 mg, 91%) using (0.35 mmol) and (201 mg, 87%) using (1 mmol) as a yellow semisolid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8.1 Hz, 1H), 7.66 (d, J = 5.5 Hz, 2H), 7.45−7.41 (m, 1H), 7.37−7.34 (m, 1H), 7.21 (d, J = 4.8 Hz, 1H), 7.11 (s, 1H), 6.99−6.92 (m, 2H), 5.30 (s, 1H), 4.37 (s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 152.3, 142.9, 133.9, 129.4, 129.2, 129.0, 127.6, 127.0, 126.2, 126.0, 125.6, 124.4, 123.9, 110.2, 31.2. IR (neat) 1262, 1632, 3054, 3524 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{15}H_{13}OS$ (M + H)$^+$ 241.0687, found 241.0686.

*3-(3-Phenylpropyl)naphthalen-2-ol (**3r**).* Prepared according to general procedure A and A′, using 3-phenyl-1-propanol (48 mg, 0.35 mmol)/(136 mg, 1 mmol) to afford 3-(3-phenylpropyl)naphthalen-2-ol **3o** (72 mg, 78%) using (0.35 mmol) and (185 mg, 71%) using (1 mmol) as a white solid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). Melting point: 60−62 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 7.9 Hz, 1H), 7.49 (d, J = 8.1 Hz, 1H), 7.45 (s, 1H), 7.19 (m, 7H), 6.88 (s, 1H), 4.96 (s, 1H), 2.70 (t, J = 7.6 Hz, 2H), 2.61 (t, J = 7.7 Hz, 2H), 1.98−1.86 (m, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 152.6, 142.4, 133.4, 130.8, 129.3, 128.8, 128.6, 128.5, 127.3, 125.9, 125.8, 123.7, 109.5, 35.8, 31.3, 30.2. IR (neat) 1264, 1515, 2930, 3527 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{19}H_{19}O$ (M + H)$^+$ 263.1436, found 263.1429.

*3-Benzyl-7-methoxynaphthalen-2-ol (**3s**).* Prepared according to general procedure A and A′, using benzyl alcohol (38 mg, 0.35 mmol)/(108 mg, 1 mmol) to afford 3-benzyl-7-methoxynaphthalen-2-ol **3s** (81 mg, 88%) using (0.35 mmol) and (225 mg, 85%) using (1 mmol) as a white solid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). Melting point: 136−138 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.6 Hz, 1H), 7.49 (s, 1H), 7.32−7.21 (m, 5H), 7.02 (s, 1H), 6.98−6.95 (m, 2H), 4.97 (s, 1H), 4.12 (s, 2H), 3.88 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 158.0, 153.2, 140.0, 135.0, 129.7, 129.0, 128.9, 128.8, 126.8, 126.5, 124.7, 116.4, 109.5, 104.4, 55.4, 36.9. IR (neat) 1227, 1593, 2354, 2920, 3360 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{18}H_{17}O_2$ (M + H)$^+$ 265.1229, found 265.1223.

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*7-Methoxy-3-(4-methylbenzyl)naphthalen-2-ol (**3t**).* Prepared according to general procedure A and A′, using 4-methylbenzyl alcohol (43 mg, 0.35 mmol)/(122 mg, 1 mmol) to afford 7-methoxy-3-(4-methylbenzyl)naphthalen-2-ol **3t** (90 mg, 92%) using (0.35 mmol) and (242 mg, 87%) using (1 mmol) as a brown solid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). Melting point: 135−134 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.8 Hz, 1H), 7.51 (s, 1H), 7.14 (q, J = 8.1 Hz, 4H), 7.03 (s, 1H), 7.00−6.95 (m, 2H), 5.03 (s, 1H), 4.09 (s, 2H), 3.90 (s, 3H), 2.33 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 157.9, 153.2, 136.8, 136.1, 135.0, 129.6, 129.5, 129.0, 128.8, 127.0, 124.6, 116.4, 109.6, 104.4, 55.3, 36.5, 21.2. IR (neat) 1219, 1514, 1635, 2925, 3673 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{19}H_{19}O_2$ $(M + H)^+$ 279.1385, found 279.1380.

*3-(4-Fluorobenzyl)-7-methoxynaphthalen-2-ol (**3u**).* Prepared according to general procedure A and A′, using 4-fluorobenzyl alcohol (44 mg, 0.35 mmol)/(126 mg, 1 mmol) to afford 3-(4-fluorobenzyl)-7-methoxynaphthalen-2-ol **3u** (86 mg, 87%) using (0.35 mmol) and (235 mg, 83%) using (1 mmol) as a white solid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). Melting point: 136−138 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.8 Hz, 1H), 7.47 (s, 1H), 7.24−7.19 (m, 2H), 7.01 (s, 1H), 7.00−6.94 (m, 4H), 5.00 (s, 1H), 4.08 (s, 2H), 3.89 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 161.7 (d, J = 244.1 Hz), 158.1, 153.0, 135.9 (d, J = 3.1 Hz), 135.1, 130.3 (d, J = 7.8 Hz), 129.6, 129.0, 126.8, 124.7, 116.5, 115.4 (d, J = 21.2 Hz).109.4, 104.4, 55.4, 36.0. IR (neat) 1221, 1507, 1636, 2853, 3524 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{18}H_{16}FO_2$ $(M + H)^+$ 283.1134, found 283.1129.

*3-Benzyl-6-methoxynaphthalen-2-ol (**3v**).* Prepared according to general procedure A and A′, using benzyl alcohol (38 mg, 0.35 mmol)/(108 mg, 1 mmol) to afford 3-benzyl-6-methoxynaphthalen-2-ol **3v** (66 mg, 72%) using (0.35 mmol) and (180 mg, 68%) using (1 mmol) as a white solid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). Melting point: 95−97 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (d, J = 8.9 Hz, 1H), 7.38 (s, 1H), 7.29 (d, J = 4.5 Hz, 1H), 7.25−7.15 (m, 5H), 7.00−6.95 (m, 2H), 4.89 (s, 1H), 4.06 (s, 2H), 3.79 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 156.3, 150.9, 140.0, 130.1, 130.0, 129.0, 129.0, 128.8, 128.6, 127.5, 126.5, 118.8, 110.4, 105.8, 55.4, 37.0. IR (neat) 1263, 1515, 1609, 2927, 3672 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{18}H_{17}O_2$ $(M + H)^+$ 265.1229, found 265.1217.

*6-Methoxy-3-(3-methylbenzyl)naphthalen-2-ol (**3w**).* Prepared according to general procedure A and A′, using 3-methylbenzyl alcohol (43 mg, 0.35 mmol)/(122 mg, 1 mmol) to afford 6-methoxy-3-(3-methylbenzyl)naphthalen-2-ol **3w** (49 mg, 50%) using (0.35 mmol) and (155 mg, 56%) using (1 mmol) as a yellow semisolid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 8.8 Hz, 1H), 7.49 (s, 1H), 7.23 (m, 1H), 7.11−7.07 (m, 6H), 5.11 (s, 1H), 4.13 (s, 2H), 3.90 (s, 3H), 2.34 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 156.2, 151.0, 139.8, 138.4, 130.1, 130.0, 129.7, 129.0, 128.7, 128.6, 127.5, 127.3, 126.0, 118.7, 110.4, 105.8, 55.4, 37.0, 21.5. IR (neat) 1249, 1609, 2918, 3398 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{19}H_{18}O_2$ $(M)^+$ 278.1307, found 278.1295.

*3-Benzyl-6-bromonaphthalen-2-ol (**3x**).* Prepared according to general procedure A and A′, using benzyl alcohol (38 mg, 0.35 mmol)/(108 mg, 1 mmol) to afford 3-benzyl-6-bromonaphthalen-2-ol **3x** (60 mg, 54%) using (0.35 mmol) and (156 mg, 50%) using (1 mmol) as a white solid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). Melting point: 95−97 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.40−7.31 (m, 3H), 7.25−7.09 (m, 5H), 6.94 (m, 1H), 5.06 (s, 1H), 4.03 (s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 152.9, 139.5, 132.2, 130.8, 130.3, 129.5, 129.3, 129.0, 128.9, 128.8, 127.7, 126.7, 117.3, 110.1, 36.9. IR (neat) 1264, 1514, 3057, 3563 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{17}H_{14}BrO$ $(M + H)^+$ 313.0228, found 313.0235.

*6-Bromo-3-(3-chlorobenzyl)naphthalen-2-ol (**3y**).* Prepared according to general procedure A and A′, using 3-chlorobenzyl alcohol (50 mg, 0.35 mmol)/(142 mg, 1 mmol) to afford 6-bromo-3-(3-chlorobenzyl)naphthalen-2-ol **3y** (30 mg, 25%) using (0.35 mmol) and (100 mg, 29%) using (1 mmol) as a white solid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). Melting point: 118−120 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 1.6 Hz, 1H), 7.51 (d, J = 8.7 Hz, 1H), 7.46−7.44 (m, 2H), 7.26−7.20 (m, 3H), 7.15−7.12 (m, 1H), 7.07 (s, 1H), 5.26 (s, 1H), 4.11 (s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 152.7, 141.9, 134.5, 132.2, 130.3, 130.2, 129.9, 129.5, 129.5, 129.1, 129.0, 127.6, 127.2, 126.7, 117.4, 110.0, 36.5. IR (neat) 1227, 1593, 2920, 3360 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{17}H_{13}BrClO$ $(M + H)^+$ 346.9838, found 346.9853.

*2-Benzylnaphthalen-1-ol (**6a**).* Prepared according to general procedure C and C′, using benzyl alcohol (76 mg, 0.70 mmol)/(216 mg, 2 mmol) to afford 2-benzylnaphthalen-1-ol **6a** (68 mg, 83%) using (0.35 mmol) and (185 mg, 79%) using (1 mmol) as a white solid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). Melting point: 72−74 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03−8.01 (m, 1H), 7.74−7.70 (m, 1H), 7.37 (m, 3H), 7.25−7.15 (m, 6H), 5.06 (s, 1H), 4.09 (s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 149.1, 139.4, 133.9, 129.1, 129.0, 128.7, 127.8, 126.9, 125.9, 125.5, 125.0, 121.2, 120.7, 120.0, 36.9. IR (neat) 1264, 1699, 3055, 3649 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{17}H_{15}O$ $(M + H)^+$ 235.1123, found 235.1121.

*2-(4-Methylbenzyl)naphthalen-1-ol (**6b**).* Prepared according to general procedure C and C′, using 4-methylbenzyl alcohol (86 mg, 0.70 mmol)/(244 mg, 2 mmol) to afford 2-(4-methylbenzyl)naphthalen-1-ol **6b** (42 mg, 48%) using (0.35 mmol) and (125 mg, 50%) using (1 mmol) as a yellow solid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). Melting point: 68−70 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12−8.10 (m, 1H), 7.81−7.79 (m, 1H), 7.48−7.43 (m, 3H), 7.29 (d, J = 8.3 Hz, 1H), 7.14 (q, J = 8.2 Hz, 4H), 5.18 (s, 1H), 4.14 (s, 2H), 2.33 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 149.2, 136.6, 136.2, 133.9, 129.8, 129.1, 128.6, 127.8, 125.9, 125.5, 125.0, 121.3, 120.5, 120.2, 36.6, 21.1. IR (neat) 1264, 1652, 2924, 3665 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{18}H_{17}O$ $(M + H)^+$ 249.1279, found 249.1275.

*2-(3-Methylbenzyl)naphthalen-1-ol (**6c**).* Prepared according to general procedure C and C′, using 3-methylbenzyl alcohol (86 mg, 0.70 mmol)/(244 mg, 2 mmol) to afford 2-(3-methylbenzyl)naphthalen-1-ol **6c** (50 mg, 58%) using (0.35 mmol) and (136 mg, 55%) using (1 mmol) as a yellow semisolid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01−7.99 (m, 1H), 7.70−7.66 (m, 1H), 7.36−7.31 (m, 3H), 7.17 (d, J = 8.3 Hz, 1H), 7.10−7.06 (m, 1H), 6.94 (d, J = 7.5 Hz, 3H), 5.10 (s, 1H), 4.00 (s, 2H), 2.18 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 149.2, 139.3, 138.8, 133.9, 129.4, 129.1, 129.0, 127.8, 127.7, 125.9, 125.7, 125.4, 125.0, 121.3, 120.6, 120.1, 36.9, 21.5. IR (neat) 1263, 1657, 2921, 3525 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{18}H_{17}O$ $(M + H)^+$ 249.1279, found 249.1283.

*2-(4-Methoxybenzyl)naphthalen-1-ol (**6d**).* Prepared according to general procedure C and C′, using 4-methoxybenzyl alcohol (97 mg, 0.70 mmol)/(276 mg, 2 mmol) to afford 2-(4-methoxybenzyl)-naphthalen-1-ol **6d** (61 mg, 66%) using (0.35 mmol) and (185 mg, 70%) using (1 mmol) as a yellow solid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). Melting point: 79−81 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10−8.06 (m, 1H), 7.78−7.75 (m, 1H), 7.44−7.39 (m, 3H), 7.23 (d, J = 5.8 Hz, 1H), 7.14 (d, J = 8.8 Hz, 2H), 6.83−6.80 (m, 2H), 5.15 (s, 1H), 4.08 (s, 2H), 3.75 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 158.6, 149.2, 133.9, 131.2, 129.7, 129.0, 127.8, 125.9, 125.5, 125.0, 121.3, 120.5, 120.2, 114.5, 55.4, 36.2. IR (neat) 1242, 1595, 2921, 3471 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{18}H_{17}O_2$ $(M + H)^+$ 265.1229, found 265.1223.

*2-(Benzo[d][1,3]dioxol-5-ylmethyl)naphthalen-1-ol (**6e**).* Prepared according to general procedure C and C′, using piperonyl alcohol (106 mg, 0.70 mmol)/(304 mg, 2 mmol) to afford 2-(benzo[*d*][1,3]dioxol-5-ylmethyl)naphthalen-1-ol **6e** (54 mg, 56%) using (0.35 mmol) and (156 mg, 56%) using (1 mmol) as a yellow solid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). Melting point: 94−96 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13−8.09 (m, 1H), 7.80−7.82 (m, 1H), 7.49−7.43 (m, 3H), 7.28 (d, J = 8.3 Hz, 1H), 6.75 (s, 2H), 6.71 (s, 1H), 5.92 (s, 2H), 5.25 (s, 1H), 4.08 (s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 149.2, 148.4, 146.6, 133.9, 133.2, 128.9, 127.8, 125.9, 125.5, 124.9, 121.4, 121.2, 120.6, 120.1, 109.2, 108.6, 101.2, 36.8. IR (neat) 1239, 1239, 1391, 1486, 2923, 3400 cm^{-1}.

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HRMS (ESI-TOF) m/z calculated for $C_{18}H_{15}O_3$ $(M + H)^+$ 279.1021, found 279.1021.

*2-(3-Chlorobenzyl)naphthalen-1-ol (**6f**).* Prepared according to general procedure C and C′, using hexylalcohol (97 mg, 0.70 mmol)/(285 mg, 2 mmol) to afford 2-(3-chlorobenzyl)naphthalen-1-ol **6f** (100 mg, 47%) using (0.35 mmol) and (120 mg, 45%) using (1 mmol) as a white solid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). Melting point: 74−76 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10−8.03 (m, 1H), 7.82 (dd, J = 6.7, 2.7 Hz, 1H), 7.52−7.43 (m, 3H), 7.23 (m, 4H), 7.14−7.12 (m, 1H), 5.15 (s, 1H), 4.15 (s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 148.9, 141.9, 134.8, 133.9, 130.1, 129.1, 128.8, 128.0, 126.9, 126.8, 126.1, 125.7, 124.8, 121.0, 120.8, 119.6, 36.3. IR (neat) 1264, 1396, 1575, 1716, 2926, 3400 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{17}H_{13}ClO$ $(M)^+$ 268.0655, found 268.0637.

*2-(4-Fluorobenzyl)naphthalen-1-ol (**6g**).* Prepared according to general procedure C and C′, using 4-fluorobenzyl alcohol (88 mg, 0.70 mmol)/(252 mg, 2 mmol) to afford 2-(4-fluorobenzyl)naphthalen-1-ol **6g** (48 mg, 55%) using (0.35 mmol) and (150 mg, 59%) using (1 mmol) as a yellow solid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). Melting point: 75−77 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.9−8.07 (m, 1H), 7.83−7.80 (m, 1H), 7.51−7.43 (m, 3H), 7.27−7.25 (m, 1H), 7.22−7.19 (m, 2H), 7.01−6.97 (m, 2H), 5.13 (s, 1H), 4.14 (s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 161.8 (d, J = 245.0 Hz), 148.9, 135.2 (d, J = 3.2 Hz), 133.9, 130.1 (d, J = 7.8 Hz), 128.8, 127.9, 126.0, 125.7, 124.8, 121.0, 120.8, 120.0, 115.8 (d, J = 21.4 Hz), 35.9. IR (neat) 1266, 1507, 1652, 3058, 3565 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{17}H_{14}FO$ $(M + H)^+$ 253.1028, found 253.1027.

*2-(3-(Trifluoromethyl)benzyl)naphthalen-1-ol (**6h**).* Prepared according to general procedure C and C′, using 3-(trifluoromethyl)benzyl alcohol (123 mg, 0.70 mmol)/(352 mg, 2 mmol) to afford 2-(3-(trifluoromethyl)benzyl)naphthalen-1-ol **6h** (51 mg, 48%) using (0.35 mmol) and (136 mg, 45%) using (1 mmol) as a white solid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). Melting point: 85−87 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (m, 1H), 7.83 (dd, J = 7.0, 2.3 Hz, 1H), 7.54−7.45 (m, 5H), 7.40 (m, 2H), 7.26 (m, 1H), 5.17 (s, 1H), 4.23 (s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 148.7, 141.0, 133.9, 132.1, 131.1 (q, J = 32 Hz), 129.2, 128.7, 128.1, 126.1, 125.8, 125.5 (q, J = 3.5 Hz), 124.7, 124.3 (q, J = 271 Hz), 123.5 (q, J = 3.6 Hz), 121.1, 120.2, 119.8, 36.2. IR (neat) 1034, 1239, 1486, 1574, 2923, 3500 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{18}H_{14}F_3O$ $(M + H)^+$ 303.0997, found 303.0996.

*2-(Thiophen-2-ylmethyl)naphthalen-1-ol (**6i**).* Prepared according to general procedure C and C′, using 2-thiophenemethanol (80 mg, 0.70 mmol)/(228 mg, 2 mmol) to afford 2-(thiophen-2-ylmethyl)-naphthalen-1-ol **6i** (59 mg, 70%) using (0.35 mmol) and (151 mg, 67%) using (1 mmol) as a yellow solid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). Melting point: 56−58 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14−8.12 (m, 1H), 7.82 (m, 1H), 7.50−7.46 (m, 3H), 7.33 (d, J = 8.4 Hz, 1H), 7.21 (d, J = 4.7 Hz, 1H), 6.95 (t, J = 4.2 Hz, 1H), 6.90 (d, J = 2.4 Hz, 1H), 5.36 (d, J = 3.2 Hz, 1H), 4.35 (s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 149.2, 142.6, 134.0, 128.4, 127.9, 127.1, 126.1, 125.6, 125.6, 125.0, 121.2, 120.8, 119.8, 31.5. IR (neat) 3612, 3059, 1512, 1392, 1266 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{15}H_{13}SO$ $(M + H)^+$ 241.0687, found 241.0668.

*2-Methyl-4,5-dihydro-3H-benzo[e]indole (**8a**).* Prepared according to general procedure D and D′, using 2-aminopropan-1-ol (26 mg, 0.35 mmol)/(75 mg, 1 mmol) to afford 2-methyl-4,5-dihydro-3*H*-benzo-[*e*]indole **8a** (43 mg, 67%) using (0.35 mmol) and (120 mg, 65%) using (1 mmol) as a brown liquid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.34 (d, J = 7.6 Hz, 1H), 7.20 (dd, J = 15.1, 7.4 Hz, 2H), 7.06−7.02 (m, 1H), 6.17 (s, 1H), 3.01 (t, J = 7.8 Hz, 2H), 2.76 (t, J = 7.8 Hz, 2H), 2.29 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 133.6, 132.9, 128.0, 127.9, 127.2, 126.7, 124.1, 121.4, 118.5, 101.2, 29.8, 21.8, 13.2. IR (neat) 1375, 1536, 1699, 2925, 3401 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{13}H_{13}N$ $(M)^+$ 183.1048, found 183.1042.

*2-Ethyl-4,5-dihydro-3H-benzo[e]indole (**8b**).* Prepared according to general procedure D and D′, using 2-amino-1-butanol (31 mg, 0.35 mmol)/(89 mg, 1 mmol) to afford 2-ethyl-4,5-dihydro-3*H*-benzo[*e*]-indole **8b** (43 mg, 62%) using (0.35 mmol) and (128 mg, 65%) using (1 mmol) as a brown solid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). Melting point: 89−91 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.35 (d, J = 7.6 Hz, 1H), 7.20 (dd, J = 15.7, 7.8 Hz, 2H), 7.05−7.01 (m, 1H), 6.20 (d, J = 2.2 Hz, 1H), 3.02 (t, J = 7.7 Hz, 2H), 2.78 (t, J = 7.7 Hz, 2H), 2.65 (q, J = 7.6 Hz, 2H), 1.30 (d, J = 7.6 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 133.9, 133.6, 132.9, 127.9, 127.8, 126.7, 124.1, 121.4, 118.3, 99.5, 29.8, 21.9, 21.1, 13.8. IR (neat) 1456, 1538, 1699, 2925, 3402 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{14}H_{15}N$ $(M)^+$ 197.1204, found 197.1188.

*2-(sec-Butyl)-4,5-dihydro-3H-benzo[e]indole (**8c**).* Prepared according to general procedure D and D′, using 2-amino-3-methylpentan-1-ol (41 mg, 0.35 mmol)/(117 mg, 1 mmol) to afford 2-(*sec*-butyl)-4,5-dihydro-3*H*-benzo[*e*]indole **8c** (42 mg, 53%) using (0.35 mmol) and (125 mg, 55%) using (1 mmol) as a yellow semisolid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (s, 1H), 7.33 (d, J = 7.7 Hz, 1H), 7.17 (dd, J = 16.2, 7.9 Hz, 2H), 7.00 (td, J = 7.4, 1.1 Hz, 1H), 6.17 (d, J = 2.5 Hz, 1H), 3.01 (t, J = 7.7 Hz, 2H), 2.79 (m, 2H), 2.68 (h, J = 7.0 Hz, 1H), 1.70−1.53 (m, 2H), 1.29 (d, J = 6.9 Hz, 3H), 0.95 (t, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 137.5, 133.7, 132.7, 127.9, 127.5, 126.7, 124.1, 121.4, 118.1, 99.0, 34.5, 30.3, 29.8, 22.0, 20.2, 12.0. IR (neat) 1278, 1514, 1698, 2961, 3407 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{16}H_{19}N$ $(M)^+$ 225.1517, found 225.1511.

*2-Benzyl-4,5-dihydro-3H-benzo[e]indole (**8d**).* Prepared according to general procedure D and D′, using (*S*)-(−)-2-Amino-3-phenyl-1-propanol (53 mg, 0.35 mmol)/(151 mg, 1 mmol) to afford 2-benzyl-4,5-dihydro-3*H*-benzo[*e*]indole **8d** (55 mg, 61%) using (0.35 mmol) and (150 mg, 58%) using (1 mmol) as a pink solid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). Melting point: 88−90 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.34−7.26 (m, 6H), 7.19−7.13 (m, 2H), 7.03−6.99 (m, 1H), 6.25 (s, 1H), 3.99 (s, 2H), 2.98 (t, J = 7.7 Hz, 2H), 2.73 (t, J = 7.7 Hz, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 139.6, 133.5, 132.9, 130.3, 128.9, 128.8, 128.7, 128.0, 126.8, 126.6, 124.3, 121.5, 118.5, 102.0, 34.4, 29.8, 21.9. IR (neat) 1453, 1516, 1699, 2927, 3402 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{19}H_{18}N$ $(M + H)^+$ 260.1439, found 260.1429.

*2-(2-(Methylthio)ethyl)-4,5-dihydro-3H-benzo[e]indole (**8e**).* Prepared according to general procedure D and D′, using (*S*)-(−)-methioninol (47 mg, 0.35 mmol)/(135 mg, 1 mmol) to afford 2-(2-(methylthio)ethyl)-4,5-dihydro-3*H*-benzo[*e*]indole **8e** (45 mg, 53%) using (0.35 mmol) and (122 mg, 50%) using (1 mmol) as a yellow semisolid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.32 (d, J = 7.5 Hz, 1H), 7.18 (dd, J = 15.4, 7.4 Hz, 2H), 7.04−7.00 (m, 1H), 6.21 (s, 1H), 3.00 (t, J = 7.7 Hz, 2H), 2.91 (t, J = 7.0 Hz, 2H), 2.82−2.76 (m, 4H), 2.17 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 133.5, 132.9, 130.6, 128.4, 127.9, 126.7, 124.2, 121.4, 118.3, 101.1, 34.7, 29.8, 27.6, 21.9, 15.7. IR (neat) 1367, 1515, 1699, 2918, 3397 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{15}H_{18}NS$ $(M + H)^+$ 244.1160, found 244.1149.

*8-Methoxy-2-methyl-4,5-dihydro-3H-benzo[e]indole (**8f**).* Prepared according to general procedure D and D′, using 2-amino-propan-1-ol (26 mg, 0.35 mmol)/(75 mg, 1 mmol) to afford 8-methoxy-2-methyl-4,5-dihydro-3*H*-benzo[*e*]indole **8f** (39 mg, 52%) using (0.35 mmol) and (111 mg, 52%) using (1 mmol) as a yellow semisolid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (s, 1H), 7.06 (d, J = 8.2 Hz, 1H), 6.88 (d, J = 2.6 Hz, 1H), 6.56 (dd, J = 8.1, 2.6 Hz, 1H), 6.13 (d, J = 1.3 Hz, 1H), 3.83 (s, 3H), 2.93 (t, J = 7.7 Hz, 2H), 2.74 (t, J = 7.7 Hz, 2H), 2.29 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 158.8, 134.8, 128.6, 128.5, 127.3, 125.3, 118.6, 109.0, 107.6, 101.3, 55.4, 29.0, 22.1, 13.3. IR (neat) 1277, 1507, 1617, 2931, 3197 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{14}H_{16}NO$ $(M + H)^+$ 214.1232, found 214.1224.

*7-Bromo-2-ethyl-4,5-dihydro-3H-benzo[e]indole (**8g**).* Prepared according to general procedure D and D′, using 2-amino-1-butanol (31 mg, 0.35 mmol)/(89 mg, 1 mmol) to afford 2-benzyl-7-bromo-4,5-dihydro-3*H*-benzo[*e*]indole **8g** (51 mg, 53%) using (0.35 mmol) and (152 mg, 55%) using (1 mmol) as a yellow semisolid after silica gel

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column chromatography (EtOAc/*n*-hexane = 10:90). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.30−7.28 (m, 2H), 7.18−7.16 (m, 1H), 6.13 (s, 1H), 2.96 (t, J = 7.8 Hz, 2H), 2.75 (t, J = 7.7 Hz, 2H), 2.63 (q, J = 7.6 Hz, 2H), 1.29 (t, J = 7.6 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 135.1, 134.3, 132.7, 130.7, 129.5, 127.8, 122.9, 117.6, 117.0, 99.5, 29.6, 21.7, 21.0, 13.8. IR (neat) 1263, 1521, 1699, 2926, 3415 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{14}H_{14}BrN$ $(M)^+$ 275.0310, found 275.0306.

2-Benzyl-7-bromo-4,5-dihydro-3H-benzo[e]indole (**8h**). Prepared according to general procedure D and D′, using (*S*)-(−)-2-Amino-3-phenyl-1-propanol (53 mg, 0.35 mmol)/(151 mg, 1 mmol) to afford 2-benzyl-7-bromo-4,5-dihydro-3*H*-benzo[*e*]indole **8h** (59 mg, 50%) using (0.35 mmol) and (152 mg, 45%) using (1 mmol) as a yellow semisolid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.35−7.30 (m, 2H), 7.29−7.21 (m, 5H), 7.14 (d, J = 7.8 Hz, 1H), 6.18 (d, J = 2.3 Hz, 1H), 3.96 (s, 2H), 2.92 (t, J = 7.8 Hz, 2H), 2.70 (t, J = 7.8 Hz, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 139.3, 135.0, 132.5, 130.7, 130.7, 129.5, 128.8, 128.8, 128.7, 126.7, 122.9, 117.7, 117.1, 101.8, 34.4, 29.5, 21.7. IR (neat) 1140, 1195, 2919, 3411 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{19}H_{17}BrN$ $(M + H)^+$ 338.0544, found 338.0519.

2-Benzyl-7-methoxy-4,5-dihydro-3H-benzo[e]indole (**8i**). Prepared according to general procedure D and D′, using (*S*)-(−)-2-Amino-3-phenyl-1-propanol (53 mg, 0.35 mmol)/(151 mg, 1 mmol) to afford 2-benzyl-7-methoxy-4,5-dihydro-3*H*-benzo[*e*]indole **8i** (46 mg, 46%) using (0.35 mmol) and (146 mg, 50%) using (1 mmol) as a yellow semisolid after silica gel column chromatography (EtOAc/*n*-hexane = 10:90). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.27−7.21 (m, 7H), 6.73 (s, 1H), 6.17 (d, J = 2.3 Hz, 1H), 3.96 (s, 2H), 3.78 (s, 3H), 2.94 (t, J = 7.7 Hz, 2H), 2.70 (t, J = 7.7 Hz, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 156.8, 139.6, 134.5, 130.1, 128.9, 128.7, 127.3, 126.5, 122.2, 118.2, 114.4, 111.3, 101.6, 55.4, 34.4, 30.1, 21.8. IR (neat) 1246, 1523, 2919, 3407 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{20}H_{19}NO$ $(M)^+$ 289.1467, found 289.1455.

2-Methyl-4,5-dihydro-1H-benzo[g]indole (**9a**). Prepared according to general procedure E and E′, using 2-aminopropan-1-ol (26 mg, 0.35 mmol)/(75 mg, 1 mmol) to afford 2-methyl-4,5-dihydro-1*H*-benzo[*g*]indole **9a** (30 mg, 47%) using (0.35 mmol) and (86 mg, 47%) using (1 mmol) as purple solid after silica gel column chromatography (EtOAc/*n*-hexane = 20:80). Melting point: 69−71 °C. (lit[21] = 70−72 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.21−7.16 (m, 2H), 7.09 (d, J = 6.7 Hz, 1H), 7.03 (td, J = 7.4, 1.3 Hz, 1H), 5.83 (d, J = 1.5 Hz, 1H), 2.93 (t, J = 7.6 Hz, 2H), 2.71 (t, J = 7.6 Hz, 2H), 2.34 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 134.5, 129.6, 128.8, 128.4, 126.6, 126.5, 124.5, 121.0, 117.7, 106.4, 30.2, 22.0, 13.4. IR (neat) 1290, 1509, 1651, 2927, 3308 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{13}H_{13}N$ $(M)^+$ 183.1048, found 183.1044.

2-Ethyl-4,5-dihydro-1H-benzo[g]indole (**9b**). Prepared according to general procedure E and E′, using 2-amino-1-butanol (31 mg, 0.35 mmol)/(89 mg, 1 mmol) to afford 2-ethyl-4,5-dihydro-1*H*-benzo[*g*]-indole **9b** (36 mg, 52%) using (0.35 mmol) and (99 mg, 50%) using (1 mmol) as a pale brown oil after silica gel column chromatography (EtOAc/*n*-hexane = 20:80). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.19 (t, J = 8.3 Hz, 2H), 7.11 (d, J = 7.4 Hz, 1H), 7.04 (td, J = 7.4, 1.3 Hz, 1H), 5.88 (s, 1H), 2.95 (t, J = 7.6 Hz, 2H), 2.72 (m, 4H), 1.32 (td, J = 7.6, 1.3 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 135.4, 134.5, 129.6, 128.3, 126.5, 126.4, 124.5, 120.7, 117.7, 104.7, 30.2, 22.0, 21.3, 13.8. IR (neat) 1268, 1512, 1698, 2929, 3504 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{14}H_{15}N$ $(M)^+$ 197.1204, found 197.1200.

2-(sec-Butyl)-4,5-dihydro-1H-benzo[g]indole (**9c**). Prepared according to general procedure E and E′, using 2-amino-3-methylpentan-1-ol (41 mg, 0.35 mmol)/(117 mg, 1 mmol) to afford 2-(*sec*-butyl)-4,5-dihydro-1*H*-benzo[*g*]indole **9c** (38 mg, 49%) using (0.35 mmol) and (102 mg, 45%) using (1 mmol) as a yellow semisolid after silica gel column chromatography (EtOAc/*n*-hexane = 20:80). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.19 (t, J = 7.2 Hz, 2H), 7.13 (d, J = 7.1 Hz, 1H), 7.06−7.00 (m, 1H), 5.86 (d, J = 2.3 Hz, 1H), 2.95 (t, J = 7.6 Hz, 2H), 2.74 (m, 3H), 1.76−1.56 (m, 2H), 1.31 (d, J = 6.9 Hz, 3H), 0.97 (t, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 139.0, 134.5, 129.7, 128.3, 126.5, 126.1, 124.4, 120.5, 117.7, 104.0, 34.7, 30.4, 30.2, 22.1, 20.3, 12.0. IR (neat) 1267, 1511, 1653, 2928, 3329 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{16}H_{19}N$ $(M)^+$ 225.1517, found 225.1513.

2-Benzyl-4,5-dihydro-1H-benzo[g]indole (**9d**). Prepared according to general procedure E and E′, using (*S*)-(−)-2-Amino-3-phenyl-1-propanol (53 mg, 0.35 mmol)/(151 mg, 1 mmol) to afford 2-benzyl-4,5-dihydro-1*H*-benzo[*g*]indole **9d** (40 mg, 44%) using (0.35 mmol) and (130 mg, 50%) using (1 mmol) as a pale brown oil after silica gel column chromatography (EtOAc/*n*-hexane = 20:80). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.38−7.34 (m, 2H), 7.30−7.26 (m, 3H), 7.20−7.13 (m, 2H), 7.04−7.00 (m, 2H), 5.90 (d, J = 2.2 Hz, 1H), 4.03 (s, 2H), 2.94 (t, J = 7.6 Hz, 2H), 2.73 (t, J = 7.7 Hz, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 139.4, 134.6, 131.7, 129.5, 128.8, 128.8, 128.4, 127.3, 126.7, 126.5, 124.7, 120.7, 117.9, 107.0, 34.5, 30.1, 22.0. IR (neat) 1454, 1694, 2926, 3312 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{19}H_{17}N$ $(M)^+$ 259.1361, found 259.1354.

2-(2-(Methylthio)ethyl)-4,5-dihydro-1H-benzo[g]indole (**9e**). Prepared according to general procedure E and E′, using (*S*)-(−)-methioninol (47 mg, 0.35 mmol)/(135 mg, 1 mmol) to afford 2-(2-(methylthio)ethyl)-4,5-dihydro-1*H*-benzo[*g*]indole **9e** (39 mg, 46%) using (0.35 mmol) and (102 mg, 42%) using (1 mmol) as a pink solid after silica gel column chromatography (EtOAc/*n*-hexane = 20:80). Melting point: 66−68 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.18 (t, J = 7.0, 1.3 H, 2H), 7.15−7.12 (m, 1H), 7.03 (td, J = 7.4, 1.3 Hz, 1H), 5.88 (d, J = 2.2 Hz, 1H), 2.97−2.91 (m, 4H), 2.81 (t, J = 7.3 Hz, 2H), 2.71 (t, J = 7.6 Hz, 2H), 2.17 (s, 3H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 134.6, 132.0, 129.5, 128.3, 127.0, 126.5, 124.7, 120.5, 118.0, 106.0, 34.7, 30.1, 27.8, 21.9, 15.7. IR (neat) 1256, 1507, 1608, 2924, 3269 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{15}H_{18}NS$ $(M + H)^+$ 244.1160, found 244.1146.

2-Benzyl-3H-benzo[e]indole (**10a**). Prepared according to general procedure F, using 2-benzyl-4,5-dihydro-3*H*-benzo[*e*]indole **8d** (39 mg, 0.15 mmol) to afford 2-benzyl-3*H*-benzo[*e*]indole **10a** (9 mg, 24% yield) White solid after silica gel column chromatography (EtOAc/*n*-hexane = 10:80). Melting point: 123−125 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 8.2 Hz, 1H), 8.08 (s, 1H), 7.88 (d, J = 8.1 Hz, 1H), 7.53 (m, 2H), 7.42−7.33 (m, 4H), 7.30 (d, J = 7.0 Hz, 3H), 6.88 (d, J = 1.3 Hz, 1H), 4.23 (s, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 138.9, 136.0, 132.5, 129.2, 129.0, 128.9, 128.6, 128.0, 126.9, 125.7, 123.5, 123.3, 123.1, 122.2, 112.5, 100.6, 34.9. IR (neat) 1182, 1300, 1735, 2850, 2918, 3400 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{19}H_{15}N$ $(M)^+$ 257.1204, found 257.1200.

(E)-2-(4-Methylbenzylidene)-3,4-dihydronaphthalen-1(2H)-one (**11a**).[19] Prepared according to procedure G, using tetralone **5a** (300 mg, 2.05 mmol, 1.0 equiv), aldehyde **7aa** (296 mg, 2.46 mmol, 1.2 equiv), NaOH (164 mg, 41.0 mmol, 2.0 equiv) to provide **11a** (475 mg, 93% isolated yield) as a yellow solid after silica gel column chromatography (EtOAc/*n*-hexane = 20:80). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (dd, J = 7.7, 1.0 Hz, 1H), 7.87 (s, 1H), 7.49 (td, J = 7.5, 1.2 Hz, 1H), 7.38−7.34 (m, 3H), 7.25 (m, 3H), 3.14 (td, J = 6.5, 1.5 Hz, 2H), 2.95 (t, J = 6.6 2H), 2.40 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 188.0, 143.3, 138.9, 136.9, 134.8, 133.6, 133.3, 133.0, 130.1, 129.3, 128.3, 128.2, 127.1, 28.9, 27.3, 21.5. The data for this compound **11a** are in agreement with the reported compound.

4-Methylbenzaldehyde (**2aa**).[20] Prepared according to procedure A, 4-methylbenzyl alcohol **2a** (43 mg, 0.35 mmol, 1.0 equiv), NaOH (42 mg, 1.05 mmol, 3 equiv) to provide **2aa** (8.5 mg, 20% isolated yield) as a yellow liquid after silica gel column chromatography (EtOAc/*n*-hexane = 10:80).). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.95 (s, 1H), 7.76 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 7.8 Hz, 2H), 2.43 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 192.1, 145.6, 134.2, 129.9, 129.8, 21.9. The data for this compound **2aa** are in agreement with the reported compound.

3-(4-Methylbenzyl)naphthalene-1,2-dione (**14a**).[22] Prepared according to procedure H, using tetralone **5a** (62 mg, 0.25 mmol, 1.0 equiv), CuI (2.47 mg, 0.025 mmol) to provide **14a** (47 mg, 72% isolated yield) as a yellow solid after silica gel column chromatography (EtOAc/*n*-hexane = 10:80). Melting point: 92−94 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 7.1 Hz, 1H), 7.56 (td, J = 7.6, 1.4 Hz, 1H), 7.40 (td, J = 7.6, 1.1 Hz, 1H), 7.19 (d, J = 7.4 Hz, 1H), 7.14 (s, 4H), 6.97

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(s, 1H), 3.73 (d, J = 1.1 Hz, 2H), 2.34 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): 181.0, 179.4, 141.7, 140.4, 136.5, 136.0, 135.4, 134.7, 130.7, 130.1, 130.1, 129.6, 129.6, 129.4, 34.9, 21.2. IR (neat) 1257, 1664, 1698, 1733, 2360, 2918 cm^{-1}. HRMS (ESI-TOF) m/z calculated for $C_{18}H_{15}O_2$ $(M + H)^+$ 263.1072, found 263.1073.

3-(3-Methylbut-2-en-1-yl)naphthalene-1,2-dione (14b).[22] Prepared according to procedure H, using 3-(3-methylbut-2-en-1-yl)naphthalen-2-ol **3o** (53 mg, 0.25 mmol, 1.0 equiv), CuI (2.47 mg, 0.025 mmol) to provide **14b** (35 mg, 62% isolated yield) as a yellow solid after silica gel column chromatography (EtOAc/*n*-hexane = 10:80). Melting point: 116−118 °C. The data for this compound **14b** are in agreement with the reported compound. ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 7.3 Hz, 1H), 7.59 (td, J = 7.6, 1.3 Hz, 1H), 7.41 (t, J = 7.6 Hz, 1H), 7.27 (d, J = 7.6 Hz, 1H), 7.11 (s, 1H), 5.24−5.19 (m, 1H), 3.13 (d, J = 7.4 Hz, 2H), 1.78 (s, 3H), 1.68 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 181.4, 179.6, 140.6, 139.8, 134.0, 135.7, 130.7, 130.1, 129.9, 129.4, 119.2, 27.7, 26.0, 18.0. IR (neat) 1694, 1733, 2361, 2920 cm^{-1}.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.2c00779.

Copies of ^1H and ^{13}C NMR spectra and crystallographic data (PDF)

FAIR data, including the primary NMR FID files, for compounds **3a**, **3b**, **3c**, **3d**, **3e**, **3f**, **3g**, **3h**, **3i**, **3j**, **3k**, **3l**, **3m**, **3n**, **3o**, **3p**, **3q**, **3r**, **3s**, **3t**, **3u**, **3v**, **3w**, **3x**, **3y**, **6a**, **6b**, **6c**, **6d**, **6e**, **6f**, **6g**, **6h**, **6i**, **8a**, **8b**, **8c**, **8d**, **8e**, **8f**, **8g**, **8h**, **8i**, **9a**, **9b**, **9c**, **9d**, **9e**, **10a**, **11a**, **2aa**, **14a**, and **14b** (ZIP)

Accession Codes

CCDC 2150250 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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