Novel Strategies for C-H Bond Functionalization of Alkynes, Arenes and Carbonyl Compounds via Copper and Scandium Catalysis

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Dedicated to My Family,

Friends and Teachers

भारतीय विज्ञान शिक्षा एवं अनुसंधान संस्थान, पुणे
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CERTIFICATE

This is to certify that the work incorporated in this thesis entitled ***"Novel Strategies for C-H Bond Functionalization of Alkynes, Arenes and Carbonyl Compounds via Copper and Scandium Catalysis"*** submitted by **Mr. Balu Shankar Navale** carried out by candidate at Indian Institute of Science Education and Research (IISER), Pune, under my supervision. 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.

Date: 26th April, 2019, Pune

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Declaration

I declare that this written submission represents my ideas in my own words and where others' ideas have been included; I have adequately cited and referenced the original sources. I also declare that I have adhered to all principles of academic honesty and integrity and have not misrepresented or fabricated or falsified any idea/data/fact/source in my submission. I understand that violation of the above will be cause for disciplinary action by the Institute and can also evoke penal action from the sources which have thus not been properly cited or from whom proper permission has not been taken when needed.

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Balu Shankar Navale

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ABBREVIATIONS

α	Alpha
ß	Beta
γ	Gamma
°C	degrees Celsius
µ	micro
Å	angstrom
Ac	Acetyl
acac	Acetylacetone
AcOH	Acetic acid
AIBN	Azobisisobutyronitrile
aq	aqueous
Ar	Aryl
atm	atmosphere
Boc	tert-butyldicarbonate
bpy	2,2'-Bipyridine
bs	broad singlet
Bu	Butyl
calcd.	Calculated
Cat.	Catalytic
CBTF	4-Chlorobenzotrifluoride
CD_3OD	Duterated methanol
$CDCl_3$	Duterated chloroform
$CHCl_3$	Chloroform
cm^{-1}	wavenumber(s)
conc.	Concentrated
COD	1,5-cyclooctadiene
Cp*	Pentamethylcyclopentadienyl
d	doublet (NMR)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DCM	Dichloromethane

dd	doublet of doublet
DDQ	2,3-Dichloro-5,6-dicyanobezoquinone
DIPEA	*N*,*N*-Diisopropylethylamine
DMA	Dimethylacetamide
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-dimethyl formamide
DMSO	Dimethylsulfoxide
DMSO-d6	Duterated dimethyl sulfoxide
DTBP	Di-tert-butyl peroxide
equiv.	equivalents
ESI TOF	Electrospray ionisation time-of-flight
ESMS	Electrospray mass spectrometry
esp	*α*,*α*,*α′*,*α′*-tetramethyl-1,3-benzenedipropionic acid
Et	Ethyl (CH_3CH_2)
EtOH	Ethanol
EtOAc	Ethyl acetate
FTIR	Fourier-transform infrared spectroscopy
g	gram(s)
GC	Gas Chromatography
h	hour(s)
HCl	Hydrochloric acid
hfacac	Hexafluoroacetylacetone
HRMS	High Resolution Mass Spectrometry
Hz	Hertz
i-, iso-	Isomeric (branched alkyl chain)
^{i}Bu	isobutyl
^{i}Pr	isopropyl
IR	infrared spectroscopy
J	Spin coupling constant (in NMR spectroscopy)
L	Ligand
LA	Lewis acid
lit.	literature
m	meta
M	molar (mol L^{-1})

m	multiplet (in NMR)
M	Metal
m/z	mass to charge ratio
Me	Methyl (CH_3)
MeCN	Acetonitrile
MeOH	Methanol
mg	milligram
min	minute(s)
mL	millilitres
mmol	millimoles
mol	mole(s); molecular (as in mol. weight)
mp	melting point
MS	Molecular Sieves
NMR	Nuclear Magnetic Resonance
o	ortho
p	para
pfb	perfluorobutyrate
Ph	Phenyl (C_6H_5)
1,10-Phen	1,10-Phenanthroline
Phen	Phenanthroline
PivOH	Pivalic acid
ppm	parts per million
Pr	Propyl
Py	pyridine
q	quartet (NMR)
quin.	Quintet
R-BPCP	(*R*)-(1-(biphenyl)-2,2-diphenylcyclopropanecarboxylate)
R_f	retention factor (in chromatography)
rt	room temperature
s	singlet (NMR)
$Sc(OTf)_3$	Scandium(III) triflate
S-DOSP	1-[[4-alkyl(C11-C13)phenyl]sulfonyl]-(2*S*)-pyrrolidinecarboxylate
t	triplet (NMR)
t-, tert-	Tertiary (branched alkyl chain)

^{t}Bu	tert-butyl
TBDPS	tert-Butyldiphenylsilyl
TBHP	tert-Butyl hydroperoxide
TMEDA	Tetramethylethylenediamine
td	triplet of doublet
Tf	trifluoromethanesulphonyl (triflyl)
OTf	triflate
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
TPA	Triphenylacetate
UV	ultraviolet
vis	visible
X	Heteroatom
δ	chemical shift in ppm downfield from trimethylsilane

SYNOPSIS

The thesis entitled "***Novel Strategies for C-H Bond Functionalization of Alkynes, Arenes and Carbonyl Compounds via Copper and Scandium Catalysis***" comprises of five chapters.

Chapter 1: ***Introduction to Transition Metal-Catalyzed C-H Bond Functionalization Reactions***

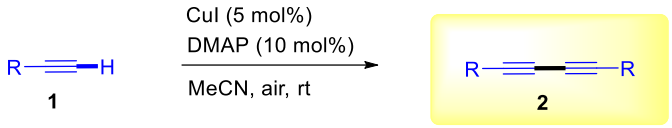
This chapter gives a brief overview of C-H bond functionalization reactions using different transition metal catalysts and its importance over traditional C-C bond forming reactions. Due to high C-H bond dissociation energy, site and chemoselective C-H bond functionalization approach is a great challenge and a topic of broad interest in organic synthesis. This chapter presents the important and useful methods of C-H bond functionalization based on transition metal-catalyzed oxidative coupling reactions and C-H bond functionalizations using α-diazocarbonyl compounds. The different types of C-H bond functionalizations and related reactions have been discussed in detail in this chapter.

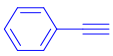
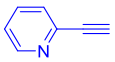
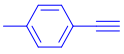
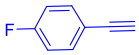
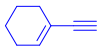
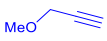
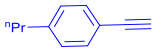
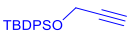
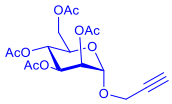
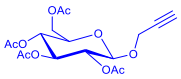
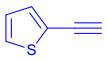
Chapter 2: ***Copper(I) Iodide-Catalyzed Oxidative C-H Bond Functionalization of Terminal Alkynes***

In this chapter, we describe the use of convenient catalytic system comprising of CuI and DMAP for the effective oxidative homo- and heterocoupling of terminal alkynes under aerobic conditions at room temperature. The chapter presents selected protocols for the oxidative homo- and heterocoupling of terminal alkynes. At the outset of our investigation, we selected phenyl acetylene **1a** as a model substrate for the C-H bond functionalization via oxidative homocoupling reaction using copper(I) salts and base at room temperature under aerobic conditions for the initial study. Different catalytic systems were screened in different solvents to optimize the reaction conditions to obtain the corresponding homocoupled product **2a**. Based on the exhaustive screening, CuI (5 mol%), DMAP (10 mol%) and air as an oxidant at ambient temperature in acetonitrile emerged as the optimum reaction conditions. Under the optimum reaction conditions, phenylacetylene **1a** reacted smoothly to afford the corresponding homocoupled product **2a** in excellent yield.

Encouraged by the initial success, we then planned to generalize the protocol by exploring the broader substrate scope. Different terminal alkynes (**1a-1m**) were utilized in the homocoupling reaction under optimized reaction conditions to afford the corresponding 1, 3-diynes (**2a-2m**) in good to excellent yields in short time (up to 98%, Table 2.1).

Table 2.1 CuI-DMAP catalyzed homocoupling of terminal alkynes[a-c]



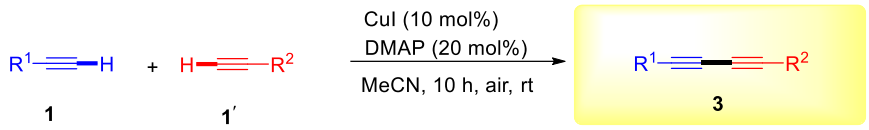
Entry	1	2	Time (h)	Yield[b] (%)	Entry	1	2	Time (h)	Yield[b] (%)
1		**2a**	1	97	8		**2h**	1.5	87
2		**2b**	1	98	9		**2i**	1	92
3		**2c**	1.5	85	10		**2j**	1.5	82
4		**2d**	1	87	11		**2k**	1.5	94
5		**2e**	1	96	12		**2l**	1.5	87[c]
6		**2f**	1	90	13		**2m**	3.5	71[c]
7		**2g**	1	94					

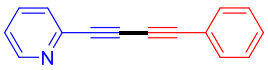
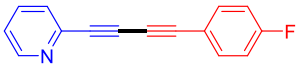
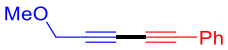
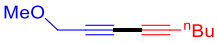
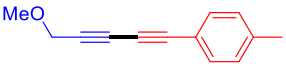
[a]Reaction conditions: Terminal alkynes **1** (1 mmol, 1 equiv.), CuI (5 mol%), DMAP (10 mol%) in MeCN (4 mL) air; the reaction was monitored by TLC. [b]Isolated yield after column chromatography; [c]10 mol% CuI and 20 mol% DMAP was used.

Encouraged by the initial success with homocoupling, further we explored this protocol by utilizing our catalytic system to the cross-coupling of two different terminal alkynes. Later, two different terminal alkynes (ratio 1:5) were subjected to the coupling reaction with an increased amount of catalyst loading CuI (10 mol%) and DMAP (20 mol%) in acetonitrile

under aerobic conditions to afford the corresponding cross-coupled products (**3a-3e)** in very good yields (up to 85%, Table 2.2)

Table 2.2 Synthesis of unsymmetric conjugated diynes[a,b]



Entry	R^1	R^2	R^1–R^2	3	Yield[b] (%)
1	**1h**	**1a**		**3a**	82
2	**1h**	**1i**		**3b**	85
3	**1d**	**1a**		**3c**	72
4	**1d**	**1c**		**3d**	70
5	**1d**	**1c**		**3e**	74

[a]Reaction conditions: Terminal alkynes **1** (1 mmol, 1 equiv.), terminal alkynes **1′** (5 mmol, 5 equiv.), CuI (10 mol%), DMAP (20 mol%) in MeCN (6 mL) air; the reaction was monitored by TLC. [b]Isolated yield after purification by column chromatography.

The protocol proved to mild and a wide range of functional groups tolerated the reaction conditions of both homo- and heterocouplings. It is also important to note that the coupling proceeds smoothly without any requirement of metal co-catalysts, unlike the previously reported procedures.

We have successfully demonstrated a practical and convenient catalyst system (CuI-DMAP) for the effective homo- and heterocoupling of terminal alkynes. The reaction procceds under aerobic conditions at room temperature. We have also effectively utilized easily available, inexpensive and non-hazardous DMAP for the smooth coupling of terminal alkynes. It is important to note that we have successfully avoided the use of excess base and metal co-catalysts unlike previously reported procedures. This protocol proved to be practical, economical and environmentally friendly.

Chapter 3: *Scandium-Catalyzed C-H Bond Functionalization of Arenes with α-Aryl-α-diazoacetates*

This chapter deals with the C-H bond functionalization of arenes as well as arenes bearing olefin or alkyne functionality with propargyl *α*-aryl-*α*-diazoacetates via scandium catalysis. This chapter is further subdivided into two sections.

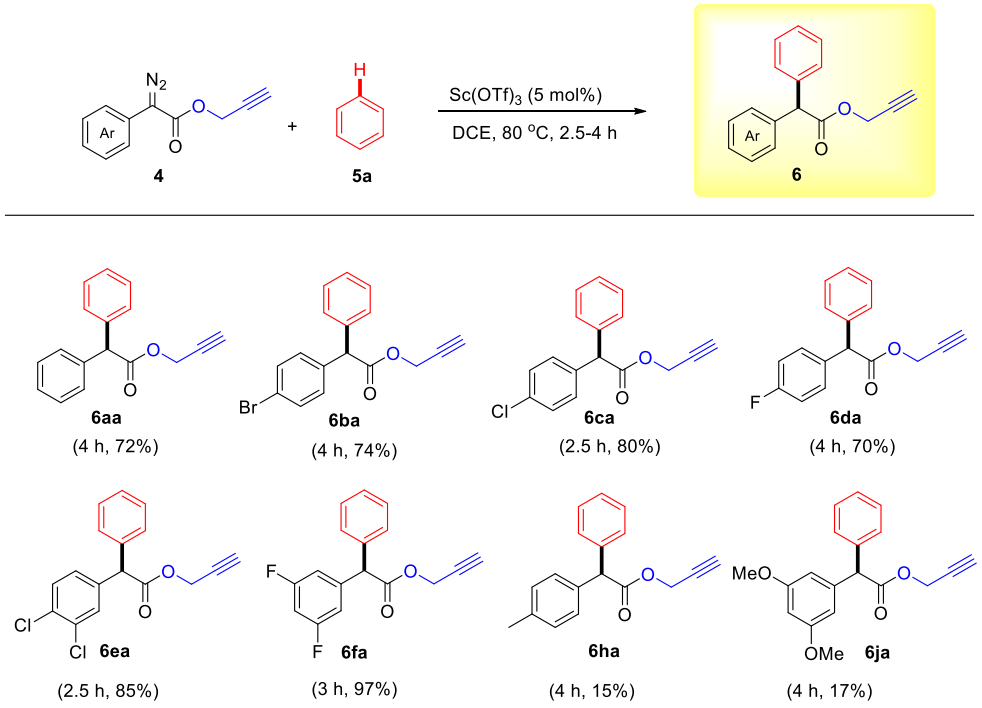
Section A: *Scandium(III) Triflate-Catalyzed Chemo- and Regioselective C-H Bond Functionalization of Arenes with Propargyl α-Aryl-α-diazoacetates*

Catalytic C-H bond functionalization is one of the most important and greener methods for the synthesis of complex organic molecules. This section deals with the C-H bond functionalization of arenes. We have explored the use of propargyl *α*-aryl-*α*-diazoacetates as robust and useful new class of reagents for the C-H bond functionalization of arenes. This section begins with a brief overview of C-H bond functionalization of different arenes with *α*-diazocarbonyl compounds via transition metal catalysis. *α*-Diarylacetates are important motifs present in many biologically active compounds and natural products, and this molecular scaffold has been utilized in the synthesis of various drug molecules. Synthesis of *α*-diarylacetates via C-H bond functionalization starting from unactivated arenes and electronically deactivated arenes by modifying catalyst and *α*-diazocarbonyl compounds remains an interesting area for the synthetic organic chemist.

In this regard, we commenced our study starting from ethyl *α*-phenyl-*α*-diazoacetate **4a′** and unactivated arene such as benzene **5a** as model substrates. Further, the reactions were screened in the presence of various metal catalysts, co-catalysts and modified *α*-aryl-*α*-diazoacetates at room temperature as well as under refluxing condition in different solvents. Based on the screening of various metal catalysts along with the modified *α*-aryl-*α*-diazoacetates/co-catalysts, in different solvents and temperature, $Sc(OTf)_3$ (5 mol%), benzene **5a** (10 equiv.) and propargyl *α*-phenyl-*α*-diazoacetate **4a** (1 equiv.) in dichloroethane at 80 ^{o}C emerged as an optimal reaction condition. Based on the experimental studies, propargyl *α*-phenyl-*α*-diazoacetate **4a** proved to be a very useful modified reagent for the desired C-H bond functionalization reaction. Under the optimal reaction conditions, propargyl *α*-phenyl-*α*-diazoacetate **4a** reacted smoothly with benzene **5a** by affording the corresponding C-H bond functionalized product **6aa** in good yield (72%, Table 3A.1). Further, the structure of the compound **6aa** was unambiguously confirmed by single crystal X-ray analysis. Encouraged

by the initial success, we treated unactivated arene such as benzene **5a** with various propargyl *α*-aryl-*α*-diazoacetates (**4a-4f, 4h, 4j**) under the optimum reaction conditions to afford the corresponding desired products (**6aa-6fa, 6ha, 6ja**) in modest to excellent yields (up to 97%, Table 3A.1)

Table 3A.1 C-H bond functionalization of benzene[a,b]

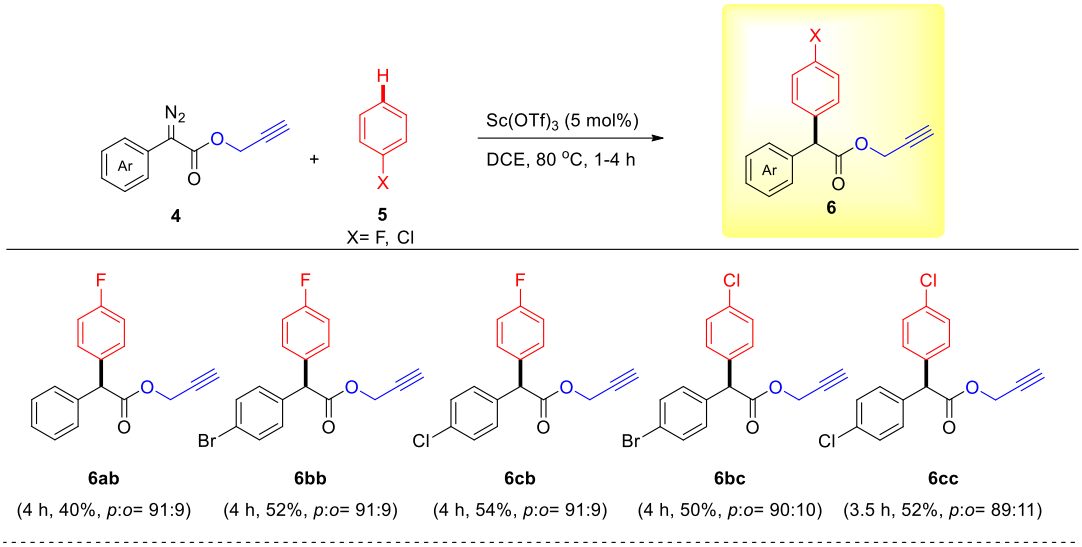


[a]Reaction conditions: Propargyl *α*-aryl-*α*-diazoacetate **4** (0.5 mmol, 1 equiv.), benzene **5a** (5 mmol, 10 equiv.) and $Sc(OTf)_3$ (5 mol%) was added in DCE (2.5 mL) under inert atmosphere and reaction mixture was refluxed at 80 °C; the reaction was monitored by TLC. [b]Isolated yield after purification by column chromatography (Time and yields are given in parenthesis).

After the initial success in C-H bond functionalization of an unactivated arene, we turned our attention to explore this method for the relatively challenging C-H bond functionalization of mildly deactivated arenes. Gratifyingly we were able to functionalize mildly deactivated arenes such as fluorobenzene **5b** and chlorobenzene **5c**. Fluorobenzene **5b** reacted with various propargyl *α*-aryl-*α*-diazoacetates (**4a, 4b, 4c**) under the optimal reaction conditions to give the corresponding desired products (**6ab, 6bb, 6cb**) in moderate yields with excellent regioselectivity (up to 54% yield, up to 91:9 *p*:*o* ratio, Table 3A.2). Likewise, the chlorobenzene **5c** reacted smoothly with propargyl *α*-aryl-*α*-diazoacetates (**4b, 4c**) under the optimal reaction conditions to give the corresponding desired products (**6bc, 6cc**) in

moderate yields with very good regioselectivity (up to 52% yield, up to 90:10 *p*:*o* ratio, Table 3A.2).

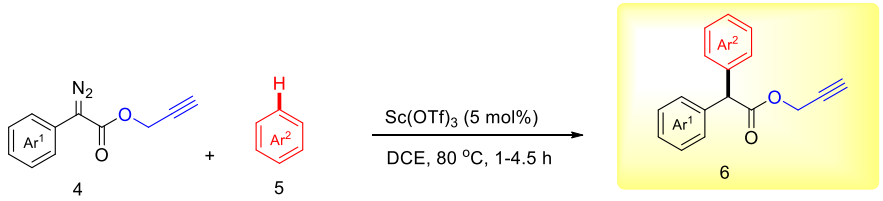
Table 3A.2 C-H bond functionalization of mildly deactivated arenes[a,b]

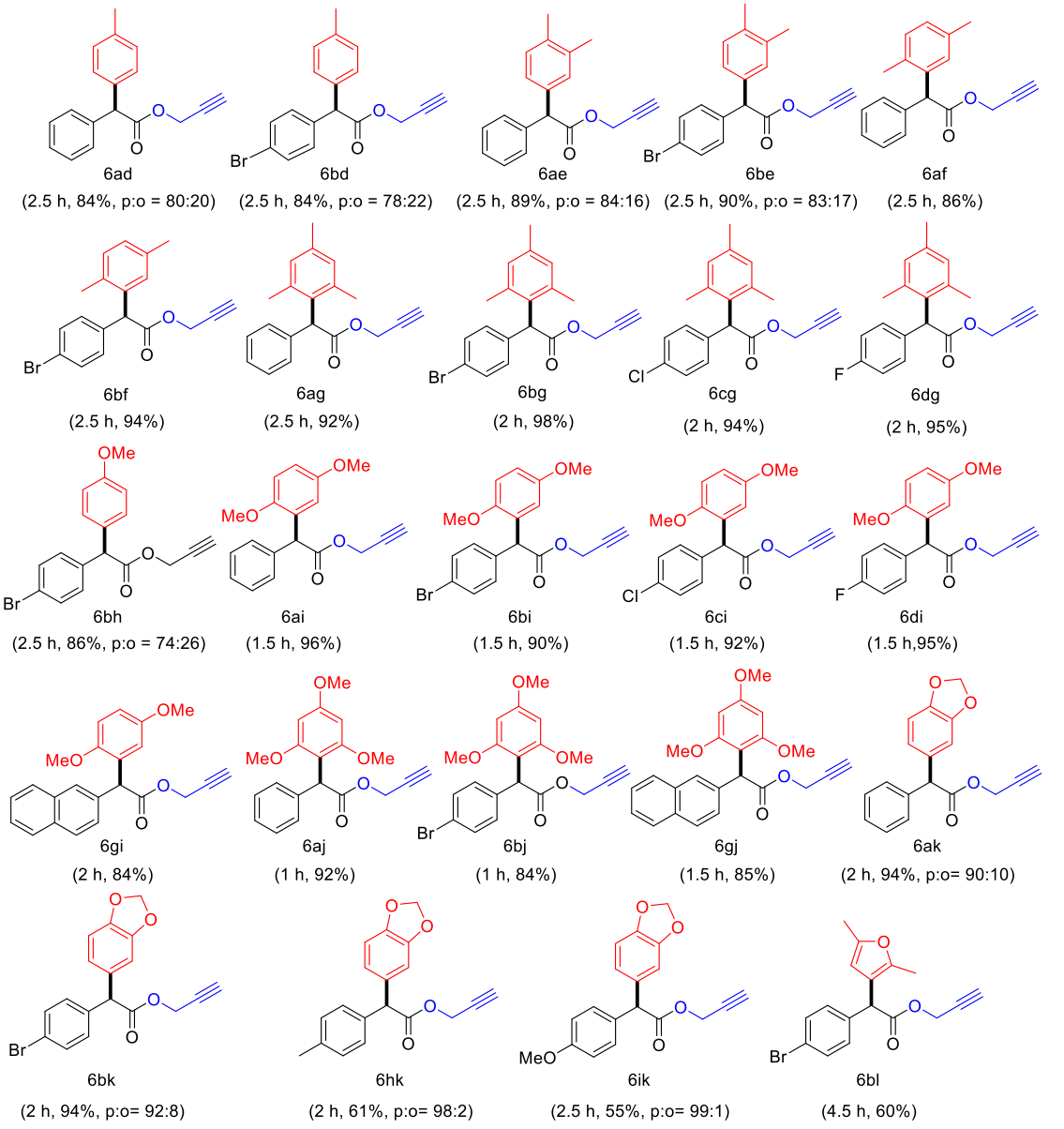


[a]Reaction conditions: Propargyl *α*-aryl-*α*-diazoacetates **4** (0.5 mmol, 1 equiv.), arene **5** (10 equiv.), and $Sc(OTf)_3$ (5 mol%) was added in DCE (2.5 mL) under inert atmosphere and reaction mixture was refluxed at 80 °C; the reaction was monitored by TLC. [b]Isolated yield after purification by column chromatography (Time and yields are given in parenthesis).

Later, we explored this method for the chemoselective C-H bond functionalization of electron rich arenes. C-H bond functionalization of electron rich arenes (**5d-5l**) under the optimum reaction conditions furnished the desired products **6** in moderate to excellent yields with good to excellent regioselectivity (up to 98% yield, up to 99:1 *p*:*o* ratio, Table 3A.3). Mildly activated arene such as toluene **5d** reacted with propargyl *α*-aryl-*α*-diazoacetates (**4a-4b**) under the optimal reaction conditions to afford the corresponding desired products (**6ad-6bd**) in good yields with good regioselectivity (up to 84% yield, up to 80:20 *p*:*o* ratio, Table 3A.3). *o*-Xylene **5e** and *p*-xylene **5f** reacted smoothly with propargyl *α*-aryl-*α*-diazoacetates (**4a-4b**) under the optimal reaction conditions to afford the corresponding desired products (**6ae-6be, 6af-6bf**) in good to excellent yields with very good regioselectivity (up to 94% yield, Table 3A.3). Mesitylene **5g**, when treated with propargyl α-aryl-α-diazoacetates (**4a-4d**) under optimal reaction condition, furnished the corresponding products (**4ag-4dg**) in excellent yields (up to 98% yield, Table 3A.3). Under the optimal reaction conditions, the activated arene such as anisole **5h** reacted smoothly with the propargyl *α*-(4-bromophenyl)-*α*-diazoacetate **4b** to afford the corresponding desired product **6bh** in very good yield.

Table 3A.3 Chemoselective C-H bond functionalization of electronically activated arenes[a,b]

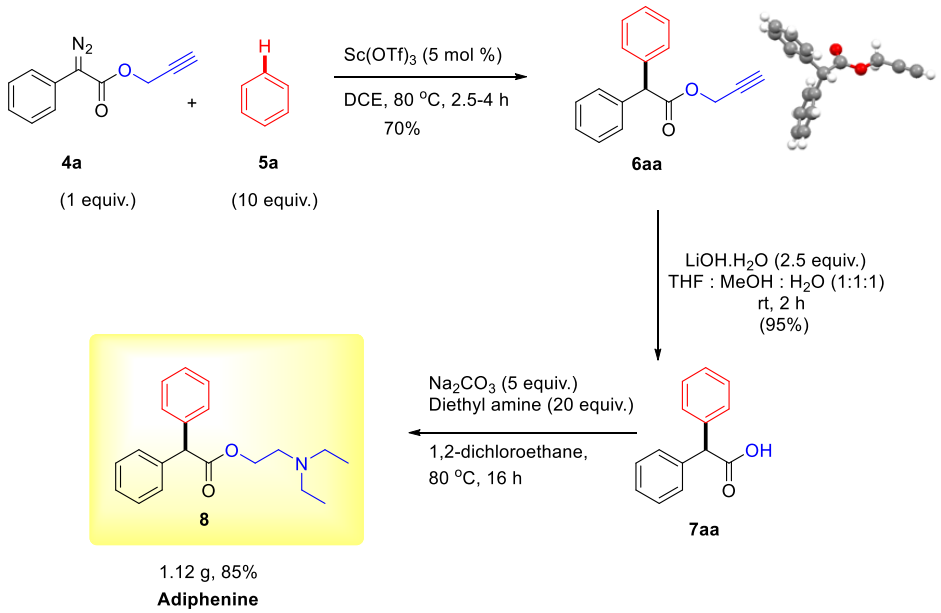




[a]Reaction conditions: Propargyl *α*-aryl-*α*-diazoacetates **4** (0.5 mmol, 1equiv.), arene **5** (10 equiv.) and $Sc(OTf)_3$ (5 mol%) was added in DCE (2.5 mL) under inert atmosphere and reaction mixture was refluxed at 80 °C; the reaction was monitored by TLC. [b]Isolated yield after purification by column chromatography (Time and yields are given in parenthesis).

Activated arene such as 1,4-dimethoxybenzene **5i** reacted with various propargyl *α*-aryl-*α*-diazoacetates (**4a-4d, 4g**) and afforded the corresponding desired products (**6ai-6di, 6gi**) in excellent yields (up to 96%, Table 3A.3) under optimized reaction conditions. Highly activated arene such as 1,3,5-trimethoxybenzene **5j** reacted with propargyl *α*-aryl-*α*-diazoacetates (**4a, 4b, 4g)** to furnish the corresponding C-H bond functionalization products (**6aj, 6bj, 6gj**) in very good yields (up to 92%, Table 3A.3). 1,3-Benzodioxole **5k** also reacted smoothly with various propargyl *α*-aryl-*α*-diazoacetates (**6a,6b, 6h, 6i**) under the optimal reaction conditions to afford the corresponding desired products (**6ak, 6bk, 6hk, 6ik**) in moderate to excellent yields and excellent regioselectivity (up to 94% yield, up to 99:1 *p*:*o* ratio, Table 3A.3). Heteroaromatic arene such as 2,5-dimethylfuran **5l**, when treated with propargyl α-aryl-α-diazoacetates **4b** under optimal conditions, afforded the C-H functionalization product **6bl** in 60% yield (see Table 3A.3).

To have the wider application and for the practicability, we have explored this protocol for the gram scale synthesis of *α*-diarylacetates (**6aa, 6ca, 6ea, 6bi**). The method proved to be reproducible on a gram scale. Further, this protocol was successfully employed for the synthesis of adiphenine **8**, a nicotinic receptor inhibitor (an antispasmodic drug) on a gram scale (Scheme 3A.1).



Scheme 3A.1: Synthesis of Adiphenine

Further, to have some insight into the mechanism, kinetic isotopic effect studies have also been carried out. Experimental observations indicated that cleavage of C-H bond of arenes is not a rate-determining step.

In this section, we have developed novel scandium catalyzed highly chemoselective C-H bond functionalization of arenes, unactivated arenes and mildly deactivated arenes with propargyl α-aryl-α-diazoesters to obtain synthetically and biologically important α-diarylacetate compounds in good to excellent yields.

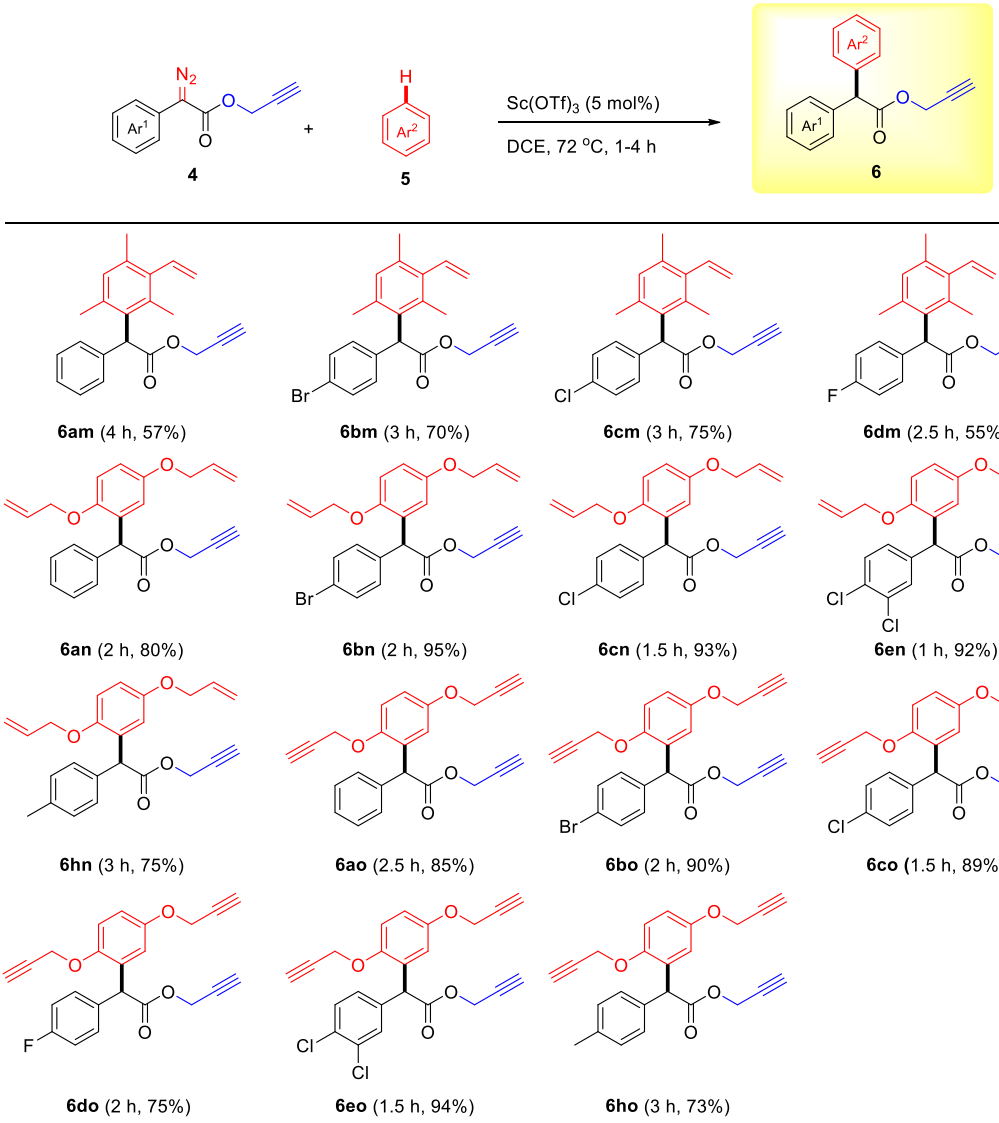
Section B: ***Chemoselective C-H Bond Functionalization of Arenes Bearing Olefin or Alkyne Functionality with Propargyl α-Aryl-α-diazoacetates via Scandium Catalysis***

This section describes the chemoselective C-H bond functionalization of arenes bearing olefin or alkyne functionality via scandium catalysis. The section begins with a brief introduction to the reactions of arenes bearing olefin or alkyne functionality with α-diazocarbonyl compounds under transition metal catalysis. It is very important to note that arenes bearing olefin functionality usually undergoes cyclopropanation reaction with α-diazocarbonyl compounds in the presence of transition metal catalysts. Also, arenes bearing alkyne functionality usually undergoes cyclopropenation reaction with α-diazocarbonyl compounds in the presence of transition metal catalysts. In this regard, developing a protocol for the chemoselective C-H bond functionalization of arenes bearing olefin or alkyne functionality is challenging.

We planned to explore the reactivity of propargyl α-aryl-α-diazoacetates **4** with arenes **5** bearing olefin or alkyne functionality under scandium catalysis. To explore the feasibility, we screened various transition metal catalysts. Based on the screening of various catalysts and solvents, $Sc(OTf)_3$ (5 mol%), propargyl α-(4-bromophenyl)-α-diazoacetate **4b** (1 equiv.), arene **5m** (10 equiv.) in DCE at 72 ^oC emerged as optimum reaction conditions. Later, for the wider substrate scope and to generalize the protocol, different propargyl α-aryl-α-diazoacetates (**4a-4d**) were treated with arene **5m** bearing olefin functionality under the optimal reaction conditions to afford the corresponding desired products (**6am-6dm**) in moderate to good yields (up to 75%, Table 3B.1). 1,4-Bis(allyloxy)benzene **5n** also smoothly underwent chemoselective C-H bond functionalization with various propargyl α-aryl-α-diazoacetates (**4a-4c, 4e, 4h**) under optimized reaction conditions to give the corresponding desired products (**6an-6cn, 6en, 6hn**) in good to excellent yields (up to 95%, Table 3B.1). The treatment of 1,4-

bis(propargyloxy)benzene **5o** bearing alkyne functionality with different propargyl α-aryl-α-diazoacetates (**4a-4e, 4h**) furnished the corresponding C-H bond functionalization products (**6ao-6eo**, **6ho**) exclusively in good to excellent yields (up to 94% yield, Table 3B.1). During this transformations, we did not observe any isolable cyclopropanation and cyclopropenation by-products.

Table 3B.1 C-H bond functionalization of arenes containing multiple bonds[a,b]



[a]Reaction conditions: Propargyl α-aryl-α-diazoacetate **4** (0.5 mmol, 1 equiv.), arene **5** (10 equiv.) and $Sc(OTf)_3$ (5 mol%) was added in DCE (2.5 mL) under inert atmosphere; the reaction was monitored by TLC. [b]Isolated yield after purification by column chromatography (Time and yield are given in parenthesis).

In this section, we have successfully demonstrated a highly chemoselective C-H bond functionalization of arenes bearing olefin or alkyne functionality with newly developed reagent

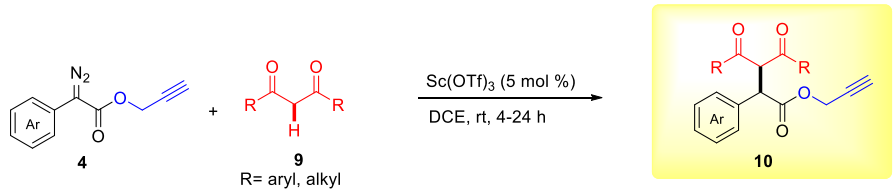
propargyl *α*-aryl-*α*-diazoacetates via scandium catalysis. The protocol proved to be practical, and it avoids the use of expensive catalysts and ligands.

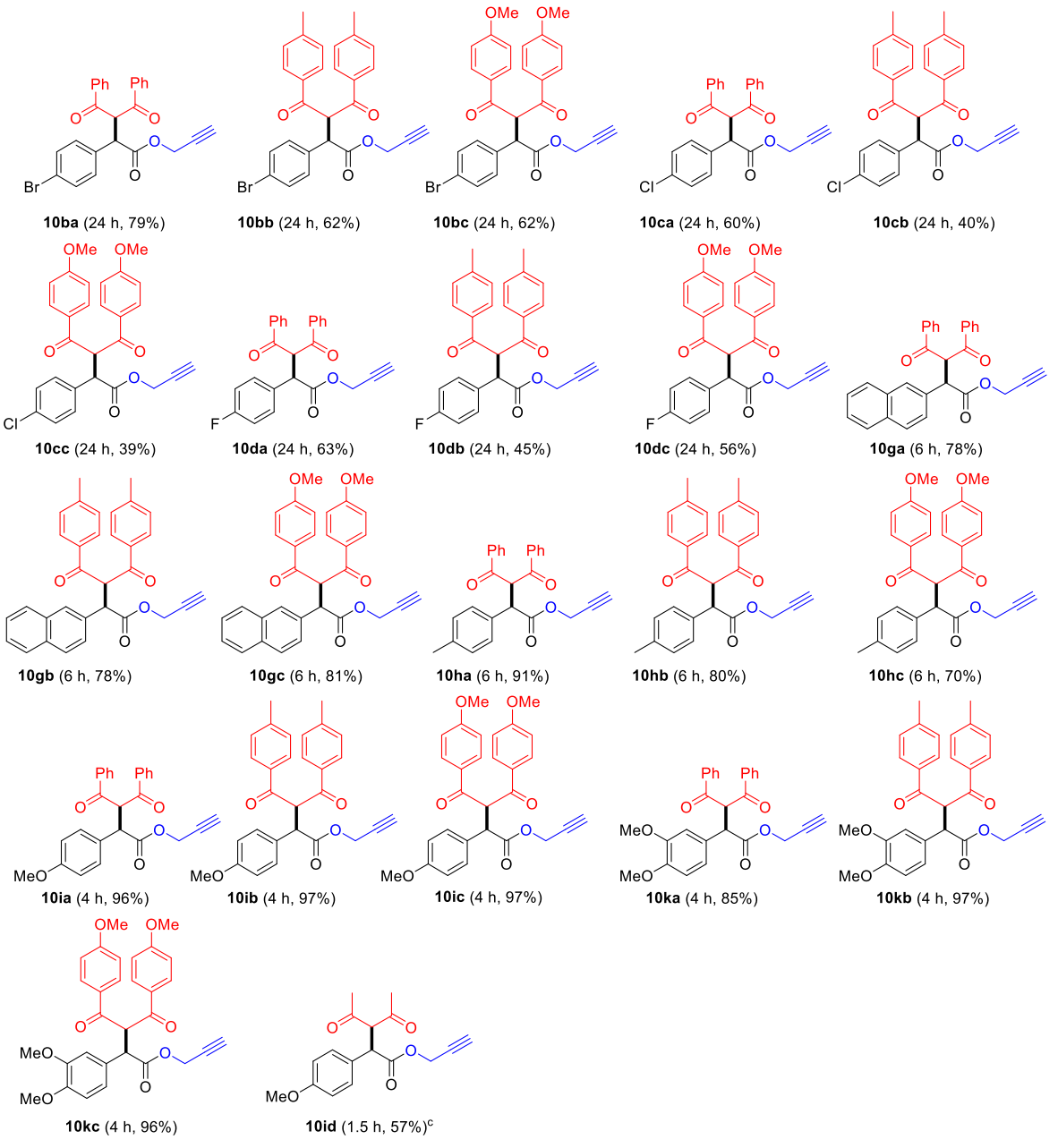
Chapter 4: *Propargyl α-Aryl-α-diazoacetates as Robust Reagents for the Effective C-H Bond Functionalization of 1,3-Diketones via Scandium Catalysis*

This chapter deals with the scandium catalyzed C-H bond functionalization of 1,3-diketones with propargyl *α*-aryl-*α*-diazoacetates at room temperature. The chapter gives an account on transition metal-catalyzed C-H bond functionalization of 1,3-dicarbonyl compounds. We have explored the use of propargyl *α*-aryl-*α*-diazoacetates as robust and useful new class of reagents for the C-H bond functionalization of 1,3-diketones.

At the outset, we began our investigation by choosing ethyl *α*-(4-methoxyphenyl)-α-diazoacetate **4i'** and 1,3-diketone **9a** (dibenzoylmethane) as model substrates. Based on the exhaustive screening, propargyl *α*-aryl-*α*-diazoacetates **4** (0.5 mmol), 1,3-diketone **9** (0.75 mmol), $Sc(OTf)_3$ (5 mol%) in DCE at room temperature proved to be the optimum reaction conditions. Encouraged by the initial success, we planned to explore the reactivity and scope of different propargyl *α*-aryl-*α*-diazoacetates **4** for the effective C-H bond functionalization of 1,3-diketones **9**. Moderately deactivated propargyl *α*-aryl-*α*-diazoacetates (**4b-4d**) reacted smoothly with different 1,3-diketones (**9a-9c**) under optimum reaction conditions to afford the corresponding desired products (**10ba-10dc**) in moderate to good yields (up to 79% yield, Table 4.1). Likewise, unactivated propargyl *α*-aryl-*α*-diazoacetate **4g** reacted with various 1, 3-diketones (**9a-9c**) under optimized reaction conditions to afford the corresponding desired products (**10ga-10gc**) in good yields (see Table 4.1). Electronically activated propargyl *α*-aryl-*α*-diazoesters (**4h-4i, 4k**) also reacted smoothly with different 1,3-diketones (**9a-9c**) under optimum reaction conditions to afford the corresponding desired products (**10ha-10ic, 10ka-10kc**) in good to excellent yields (up to 81% yield, Table 4.1). While the aliphatic 1,3-diketone such as 2,4-pentandione (**9d**) reacted with propargyl *α*-(4-methoxyphenyl)-*α*-diazoacetate **4i** at slightly higher temperature 50 ^{o}C to afford the corresponding C-H bond functionalization product (**10id**) in 57% yield (see Table 4.1).

Table 4.1 C-H bond functionalization of 1,3-diketones[a,b]





[a]Reaction conditions: Solution of *α*-aryl-*α*-diazoacetates **4** (0.5 mmol, 1 equiv.) in 1 mL DCE was added to the solution of $Sc(OTf)_3$ (5 mol%) and 1,3-diketone **9** (1.5 equiv., 0.75 mmol) in 2 mL DCE over 30 min at room temperature. [b]Isolated yield after purification by column chromatography (Time and yield are given in parenthesis), [c] the reaction was carried out at 50 °C.

In this chapter, we have successfully developed the new reagent-catalyst controlled effective C-H bond functionalization reaction to afford 1,3-dicarbonyl alkylation via scandium catalysis. We have developed a new series of *α*-aryl-*α*-diazoacetates with propargyl ester as the robust acceptor group and employed them as reagents for the effective C-H bond functionalization of 1,3-diketones at room temperature. The protocol avoids the use of excess, expensive catalysts, and ligands under practical reaction conditions at room temperature. The practicality of the protocol has been demonstrated by the gram scale synthesis.

Chapter 5: *Scandium(III) Triflate-Catalyzed One-Pot Synthesis of γ-Keto Esters from ß-Keto Acids and Propargyl α-Aryl-α-diazoacetates*

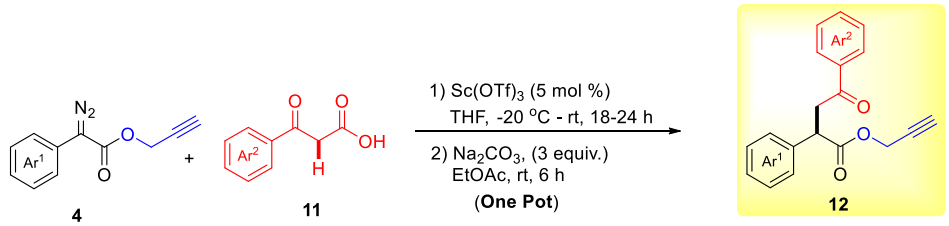
This chapter deals with the synthesis of *α*-substituted *γ*-keto esters starting from *ß*-keto acids and *α*-aryl-*α*-diazoacetates by exploring scandium catalysis. The chapter begins with an introduction to the synthesis of *γ*-keto esters by various traditional methods. Although various methods are available for the synthesis of *γ*-keto esters, novel catalytic methods are still in demand to widen the substrate scope. Likewise, the easy availability of starting materials and the cost-effective strategies are required to enhance the practicality of the protocols.

Based on the previous research findings we hypothesized that the reaction of *ß*-keto acids **11** and propargyl *α*-aryl-*α*-diazoacetates **4** under scandium catalysis might result in the formation of corresponding *γ*-keto esters. To validate the hypothesis, we chose propargyl *α*-(4-methoxyphenyl)-*α*-diazoacetate **4i** and benzoylacetic acid **11a** as model substrates. Based on the exhaustive screening, propargyl *α*-(4-methoxyphenyl)-*α*-diazoacetate **4i** (1 equiv.), *ß*-keto acid **11a** (2.5 equiv.), $Sc(OTf)_3$ (5 mol%) in dry tetrahydrofuran (-20 ^oC to room temperature, 24 h) proved to be the optimal reaction conditions. It was gratifying to note that under the optimal reaction conditions propargyl *α*-(4-methoxyphenyl)-*α*-diazoacetate **4i** and *ß*-keto acid **11a** reacted smoothly to afford the corresponding *α*-substituted *γ*-keto ester **12ia** in good yield (76% yield, Table 5.1).

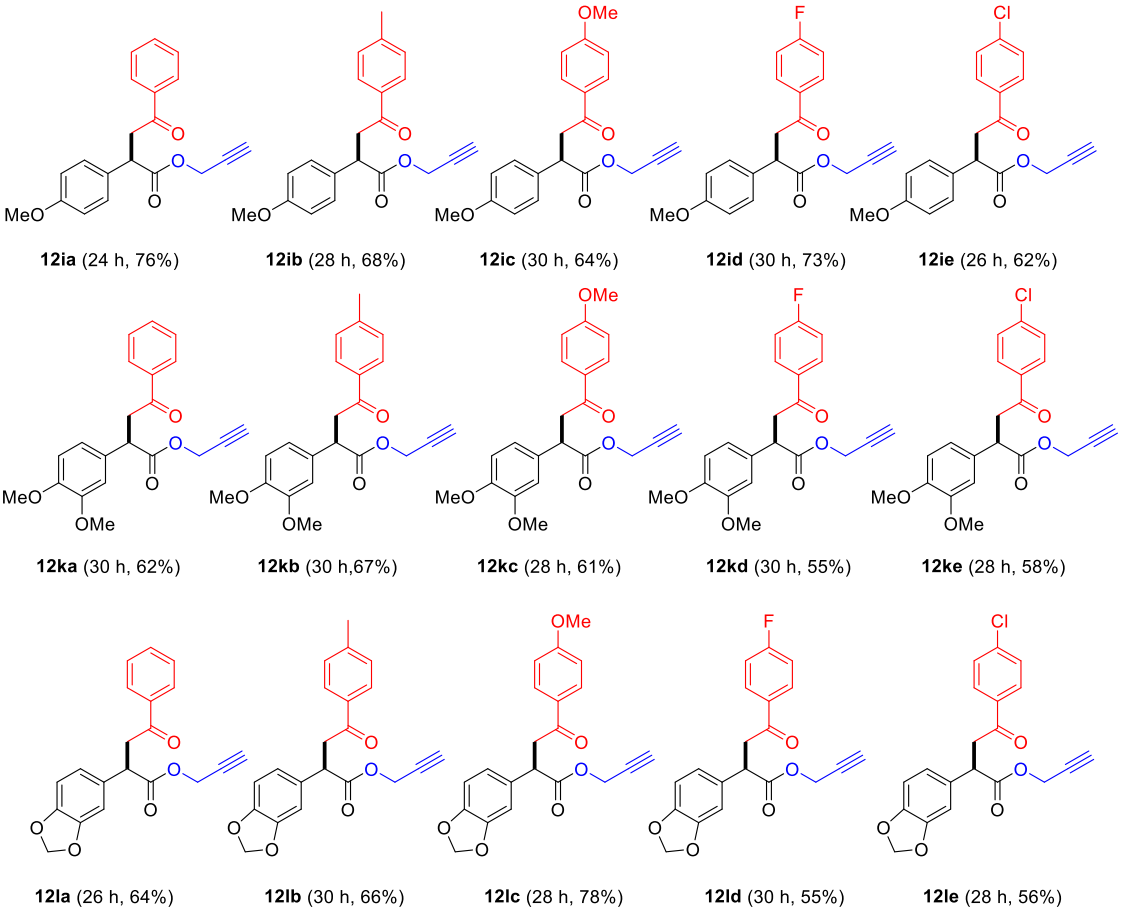
Encouraged by the initial result, we planned to generalize the protocol by exploring substrate scope for this reaction. The various propargyl *α*-aryl-*α*-diazoacetates (**4i**, **4k**, **4l**) reacted smoothly with different aromatic *ß*-keto acids (**11a-11e**) under the optimal reaction conditions to afford the corresponding desired products *α*-substituted *γ*-keto esters (**12ia-12ie**, **12ka-12le**) in moderate to good yields (up to 78%, see Table 5.1). It is very significant to

note that effective C-H bond functionalization, decarboxylation took place in one pot to afford the desired products α-substituted γ-keto esters.

Table 5.1 C-H bond functionalization of β-keto acids[a,b]



4 **11** **12**



12ia (24 h, 76%) **12ib** (28 h, 68%) **12ic** (30 h, 64%) **12id** (30 h, 73%) **12ie** (26 h, 62%)

12ka (30 h, 62%) **12kb** (30 h,67%) **12kc** (28 h, 61%) **12kd** (30 h, 55%) **12ke** (28 h, 58%)

12la (26 h, 64%) **12lb** (30 h, 66%) **12lc** (28 h, 78%) **12ld** (30 h, 55%) **12le** (28 h, 56%)

[a]Reaction conditions: 1) Solution of α-aryl-α-diazoacetates **4** (0.5 mmol, 1 equiv.) in 1.5 mL THF was added to the solution of $Sc(OTf)_3$ (5 mol%) and ß-keto acid **11** (2.5 equiv.) in 2 mL THF over 45 min under inert atmosphere; the reaction was monitored by TLC. 2) Na_2CO_3 (3 equiv.), EtOAc (4 mL) open atmosphere, [b]Isolated yield after purification by column chromatography (Time and yields are given in parenthesis).

In this chapter, we have successfully developed scandium(III) triflate-catalyzed the highly chemoselective one-pot synthesis of the α-substituted γ-keto ester using propargyl α-aryl-α-diazoacetates and ß-keto acids. The protocol avoids the use of expensive catalysts and ligands under practical reaction conditions. The practicality of the protocol has been demonstrated by the gram scale synthesis.

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(*Numbers of the substrates and products in the synopsis are different from those in the thesis. Please note that compound numbers have been assigned for the convenience in every chapter and number of few compounds may vary from chapter to chapter*)

Publications

1. **Balu S. Navale,** Ramakrishna G. Bhat* "Copper(I) iodide–DMAP catalyzed homo- and heterocoupling of terminal alkynes." *RSC Adv*. **2013**, *3*, 5220.

2. **Balu S. Navale,** Ramakrishna G. Bhat* "Scandium(III) triflate-catalyzed chemo- and regioselective C-H bond functionalization of arenes with propargyl *α*-aryl-*α*-diazoacetates." *Manuscript is communicated.*

3. **Balu S. Navale,** Debasish Laha, Ramakrishna G. Bhat* "Chemoselective C-H Bond functionalization of arenes bearing olefin or alkyne functionality with Propargyl *α*-Aryl-*α*-diazoacetates via Scandium Catalysis." *Manuscript under preparation.*

4. **Balu S. Navale,** Debasish Laha, Ramakrishna G. Bhat* "Propargyl *α*-aryl-*α*-diazoacetates as robust reagents for the effective C-H bond functionalization of 1,3-diketones via scandium catalysis. *Manuscript is communicated.*

5. **Balu S. Navale,** Debasish Laha, Ramakrishna G. Bhat* "Scandium(III) triflate-catalyzed one-pot synthesis of *γ*-keto esters from *ß*-keto acids and propargyl *α*-aryl-*α*-diazoacetates." *Manuscript under preparation.*

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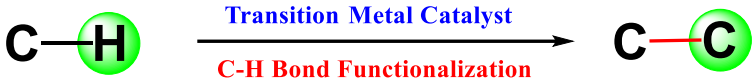
Chapter 1

Introduction to Transition Metal-Catalyzed C-H Bond Functionalization Reactions



Introduction to Transition Metal-Catalyzed C-H Bond Functionalization Reactions

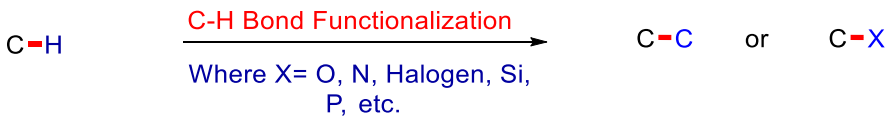
1

This chapter gives a brief overview of C-H bond functionalization reactions using transition metal catalysts and their importance over traditional C-C bond forming reactions. Due to high C-H bond dissociation energy, C-H bond functionalization is considered to be a highly challenging approach in organic synthesis. The important methods of C-H bond functionalization based on transition metal catalyzed oxidative coupling reactions and C-H bond functionalization using α-diazocarbonyl compounds have been discussed in detail.

1.1 C-H bond functionalization reactions

C-H bond functionalization of organic compounds is a powerful method for constructing new carbon-carbon (C-C) and carbon-heteroatom (C-X) bonds. C-H bond functionalization is a process in which the conversion of carbon-hydrogen bond into carbon-carbon bond or carbon-heteroatom bond is carried out irrespective of method and mechanism. (Scheme 1.1). As early as 1965 C-H bond functionalization reactions were demonstrated and nowadays these C-H bond functionalization reactions have become a powerful tool for constructing new carbon-carbon and carbon-heteroatom bond.[1] C-H bond functionalization is an important emerging field for the functionalization of organic compounds containing unreactive carbon-hydrogen bond. C-H bond functionalization earns significant attention from synthetic chemists due to its applications in the organic synthesis. C-H bond functionalization methods have been successfully employed in the synthesis of many natural products and biologically active compounds.[2] This has tremendous importance as some of these methods are greener and economic and reduces huge waste in the chemical synthesis.[3] The extensive variations and modifications have been carried out in C-H bond functionalization reactions to achieve a greater selectivity and improvement in yields of desired products.[1]

Development of novel catalyst system for the functionalization of the unreactive C-H bonds is a major challenge and of great interest to synthetic organic chemists. C-H bond functionalization involves different types of intermediates based on the mechanisms of the reactions. Some of the typical intermediates are organometallic intermediates, carbenoid or ionic intermediates.[1d,2f] The direct C-H bond functionalization reduces the number of synthetic steps and also the preactivation of starting materials is avoided thereby increasing the overall atom-efficiency.



Scheme 1.1 C-H bond functionalization

1.2 Challenges in C-H bond functionalization

Reactivity and selectivity are the two major and important challenges of C-H bond functionalization reaction. Most of the C-H bonds have high bond dissociation energies, and due to this, they are mostly inert for the required functionalizations (Figure 1.1).[4] Also, the C-H bond cleavage has a higher kinetic barrier, due to this reason C-H bond functionalization is a challenging process as well. Due to high bond dissociation energy for different C-H bonds, the conversion of the C-H bond to C-C or C-X bond is thermodynamically unfavorable process. Functionalization of alkyne C-H bond as well as arene C-H bond is difficult due to their relatively high bond dissociation energy.

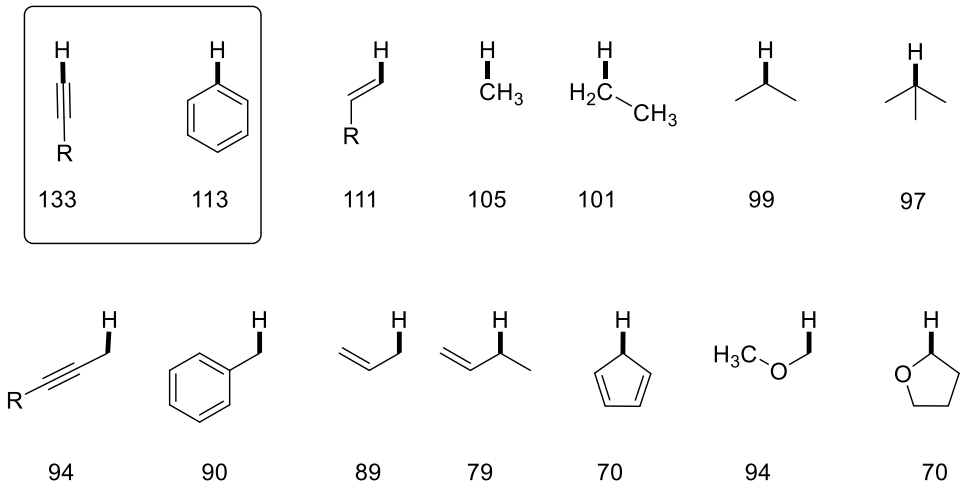
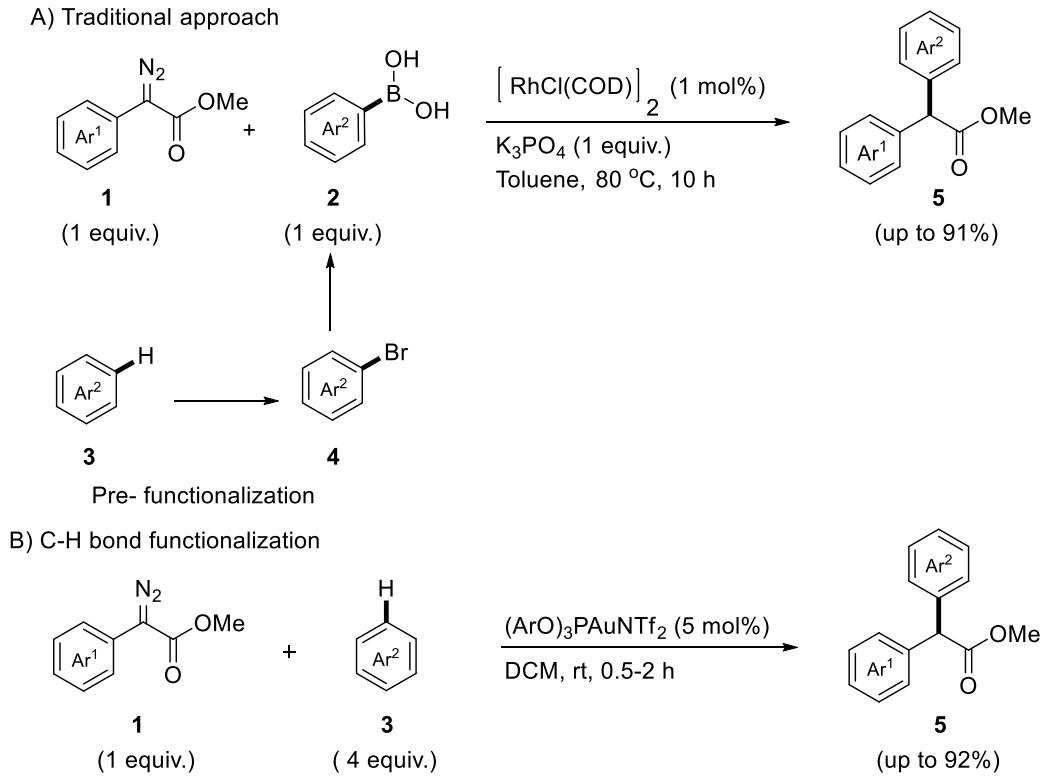


Figure 1.1 Bond dissociation energy of C-H bonds in kcal/mol

Another major challenge is to achieve the selectivity during C-H bond functionalization reactions. Likewise, most of the organic compounds will have different C-H bonds with comparatively similar bond energies and steric factors. Hence, achieving regioselective functionalization of C-H bond is very important and useful. Regioselectivity in C-H bond functionalization is generally achieved by controlling the electronic/steric properties of substrates or by using specific directing group which coordinates with a metal catalyst to bring about the functionalization.[1d]

1.3 Traditional methods versus C-H bond functionalization

The construction of new carbon-carbon or carbon-heteroatom bond is carried out by either using a traditional approach or C-H bond functionalization. The traditional method requires pre-functionalized starting materials and multiple steps to obtain a target molecule. It also generates a lot of waste during multistep synthesis thereby leading to environmental pollution. As an example, a traditional method has been compared with the direct C-H bond functionalization for the synthesis of diaryl acetate **5** starting from *α*-aryl-*α*-diazoacetate **1** (Scheme 1.2)

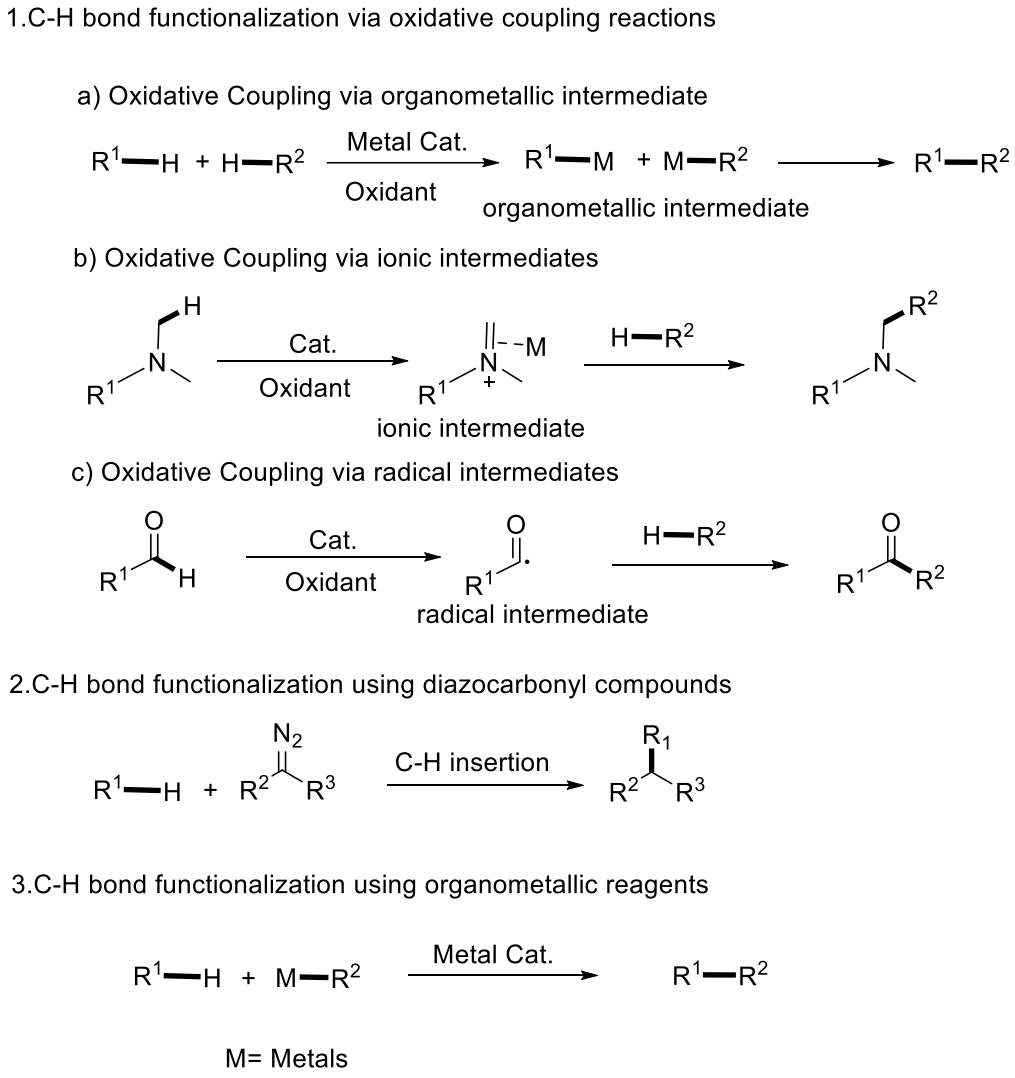


Scheme 1.2 Traditional method versus C-H bond functionalization

Anbarasan and co-workers reported the synthesis of *α*-diarylacetates **5** following a traditional route using pre-functionalized substrate aryl boronic acids **2.** Usually, aryl boronic acids **2** are synthesized starting from arenes **3** in a couple of steps. This traditional approach required the use of excess reagents to obtain the desired product **5** (Scheme 1.2 A).[5a] While, Xi et al. reported the synthesis of *α*-diarylacetates **5** by exploring the C-H bond functionalization strategy starting from simple and easily available arenes **3** and *α*-aryl-*α*-diazoacetate **1** in the presence of gold catalyst to obtain the desired product **5** in one pot (Scheme 1.2B).[5b]

1.4 Classification of C-H bond functionalization reactions

Based on the available plausible and proved mechanisms in the literature, the C-H bond functionalization reactions are further classified into the following types *viz.*1) C-H bond functionalization using oxidative coupling reactions, which is further subdivided into three types, namely, a) oxidative coupling via organometallic intermediates b) oxidative coupling via ionic intermediates c) oxidative coupling via radical intermediates. (2) C-H bond functionalization using *α*-diazocarbonyl compounds and lastly (3) C-H bond functionalization using organometallic reagents (Scheme 1.3).[1d]



Scheme 1.3 Classification of C-H bond functionalization reactions

As most of the thesis work is based on the C-H bond functionalization via oxidative coupling reaction involving organometallic intermediates and C-H bond functionalization using α-diazocarbonyl compounds, some of the selected examples of these types have been discussed in this chapter.

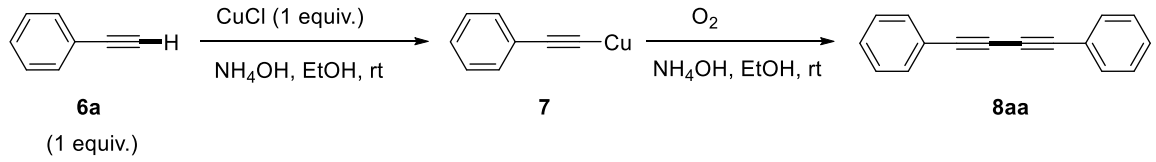
1.4.1 C-H bond functionalization using oxidative coupling reactions

The C-H bond functionalization using oxidative coupling reaction is further subdivided into following subtypes.

1.4.1a Oxidative coupling via organometallic intermediates

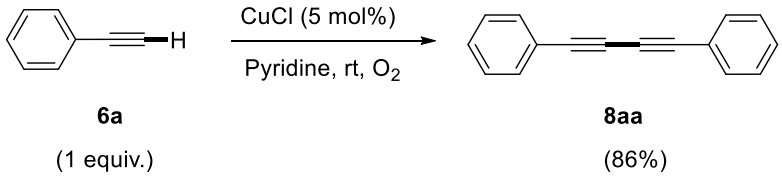
Oxidative coupling reaction that involves organometallic intermediate is one of the important methods for C-H bond functionalization. The oxidative coupling involves two simple hydrocarbons, and pre-functionalized starting materials are not required for the construction of a new carbon-carbon bond. This approach is greener and more economical as it avoids the use of pre-functionalized starting materials.[6] As mentioned earlier, due to the inert nature of the C-H bond and to achieve chemoselectivity/ regioselectivity during the C-H bond functionalization makes it a challenging task and is one of the important fields in organic synthesis. The researchers have utilized different metal catalysts and various oxidants for this type of C-H bond functionalization. Some of the important selected examples of this type of C-H bond functionalization are discussed.

C-H bonds present in the hydrocarbons have different types of hybridizations, i.e., Csp-H, Csp^2-H and Csp^3-H. The C-H bonds with same or different hybridizations have been explored in the oxidative coupling reactions to achieve the chemo- and regioselectivity. As early as 1869, Glaser reported the oxidative coupling of phenylacetylene **6a** using a stoichiometric amount of copper chloride and oxygen as an oxidant to afford the conjugated 1,3-diyne **8aa** (Scheme 1.4).[7a]



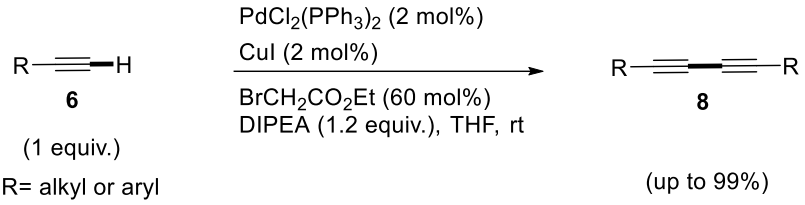
Scheme 1.4 C-H bond functionalization using Glaser coupling

In 1960, Hay reported the synthesis of conjugated 1,3-diyne **8aa** via an oxidative coupling reaction of phenylacetylene **6a** in the presence of catalytic amount of copper chloride (5 mol%) and oxygen as an oxidant. The use of pyridine was necessary for the transformation to afford the desired product in good yield (Scheme 1.5).[7b]



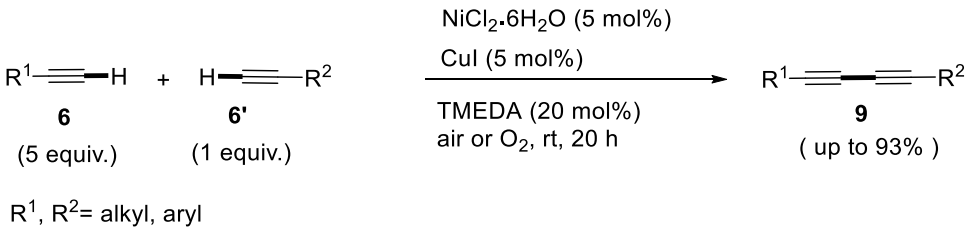
Scheme 1.5 Hay coupling for the C-H bond functionalization

Glaser coupling and related modified methods have been proved to be important for the synthesis of conjugated symmetric 1,3-diynes **8**, as these protocols avoid the use of pre-functionalized alkynes.[7c] Later, the Glaser type coupling was further modified to increase the efficiency by using other transition metals such as palladium or nickel as co-catalyst along with the copper salts.[7d-7e] In 2002, Lie et al. reported the synthesis of aliphatic and aromatic conjugated symmetric 1,3 diynes **8** by using Pd/Cu co-catalyzed oxidative homocoupling of terminal alkynes **6** to in excellent yields (up to 99%, Scheme 1.6).[7d]



Scheme 1.6 Pd and Cu catalyst system for homocoupling of terminal alkynes

Heterocoupling is relatively more challenging, and the coupling of two different terminal alkynes **6** usually leads to unwanted homocoupling products **8**. The desired heterocoupling products can be synthesized in good yields by using one of the terminal alkyne in excess. In 2009, Lei and co-workers developed a method for the synthesis of conjugated unsymmetrical 1,3-diynes **9** by using $NiCl_2$ and CuI as catalysts in the presence of base TMEDA and air as an oxidant to obtain the desired unsymmetrical 1,3-diynes in good to excellent yields (Scheme 1.7).[7e] Aliphatic, as well as aromatic conjugated unsymmetrical 1,3-diynes, were successfully synthesized by this method.

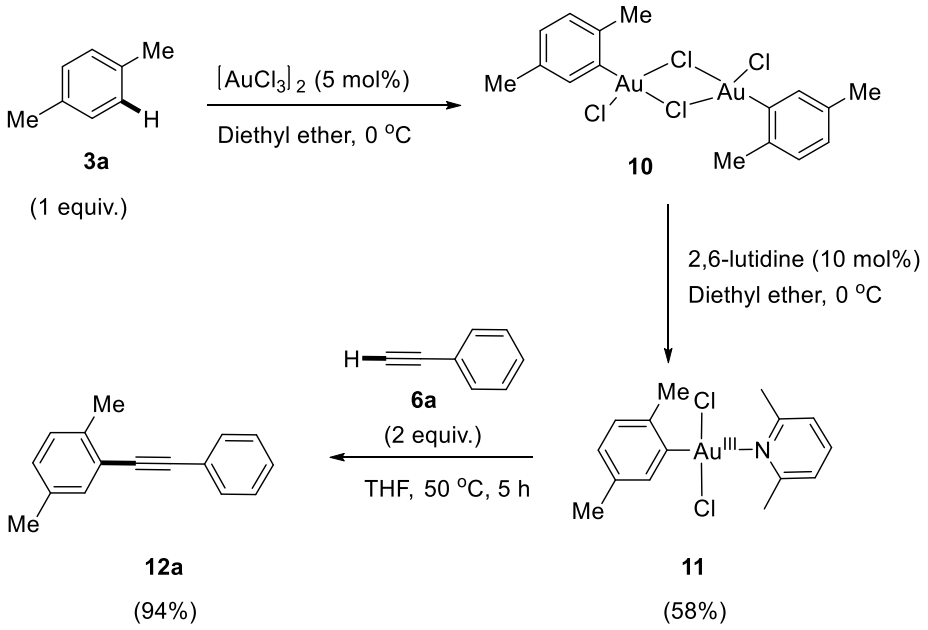


Scheme 1.7 Heterocoupling of terminal alkynes

The efficient formation of Csp-Csp^2 bond is an important step in the synthesis of arylalkynes **12**. Traditionally arylalkyne moieties have been synthesized by using Sonogashira coupling between aryl halides and terminal alkynes. However, in Sonogashira coupling pre-functionalized aromatic compounds are required to afford the desired coupled

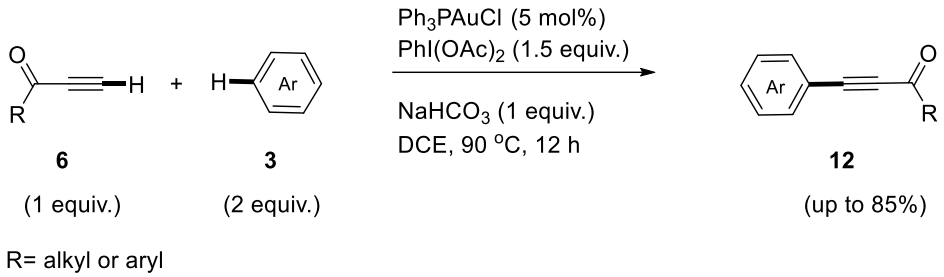
products.[8a,b] The oxidative cross-coupling between arenes and terminal alkynes via double C-H bond functionalization have been reported in the recent years. This method avoids the use of pre-functionalized starting materials. Some of the important examples are discussed here.

In 2001, Fuchita and co-workers reported the synthesis of arylgold (III) complex **10** from simple arene **3a** via the C-H bond activation. Further, the arylgold (III) complex **10** upon reaction with 2,6-lutidine results in the active gold complex **11**. The reaction of this gold complex **11** with phenylacetylene **6a** afforded the desired product arylalkyne **12a** in excellent yields (Scheme 1.8).[8c] However, the stoichiometric amount of gold complex **11** was necessary for the conversion. This useful transformation paved the way for the catalytic version of oxidative coupling reactions between terminal alkynes and simple unactivated arenes.



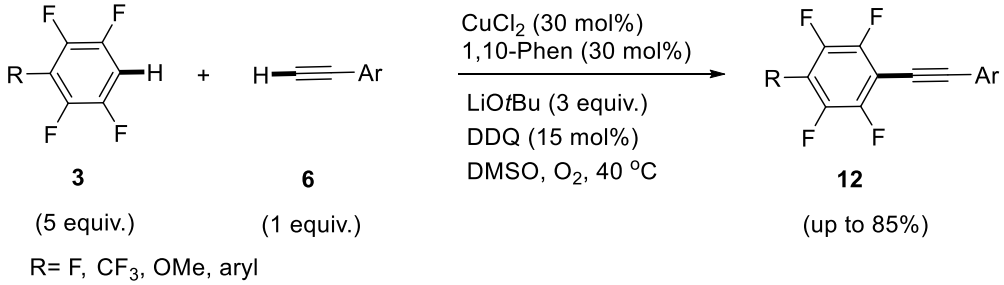
Scheme 1.8 C-H bond functionalization via gold complex

Nevado and co-workers in 2010, reported the oxidative coupling reaction between terminal alkynes **6** and electron-rich arenes **3** by using a gold catalyst.[8d] Electron rich arenes, as well as heteroarenes, reacted with the electron deficient terminal alkynes **6** in the presence of catalytic amount of Ph_3PAuCl (5 mol%)and $PhI(OAc)_2$ as an oxidant to furnish the desired products **12** in good yields (Scheme 1.9).



Scheme 1.9 Gold-catalyzed C-H bond functionalization of terminal alkynes

In 2010, Su and co-workers carried out the copper-catalyzed C-H bond functionalization of terminal alkynes **6** with the electron deficient polyfluoroarenes **3**. Polyfluoroarenes **3** in the presence of catalytic amount of $CuCl_2$, 1,10-phenanthroline as ligand and other additives reacted with the terminal alkynes **6** to afford the desired arylalkynes **12** in very good yield (up to 85%, Scheme 1.10).[9] The reaction was carried out in the presence of a readily available copper catalyst.

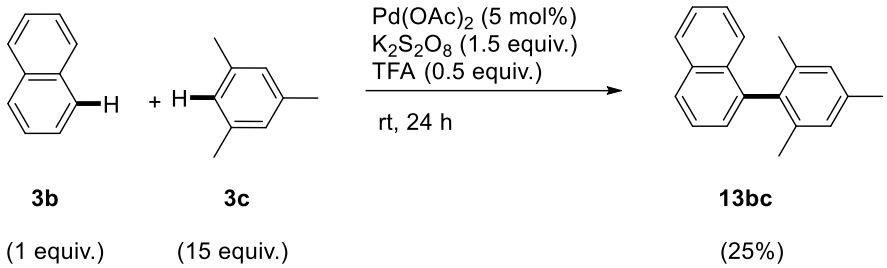


Scheme 1.10 Copper catalyzed C-H bond functionalization of electron deficient arenes

The formation of the Csp^2-Csp^2 bond is a key step in the synthesis of biaryl compounds. Biaryl compounds have also been synthesized using traditional coupling reactions such as Suzuki coupling, Stille coupling, Hiyama coupling, and Negishi coupling.[10] However, these coupling reactions require the use of pre-functionalized aromatics such as aryl halides and organometallic reagents along with the transition metal catalysts. Although these methods are very popular and common for the synthesis of biaryl moieties, however, it requires pre-functionalized starting materials and proves to be less economical. The direct oxidative cross-coupling reactions between two simple arenes would be the most economical approach for the synthesis of biaryl compounds as it avoids prefunctionalization of arenes and more number of steps. To achieve the selectivity in cross-coupling reactions between two simple arenes by using simple catalytic system remains as a challenging task for the synthetic

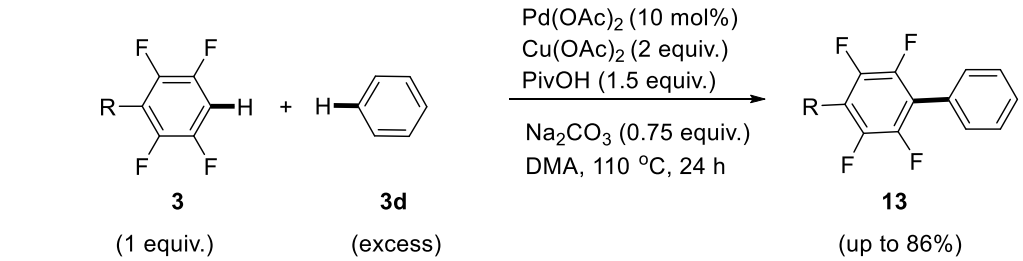
organic chemists.[11a] Some of the important selected examples for the synthesis of biaryl compounds via arene C-H bond functionalization have been discussed below.

In 2006 Li et al. reported the oxidative coupling reaction between two different arenes in the presence of $Pd(OAc)_2$ as a catalyst along with $K_2S_2O_8$ as an oxidant. One of the arenes **3c** was taken in excess for this reaction to afford the desired product **13bc**. Although the yield of the desired product **13bc** was poor, yet this method demonstrated the strength of the protocol for the coupling of two unactivated arenes via the oxidative coupling reaction (Scheme 1.11).[11b]



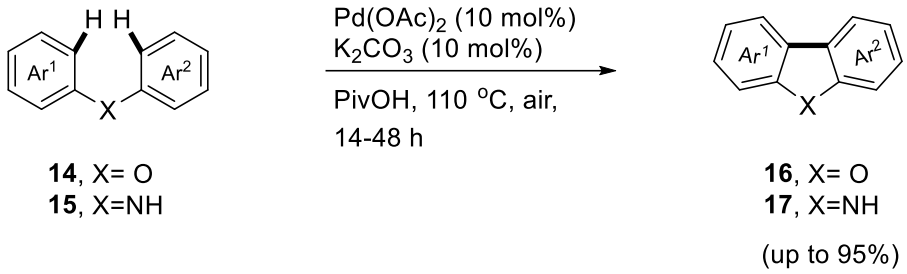
Scheme 1.11 Pd-catalyzed oxidative cross-coupling between two different arenes

Later, Su and co-workers developed a useful method for the synthesis of biaryls via the oxidative cross-coupling between polyfluoroarenes **3** and simple unactivated arene such as benzene **3d**. They utilized the catalytic amount of $Pd(OAc)_2$ (10 mol %) along with $Cu(OAc)_2$ as an oxidant to afford the desired products **12** in good yields (Scheme 1.12).[11c]



Scheme 1.12 C-H functionalization of fluorinated arenes

In 2008, Fagnou and co-workers reported an intramolecular oxidative coupling reaction of diaryl ethers **14** as well as diarylamine **15** using the catalytic amount of $Pd(OAc)_2$ and mild base to afford the corresponding cyclization products dibenzofurans **16** and carbazoles **17** respectively in good to excellent yields (Scheme 1.13).[11d]



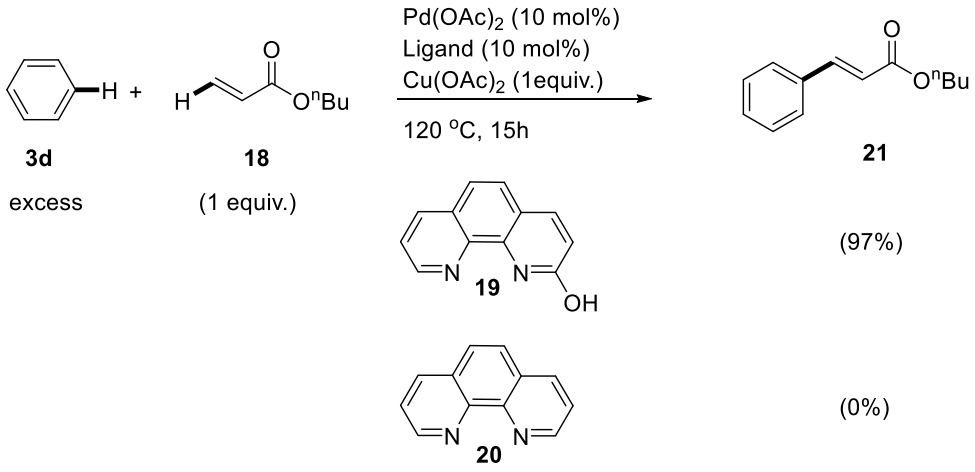
14, X= O
15, X=NH

16, X= O
17, X=NH

(up to 95%)

Scheme 1.13 Intramolecular oxidative C-H bond functionalization of arenes

Substituted olefins are valuable building blocks, and the synthesis of this scaffold via economically viable routes are of prime importance. The oxidative Heck type alkenylation of simple arenes would be a more economical approach for the synthesis of substituted olefins. In the year 2014, Duan and co-workers reported the oxidative cross-coupling between arene such as benzene **3d** and acrylate **18** in the presence of catalytic amount of $Pd(OAc)_2$, 2-hydroxy-1,10-phenanthroline **19** as a ligand and copper acetate as an oxidant to furnish the desired product **21** in 97% yield.[12] The ligand, 2-hydroxy-1,10-phenanthroline **19** proved to be crucial and played an important role in this reaction. Similar ligand such as 1,10-phenanthroline **20** was not effective for this transformation (Scheme 1.14).



3d
excess

18
(1 equiv.)

19

20

21

(97%)

(0%)

Scheme 1.14 The ligand effect in the oxidative cross-coupling

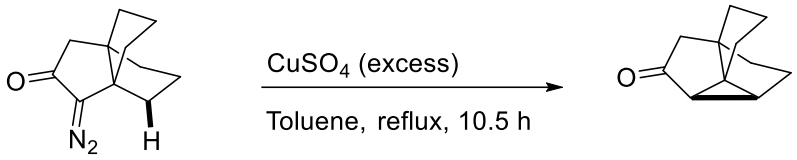
1.4.2 C-H bond functionalization using *α*-diazocarbonyl compounds

α-diazocarbonyl compounds are very useful and versatile precursors in synthetic organic chemistry.[13] These compounds can be easily prepared from readily available starting materials. *α*-diazocarbonyl compounds are very useful building blocks in synthetic organic chemistry due to its reactivity and wide applications in various chemical transformations. *α*-

diazocarbonyl compounds have been used in the synthesis of different natural products and biologically active compounds.[14] During a chemical reaction, the α-diazocarbonyl compound liberates the nitrogen molecule to afford a reactive intermediate either due to the presence of a catalyst or due to the thermal or photochemical conditions. The α-diazocarbonyl compounds usually leads to the formation of reactive intermediates such as free carbene, metal carbenoid, diazonium cations, zwitterionic intermediate or ylide.[13d] α-Diazocarbonyl compounds have been utilized in different reactions such as Wolf rearrangement, cyclopropanation of alkenes and alkynes, Buchner reaction and in X-H insertion (X = O, N, S, C, Si, etc.) reactions.[13d]

The use of α-diazocarbonyl compounds has been explored in the catalytic C-H bond functionalization reactions to construct new carbon-carbon bonds. The development of new catalyst-reagent systems and the modifications of these for the reactivity of α-diazocarbonyl compounds remains an interesting area of research in fields of C-H bond functionalization. The transition metal catalyzed C-H bond functionalization using α-diazocarbonyl compounds is one of the most important strategy nowadays to construct the carbon-carbon bond. Some of the selected examples of intramolecular and intermolecular C-H bond functionalization utilizing α-diazocarbonyl compounds have been discussed here.

In 1942, Meerwein et al. reported the first C-H bond functionalization reaction using the α-diazocarbonyl compound.[15a] In the year 1983, Wrobel et al. reported the copper sulfate-mediated intramolecular C-H bond insertion reaction of the α-diazo ketone **21** in the synthesis of modhephene **22**. The reaction was carried out using an excess amount of copper sulfate under refluxing condition in toluene (Scheme 1.15).[15b]

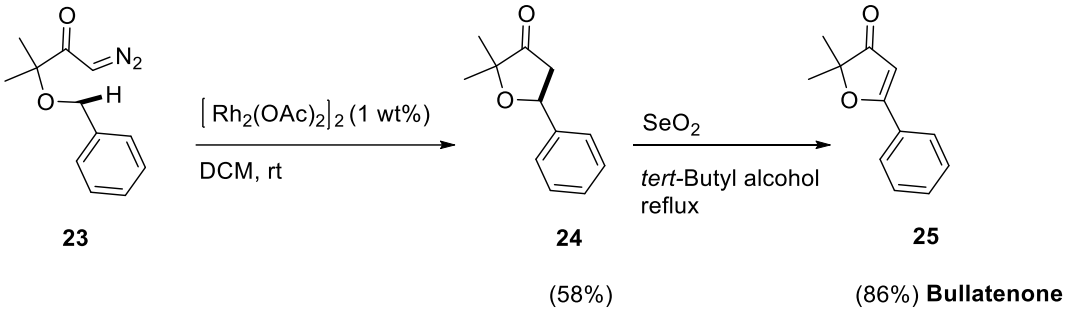


21 (1 equiv.) → **22** (76%)

Scheme 1.15 Copper sulfate-mediated C-H bond functionalization of α-diazo ketone

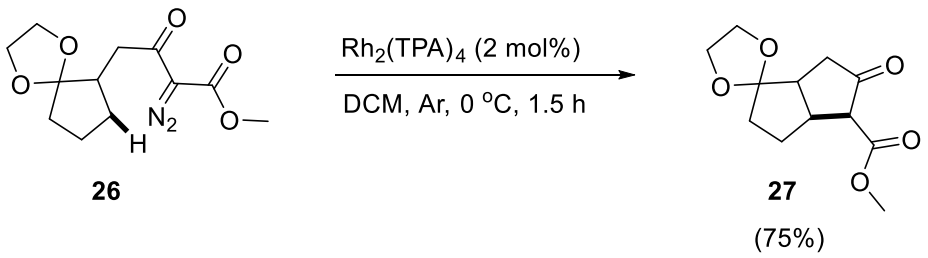
In 1989, Adams and co-workers utilized the C-H bond functionalization strategy for the synthesis of bullatenone. They carried out the C-H functionalization of benzylic C-H bond adjacent to the ether oxygen in the presence of other aliphatic carbon-hydrogen bonds.

α-Diazocarbonyl compound **23** underwent an intramolecular C-H insertion reaction in the presence of rhodium catalyst (1 wt%) to furnish the corresponding cyclized product **24** which upon further oxidation with selenium dioxide afforded the bullatenone **25** (Scheme 1.16).[15c]



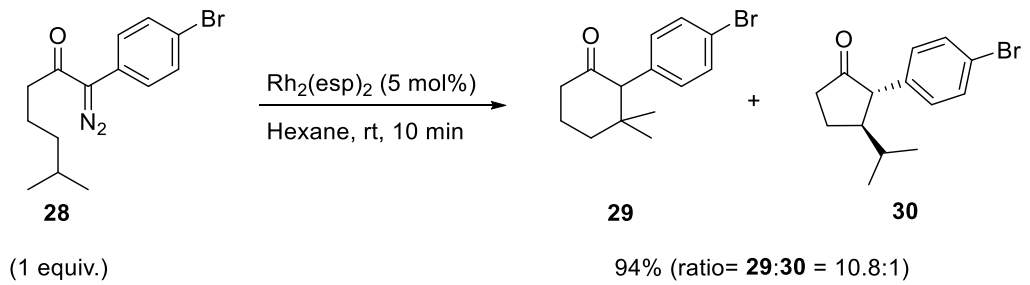
Scheme 1.16 Synthesis of bullatenone via C-H bond functionalization strategy

In 1992, Ikegami and co-workers reported the rhodium catalyzed intramolecular C-H bond functionalization of *α*-diazocarbonyl compound **26** to furnish the tricyclic compound **27**. Ikegami and co-workers screened a variety of rhodium catalysts for this transformation. Bulkier ligand such as triphenylacetate enhanced the selectivity in this transformation (Scheme 1.17).[15d]



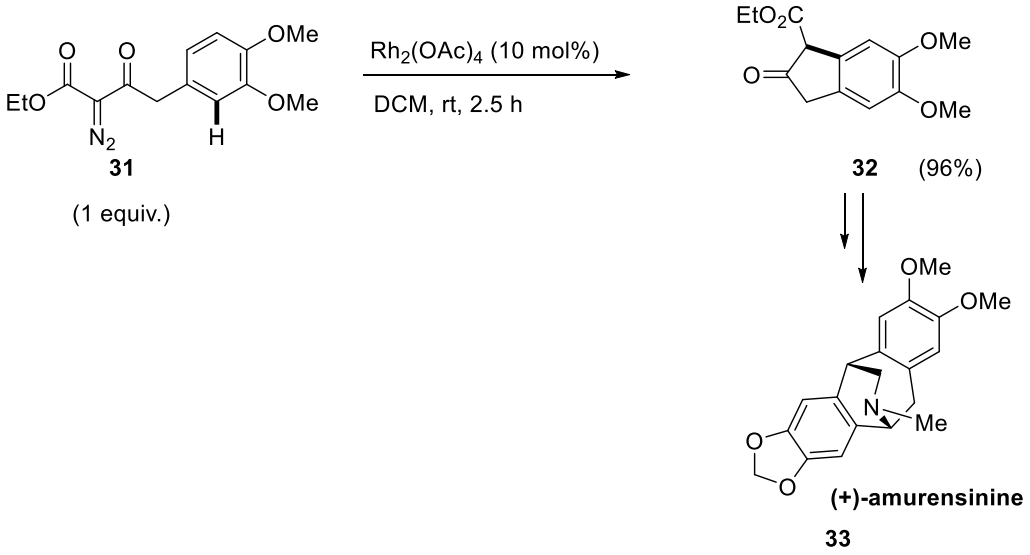
1.17 Rhodium-catalyzed C-H bond functionalization of *α*-diazocarbonyl compound

Recently, Taber and co-workers carried out the rhodium catalyzed synthesis of substituted cyclohexanone **29** and substituted cyclopentanone **30** starting from *α*-diazo ketone **28**. *α*-diazo ketone **28** underwent a highly selective C-H bond functionalization in the presence of $Rh_2(esp)_2$ (5 mol%). It was observed that the six-membered ring formation was dominant over the five-membered ring formation (Scheme 1.18).[15e]



Scheme 1.18 Rhodium-catalyzed intramolecular C-H bond functionalization

In 2006, Stoltz and co-workers successfully applied the rhodium catalyzed intramolecular C-H bond functionalization strategy for the synthesis of (+)-amurensinine. The key step in the total synthesis was the intramolecular Csp^2-H bond functionalization of arene part with the α-diazocarbonyl compound **31**. In the presence of the $Rh_2(OAc)_4$ compound **31** underwent intramolecular cyclization to afford the desired product **32** in 96% yield. The protocol successfully explored the use of α-diazocarbonyl compounds in natural product synthesis via C-H bond functionalization (Scheme 1.19).[15f]

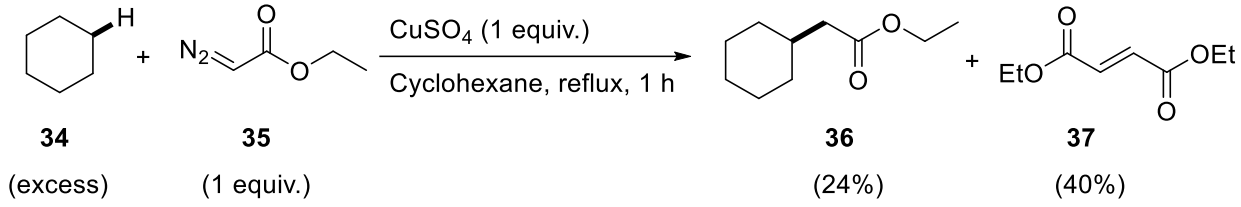


Scheme 1.19 Rhodium-catalyzed intramolecular C-H bond functionalization of arene

Intermolecular C-H bond functionalization using α-diazocarbonyl compound is a relatively more challenging task due to the competitive dimerization reaction of α-diazocarbonyl compounds.[13a] Nowadays, intermolecular C-H bond functionalization using diazo compounds have been extensively studied, and many research groups are working in this field to achieve chemoselectivity and regioselectivity with high efficiency.[13d,15] Different transition metal catalysts have been proved to be very useful for carbenoid based C-H bond

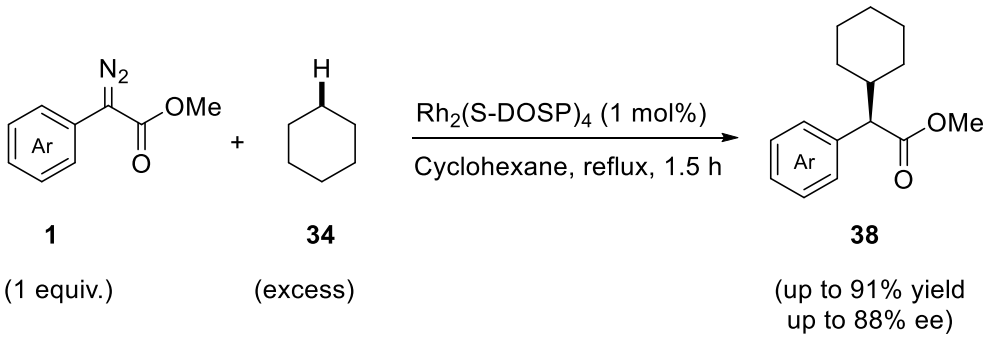
functionalization reactions.[14] To achieve high chemoselectivity, and regioselectivity a variety of modified diazocarbonyl compounds have been synthesized. Likewise, the development of newer catalyst-reagent systems remains an interesting and challenging area for a synthetic organic chemist. Some of the important contributions in the intermolecular C-H bond functionalization using *α*-diazocarbonyl compounds has been presented.

In 1974, Scott and co-workers reported the very first copper catalyzed C-H bond insertion reaction of cyclohexane **34** with ethyl diazoacetate **35**. Along with the C-H bond insertion product **36**, the carbene dimerization side product **37** was formed in major amount during this transformation. Although the yield of the desired product **36** was poor, yet the strategy proved the concept of intermolecular C-H bond insertion reaction (Scheme 1.20).[16a]



Scheme 1.20 C-H bond functionalization of cyclohexane

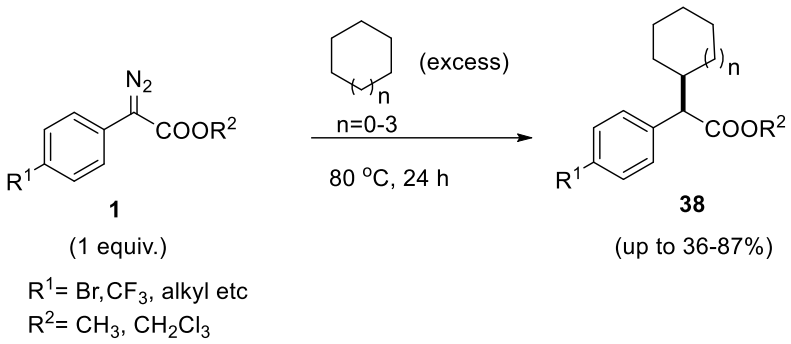
In 1997, Davies and co-workers carried out the highly enantioselective C-H bond functionalization of cyclohexane **34** using chiral rhodium(II) tetraprolinate catalyst-Rh_2((S)-DOSP)$_4$ and donor/acceptor-type methyl *α*-aryl-*α*-diazoacetates **1** (Scheme 1.21).[16b] This transformation afforded the desired products **38** in good to excellent yields with very good



Scheme 1.21 Rhodium-catalyzed C-H bond functionalization of cyclohexane

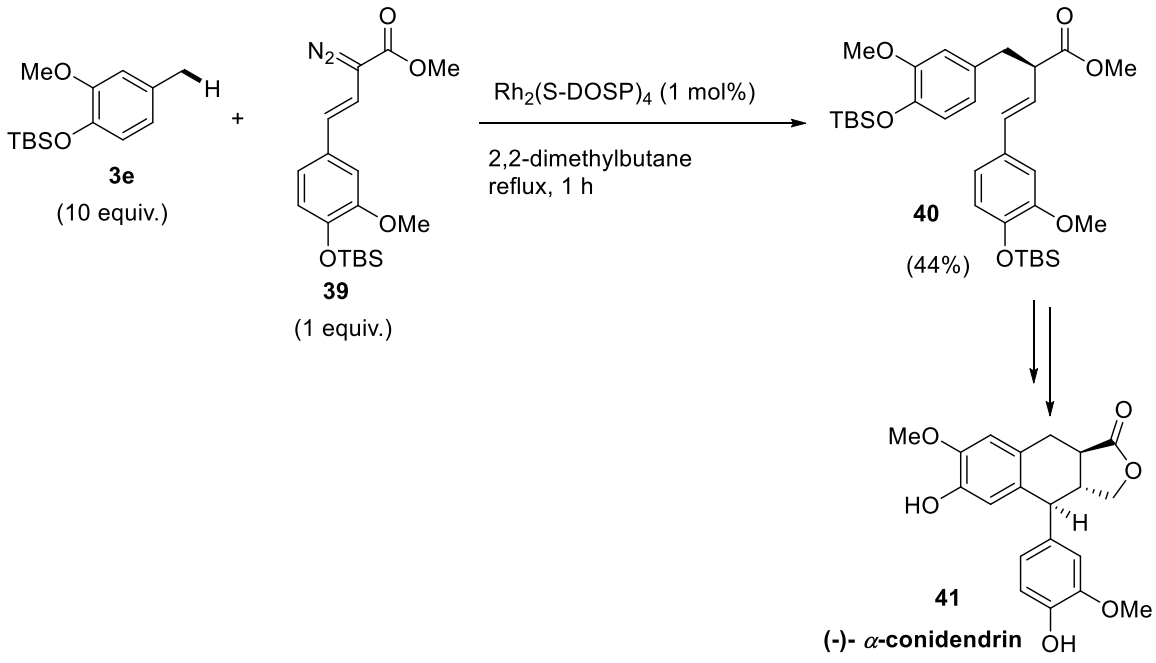
enantioselectivity. This was a breakthrough result in enantioselective C-H bond functionalization reactions via carbenoid formation.

In 2017, Tortoreto et al. reported the metal free C-H bond functionalization of cycloalkanes using *α*-aryl-*α*-diazoacetates **1**. *α*-Aryl-*α*-diazoacetates was refluxed in different cycloalkanes at 80 °C to furnish the corresponding desired products **38**.[16c] Various donor-acceptor type *α*-diazocarbonyl compounds were utilized in this transformation to access desired products. The reaction was believed to proceed via the formation of free carbene at a higher temperature (Scheme 1.22).



Scheme 1.22 Metal free C-H bond functionalization of alkanes

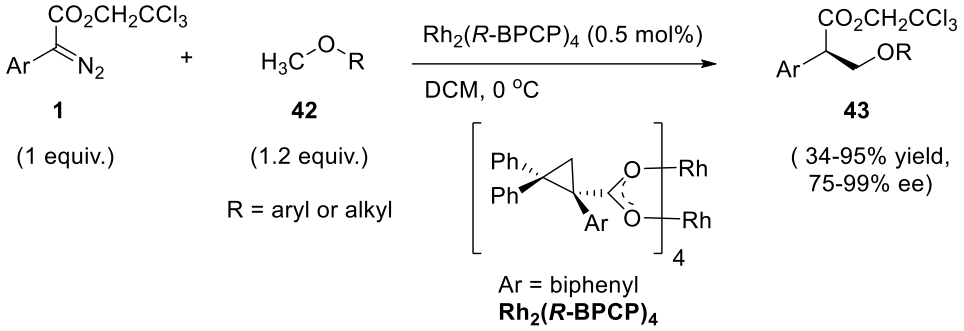
Chemoselective C-H bond functionalization of the benzylic C-H bond is challenging. Davies and co-workers reported an enantioselective intermolecular benzylic C-H bond functionalization starting from compound **3e** and *α*-diazocarbonyl compound **39** using Rh_2((S)-DOSP)$_4$ as a catalyst.[16d,e] The benzylic C-H bond was selectively functionalized in



Scheme 1.23 Synthesis of (-)-*α*-conidendrin via benzylic C-H bond functionalization

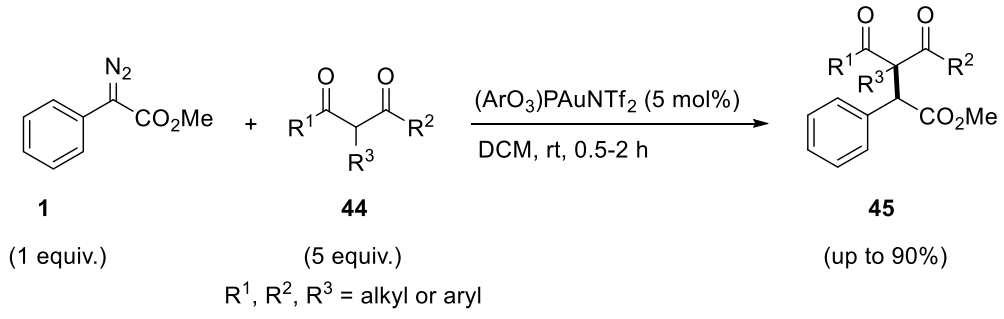
the presence of other aromatic C-H bonds. This protocol was successfully employed for the total synthesis of (-)- α-conidendrin **41** (Scheme 1.23).[16e]

Recently, Davies and co-workers carried out the highly chemoselective and enantioselective C-H bond functionalization of various methyl ethers **42** using the catalytic amount of Rh_2(*R*-BPCP)$_4$ and 2,2,2-trichloroethyl α-aryl-α-diazoacetates **1** as reagents. This transformation proceeded via rhodium (II) carbenoid intermediate. They have synthesized new α-aryl-α-diazoacetate reagent that contains 2,2,2-trichloroethyl (TCE) ester. This TCE ester group was proved to be responsible for the enhancement in regioselectivity and enantioselectivity of the C-H bond functionalization (Scheme 1.24).[16f]



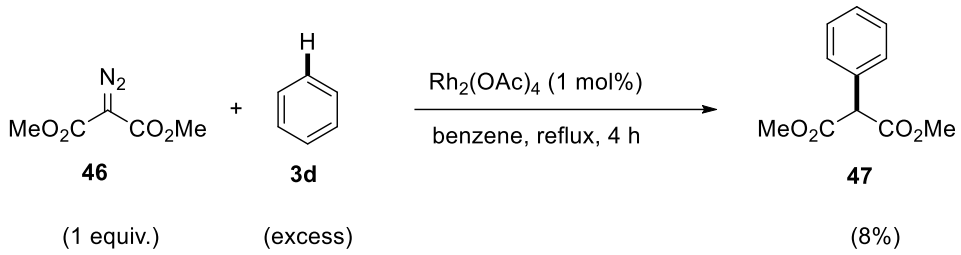
Scheme 1.24 C-H bond functionalization of various methyl ethers

In 2014, Xi et al. reported the C-H bond functionalization of 1,3-dicarbonyl compounds **44** by using a gold catalyst and methyl α-phenyl-α-diazoacetate **1** as a reagent. This protocol proved to be very useful in the direct synthesis of tricarbonyl compounds **45**. 1,3-Dicarbonyl compounds **44** were taken in excess for this transformation to afford the desired products **45** in good yields. This transformation was highly chemoselective afforded the desired C-H bond functionalization products **45** (Scheme 1.25).[16g]



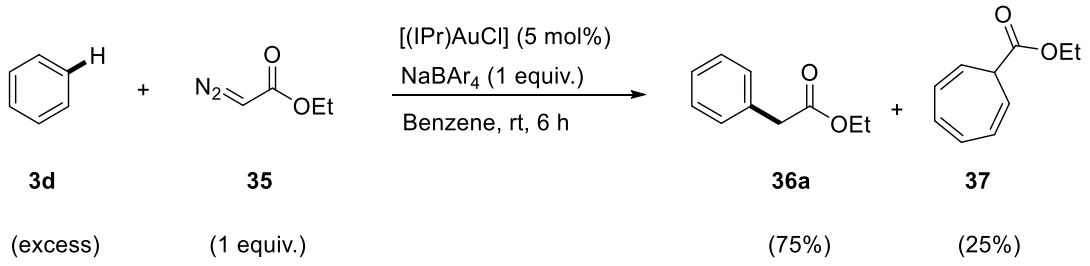
Scheme 1.25 Gold-catalyzed C-H bond functionalization of 1,3-dicarbonyl compounds

Intermolecular aromatic C-H bond functionalization using α-diazocarbonyl compounds is one of the important approaches in the field of synthetic organic chemistry. Various transition metal catalyzed C-H bond functionalization of arenes have been reported in the literature. In 2001, Livant and co-workers disclosed the aromatic C-H insertion product **47** starting from benzene and acceptor-acceptor type α-diazocarbonyl compound **46** in presence rhodium catalyst though in very low yield.[17a] Benzene was used in excess for this useful transformation (Scheme 1.26).[17a]



Scheme 1.26 Arene C-H bond functionalization using Rhodium catalyst

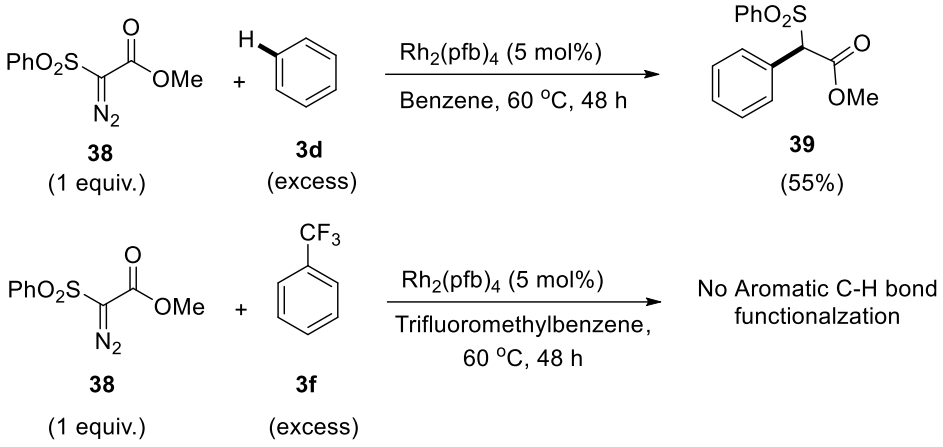
In 2005, Pérez and co-workers reported an interesting arene C-H bond functionalization of benzene **3d** with ethyl diazoacetate **35** in the presence of gold catalyst. The desired product **36a** was obtained in 75% yield along with the side product cycloheptatriene **37** (Scheme 1.27).[17b] This study demonstrated the use of gold catalyst in the aromatic C-H bond insertion reactions. This important result led to the open new area of gold-catalyzed aromatic C-H bond functionalization reactions using α-diazocarbonyl compounds.



Scheme 1.27 Benzene C-H bond functionalization with ethyl diazoacetate using a gold catalyst

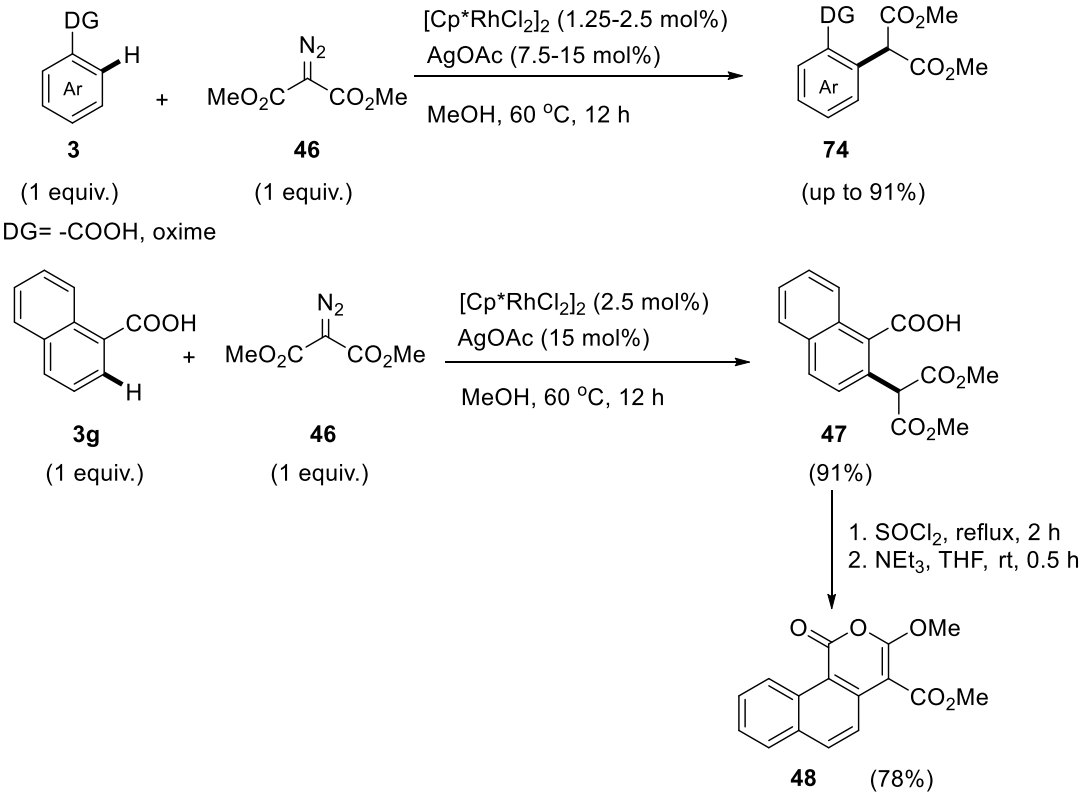
In 2009, Park et al. carried out arene C-H bond functionalization using rhodium catalyst.[17c] In this transformation, benzene **3d** underwent C-H bond functionalization with the acceptor-acceptor type α-diazocarbonyl compound **38** in the presence of catalytic amount of

$Rh_2(pfb)_4$ (5 mol%) to afford the corresponding product **39**. This reaction was carried out at 60 ^oC for two days. However, electronically deactivated arene such as trifluoromethyl benzene **3f** was found to be nonreactive under the reported conditions (Scheme 1.28).



Scheme 1.28 $Rh_2(pfb)_4$ catalyzed C-H bond functionalization of arenes

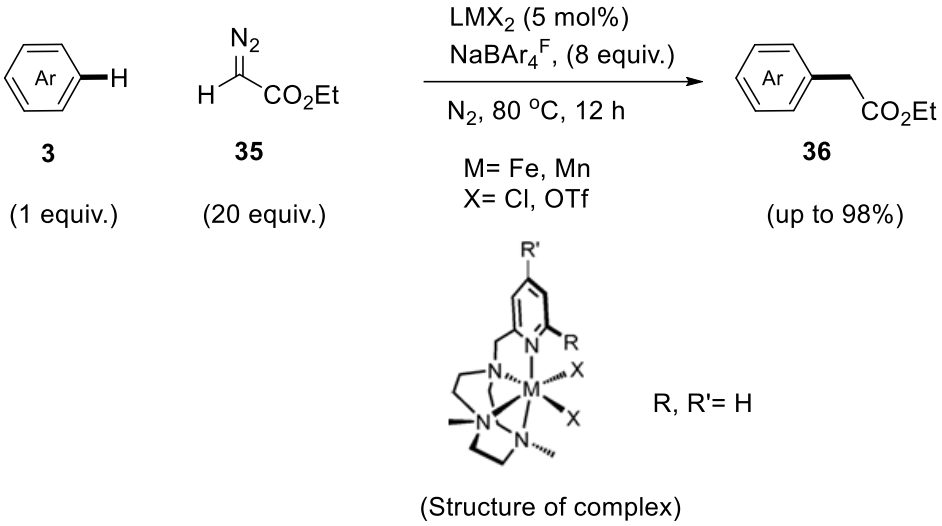
In 2012, Yu and co-workers applied the directing group strategy for the C-H bond functionalization of arenes **3** with α-diazomalonates **46** using rhodium catalyst. Aromatic



Scheme 1.29 Directing group strategy in C-H bond functionalization

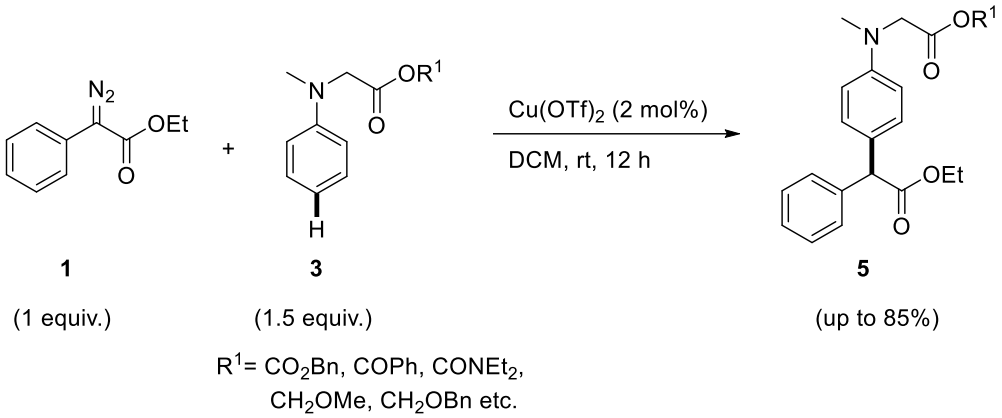
compounds containing carboxyl and oxime substituents **3** were utilized for the C-H bond functionalization. The C-H bond functionalization was highly regioselective, and the functionalization happened at the *ortho* position of the directing group to afford the desired products **47**. The functionalized product obtained was further utilized in the synthesis of isocoumarin **48** (Scheme 1.29).[17d]

Recently, Conde et al. carried out the C-H bond functionalization of simple arenes **3** with a large excess of ethyl diazoacetate **35** in the presence of iron or manganese catalyst along with co-catalyst and $NaBAr_4^F$. Arenes **3** underwent highly chemoselective C-H bond functionalization under the reaction conditions to afford the desired products **36** in good yields. The presence of $NaBAr_4^F$ was necessary for this transformation (Scheme 1.30).[17e]



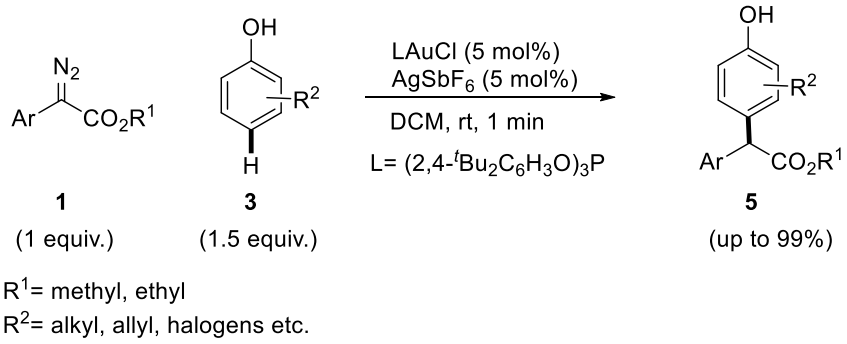
Scheme 1.30 Fe/Mn catalyzed C-H bond functionalization of arenes

Diarylacetate subunits are present in many biologically active compounds and natural products.[18] The synthesis of diarylacetates using C-H bond functionalization is an economical approach, and some of the important selected examples have been presented. In 2010, Tayama and co-workers reported the aromatic C-H bond functionalization of electronically activated *N*,*N*-disubstituted anilines **3** with phenyl diazoacetate **1** as a reagent in the presence of copper catalyst to afford the corresponding α-diarylacetates **5**. The transformation was highly chemoselective as well as regioselective. The functionalization led to the formation of *para* C-H bond functionalized product exclusively. However, the limitation of the protocol was that it worked only with electronically activated arenes with a limited substrate scope (Scheme 1.31).[19]



Scheme 1.31 Copper-catalyzed C-H bond functionalization of *N*,*N*-disubstituted aniline

Recently, Yu et al. reported a highly chemoselective C-H bond functionalization of phenols **3** with *α*-diazoesters **1** as reagents in the presence of a gold catalyst. In this transformation, C-H bond insertion took place selectively, and the anticipated O-H insertion side products were not observed during the reaction. This was the first protocol wherein, the unprotected phenols **3** were directly functionalized with *α*-diazoesters **1** using gold catalyst to afford the corresponding *α*-diarylacetates **5**. This transformation proved to be highly *para* selective (Scheme 1.32).[20]



Scheme 1.32 Gold-catalyzed C-H bond functionalization of unprotected phenols

1.5 Conclusions

Transition metal catalyzed C-H bond functionalization reactions have been proved to be environmentally benign and are gaining great importance in fields of synthetic organic chemistry. The C-H bond functionalization via oxidative coupling reactions have been widely used in synthetic organic chemistry and remains as an important research area for the synthetic chemists. Likewise, α-diazocarbonyl compounds are an important class of reagents and have been effectively explored for the C-H bond functionalization reactions. Though there are many protocols using these strategies, still there are many unmet challenges to be explored. In subsequent chapters, we have explored the C-H bond functionalization of terminal alkynes using oxidative coupling reactions as well as successfully demonstrated the use of novel modified α-diazocarbonyl compounds in C-H bond functionalization reactions.

1.6 References

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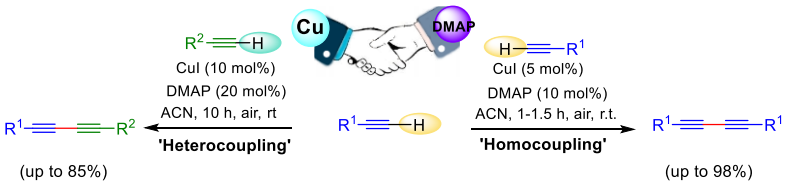
Chapter 2

Copper(I) Iodide-Catalyzed Oxidative C-H Bond Functionalization of Terminal Alkynes



Copper(I) Iodide-Catalyzed Oxidative C-H Bond Functionalization of Terminal Alkynes

2

This chapter describes the use of convenient catalyst system (CuI and DMAP) for the effective oxidative homo- and heterocoupling of terminal alkynes under aerobic conditions at room temperature. We have explored the catalytic use of DMAP for the efficient oxidative C-H bond functionalization of terminal alkynes for the first time. More importantly this catalyst system (CuI-DMAP) does not require the use of excess amount of base and specialized ligands in the oxidative coupling of terminal alkynes. Some of the salient features of this protocol are mild reaction conditions, economical, good yields and environmentally friendly.

2.1 Introduction

1,3-diyne is an important core to many molecules and is widespread in nature, and some of the molecules containing 1,3-diyne core elicits potent bioactivity against some of the major diseases (Fig 2.1).[1] 1,3-Diyne scaffolds have been extensively explored in constructing molecular boxes as high-efficiency hosts in supramolecular chemistry.[2] These conjugated diyne scaffolds have been used as essential core building blocks for the construction of advanced materials such as conjugated polymers, liquid crystals, and molecular wires.[3]

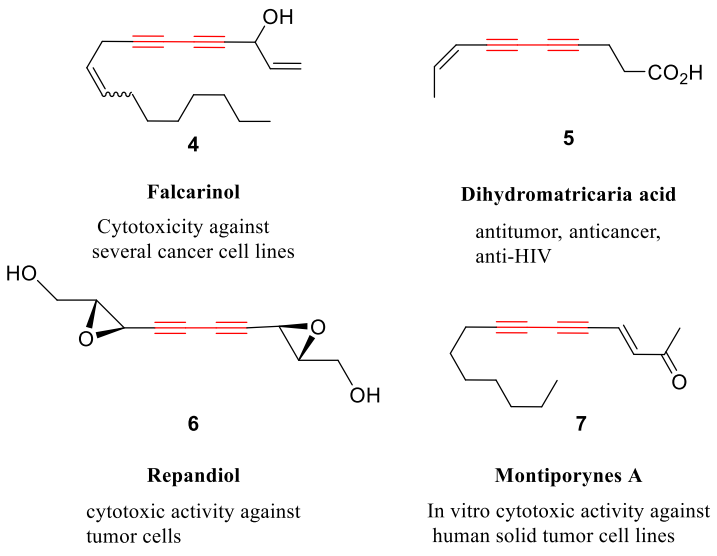
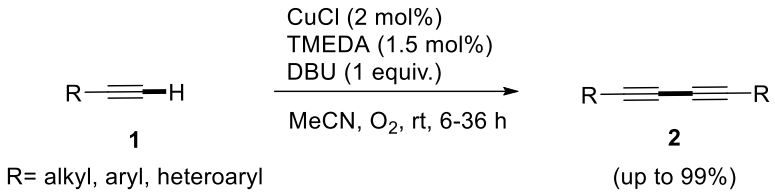


Fig 2.1 Biologically active 1,3-diynes

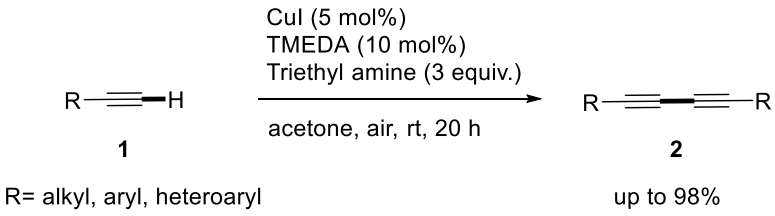
The carbon-carbon triple bond is one of the most versatile and explored functional groups in organic chemistry.[4] The design and synthesis of 1,3-diyne scaffold have been a topic of interest for a very long time since the discovery of oxidative dimerization of copper acetylides by Glaser.[5] Further this method was modified and improved by Eglinton and Galbraith in the mid 20th century.[6] Later, Hay also modified this method by using the catalytic amount of copper salt and excess of pyridine to afford the desired compound 1,3-diyne in good yield.[7]

In 2009, Beifuss and co-workers carried out an oxidative coupling reaction between terminal alkynes **1** in the presence of copper catalyst and TMEDA as a ligand along with the DBU as a base under oxygen atmosphere. Aliphatic as well as aromatic terminal alkynes underwent oxidative homocoupling reactions to afford the symmetrical 1,3-diynes **2** in good to excellent yields (Scheme 2.1).[15a]



Scheme 2.1 Ligand promoted C-H bond functionalization of terminal alkynes

In 2011, Zhang and co-workers reported the homocoupling of terminal alkynes in the presence of catalytic amount of CuI (5 mol%) and TMEDA (10 mol%) as a ligand. An excess amount of base-Et_3N and air as an oxidant was required to bring out this transformation. A variety of aliphatic as well as aromatic terminal alkynes **1** was subjected to the oxidative homocoupling reaction to afford the corresponding symmetrical 1,3-diynes **2** in good to excellent yields (Scheme 2.2).[15b]



Scheme 2.2 Cu(I) iodide-catalyzed homocoupling of terminal alkynes

Various research groups have revived this coupling by varying the metal catalysts over the past few years.[8] Glaser coupling has been further modified to increase the efficiency, by exploring the use of Pd/Cu-catalyst system for the coupling reactions[9] and also the catalyst system having a combination of Cu and Ag[10a] or Ni[10b,c] salts have been explored in the literature. Recently, the gold catalysts have been explored as an efficient catalyst for cross-coupling of terminal alkynes.[10d,e]

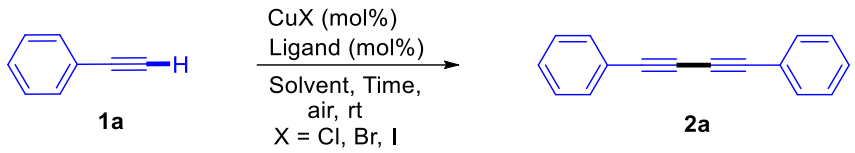
The homocoupling of terminal alkynes using copper-catalyst proved to be an attractive method as copper is readily available, less expensive and relatively environmentally friendly and less toxic.[11] Different methods for the oxidative coupling of terminal alkynes have been optimized by utilizing different copper salts, bases, and ligands. However, some of the major shortcomings of these standard methods are the use of stoichiometric amounts of copper salts,[12] excess oxidants,[13] high temperature,[12b,14] excess bases,[13c,15] co-catalysts[9f,10a,b] and low to moderate yields for aliphatic alkynes[15a]. Also, it essentially required a careful selection of the ligand-base combination for the efficient coupling. There is a great scope for the development of novel and practical protocols for the homo- and hetero-coupling of terminal alkynes.

Herein, in this chapter, we present a simple, practical and efficient catalyst system comprising of CuI-DMAP for the effective homo- and heterocoupling of terminal alkynes via the C-H bond functionalization under aerobic conditions.

2.2 Results and Discussion

In order to explore the feasibility of the coupling we commenced our initial work with phenyl acetylene **1a** as a model substrate for the C-H bond functionalization via oxidative homocoupling reaction using copper (I) salts and base at room temperature under air. As shown in Table 2.1, different catalyst systems were screened in different solvents for optimizing the reaction conditions. Based on our initial studies we observed that reaction of **1a** in presence of 2 mol% of CuI and 4 mol% of DMAP in acetonitrile afforded the 1,3-diyne **2a** in 97% in 10 hours (Entry 18, Table 2.1). Interestingly, an increase in the amount of CuI (5 mol%) and DMAP (10 mol%) furnished the compound **2a** in 97% yield in relatively shorter reaction time from 10 h to 1 h (Entry 9, Table 2.1). It was gratifying to note that in spite of the reduction in catalyst loading of CuI (1 mol%) and DMAP (2 mol%), the reaction proceed slowly by affording **2a** (69%, Entry 19, Table 2.1) in 12 h.

Table 2.1 Optimization of the reaction conditions for the coupling of terminal alkyne[a,b]



Entry	CuX (mol%)	Ligand (mol%)	Solvent	Time (h)	Yield of 2a[b] (%)
1	CuI (5)	Pyridine(10)	MeCN	3.5	21
2	CuI (5)	Pyridine(10)	CH_2Cl_2	24	10
3	CuI (5)	Pyridine(10)	Acetone	24	16
4	CuI (5)	Imidazole (10)	MeCN	18	Trace
5	CuI (5)	Imidazole (10)	Acetone	24	Trace
6	CuI (5)	Imidazole (10)	CH_2Cl_2	24	Trace
7	CuI(5)	Et_3N(10)	MeCN	24	Trace
8	CuI(5)	TMEDA(10)	MeCN	1	15
9	**CuI (5)**	**DMAP(10)**	**MeCN**	**1**	**97**
10	CuCl(5)	DMAP(10)	MeCN	1	33
11	CuBr(5)	DMAP(10)	MeCN	2.5	48
12	CuI (5)	DMAP(10)	Acetone	1	66
13	CuI (5)	DMAP(10)	CH_2Cl_2	1	22
14	CuI (5)	DMAP(10)	CH_2Cl_2	10	96
15	CuI (5)	DMAP(10)	Acetone	4	97
16	CuI (10)	DMAP(20)	MeCN	0.75	98
17	CuI (5)	DMAP(5)	MeCN	1	69
18	CuI (2)	DMAP(4)	MeCN	10	97
19	CuI (1)	DMAP(2)	MeCN	12	69
20	CuI(5)	Piperidine(10)	MeCN	1	20
28	$Cu(OAc)_2$(5)	DMAP(10)	MeCN	1	18
29	CuI (5)	No Ligand	MeCN	18	-

[a]Reaction conditions: Terminal alkynes **1a** (1 mmol, 1 equiv.), Solvent (4 mL), air; the reaction was monitored by TLC. [b]Isolated yield after column chromatography.

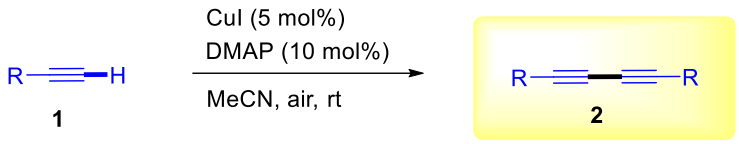
We observed that reaction of **1a** proceeded slowly in presence of catalytic amount of CuCl and CuBr (Entry 10, 11, Table 2.1). Further, different solvents were screened in order to optimize the homocoupling. It was observed that polar solvents such as acetonitrile and acetone greatly enhanced the rate of the reaction. The homocoupling **1a** was very sluggish in

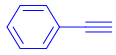
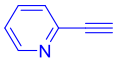
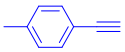
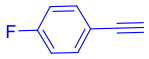
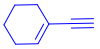
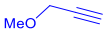
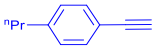
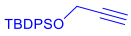
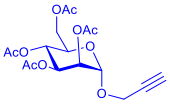
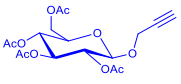
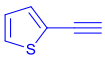
presence of TMEDA (10 mol%) and afforded **2a** in poor yield (entry 8, Table 2.1). Similarly, many other ligands proved to be not very effective in enhancing the rate of the reaction (Entry 1-8, 20, Table 2.1). We observed that the reaction failed to proceed in the absence of any ligand (Entry 21, Table 2.1). It is very important to note that combined catalyst system comprising of CuI (5 mol%) and DMAP(10 mol%) enhanced the rate of homocoupling of **1a** significantly. Based on experimental observations we believe that CuI-DMAP synergistic interactions facilitated the coupling reaction more efficiently. We also observed that reaction did not work in the absence of either of the catalysts. The presence of both CuI and DMAP proved to be necessary for the efficient oxidative Coupling. CuI (5 mol%), DMAP (10 mol%) and atmosphere of air (oxygen) as an oxidant at ambient temperature emerged as an optimum reaction condition for the homocoupling of terminal alkynes (Entry 9, Table 2.1).

Encouraged by the initial success, we turned our attention towards generalizing the protocol by extending the substrate scope under the optimized reaction conditions. Different terminal alkynes (**1a-1k**, Table-2.2) were subjected for the homocoupling reaction under the optimum reaction conditions to afford the corresponding 1,3-diynes (**2a-2k,** Table-2.2) in excellent yields (up to 98%) in relatively short time.

Bivalent sugars with a rigid linker are well known for their utility in lectin cross-binding studies.[16] In order to synthesize dimeric diyne glycosides, we prepared the peracetylated propargyl glycosides (**1l**, **1m,** Table-2.2) following the reported glycosylation procedures with propargyl alcohol.[17] These glycosides (**1l**, **1m**) containing terminal alkynes, under the homocoupling optimum reaction conditions, furnished the corresponding dimeric diyne glycosides (**2l**, **2m,** Table-2.2) in good yields (up to 87%) in relatively shorter time. The coupling of these glycosides proved to be more practical in comparison to the earlier reported procedures.[16,18]

Table 2.2 CuI-DMAP catalyzed homocoupling of terminal alkyne[a-c]

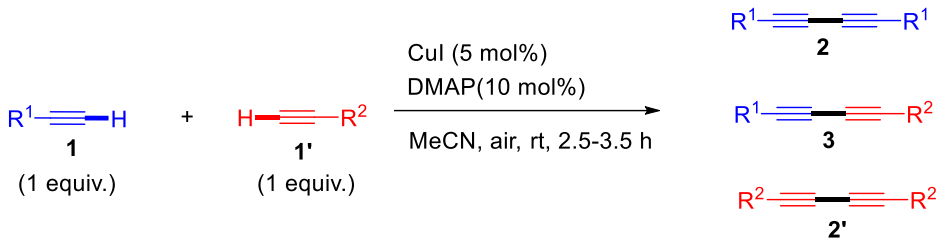


Entry	1	2	Time (h)	Yield[b] (%)	Entry	1	2	Time (h)	Yield[b] (%)
1		**2a**	1	97	8		**2h**	1.5	87
2		**2b**	1	98	9		**2i**	1	92
3		**2c**	1.5	85	10		**2j**	1.5	82
4		**2d**	1	87	11		**2k**	1.5	94
5		**2e**	1	96	12		**2l**	1.5	87
6		**2f**	1	90	13		**2m**	3.5	71[c]
7		**2g**	1	94					

[a]Reaction conditions: Terminal alkynes **1** (1 mmol, 1 equiv.), CuI (5 mol%), DMAP (10 mol%) MeCN (4 mL), air; the reaction was monitored by TLC. [b]Isolated yield after column chromatography; [c]10 mol% CuI and 20 mol% DMAP was used.

Having obtained this success, we further planned to employ this protocol cross-coupling of two different terminal alkynes. In order to study systematically, we initially treated two different terminal alkynes (**1** and **1′**) in equimolar ratio (1:1) with CuI (5 mol%) and DMAP (10 mol%) in acetonitrile at room temperature under aerobic conditions for 2.5-3.5 h. The reaction afforded the corresponding coupled products (**2, 3** and **2′**) in a very good yields (up to 96%) and up to 47% of the cross-coupled product diynes **3** (Table 2.3).

Table 2.3 Heterocoupling of terminal alkynes in equimolar ratio[a,b]



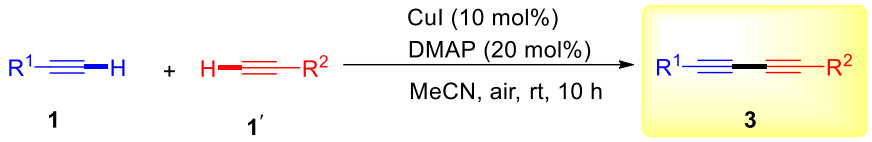
Entry	—R1	—R2	Time (h)	Overall Yield[b] (%)	Yield[b] 2 (%)	Yield[b] 3 (%)	Yield[b] 2' (%)
1	**1d**	**1a**	2.5	93	22	44	27
2	**1d**	**1b**	3	96	23	47	26
3	**1d**	**1c**	3.5	83	32	33	18

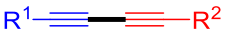
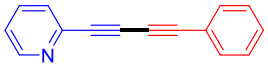
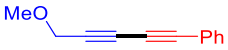
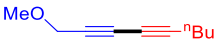
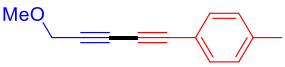
[a]Reaction conditions: Terminal alkynes **1** (1 mmol, 1 equiv.), terminal alkynes **1′** (0.5 mmol, 1 equiv.), CuI (5 mol%), DMAP (10 mol%), MeCN (4 mL), air; the reaction was monitored by TLC. [b]Isolated yield after purification by column chromatography.

Later, when two different terminal alkynes (ratio 1:5) were subjected to the coupling reaction with the increased catalytic amounts of CuI (10 mol%) and DMAP (20 mol%) in acetonitrile under aerobic conditions, the corresponding cross-coupled products (**3a-3e,** Table 2.4) were obtained in relatively very good yields (up to 85%).

The protocol tolerated a variety of functional groups under the optimized reaction conditions of both homo- and heterocoupling. It is also important to note that coupling proceeded very smoothly without the use of any metal co-catalysts or excess base unlike the previous reported procedures.[9f,10a,b]

Table 2.4 Synthesis of unsymmetric conjugated diynes[a,b]



Entry				**3**	Yield[b] %
1	**1h**	**1a**		**3a**	82
2	**1h**	**1i**		**3b**	85
3	**1d**	**1a**		**3c**	72
4	**1d**	**1c**		**3d**	70
5	**1d**	**1c**		**3e**	74

[a]Reaction conditions: Terminal alkynes **1** (1 mmol, 1 equiv.), terminal alkynes **1′** (5 mmol, 5 equiv.), CuI (10 mol%), DMAP (20 mol%), MeCN (6 mL), air; reaction was monitored by TLC. [b]Isolated yield after purification by column chromatography.

2.3 Conclusions

In conclusion, we have successfully developed a practical and efficient catalyst system comprising of CuI-DMAP for the effective homocoupling of terminal alkynes at room temperature. The homocoupling proved to be successful and the 1,3-diynes were synthesized in good to excellent yields in relatively shorter reaction time. We have also demonstrated that this newer catalyst system is also reasonably efficient in catalyzing the heterocoupling. To the best of our knowledge for the first time, we have demonstrated the use of commercially available and non-hazardous DMAP for the smooth coupling of terminal alkynes. We have also successfully avoided the use of excess base and metal co-catalysts in this protocol. This protocol proved to be practical, economical and environmentally friendly.

2.4 Experimental Section

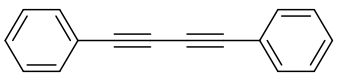
2.4.1 General

Unless otherwise noted, all reactions were carried out with distilled and dried solvents using oven-dried glassware. All reagents were purchased from commercial sources and used as received unless otherwise indicated. Thin-layer chromatography (TLC) was performed using silica gel 60 GF_{254} pre-coated aluminum backed plates (2.5 mm) with detection by UV light. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6. Chemical shifts in ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from tetramethylsilane with the solvent resonance as the internal standard or from the residual solvent peak as internal standard and *J* values are given in Hz. ^{13}C NMR spectra are reported as δ in ppm downfield from tetramethylsilane and relative to the signal of chloroform-d and DMSO-d_6. ^{13}C NMR spectra were recorded with complete proton decoupling. Mass samples were analyzed by high-resolution mass spectrometry using HRMS-TOF MS AP^{+} and HRMS ESI TOF. FT-IR spectra were obtained using a FT-IR spectrophotometer as neat and reported in cm^{-1}. Optical rotations were measured on a polarimeter. Melting points were measured in an open glass capillary and values are uncorrected.

2.4.2 General procedure A for homocoupling of terminal alkynes

A mixture of phenylacetylene **1a** (1.0 mmol), CuI (5 mol%) and DMAP (10 mol%) in acetonitrile (4 mL) was stirred at room temp temperature in the open atmosphere. The reaction mixture was stirred at room temperature for 1-1.5 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The crude product obtained was purified by column chromatography over silica gel to furnish 1,3-diyne **2a** as a white crystalline solid.

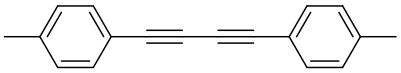
1, 4-diphenylbuta-1, 3-diyne (2a):



Compound **2a** was synthesized following the general procedure (A). The product was obtained as a white crystal (0.0981 g, 97% yield): R_f = 0.7 petroleum ether/EtOAc (95:5); m.p.:87-88 ^{o}C; IR (neat) cm^{-1}: 3017, 2925, 2144, 1480, 1436, 909, 747; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (dd, *J* = 7.8, 1.8 Hz, 4H), 7.39-7.32 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$):

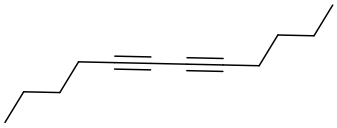
132.6, 129.3, 128.6, 121.9, 81.7, 74.0. HRMS (AP^+): Calcd for $C_{16}H_{10}(M^+)$: 202.0783, Found: 202.0784.

1,4-di-*p*-tolylbuta-1,3-diyne (2b):



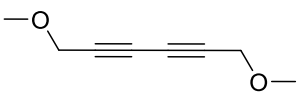
Compound **2b** was synthesized following the general procedure (A). The product was obtained as a white crystal (0.113 g, 98% yield): R_f = 0.8 petroleum ether/EtOAc (95:5); m.p.:182-183 ^oC; IR (neat) cm^{-1}: 3024, 2918, 2131, 1644, 1499, 1452, 1038, 807. ^1H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, J = 8.2 Hz, 4H), 7.14 (d, J = 8.2 Hz, 4H), 2.37 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 139.6, 132.5, 129.4, 118.9, 81.7, 73.6, 21.8. HRMS (AP^+): Calculated for $C_{18}H_{15}$ $(M+H)^+$: 231.1174, Found: 231.1182

Dodeca-5, 7-diyne (2c):



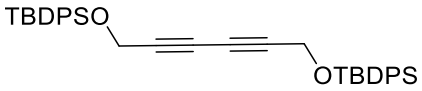
Compound **2c** was synthesized following the general procedure (A). The product was obtained as a pale yellow oil (0.069 g, 85% yield): R_f = 0.7 petroleum ether/EtOAc(85:15); IR (neat) cm^{-1}: 2931, 2868, 1709, 1460, 1248, 961, 739; ^1H NMR (400 MHz, $CDCl_3$): δ 2.25 (t, J = 6.9 Hz, 4H), 1.57–1.42 (m, 4H), 1.47–1.33 (m, 4H), 0.90 (t, J = 7.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): 77.6, 65.4, 30.5, 22.1, 19.0, 13.7; HRMS (ESI TOF): Calculated for $C_{12}H_{19}$ $(M+H)^+$: 163.1487, Found: 163.1486.

1, 6-dimethoxyhexa-2, 4-diyne (2d):



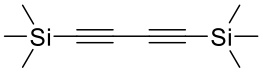
Compound **2d** was synthesized following the general procedure (A). The product was obtained as colourless oil (0.06 g, 87 % yield): R_f = 0.6 petroleum ether/EtOAc (70:30); IR (neat) cm^{-1}-2935, 2827, 2243, 1715, 1443, 1285, 1089, 933, 745; ^1H NMR (400 MHz, $CDCl_3$): δ 4.17 (s, 4H), 3.39 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): 75.3, 70.6, 60.3, 58.0; HRMS (ESI TOF): Calculated for $C_8H_{10}O_2Na$ $(M+Na)^+$: 161.0578, Found: 161.0585.

2, 2, 13, 13-tetramethyl-3, 3, 12, 12-tetraphenyl-4, 11-dioxa-3,12-disilatetradeca-6, 8-diyne (2e):



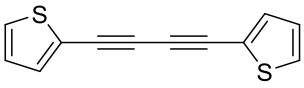
Compound **2e** was synthesized following the general procedure (A). The product was obtained as a pale yellow oil (0.282 g, 96% yield): R_f = 0.5 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 2933, 2893, 2858, 2362, 1590, 1427, 1364, 1074, 818, 695; ^1H NMR (400 MHz, $CDCl_3$): δ 7.7 (dd, J = 7.6, 1.7 Hz, 8H), 7.48 – 7.33 (m, 12H), 4.37 (s, 4H), 1.07 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): 135.7, 132.9, 130.1, 127.9, 77.4, 69.5, 53.2, 26.8, 19.3; HRMS(AP^+): Calculated for $C_{38}H_{42}O_2Si_2K$ $(M+K)^+$: 625.2360, Found: 625.2363.

1, 4-bis(trimethylsilyl)buta-1, 3-diyne (2f):



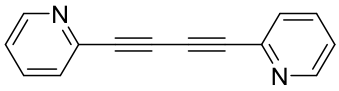
Compound **2f** was synthesized following the general procedure (A). The product was obtained as a white solid (0.0875 g, 90% yield): R_f = 0.8 (petroleum ether); m.p.:108-109 ^oC; IR (neat) cm^{-1}: 2962, 2362, 2065, 1462, 1410, 1248, 835, 745.;^1H NMR (400 MHz, $CDCl_3$): δ 0.19 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): 88.1, 86.1, -0.4 (Me_3Si). HRMS (ESI TOF): Calculated for $C_{10}H_{19}Si_2$ $(M+H)^+$: 195.1025, Found: 195.1024.

1, 4-di(thiophen-2-yl)buta-1,3-diyne (2g):



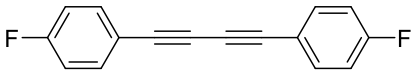
Compound **2g** was synthesized following the general procedure (A). The product was obtained as as yellow solid (0.101 g, 94% yield): R_f = 0.5 petroleum ether/EtOAc (95:5); m.p.-90-91 ℃; IR (neat) cm^{-1}: 3098, 2200, 2136, 1808, 1547, 1217, 893, 705; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.29 (m, 4H), 7.00 (dd, J = 5.1, 3.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 134.5, 129.1, 127.4, 122.0, 77.9, 76.8; HRMS (ESI TOF): Calculated for $C_{12}H_7S_2$ $(M+H)^+$: 214.9989, Found: 214.9992.

1, 4-di(pyridin-2-yl)buta-1,3-diyne (2h):



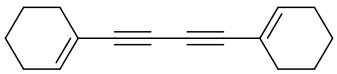
Compound **2h** was synthesized following the general procedure (A). The product was obtained as a white solid (0.089 g, 87% yield): R_f = 0.4 petroleum ether/EtOAc (85:15); m.p.:116-117 °C; IR (neat) cm^{-1}: 3053, 2997, 2216, 1570, 1455, 988, 751, 683; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 5.1 Hz, 2H), 7.69 (td, *J* = 7.8, 1.8 Hz, 2H), 7.55 (d, *J* = 7.8 Hz, 2H), 7.33 – 7.22 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.5, 142.0, 136.3, 128.5, 123.9, 81.0, 73.3; HRMS (ESI TOF): Calculated for $C_{14}H_9N_2$ $(M+H)^+$: 205.0766 Found: 205.0770.

1, 4-bis(4-fluorophenyl)buta-1,3-diyne (2i):



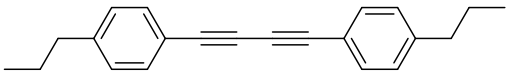
Compound **2i** was synthesized following the general procedure (A). The product was obtained as a white solid (0.110 g, 92% yield): R_f = 0.7 petroleum ether/EtOAc (95:5); m.p.192-193 °C; IR (neat) cm^{-1}: 2925, 2854, 2363, 2141, 1589, 1498, 1222, 1155, 825, 693; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 – 7.45 (m, 4H), 7.04 (t, *J* = 8.7 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) (F-coupled spectrum): δ 163.2 (d, *J* = 252.0 Hz), 134.7 (d, *J* = 8.6 Hz), 117.9, 116.1 (d, *J* = 22.2 Hz), 80.6, 73.7; HRMS (AP^+): Calculated for $C_{16}H_8F_2$ $(M)^+$: 238.0594, Found: 238.0599.

1, 4-dicyclohexenylbuta-1, 3-diyne (2j):



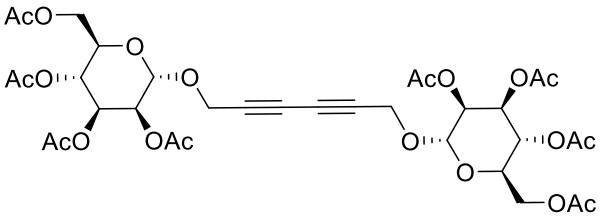
Compound **2j** was synthesized following the general procedure (A). The product was obtained as a colourless oil (0.086 g, 82% yield): R_f = 0.7 petroleum ether; IR (Neat) cm^{-1}: 2931, 2860, 2320, 2190, 1709, 1449, 1069, 753; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.32 – 6.12 (m, 2H), 2.28 – 1.95 (m, 8H), 1.60 (ddd, *J* = 18.0, 6.9, 3.0 Hz, 9H).^{13}C NMR (100 MHz, $CDCl_3$): 138.3, 120.1, 82.8, 71.7, 28.8, 26.0, 22.3, 21.5; HRMS (AP^+): Calculated for $C_{16}H_{18}$ $(M)^+$: 210.1409 Found: 210.1414.

1, 4-bis(4-propylphenyl)buta-1,3-diyne (2k):



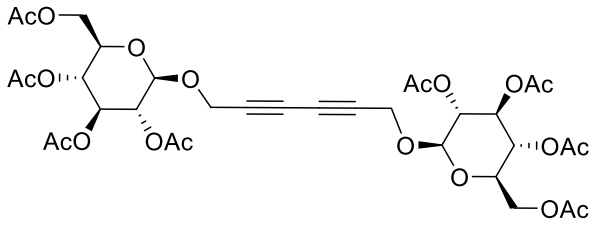
Compound **2k** was synthesized following the general procedure (A). The product was obtained as a white solid (0.135 g, 94% yield): R_f = 0.8 petroleum ether/EtOAc (95:5); m.p.: 175-177 ^{o}C; IR (neat) cm^{-1}: 2959, 2866, 1499, 1458, 1213, 747, 667; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 8.1 Hz, 4H), 7.15 (d, *J* = 8.1 Hz, 4H), 2.67 – 2.44 (m, 4H), 1.64 (sex, *J* = 7.4 Hz, 4H), 0.94 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 132.5, 128.8, 119.1, 81.7, 73.6, 38.2, 24.4, 13.9; HRMS(AP^{+}): Calculated for $C_{22}H_{22}$ (M)$^{+}$: 286.1722, Found: 286.1726.

1, 6-Bis(2,3,4,6-tetra-*O*-acetyl-*α*-D-mannopyranosyloxy)-hex-2, 4-di-yne (2l):



Compound **2l** was synthesized following the general procedure (A). The product was obtained as a white solid (0.34 g, 87% yield): R_f =0.6 Chloroform/Acetone (90:10); m.p.:53-54 ^{o}C; [α] $^{24}_{D}$ = +62 (*c* = 1.0, $CHCl_3$); IR (neat) cm^{-1}: 2924, 1743, 1369, 1217, 1045, 755. ^{1}H NMR (400 MHz, $CDCl_3$: δ 5.34 – 5.19 (m, 6H), 4.97 (s, 2H), 4.35 (s, 4H), 4.28 (dd, *J* = 12.2, 4.8 Hz, 2H), 4.09 (d, *J* = 12.3 Hz, 2H), 3.99 (s, 2H), 2.15 (s, 6H), 2.10 (s, 6H), 2.03 (s, 6H), 1.98 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 170.0, 169.97, 169.8, 96.7, 74.2, 71.0, 69.3, 69.2, 69.0, 66.0, 62.4, 55.6, 21.0, 20.9, 20.8, 20.8; HRMS(ESI TOF): Calculated for $C_{34}H_{42}O_{20}K$ (M+K)$^{+}$:809.1907 Found: 809.1911.

1, 6-Bis(2, 3, 4, 6-tetra-*O*-acetyl-*β*-D-glucopyranosyloxy)-hex-2, 4-di-yne (2m):

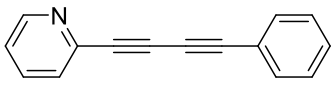


Compound **2m** was synthesized following the general procedure (A). The product was obtained as a white solid (0.274 g, 71% yield): R_f = 0.5 petroleum ether/EtOAc (30:70); m.p.:175-176 ^oC; [α] $^{25}_D$ = -37 (*c* = 1.0, $CHCl_3$); IR (neat) cm^{-1}: 2955, 1745, 1435, 1369, 1211, 1035, 753; ^1H NMR (400 MHz, $CDCl_3$): δ 5.24 (t, *J* = 9.5 Hz, 2H), 5.10 (t, *J* = 9.6 Hz, 2H), 5.01 (dd, *J* = 9.5, 8.0 Hz, 2H), 4.73 (d, *J* = 7.9 Hz, 2H), 4.45 (s, 4H), 4.27 (dd, *J* = 12.4, 4.5 Hz, 2H), 4.15 (dd, *J* = 12.4, 2.2 Hz, 2H), 3.75 (ddd, *J* = 10.0, 4.4, 2.3 Hz, 2H), 2.09 (s, 6H), 2.07 (s, 6H), 2.02 (s, 6H), 2.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 170.4, 169.6, 169.5, 98.6, 74.3, 72.8, 72.1, 71, 68.3 (2-C merged) 61.8, 56.6, 20.9, 20.8, 20.7 (2-C); HRMS (ESI TOF): Calculated for $C_{34}H_{42}O_{20}K$ $(M+K)^+$:809.1907 Found: 809.1915.

2.4.3 General procedure B for cross-coupling of two different alkynes

2-Ethynylpyridine (**1h**) (1.0 mmol), phenylacetylene (**1a**) (5.0 mmol), CuI (10 mol%) and DMAP (20 mol%) were added to acetonitrile (6 mL) at ambient temperature in the open atmosphere. The reaction mixture was stirred at room temperature for 10 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The crude product obtained was purified by column chromatography over silica gel to afford 2-(phenylbuta-1, 3-diynyl)pyridine (**3a**) as a white solid.

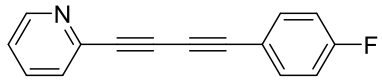
2-(phenylbuta-1, 3-diynyl)pyridine (3a):



Compound **3a** was synthesized following the general procedure (B). The product was obtained as a white solid (0.167 g, 82% yield): R_f = 0.5 petroleum ether/EtOAc (85:15); m.p.: 72-73 ^oC; IR (neat) cm^{-1}: 3053, 2997, 2216, 1570, 1040, 751. ^1H NMR (400 MHz, $CDCl_3$) δ 8.63 – 8.54 (m, 1H), 7.67 (td, *J* = 7.7, 1.7 Hz, 1H), 7.57 – 7.48 (m, 3H), 7.36 (tdd, *J* = 8.7,

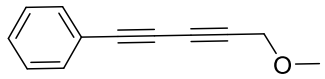
6.7, 3.6 Hz, 3H), 7.27 (ddd, *J* = 7.7, 4.8, 1.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 142.4, 136.3, 132.8, 129.7, 128.6, 128.2, 123.6, 121.4, 82.6, 80.3, 73.9, 73.6; HRMS (ESI TOF): Calculated for $C_{15}H_{10}N$ $(M+H)^+$: 204.0813, Found: 204.0820.

2-((4-fluorophenyl)buta-1, 3-diynyl)pyridine (3b):



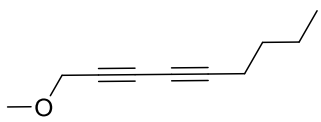
Compound **3b** was synthesized following the general procedure (B). The product was obtained as a white solid (0.19 g, 85% yield); R_f = 0.4 petroleum ether/EtOAc (85:15); m.p.:123-124 ^{o}C; IR (neat) cm^{-1}: 2925, 2854, 2214, 1888, 1500, 1221, 829, 760; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 4.7 Hz, 1H), 7.67 (td, *J* = 7.8, 1.8 Hz, 1H), 7.53 (ddd, *J* = 7.6, 4.7, 1.9 Hz, 3H), 7.30–7.24 (m, 1H), 7.09–6.96 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) (F-coupled spectrum): δ 163.3 (d, *J* = 252.2 Hz), 150.5, 142.3 136.3, 134.9 (d, *J* = 8.6 Hz), 128.2, 123.7, 117.5, 116.1 (d, *J* = 22.2 Hz), 81.5, 80.3, 73.7, 73.5; HRMS (ESI TOF): Calculated for $C_{15}H_9FN$ $(M+H)^+$: 222.0719, Found: 222.0721.

(5-methoxypenta-1, 3-diynyl)benzene (3c):



Compound **3c** was synthesized following the general procedure (B). The product was obtained as pale yellow oil (0.123 g, 72% yield): R_f = 0.6 petroleum ether/EtOAc (85:15); IR(neat) cm^{-1}: 2928, 2828, 2225, 1714, 1443, 1352, 1094, 902, 752; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 –7.46 (m, 2H), 7.41 – 7.28 (m, 3H), 4.25 (s, 2H), 3.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 132.7, 129.5, 128.6, 121.5, 78.7, 78.2, 73.4, 71.2, 60.5, 58.0; HRMS (ESI TOF): Calculated for $C_{12}H_{11}O$ $(M+H)^+$: 171.0810 Found: 171.0814.

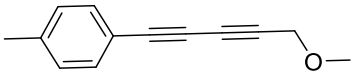
1-methoxynona-2, 4-diyne (3d):



Compound **3d** was synthesized following the general procedure (B). The product was obtained as as a colorless oil (0.106 g, 70% yield): R_f = 0.6 petroleum ether/EtOAc (85:15);

IR (neat) cm^{-1}: 2958, 2871, 2238, 1715, 1457, 1102, 973; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.15 (s, 2H), 3.38 (s, 3H), 2.28 (t, *J* = 6.9 Hz, 2H), 1.57 – 1.47 (m, 2H), 1.47 – 1.35 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 81.4, 77.4, 64.6, 60.4, 57.9, 30.3, 22.0, 19.1, 13.6; HRMS (ESI TOF): Calculated for $C_{10}H_{15}O$ $(M+H)^+$: 151.1123 Found: 151.1119.

1-(5-methoxypenta-1, 3-diynyl)-4-methylbenzene (3e):



Compound **3e** was synthesized following the general procedure (B). The product was obtained as pale yellow oil (0.136 g, 74% yield); R_f = 0.6 petroleum ether/EtOAc (85:15); IR (neat) cm^{-1}: 2928, 2827, 2234, 1714, 1445, 1353, 1094, 812; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.1 Hz, 2H), 7.13 (d, *J* = 7.9 Hz, 2H), 4.25 (s, 2H), 3.43 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9, 132.7, 129.3, 118.4, 78.5, 78.4, 72.8, 71.4, 60.5, 58.0, 21.8. HRMS (ESI TOF): Calculated for $C_{13}H_{12}O$ $(M)^+$: 184.0888, Found: 184.0885.

2.5 Appendix I: ^{1}H, ^{13}C NMR spectral data of representative compounds

Compound No.	Figure II.X	Data	Page No.
2a	Figure II.1 and II.2	^{1}H and ^{13}C	43
2b	Figure II.3 and II.4	^{1}H and ^{13}C	44
2c	Figure II.5 and II.6	^{1}H and ^{13}C	45
2h	Figure II.7 and II.8	^{1}H and ^{13}C	46
2l	Figure II.9 and II.10	^{1}H and ^{13}C	47
3a	Figure II.11 and II.12	^{1}H and ^{13}C	48
3d	Figure II.13 and II.14	^{1}H and ^{13}C	49

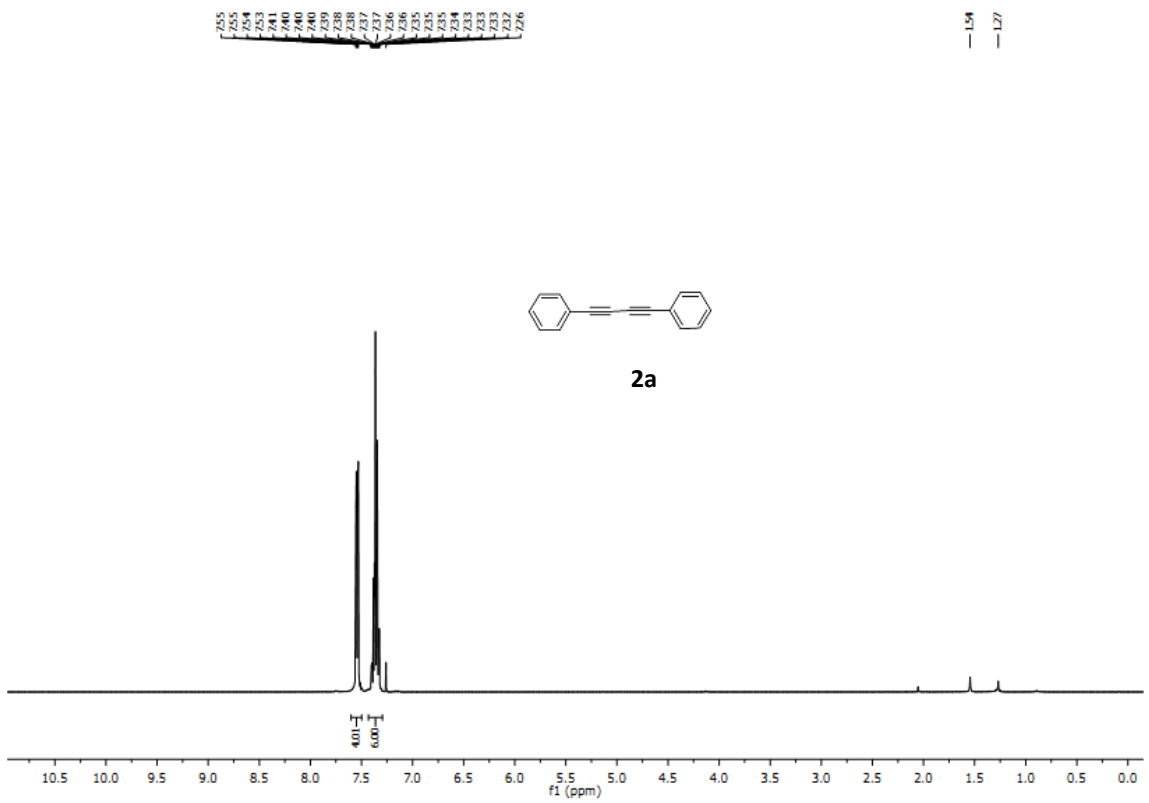


Figure II.1: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **2a**

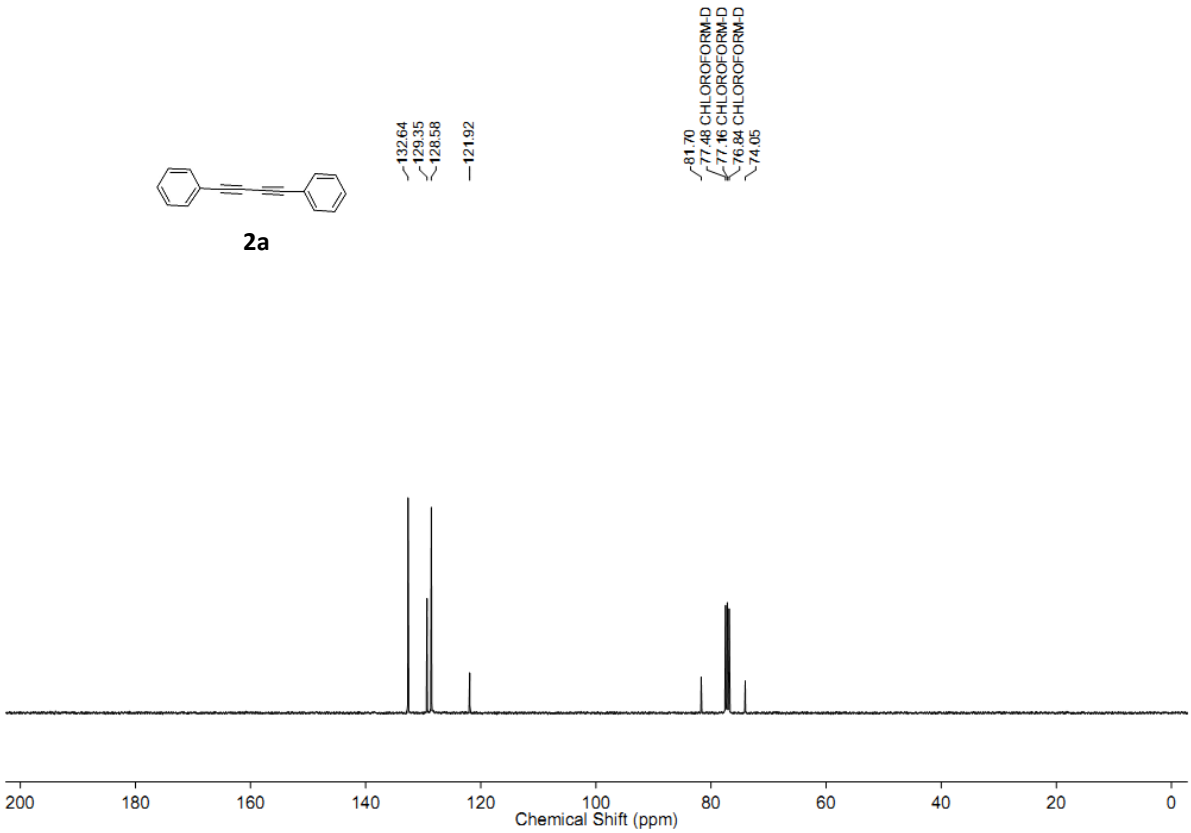


Figure II.2: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **2a**

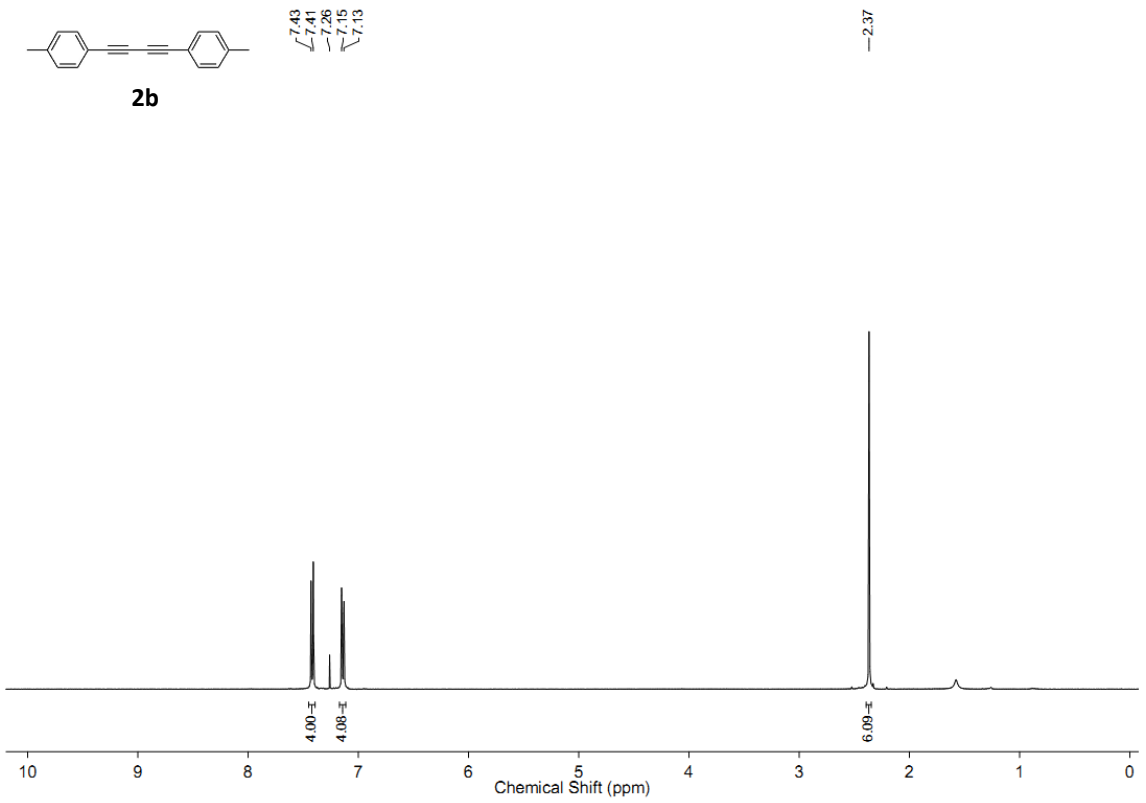


Figure II.3: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **2b**

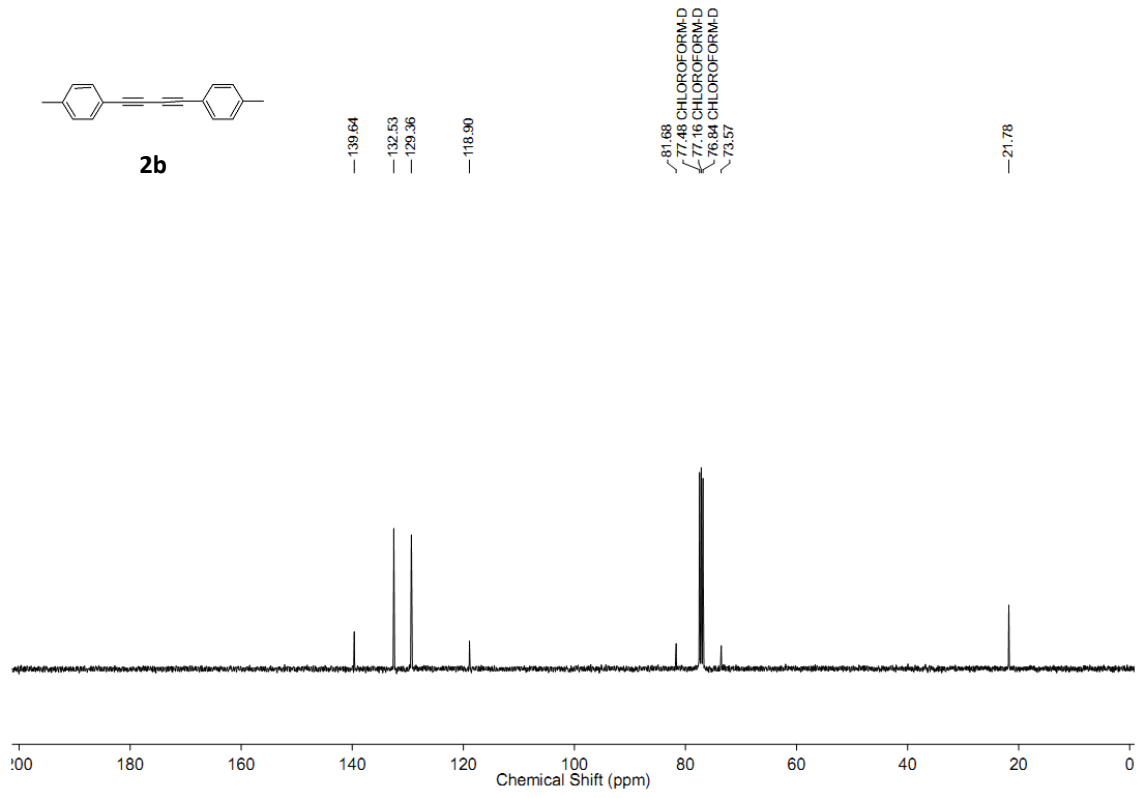


Figure II.4: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **2b**

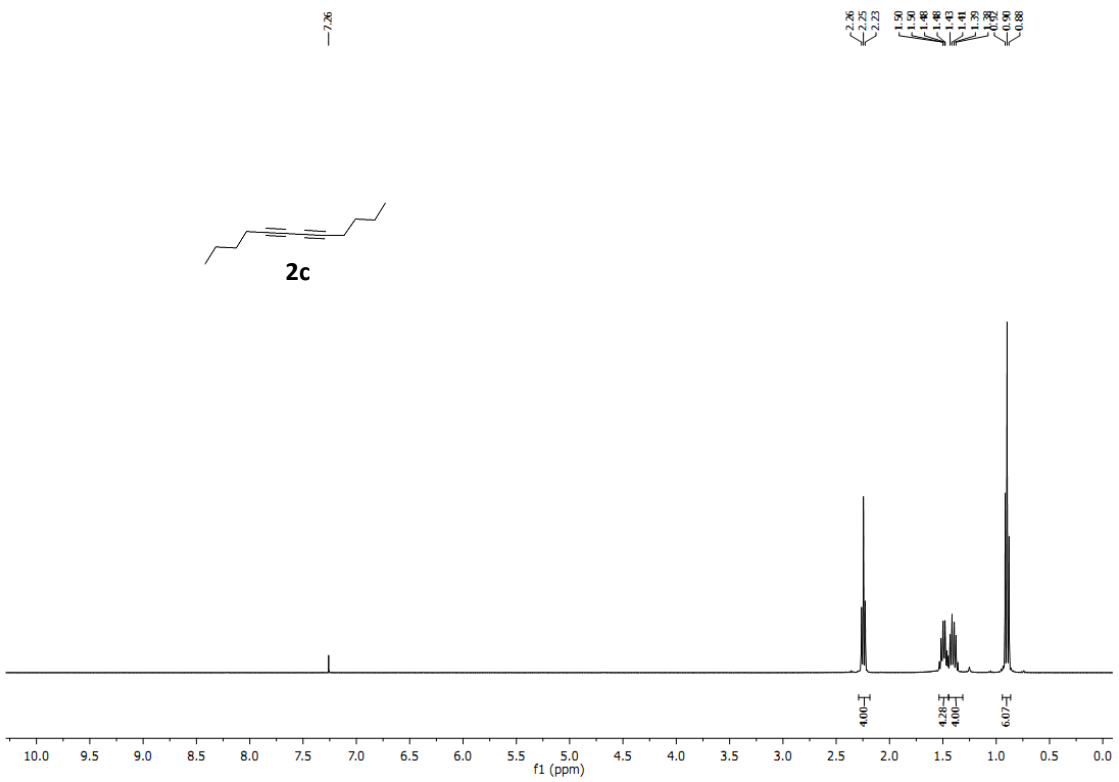


Figure II.5: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **2c**

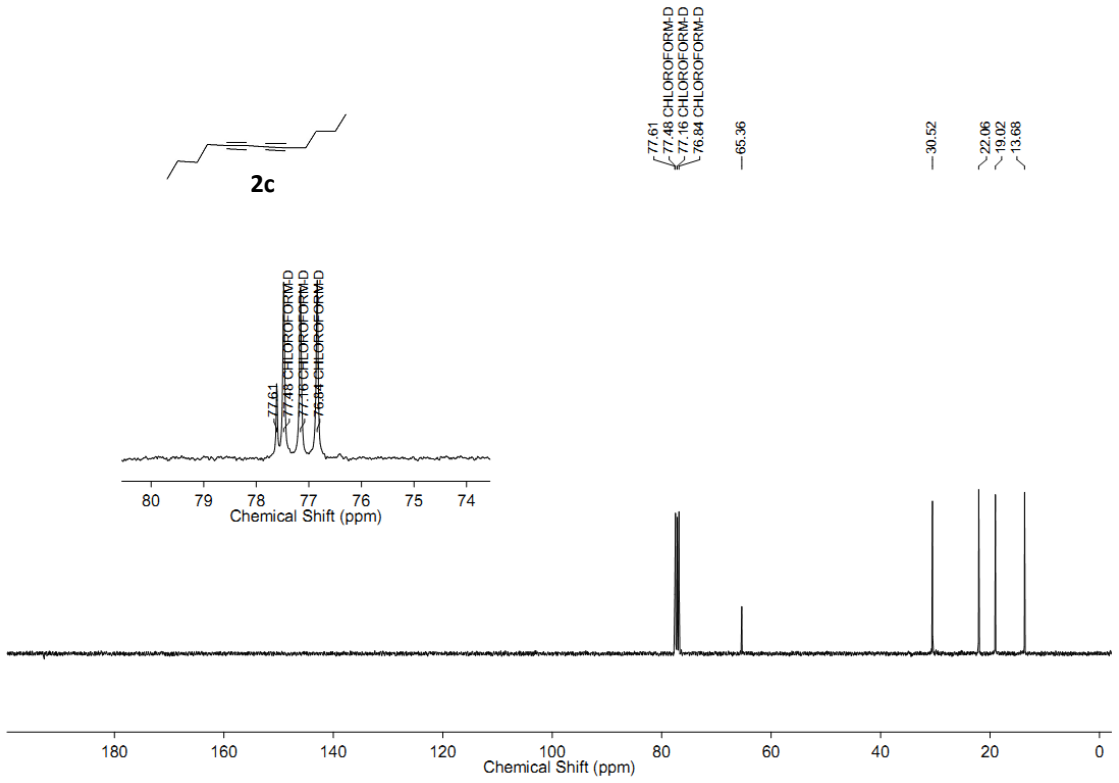


Figure II.6: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **2c**

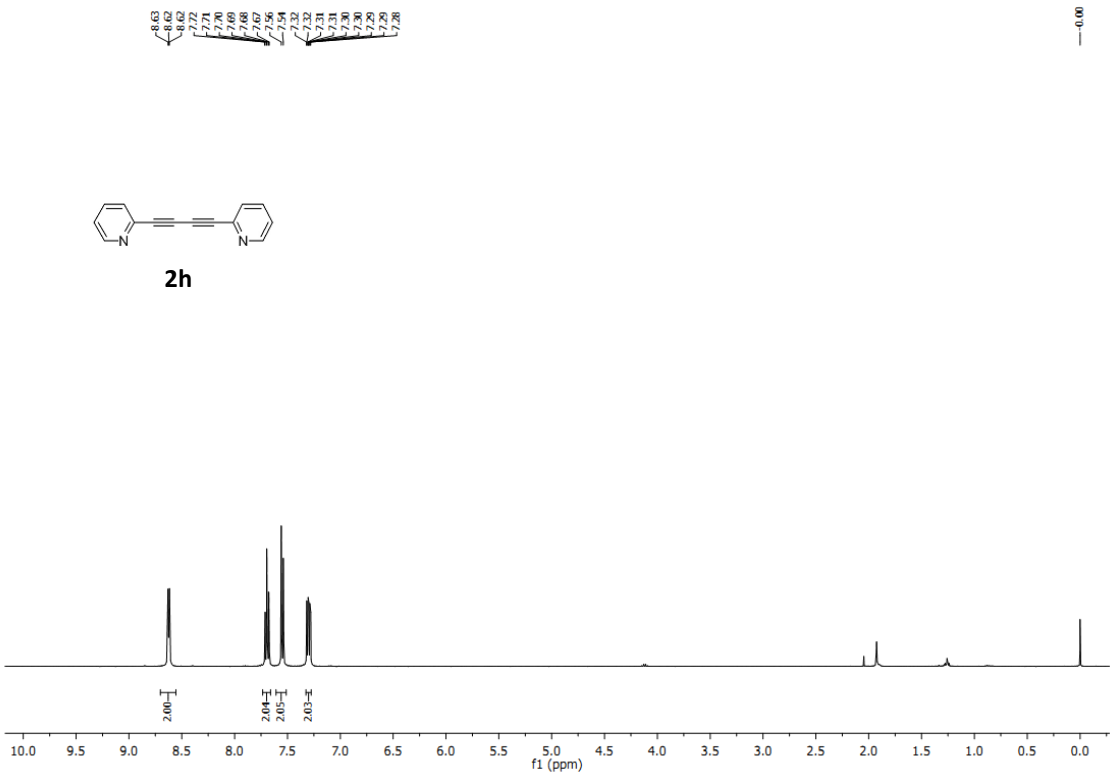


Figure II.7: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **2h**

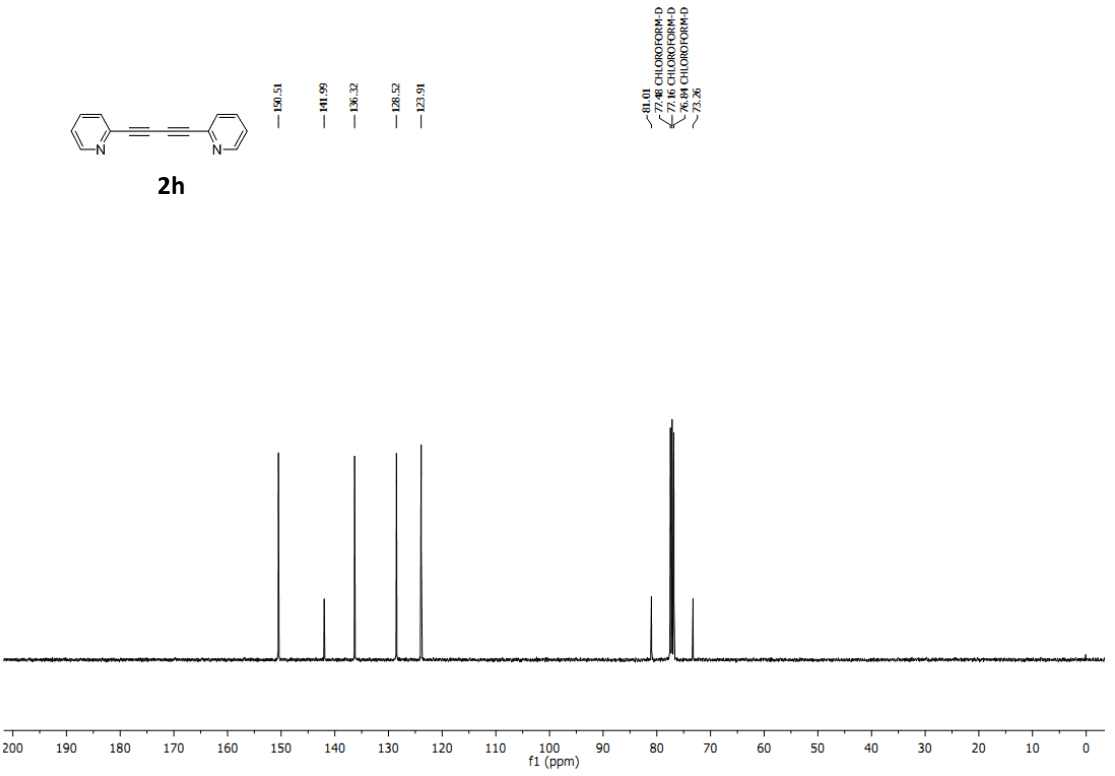


Figure II.8: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **2h**

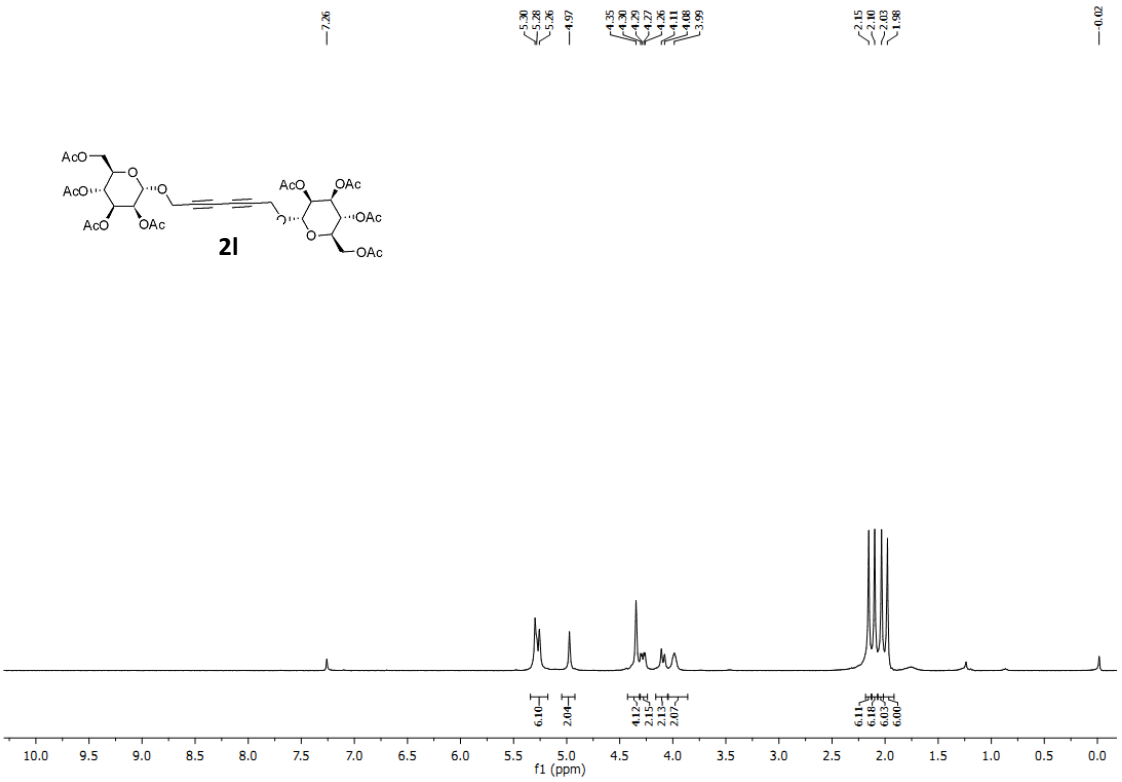


Figure II.9: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **2l**

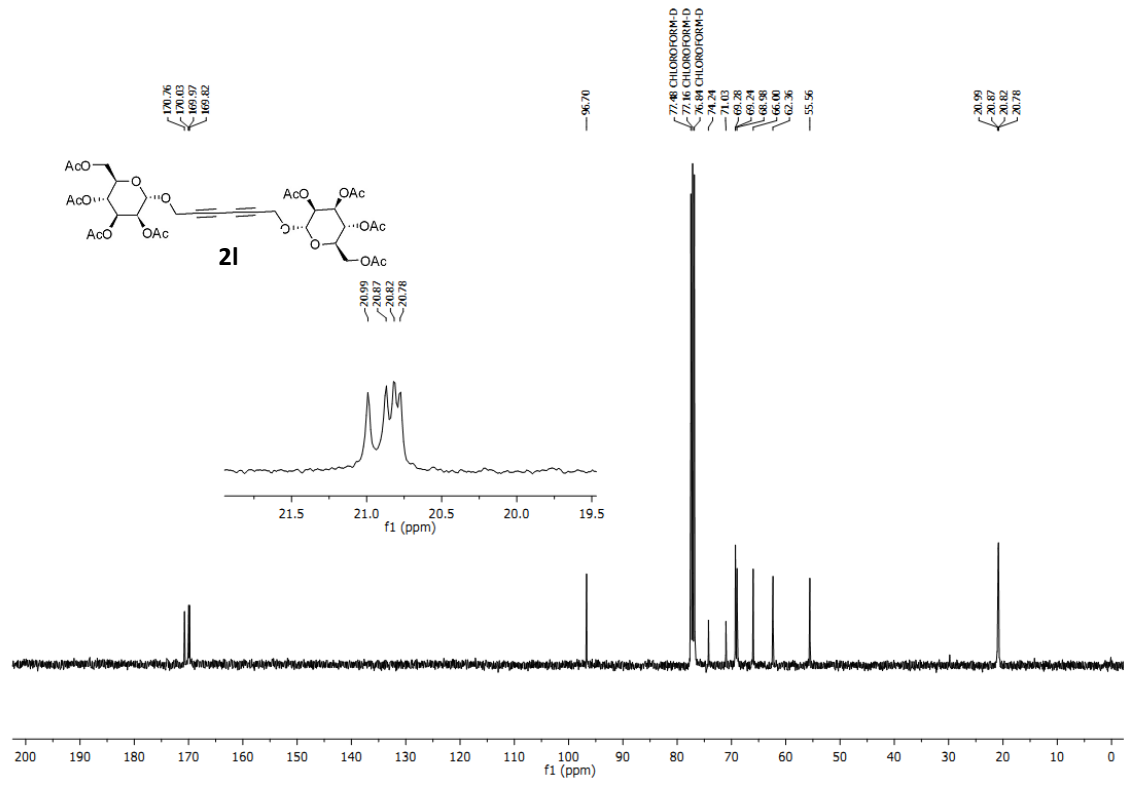


Figure II.10: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **2l**

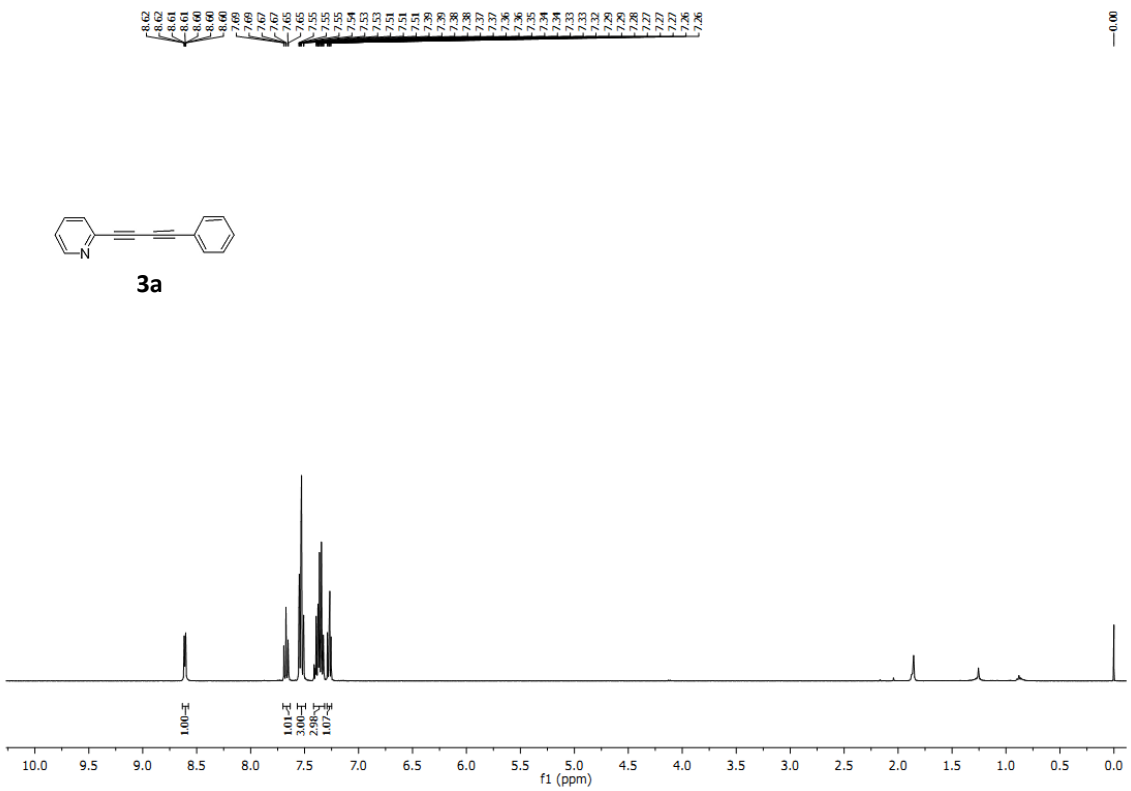


Figure II.11: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3a**

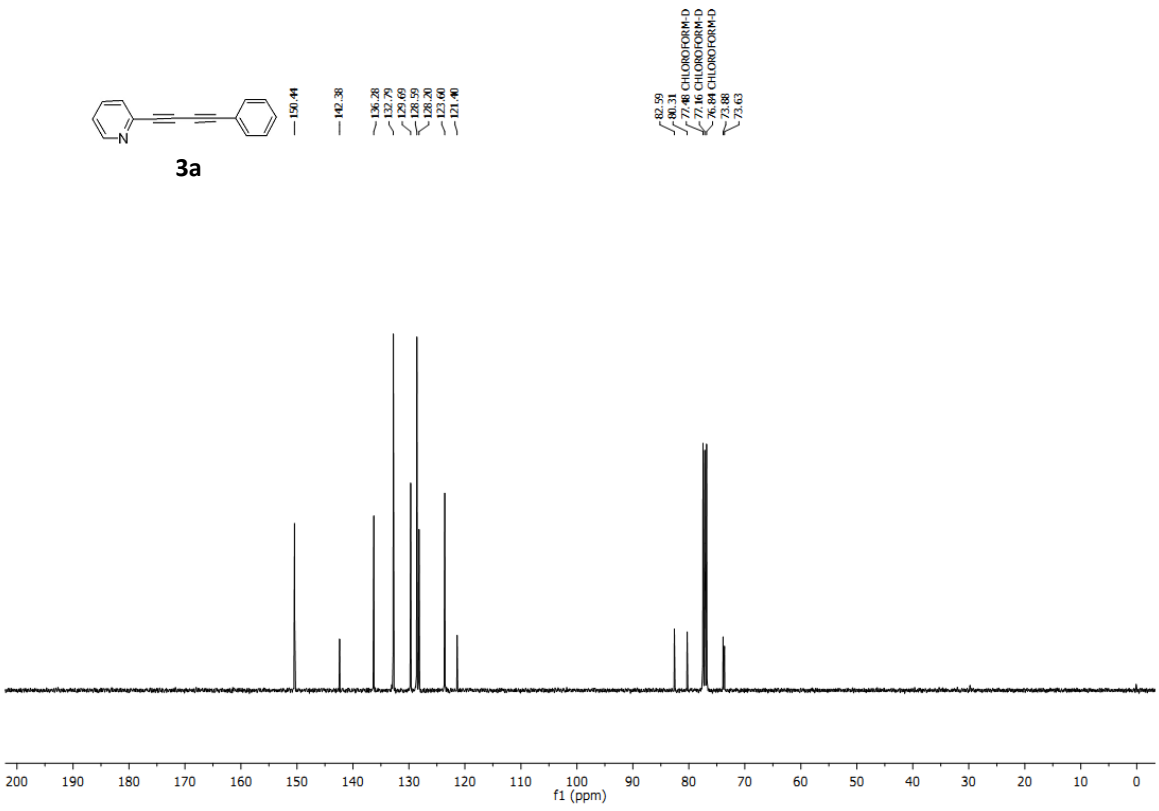


Figure II.12: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3a**

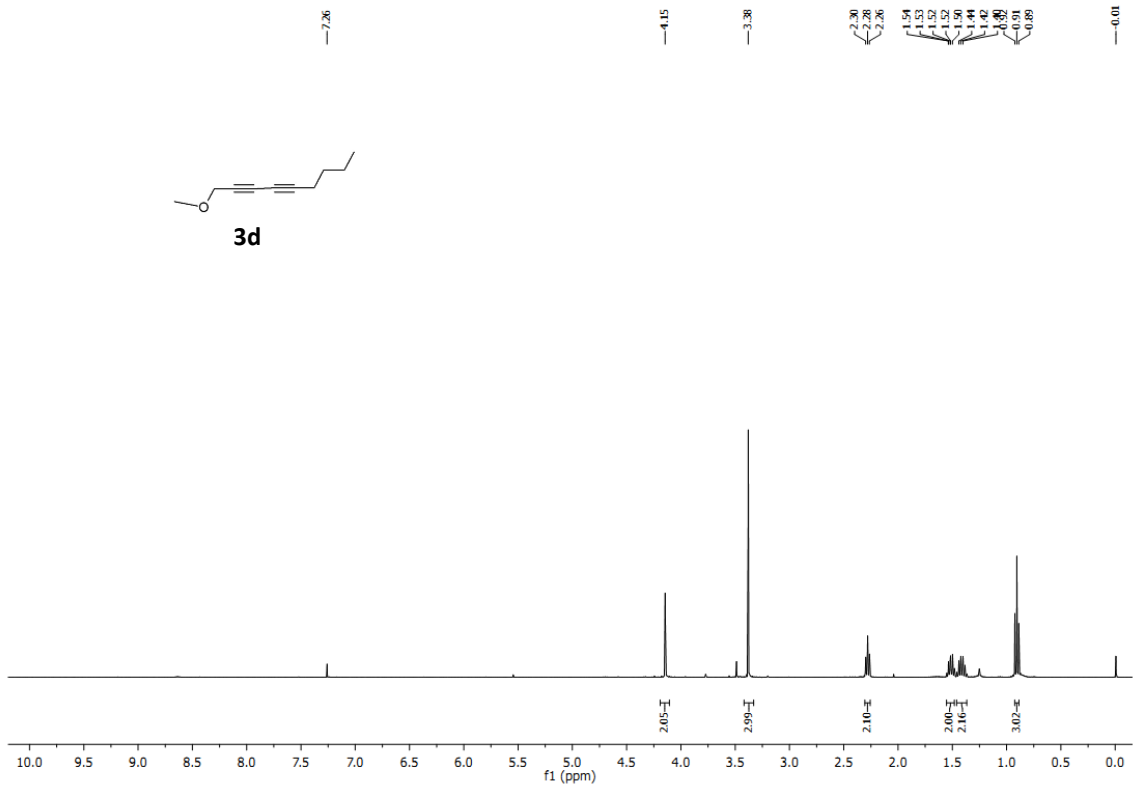


Figure II.13: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3d**

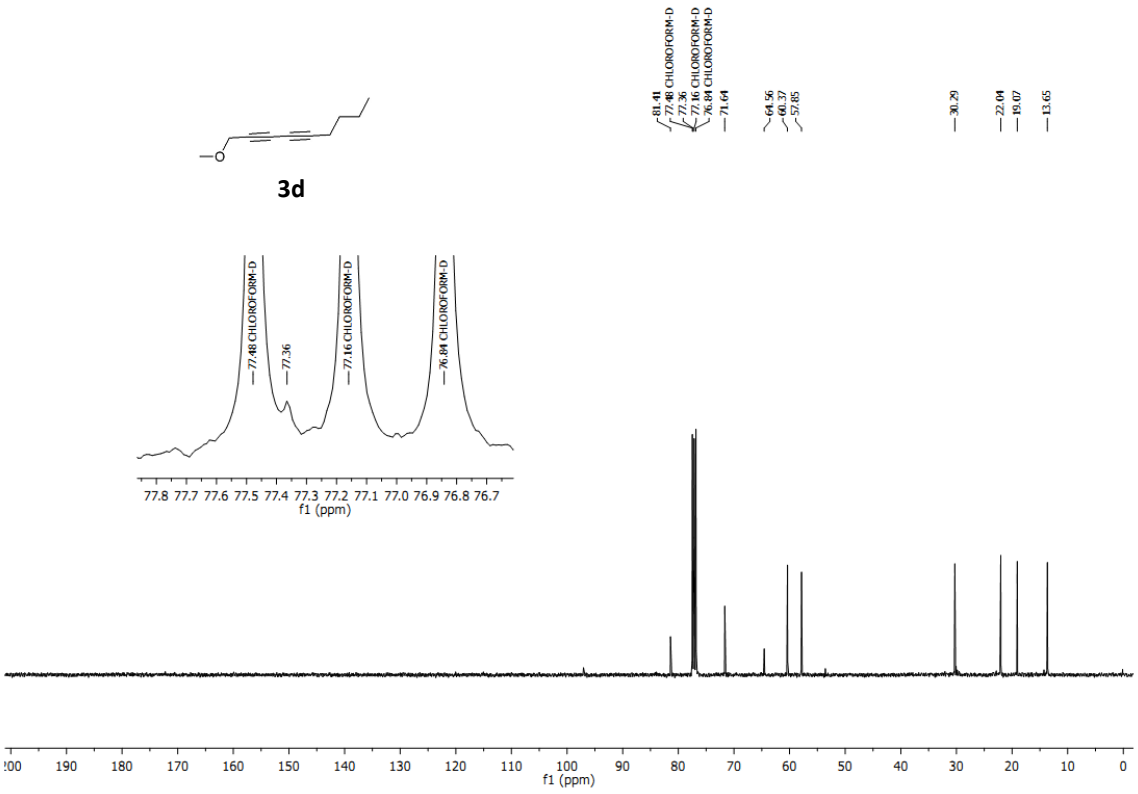


Figure II.14: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3d**

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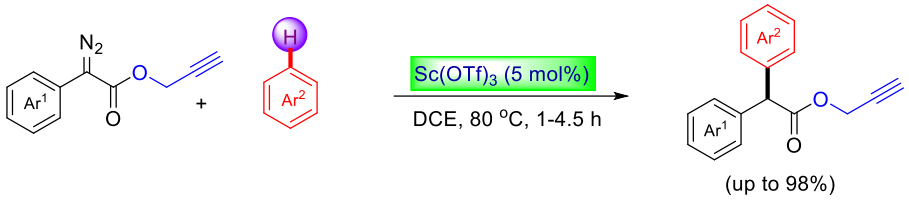
Chapter 3

Scandium-Catalyzed C-H Bond Functionalization of Arenes with α-Aryl-α-diazoacetates



(up to 98%)

- Propargyl α-aryl-α-diazoacetate-Robust reagent
- Chemo- and regioselective C-H bond functionalization
- Works with unactivated and mild deactivated arenes
- Less prone for side reactions
- Low Catalyst loading (5 mol%)
- Total of 52 examples and gram scale synthesis

Scandium-Catalyzed C-H Bond Functionalization of Arenes with α-Aryl-α-diazoacetates

3

Chemo- and regioselective C-H bond functionalization of arenes with propargyl α-aryl-α-diazoacetates is developed using scandium catalysis. Variety of unactivated, mildly deactivated and electronically activated arenes are functionalized using this protocol. The protocol avoids the use of expensive catalysts and practicality of the protocol has been demonstrated by the gram-scale synthesis of very useful α-diarylacetates.

Section-A

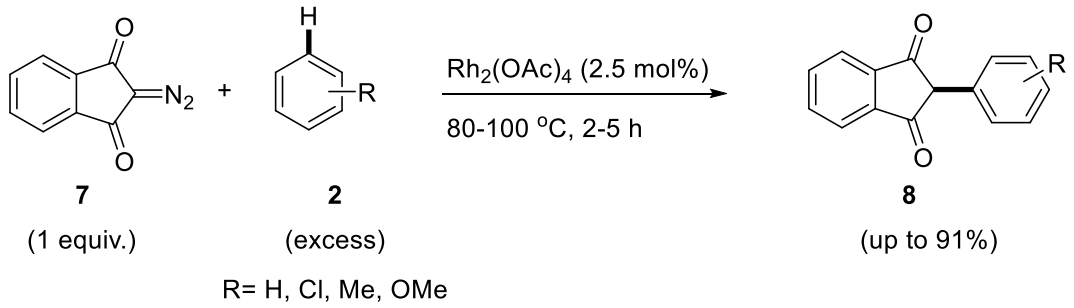
Scandium(III) Triflate-Catalyzed Chemo- and Regioselective C-H Bond Functionalization of Arenes with Propargyl α-Aryl-α-diazoacetates

3A.1 Introduction

Catalytic C-H bond functionalization is one of the most important and greener methods for the synthesis of complex organic molecules.[1] Developing catalytic methods for chemo- and regioselective C-H bond functionalization is highly desirable but challenging task for the synthetic community. Substituted benzenes are widespread and present in various biologically active compounds, and drug molecules.[2] Thus Chemo- and regioselective C-H bond functionalization of arenes are highly desirable to access bioactive compounds in minimum steps. Aromatic C-H bond functionalization using α-diazocarbonyl compounds is one of the important approaches to access substituted benzenes.[3] As the α-diazocarbonyl compounds can be easily prepared from readily available starting materials, the use of α-diazocarbonyl compounds in aromatic C-H bond functionalization made remarkable progress over the years.[3-4,9] Efforts have been made to make this method more practical with modifying catalysts, α-diazocarbonyl reagents for the aromatic C-H bond functionalizations. The transition metal complexes of rhodium,[4] gold,[5] copper,[6] and iron[7] have been widely used for the aromatic C-H bond functionalization reactions with α-diazocarbonyl compounds. Recently Ṕerez and co-workers utilized manganese catalyst for the aromatic C-H bond functionalization using α-diazocarbonyl compounds.[8] Transition metal-free C-H bond

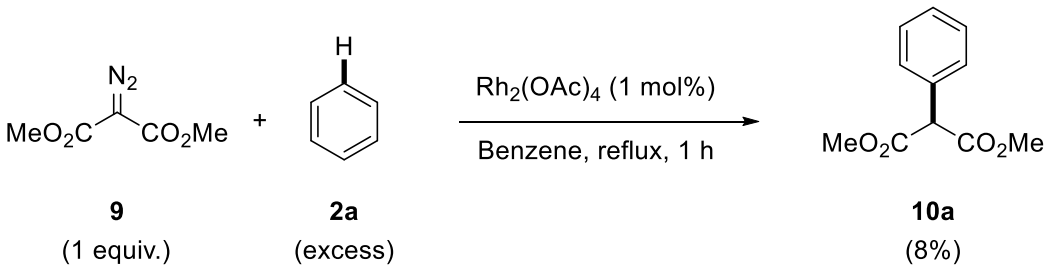
functionalization reactions of electron rich arenes have been also explored.[9] Some of the important examples for the aromatic C-H bond functionalization using *α*-diazocarbonyl compound have been dicussed here.

In 1988, Shechter and co-workers reported the rhodium-catalyzed C-H bond functionalization of arenes **2** with 2-diazo-1*H*-indene-1,3(2*H*)-dione **7**. Benzene and substituted benzenes **2** underwent the C-H bond functionalization reaction with the acceptor-acceptor type of *α*-diazocarbonyl compound **7** in the presence of catalytic amount of $Rh_2(OAc)_4$ to furnish 2-substituted 1,3-indandiones **8** in moderate to good yields. This transformation was carried out at a higher temperature (80-100 ^oC), and arenes **2** were used in excess. Arenes played the dual role as solvent as well as a substrate for the reaction (Scheme 3A.1).[4a]



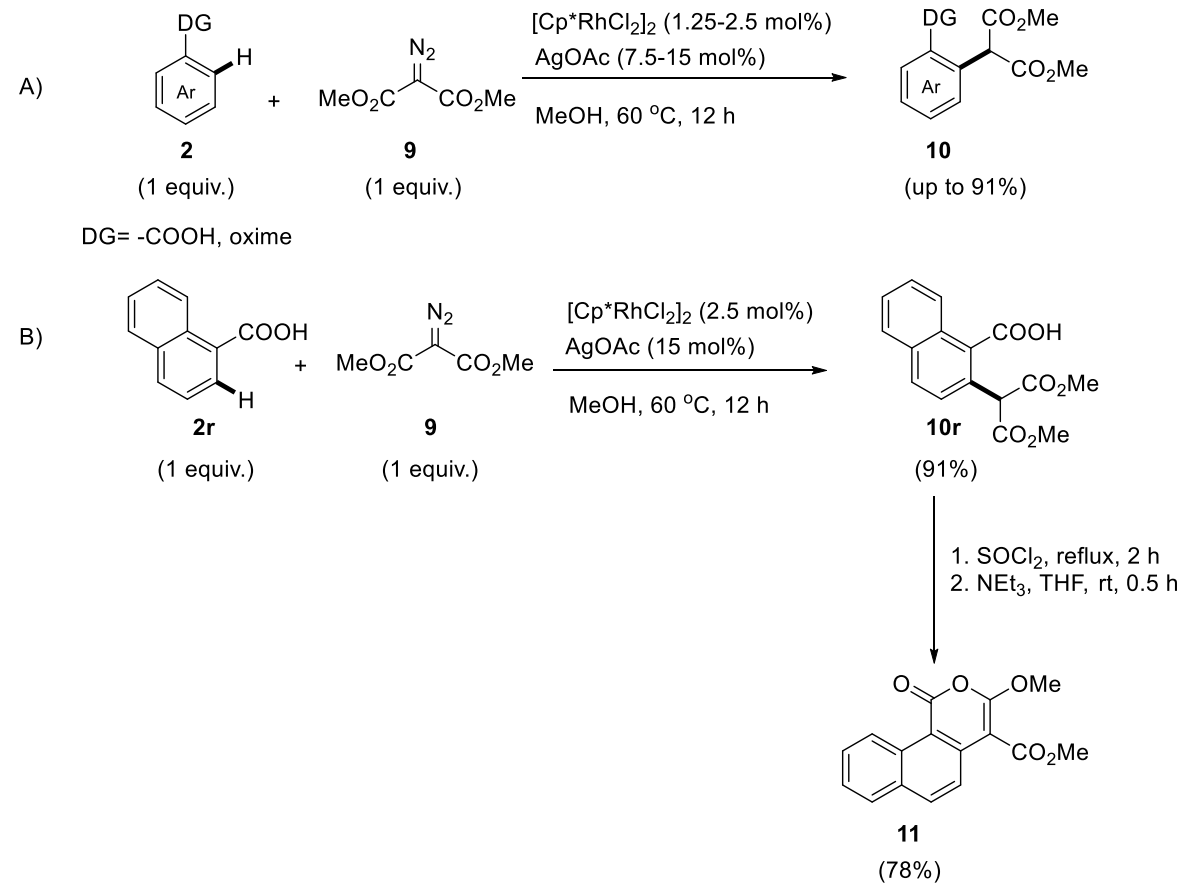
Scheme 3A.1 Rhodium-catalyzed C-H functionalization of arenes with 2-diazo-1*H*-indene-1,3(2*H*)-dione

Later in 2001, Livant and co-workers presented the synthesis of aromatic C-H insertion product **10a** by treating benzene **2a** and acceptor-acceptor type *α*-diazocarbonyl compound **9** in presence rhodium catalyst (1 mol%) in very low yield. The substrate-benzene **2a** was used in excess for this transformation (Scheme 3A.2).[4b]



Scheme 3A.2 Rhodium-catalyzed C-H bond functionalization of benzene with dimethyl 2-diazomalonate

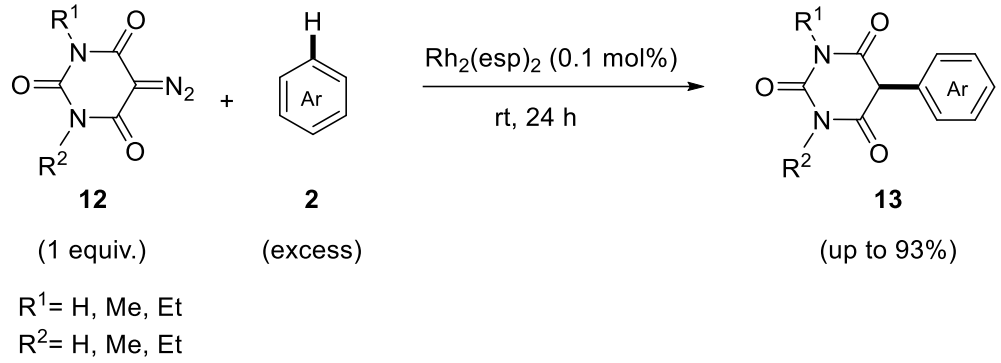
In 2012, Yu and co-workers explored the directing group strategy for the C-H bond functionalization of arenes **2** with *α*-diazomalonates **9** using rhodium catalyst. Aromatic compounds containing carboxylic and oxime functional groups as directing group (DG) **2** were functionalized using this method. This C-H bond functionalization was highly regioselective and selectively occurred at the *ortho* position of (DG) to afford the corresponding desired products **10** (Eq.A, Scheme 1.29). The functionalized product **10r** obtained in this approach was utilized further in the synthesis of isocoumarin **11** (Eq.B, Scheme 1.29).[4e]



Scheme 3A.3 Rhodium-silver co-catalyzed C-H bond functionalization of substituted arenes

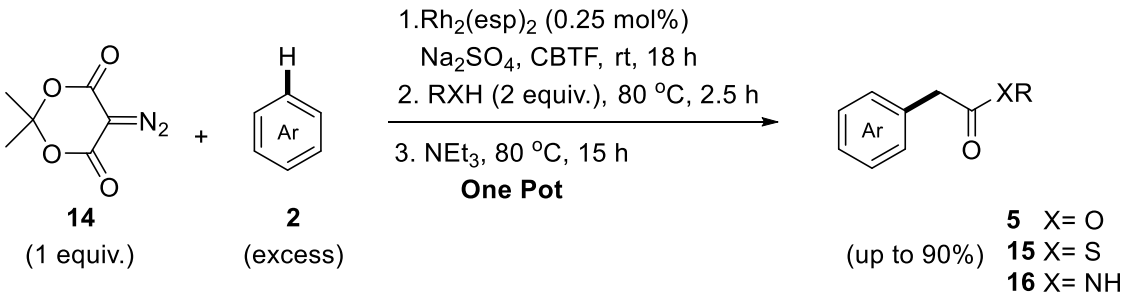
In 2015, Best et al. developed the method for the synthesis of 5-aryl barbituric acids **13** by using arenes **2** and 5-diazobarbituric acids **12** in the presence of catalytic amount of $Rh_2(esp)_2$ as a catalyst. The reaction was carried out at room temperature, and the arenes **2** were used in excess. Again, arene played the dual role of the substrate as well as a solvent for this reaction. Electronically activated arenes, neutral arenes as well as mildly deactivated arenes underwent the C-H bond functionalization reaction in the presence of catalytic amount

of $Rh_2(esp)_2$ (0.1 mol%) and 5-diazobarbituric acids **12** to furnish the corresponding 5-aryl barbituric acids **13** in good to excellent yields (Scheme 3A.4).[4g]



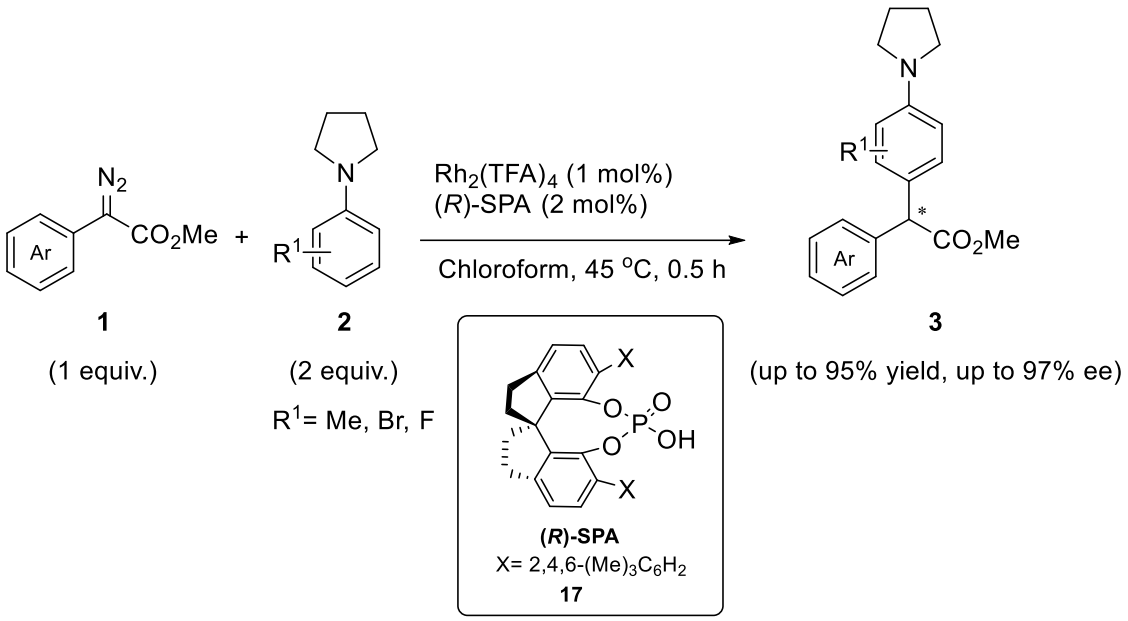
Scheme 3A.4 Rhodium-catalyzed C-H bond functionalization of arenes with 5-diazobarbituric acid

Recently in 2016, Best and co-workers reported an elegant method for the synthesis of arylacetic acid esters **5**, thioesters **15**, and amides **16**, using C-H bond functionalization strategy. The $Rh_2(esp)_2$ catalyzed arylation of Meldrum's acid-derived diazo compound **14** was the key step in the synthesis. The overall synthesis involved an one pot three steps sequence obtaining the desired products in moderate to good yields (Scheme 3A.5).[4h]



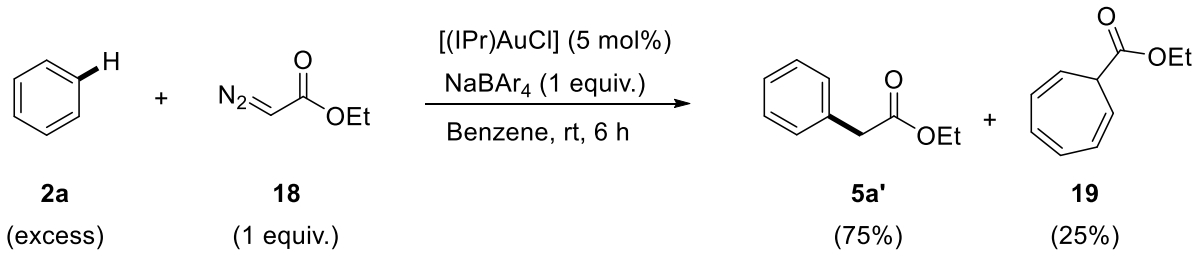
Scheme 3A.5 One-pot synthesis of arylacetic acid derivatives

In 2015, Zhou and co-workers developed the catalytic asymmetric C-H bond functionalization of aniline derivatives **2** with *α*-aryl-*α*-diazoacetates **1** in the presence of catalytic amount of $Rh_2(TFA)_4$ and chiral phosphoric acid **17**. In this transformation electronically activated arenes **2** underwent C-H bond functionalization to afford the desired products *α*-diarylacetates **3** in good yields with high enantioselectivity (Scheme 3A.6).[4j]



Scheme 3A.6 Rhodium-catalyzed asymmetric C-H bond functionalization of arenes

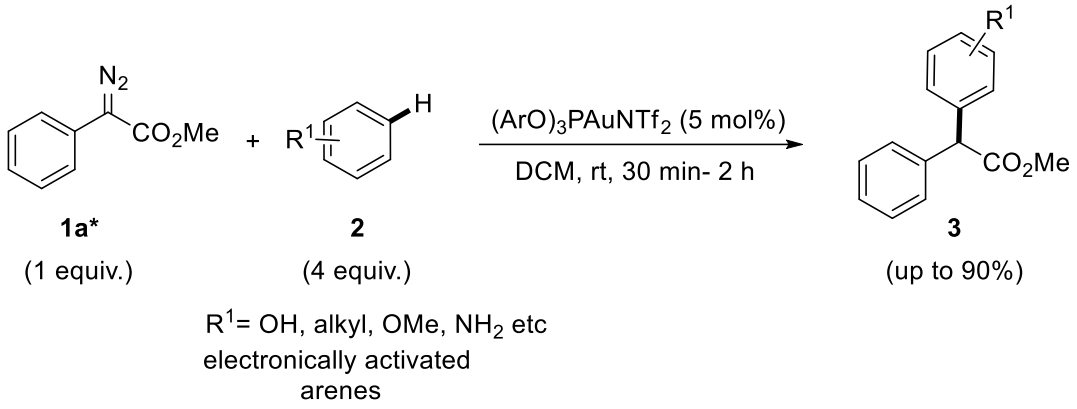
In 2005, Pérez and co-workers reported an interesting aromatic C-H bond functionalization of benzene **2a** with ethyl diazoacetate **18** in the presence of a gold catalyst. The desired product **5a′** was obtained in 75% yield along with the side product cycloheptatriene **19** (Scheme 3A.7).[5a] However, this report revealed the potential of gold catalyst in aromatic C-H bond functionalization reactions and led to a new area of gold-catalyzed aromatic C-H bond functionalization reactions using α-diazocarbonyl compounds.



Scheme 3A.7 Benzene C-H bond functionalization with ethyl diazoacetate using a gold catalyst

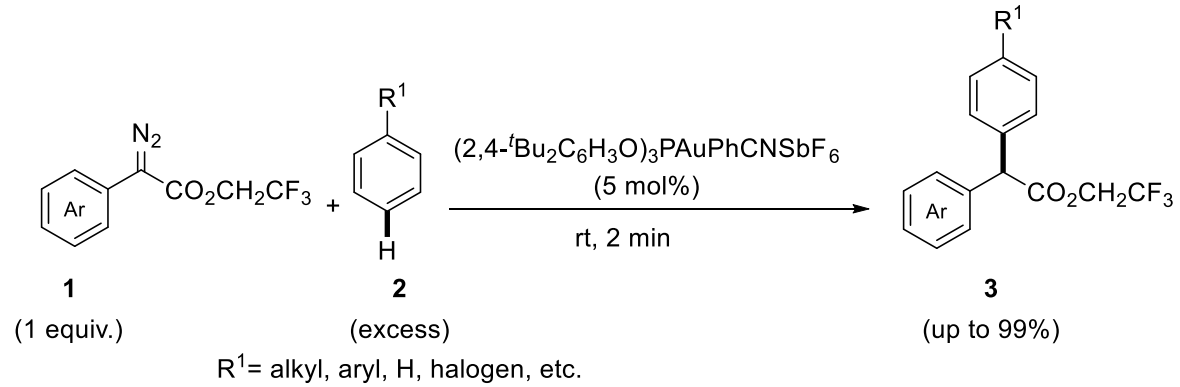
Recently, Yu et al. reported a highly chemoselective C-H bond functionalization of phenols with α-aryl-α-diazoacetates in the presence of a gold catalyst.[5d] Interestingly, under the reaction conditions, C-H insertion occurred exclusively, and the O-H insertion product was not observed. This was the first protocol wherein; the unprotected phenols were effectively functionalized by using α-aryl-α-diazoacetates and gold catalyst.

In 2014, Shi and co-workers reported the ligand-controlled gold-catalyzed C-H bond functionalization of electronically activated arenes **2** with *α*-aryl-*α*-diazoacetates **1a***. Various electronically rich arenes **2** underwent the C-H bond functionalization reaction with *α*-aryl-*α*-diazoacetates **1a*** in the presence of gold catalyst to afford the corresponding desired products *α*-diarylacetates **3**. However, this method had a limited substrate scope as the protocol worked only with the electronically activated arenes (Scheme 3A.8).[5e]



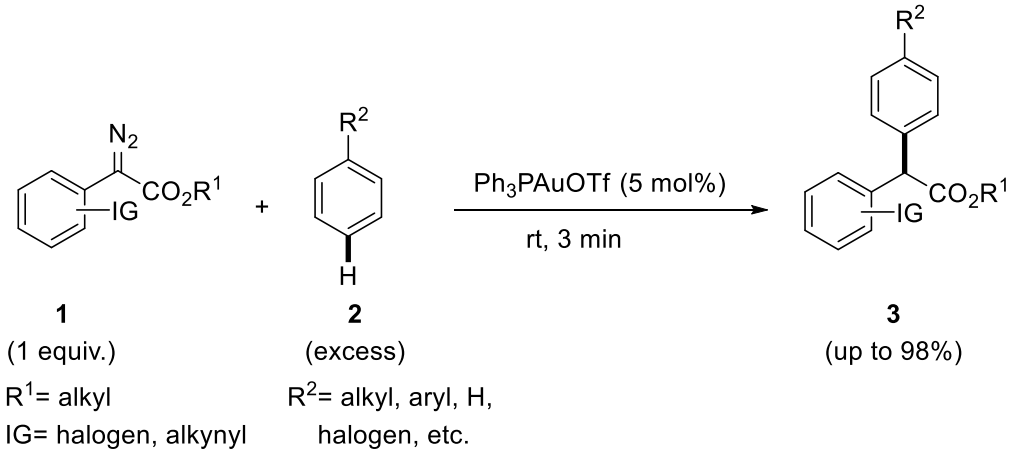
Scheme 3A.8 Gold-catalyzed C-H bond functionalization of electronically activated arenes

In 2017, Zhang and co-workers reported a novel protocol for C-H bond functionalization of arenes **2** with 2,2,2-trifluoroethyl *α*-aryl-*α*-diazoacetates **1** in the presence of gold catalyst. The combination of the 2,2,2-trifluroethyl group on the *α*-diazo ester **1** and gold catalyst played an important role in this transformation. This C-H functionalization proved to be highly *para* selective and furnished *α*-diarylacetates **3** under mild conditions in good to excellent yields (Scheme 3A.9).[5f]



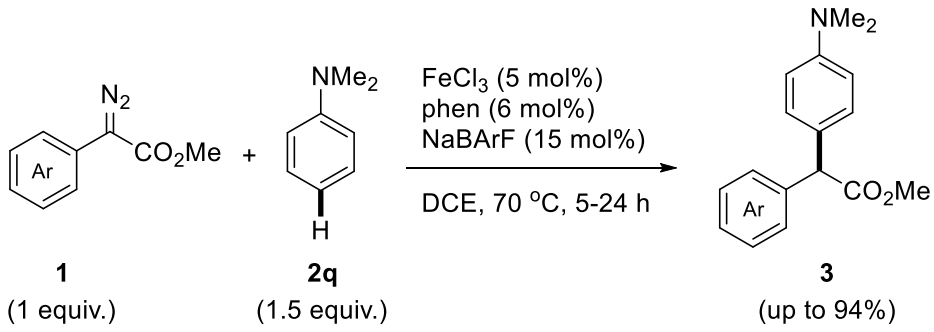
Scheme 3A.9 C-H bond functionalization of unactivated arenes using gold catalyst

Very recently, the same group developed another method for C-H bond functionalization of arenes **2** with *α*-aryl-*α*-diazoacetates **1** in the presence of gold catalyst-triphenylphosphine Gold(I) trifluoromethanesulfonate.[5g] In this protocol they used *α*-aryl-*α*-diazoacetates **1** containing electron deactivating substituents such as halogens on the phenyl ring. These substituents proved to be important for the chemoselectivity and site-selectivity of the transformation. The desired products *α*-diarylacetates **3** were obtained in good to excellent yields (Scheme 3A.10).



Scheme 3A.10 Synthesis of *α*-diarylacetates via gold catalysis

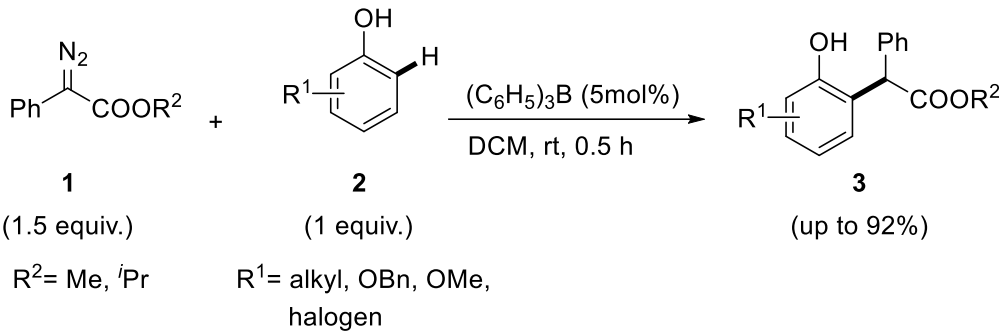
In 2016, Zhou and co-workers developed the method for C-H bond functionalization of electronically activated arene **2q** with *α*-aryl-*α*-diazoacetates **1** in the presence of an iron catalyst to afford *α*-diarylacetates **3**. This protocol required the use of ligand and additive along with the iron catalyst. This transformation proved to be highly *para* selective (Scheme 3A.11).[7b]



Scheme 3A.11 Iron-catalyzed C-H bond functionalization of *N, N*-dimethylaniline

In 2016, Zhang and co-workers developed *ortho*-selective C-H bond functionalization of unprotected phenols **2** with *α*-aryl-*α*-diazoacetates **1** in the presence of catalytic amount of

$(C_6F_5)_3B$. The reaction was carried out at room temperature to afford the desired product *α*-diarylacetates **3** in good to excellent yields. NMR studies and control experiments indicated that the hydrogen bonding interaction between phenols **2** and catalyst influenced the *ortho*-selective C-H bond functionalization (Scheme 3A.12).[9c]



Scheme 3A.12 $(C_6F_5)_3B$ catalyzed *ortho*-selective C-H bond functionalization of phenols

α-Diarylacetate is an important motif present in many biologically active compounds and natural products, and they have been utilized in the synthesis of various drug molecules (Figure 3A.1).[10] Usually, in traditional methods, *α*-diarylacetates are synthesized by using diazocarbonyl compounds, pre-functionalized aromatic compounds. These traditional synthetic routes usually increase the number of steps in the synthesis.[11] Some of the reported methods using C-H bond functionalization approach for the synthesis of *α*-diarylacetates are limited to electron rich arenes with a limited substrate scope.[4j,6,9c] Although gold catalysts have been well explored for the synthesis of *α*-diarylacetates, however, usually they are expensive, and not all of these gold catalysts are commercially available.[5] The synthesis of *α*-diarylacetates using unactivated arenes and electronically deactivated arenes by modifying the catalyst and diazocarbonyl reagent system remains an interesting area for the synthetic chemist.[5f,5g] Therefore, it is necessary to develop a new synthetic method for the functionalization of unactivated and electronically deactivated arenes using diazocarbonyl compounds and inexpensive and commercially available catalyst.

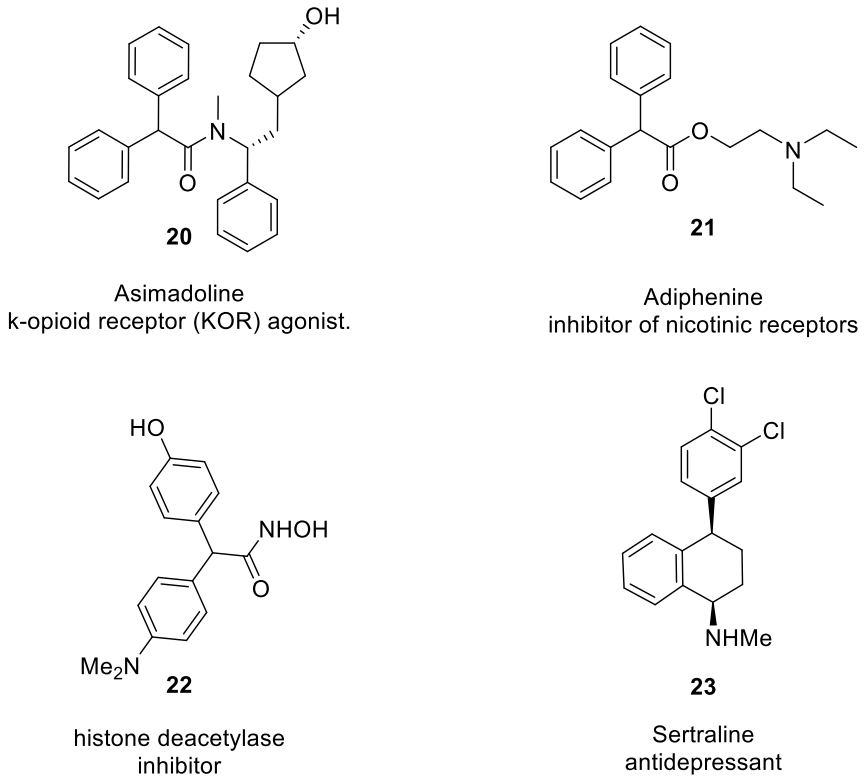


Figure 3A.1 Biologically active compounds containing geminal diaryl functionality

Some of the late transition metals have been explored for the C-H bond functionalization for their efficiency. Interestingly, early transition elements have been seldom explored in the literature due to its low reactivity. However, the synergistic combination of reagent and catalyst is very crucial for the effective C-H bond functionalization. As a part of our ongoing efforts to explore the diazocarbonyl compounds in effective C-H bond functionalization reactions using early transition elements, we planned to explore the suitable combination of the catalyst and the modified diazocarbonyl reagent. Herein, in this chapter, we describe the novel scandium catalyzed C-H bond functionalization of unactivated arenes and mildly deactivated arenes with propargyl α-aryl-α-diazoacetates as new robust reagents to synthesize useful and biologically important α-diarylacetate compounds in good to excellent yields. This methodology has been successfully applied for the synthesis of a biologically active compound such as adiphenine molecule.

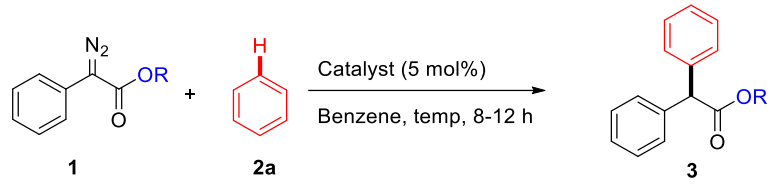
3A.2 Results and discussion

In order to explore the feasibility, we commenced our study using ethyl α-phenyl-α-diazoacetate **1a′** and unactivated arene benzene **2a** as model substrates in the presence of various metal catalysts at room temperature to refluxing conditions (80 ^{o}C) in dry benzene

(entries 1-7, Table 3A.1). Rhodium, copper and gold catalysts found to be ineffective for the C-H bond functionalization of benzene at room temperature as well as at refluxing conditions (entries 1-5, Table 3A.1). Later, when we used the catalytic amount of $Sc(OTf)_3$ for this transformation at room temperature, the starting material ethyl *α*-phenyl-*α*-diazoacetate **1a′** remained intact even after prolonged reaction time (12 h, entry 6, Table 3A.1). Interestingly, the reaction of ethyl *α*-phenyl-*α*-diazoacetate **1a′** and unactivated arene benzene **2a** in the presence of catalytic amount of $Sc(OTf)_3$ (5 mol%) at elevated temperature (80 ^oC), afforded the desired C-H bond functionalization product ethyl 2,2-diphenylacetate **3a′a** in 31% yield (entry 7, Table 3A.1). Encouraged by this preliminary results, we synthesized allyl *α*-phenyl-*α*-diazoacetate **1a′′**. The treatment of allyl *α*-phenyl-*α*-diazoacetate **1a′′** with benzene **2a** in the presence of catalytic amount of $Sc(OTf)_3$ in dry benzene at 80 ^oC, afforded the desired product allyl 2,2-diphenylacetate **3a′′a** in slightly improved yield in comparison to the the ethyl *α*-phenyl-*α*-diazoacetate **1a′** (33%, entry 8, Table 3A.1).

Initial results of the scandium catalyzed C-H bond functionalization was indeed encouraging. However, based on initial observations, we hypothesized that *α*-aryl-*α*-diazoacetate reagents **1 (1a′** and **1a′′)** may be less reactive (donor/acceptor type *α*-diazo acetates) to afford the desired products *α*-diarylacetates **3** in higher yields. Also, the catalytic activity of scandium triflate and low reactivity of unactivated arene such as benzene **2a** towards C-H bond functionalization may be the other prime causes of lower yields of **3a′a** and **3a′′a**. It is known in the literature that propargyl moiety is a weakly electron-withdrawing group[13a] and in this regard, we planned to explore the effect of propargyl group in C-H bond functionalization of unactivated arenes. To explore the feasibility and to enhance the reactivity of *α*-aryl-*α*-diazoacetate towards the C-H bond functionalization, we synthesized the propargyl *α*-phenyl-*α*-diazoacetate **1a** containing removable electron withdrawing[13a] propargyl group as an ester part. To validate our hypothesis, we treated the newly synthesized propargyl *α*-phenyl-*α*-diazoacetate **1a** with benzene **2a** in the presence of various metal catalysts at room temperature and 80 ^oC in dry benzene (entry 9-23, Table 3A.1). Most of the catalysts found to be ineffective and few cases the reactions led to the decomposition of the reagent. Also, the varying reaction temperatures from rt to 80 ^oC did not

Table 3A.1 Optimization of the reaction conditions[a-d]



Entry	Catalyst	R	Time (h)	Temp (°C)	Yield[b,c,d] (%) 3
1	$Rh_2(OAc)_4$	Ethyl	12	rt	DC
2	$Rh_2(OAc)_4$	Ethyl	4	80	DC
3	$Cu(OTf)_2$	Ethyl	12	rt	DC
4	$Cu(OTf)_2$	Ethyl	4	80	trace
5	$(ArO)_3PAuNTf_2$	Ethyl	12	rt	DC
6	$Sc(OTf)_3$	Ethyl	12	rt	NR[d]
7	$Sc(OTf)_3$	Ethyl	12	80	31%
8	$Sc(OTf)_3$	Allyl	12	80	33%
9	$Cu(OTf)_2$	Propargyl	12	80	trace
10	$(ArO)_3PAuNTf_2$	Propargyl	12	rt	DC
11	$(ArO)_3PAuNTf_2$	Propargyl	4	80	DC
12	$Sc(OTf)_3$	Propargyl	12	rt	NR
13	**$Sc(OTf)_3$**	**Propargyl**	**8**	**80**	**70%**
14	$Rh_2(OAc)_4$	Propargyl	12	rt	DC
15	Dichloro(*p*-cymene)ruthenium(II) dimer	Propargyl	12	rt	DC
16	$In(OTf)_3$	Propargyl	12	rt	NR
17	$In(OTf)_3$	Propargyl	12	80	47%
18	$Bi(OTf)_3$	Propargyl	12	rt	NR
19	$Bi(OTf)_3$	Propargyl	12	rt	10%
20	$Y(OTf)_3$	Propargyl	12	80	20%
21	$Yb(OTf)_3$	Propargyl	12	80	trace
22	$FeCl_3.6H_2O$	Propargyl	12	rt	NR
23	$FeCl_3.6H_2O$	Propargyl	12	80	19%
24	Triflic acid	Propargyl	12	rt	21%
25	Triflic acid	Propargyl	12	80	23%
26	No Catalyst	Propargyl	12	80	NR

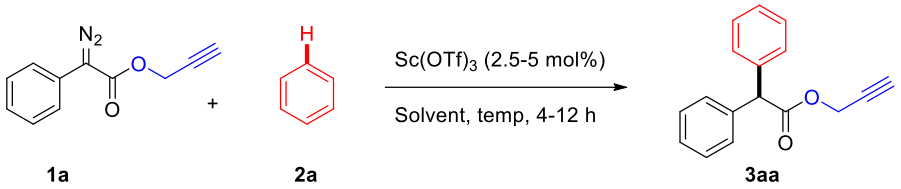
[a]Reaction conditions: a solution of *α*-aryl-*α*-diazoacetate **1** (0.5 mmol, 1 equiv.) in 1 mL benzene was added to a solution of catalyst (5 mol%) and benzene **2a** (1.5 mL) under inert atmosphere; the reaction was monitored by TLC. [b]Isolated yield after purification by column chromatography. [c]DC- decomposed, [d]NR- no reaction.

influence the outcome of the reaction in most of the cases. Gratifyingly, the reaction of propargyl *α*-phenyl-*α*-diazoacetate **1a** and benzene **2a** afforded the desired C-H bond functionalization product propargyl 2,2-diphenylacetate **3aa** in 70% yield in the presence of $Sc(OTf)_3$ (5 mol%) at 80 ^oC in 8 h (entry 13, Table 3A.1).

Further, the structure of the compound **3aa** was unambiguously confirmed by single crystal X-ray analysis.[14] This result was indeed very encouraging as the combination of $Sc(OTf)_3$ and propargyl *α*-phenyl-*α*-diazoacetate **1a** proved to be synergistic. The reactions did not work in the presence of copper and gold catalysts, and we did not observe even a trace amount of the desired products (entry 9-11, Table 3A.1). Rhodium as well ruthenium catalysts found to be ineffective for the desired direct C-H bond functionalization of benzene **2a** (entry 14-15, Table 3A.1). The reaction of benzene **2a** with propargyl *α*-phenyl-*α*-diazoacetate **1a** in the presence of other metal catalysts afforded the direct C-H bond functionalization product **3aa** either in low or moderate yields, in some cases starting materials remained intact (entry 17-23, Table 3A.1). In order to confirm the catalytic efficiency of $Sc(OTf)_3$, and to rule out the possibility of the formation of trace amount of triflic acid in situ by the hydrolysis of $Sc(OTf)_3$ if any due to the moisture and its subsequent catalysis, we carried out the reaction of **1a** and **2a** in presence of catalytic amount triflic acid (entry 24-25, Table 3A.1). However, the desired product was formed in poor yields. The C-H bond functionalization did not work in the absence of any catalysts (entry 26, Table 3A.1).

Encouraged by the preliminary results, further, we screened the reaction in various solvents at various temperature and also varied the catalytic loading of $Sc(OTf)_3$ to optimize the desired C-H bond functionalization to obtain the desired propargyl 2,2-diphenylacetate **3aa** in optimum yield (Table 3A.2). After screening various solvents (entry 1-7, Table 3A.2), dichloroethane proved to be the optimum solvent by affording the desired product in 72% yield at 80 ^oC in 4 h (entry 4, Table 3A.2). However, the polar solvents such as DMF and acetonitrile found to be disadvantageous (entry 5-6, Table 3A.2). Solvents such as ethyl acetate, nitromethane, and dichloromethane afforded the desired product **3aa** in low to moderate yields (entry 1-3, Table 3A.2). The C-H bond functionalization reaction with the lower catalyst loading $Sc(OTf)_3$ (2.5 mol%) afforded the desired product **3aa** in moderate yield in 8 h (entry 7, Table 3A.2).

Table 3A.2 Solvent screening for reactions[a,b]



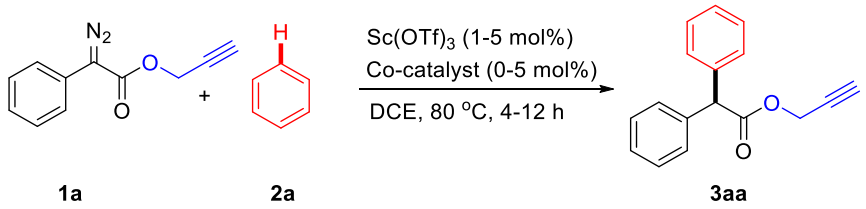
1a 2a 3aa

Entry	Solvent	$Sc(OTf)_3$ (mol%)	Temp (^oC)	Time (h)	Yield[b,c] (%)
1	EtOAc	5	78	8	39
2	Nitromethane	5	80	4	45
3	DCM	5	72	12	48
4	**DCE**	**5**	**80**	**4**	**72**
5	DMF	5	80	12	NR
6	Acetonitrile	5	80	12	NR
7	DCE	2.5	80	8	40

[a]Reaction conditions: propargyl *α*-aryl-*α*-diazoacetate **1a** (0.5 mmol, 1 equiv.), $Sc(OTf)_3$ (5 mol%), and benzene **2a** (5 mmol, 10 equiv.) was added in solvent (2.5 mL) under inert atmosphere and reaction mixture was refluxed at 72-80 ^oC; the reaction was monitored by TLC. [b]Isolated yield after purification by column chromatography. [c]NR- no reaction.

Having obtained the optimal reaction conditions in hand, we further planned to study the effect of co-catalyst in this transformation. In this regard, we screened two different silver co-catalysts along with the $Sc(OTf)_3$ to optimize the reaction (Table 3A.3). Interestingly, both $AgSbF_6$ and AgOTf found to be ineffective and led to the formation of the desired product **3aa** in lower yields (entry 1-5, Table 3A.3). However, the reaction worked smoothly in the absence of co-catalyst to afford the desired product **3aa** in good yield (72% yield, entry 6, Table 3A.3).

Table 3A.3 Co-catalyst screening for reactions[a-c]



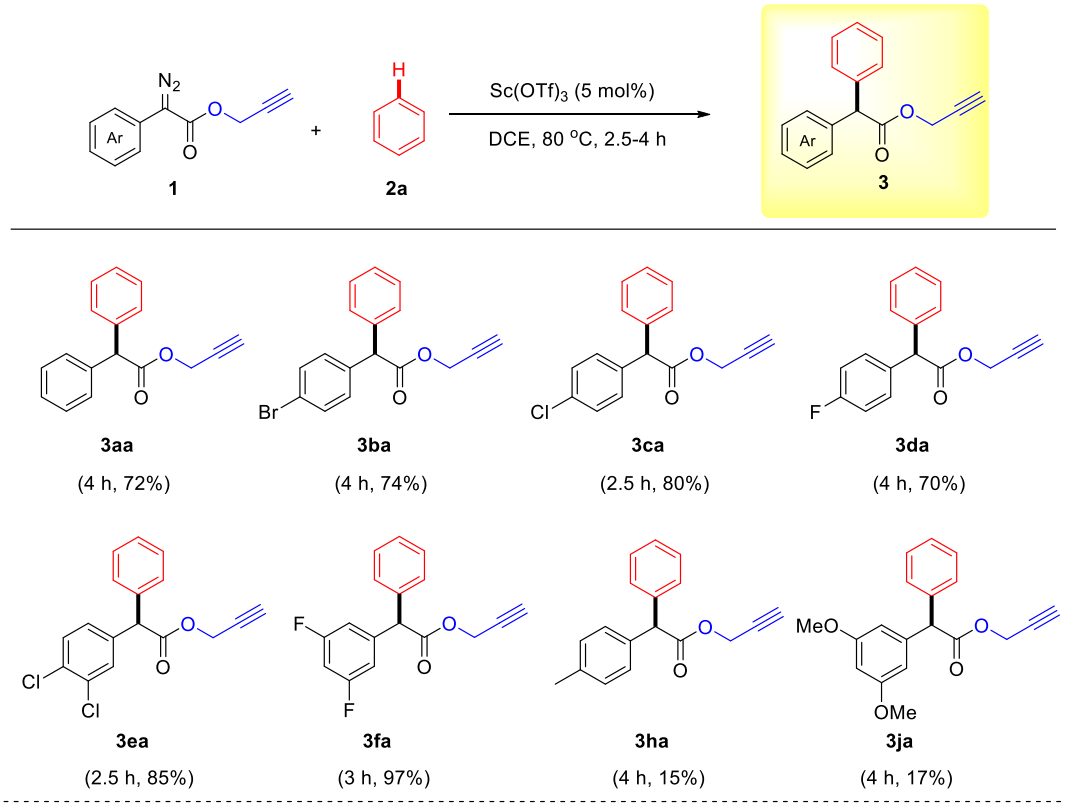
1a **2a** **3aa**

Entry	Solvent	$Sc(OTf)_3$ (mol%)	Co-catalyst (mol%)	Time (h)	Yield (%)[b,c] 3aa
1	DCE	2	$AgSbF_6$ (5)	4	20
2	DCE	5	$AgSbF_6$ (5)	2	40
3	DCE	1	$AgSbF_6$ (5)	12	10
4	DCE	5	AgOTf (5)	12	DC
5	DCE	2	AgOTf (5)	12	DC
6	**DCE**	**5**	**-**	**4**	**72**

[a]Reaction conditions: propargyl *α*-aryl-*α*-diazoacetate **1a** (0.5 mmol, 1 equiv.), benzene **2a** (5 mmol, 10 equiv.), Catalyst (1-5 mol%) and co-catalyst (5 mol%) was added in DCE (2.5 mL) under inert atmosphere and reaction mixture was refluxed at 80 °C; the reaction was monitored by TLC. [b]Isolated yield after purification by column chromatography. [c]DC- decomposed.

Having obtained the optimized reaction conditions in hand, we then focussed our attention to exploring the reagent scope of this C-H bond functionalization protocol using unactivated arene such as benzene **2a** by varying the *α*-aryl-*α*-diazoacetate reagents **1**. Benzene **2a** underwent the C-H bond functionalization reaction with different propargyl *α*-aryl-*α*-diazoacetates (**1a-1f, 1h, 1j)** to afford the desired products **(3aa-3fa, 1ha, 1ja)** in excellent yields (up to 97% yield, Table 3A.4). Propargyl *α*-aryl-*α*-diazoacetates **(1b-1f)** with weak electron-withdrawing substituents on the phenyl ring proved to be very good reagents for the C-H bond functionalization of benzene **2a** to afford the desired products (**3ba-3fa**) in good to excellent yields (up to 97% yield, Table 3A.4). While the *α*-aryl-*α*-diazoacetates (**1h, 1j**) with electron-donating substituents on the phenyl ring greatly reduced the reactivity of propargyl *α*-aryl-*α*-diazoacetates towards the C-H bond functionalization under the optimum reaction conditions to afford the desired products (**3ha**, **3ja)** in lower yields (Table 3A.4). These observations indicated that electron-withdrawing substituents on the phenyl ring of propargyl *α*-aryl-*α*-diazoacetates play a major role in tuning the reagent's reactivity and found to be most suitable diazoacetate reagents for the effective C-H bond functionalization of an unactivated arene **2a**.

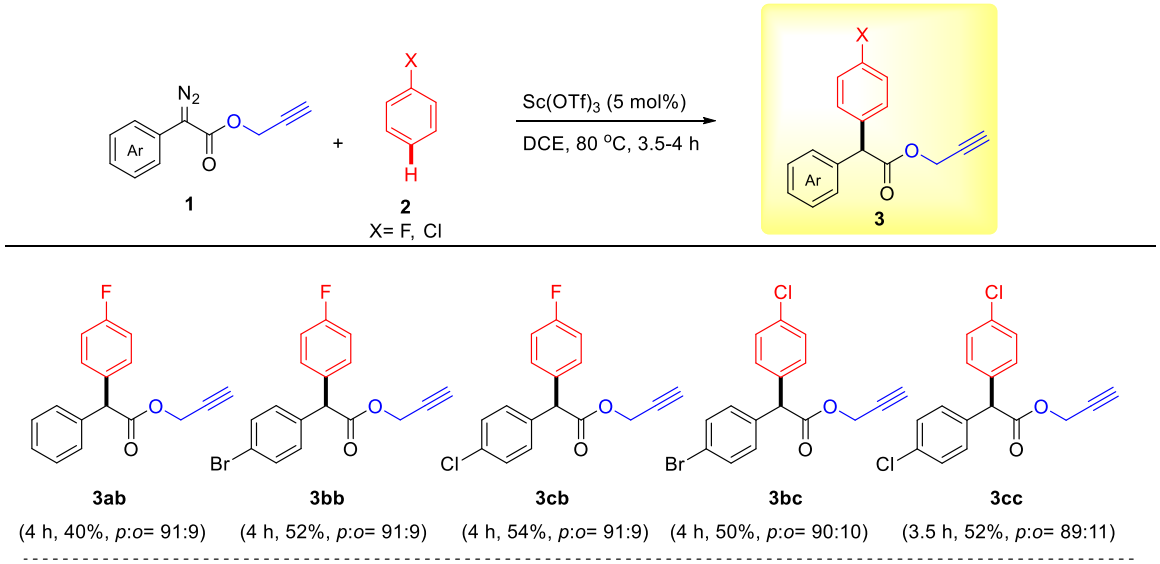
Table 3A.4 C-H bond functionalization of unactivated arene benzene[a,b]



[a]Reaction conditions: propargyl *α*-aryl-*α*-diazoacetate **1** (0.5 mmol, 1 equiv.), benzene **2a** (5 mmol, 10 equiv.) and $Sc(OTf)_3$ (5 mol%) was added in DCE (2.5 mL) under inert atmosphere and reaction mixture was refluxed at 80 °C; the reaction was monitored by TLC. [b]Isolated yield after purification by column chromatography (Time and yields are given in parenthesis).

This very important to note that C-H bond functionalization of benzene is quite challenging and many efforts have been made earlier by different stategies. The combination of the scandium triflate and propargyl *α*-aryl-*α*-diazoacetates proved to be very efficient. After the initial success on the C-H bond functionalization of an unactivated arene such as benzene, we turned our attention to explore this method for the relatively more challenging C-H bond functionalization of mildly deactivated arenes. Gratifyingly, the reactions of fluorobenzene **2b** with different propargyl *α*-aryl-*α*-diazoacetates (**1a, 1b, 1c**) under the optimal reaction conditions afforded the corresponding desired products (**3ab, 3bb, 3cb**) in moderate yields with good regioselectivity (up to 54% yield, up to 91:9 *p*:*o* ratio, Table 3A.5). Likewise, the chlorobenzene **2c** reacted smoothly with propargyl *α*-aryl-*α*-diazoacetates (**1b, 1c**) under the optimal reaction conditions to furnish the corresponding desired products (**3bc, 3cc**) in moderate yields with very good regioselectivity (up to 52% yield, up to 90:10 *p*:*o* ratio, Table 3A.5).

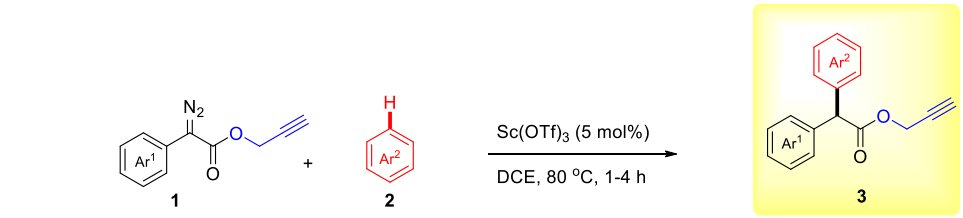
Table 3A.5 C-H bond functionalization of mild deactivated arenes[a,b]

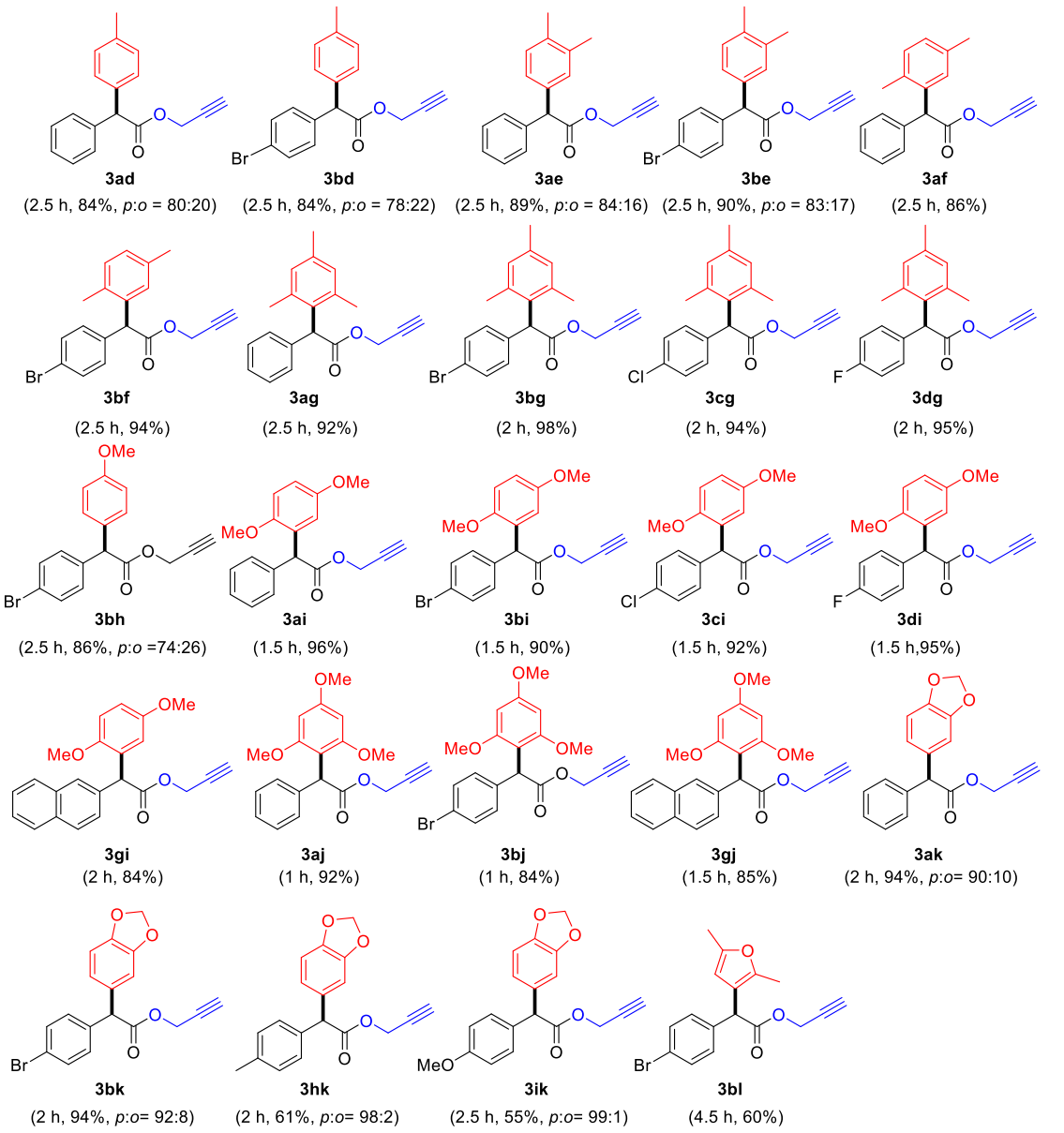


[a]Reaction conditions: propargyl *α*-aryl-*α*-diazoacetates **1** (0.5 mmol, 1 equiv.), arene **2** (10 equiv.), and $Sc(OTf)_3$ (5 mol%) was added in DCE (2.5 mL) under inert atmosphere and reaction mixture was refluxed at 80 °C; the reaction was monitored by TLC. [b]Isolated yield after purification by column chromatography (Time and yields are given in parenthesis).

Later, we explored this method for the chemoselective C-H bond functionalization of electron rich arenes. Mildly activated arene such as toluene **2d** reacted with propargyl *α*-aryl-*α*-diazoacetates (**1a-1b**) under the optimal reaction conditions to afford the corresponding desired products (**3ad-3bd**) in good yields with good regioselectivity (up to 84% yield, up to 80:20 *p*:*o* ratio, Table 3A.6). *o*-Xylene **2e** and *p*-xylene **2f** reacted smoothly with propargyl *α*-aryl-*α*-diazoacetates (**1a-1b**) under the optimal reaction conditions to afford the corresponding desired products (**3ae-3be, 3af-3bf**) in good to excellent yields (up to 94% yield, Table 3A.3). Mesitylene **5g**, when treated with propargyl *α*-aryl-*α*-diazoacetates (**1a-1d**) under optimal reaction condition, furnished the corresponding products (**3ag-3dg**) in excellent yields (up to 98% yield, Table 3A.6). Under the optimal reaction conditions, the activated arene such as anisole **2h** reacted smoothly with the propargyl *α*-aryl-*α*-diazoacetate **1b** to afford the corresponding desired product **3bh** in very good yield. Activated arene such

Table 3A.6 Chemoselective C-H bond functionalization of activated arenes[a,b]



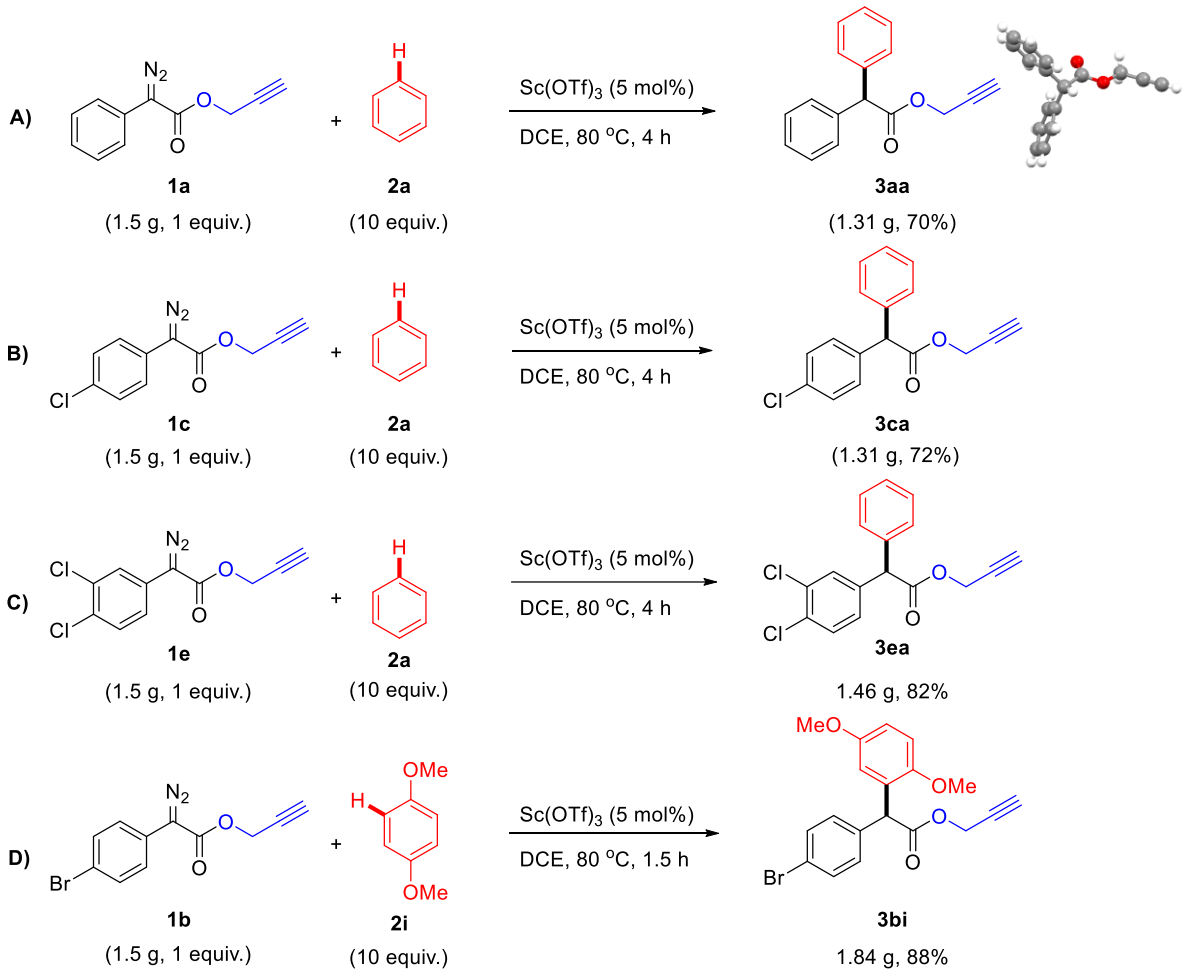


[a]Reaction conditions: propargyl α-aryl-α-diazoacetates **1** (0.5 mmol, 1equiv.), arene **2** (10 equiv.) and $Sc(OTf)_3$ (5 mol%) was added in DCE (2.5 mL) under inert atmosphere and reaction mixture was refluxed at 80 °C; the reaction was monitored by TLC. [b]Isolated yield after purification by column chromatography (Time and yields are given in parenthesis).

as 1,4-dimethoxybenzene **2i** reacted with different propargyl *α*-aryl-*α*-diazoacetates (**1a-1d, 1g**) to afford the corresponding desired products (**3ai-3di, 3gi**) in excellent yields (up to 96%, Table 3A.6) under the optimized reaction conditions.

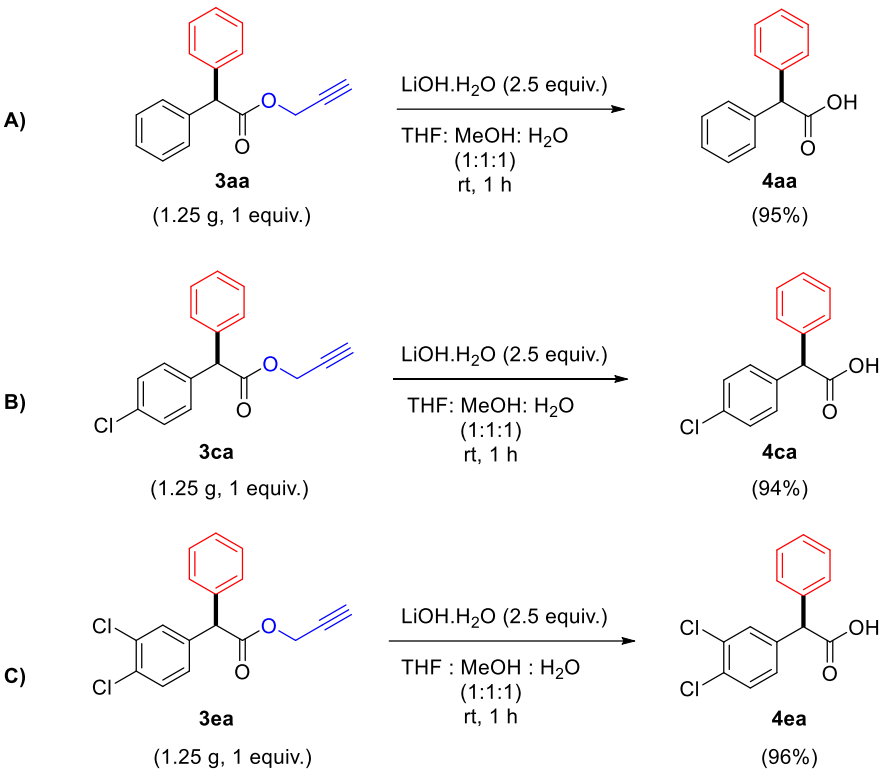
Highly activated arene such as 1,3,5-trimethoxybenzene **2j** reacted smoothly with propargyl *α*-aryl-*α*-diazoacetates (**1a, 1b, 1g)** to furnish the corresponding C-H bond functionalization products (**3aj, 3bj, 3gj**) in very good to excellent yields (up to 92%, Table 3A.6). 1,3-Benzodioxole **2k** also reacted smoothly with various propargyl *α*-aryl-*α*-diazoacetates (**1a,1b, 1h, 1i**) under the optimal reaction conditions to afford the corresponding desired C-H functionalized products (**3ak, 3bk, 3hk, 3ik**) in moderate to excellent yields with excellent regioselectivity (up to 94% yield, up to 99:1 *p*:*o* ratio, Table 3A.6). It is very important to note that C-H bond functionalization of 1,3-benzodioxole **2k** worked smoothly with *α*-(4-methoxyphenyl)-*α*-diazoacetate **1i,** unlike the previous procedure.[5e] Even the heteroaromatic arene such as 2,5-dimethylfuran **2l**, when treated with propargyl *α*-aryl-*α*-diazoacetate **1b** under the optimal reaction conditions afforded the C-H functionalization product **3bl** in 60% yield (see Table 3A.6). We demonstrated the robustness of this protocol using different arenes and propargyl *α*-aryl-*α*-diazoacetates. It is also very significant to note that substrates containing Csp^3-H bonds underwent chemo-selective C-H bond functionalization of arenes exclusively.[13b-13d]

To demonstrate the practicality and the generality of the protocol, we further explored this protocol for the gram-scale synthesis of few *α*-diarylacetates. Reactions of propargyl *α*-aryl-*α*-diazoacetates (**1a**, **1c**, **1e**, and **1b**) and arenes (**2a** and **2i**) on a gram-scale afforded the corresponding *α*-diarylacetates (**3aa**, **3ca**, **3ea**, **3bi**) in very good yields under the optimal conditions (up to 88% yield, Scheme 3A.13). The protocol proved to be effective on a gram-scale and found to be reproducible.



Scheme 3A.13 Gram-scale synthesis of α-diarylacetates

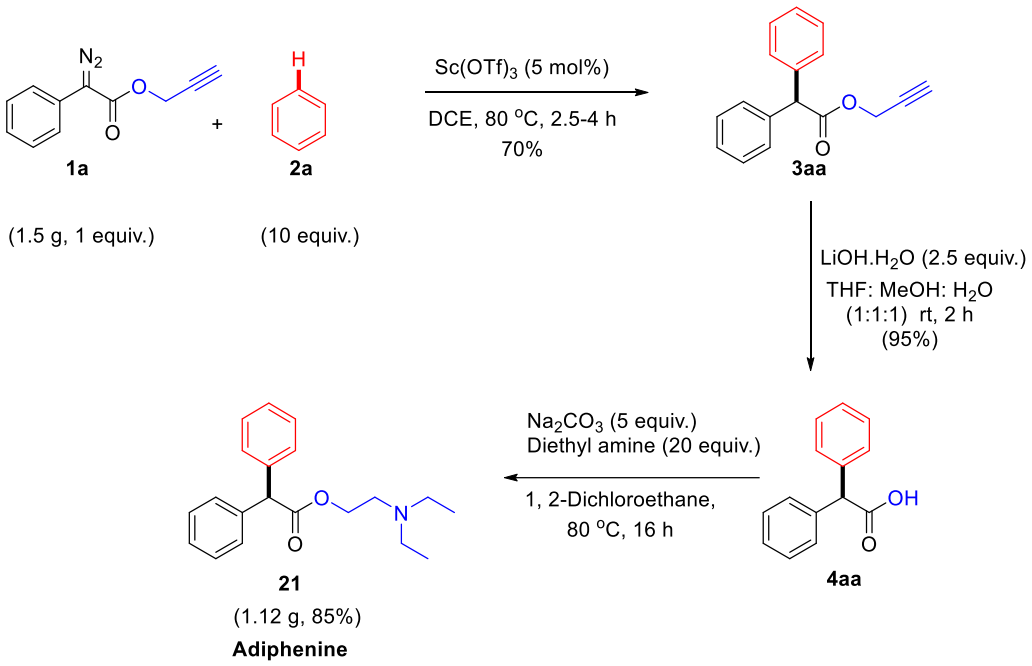
Finally, the hydrolysis of propargyl α-diarylacetates (**3aa**, **3ca, 3ea**) was carried out using $LiOH.H_2O$ (2.5 equiv.) in ethanol- tetrahydrofuran-water (1:1:1) mixture at room temperature in 1 h, to furnish the corresponding α-diarylacids (**4aa**, **4ca**, and **4ea**) in excellent yields (up to 96% yield, Scheme 3A.14). The easy removal of propargyl ester under mild condition proved to be useful for the further synthetic transformations.



Scheme 3A.14 Hydrolysis of propargyl esters

3A.2.1 Application: Gram-scale synthesis of Adiphenine-an antispasmodic drug

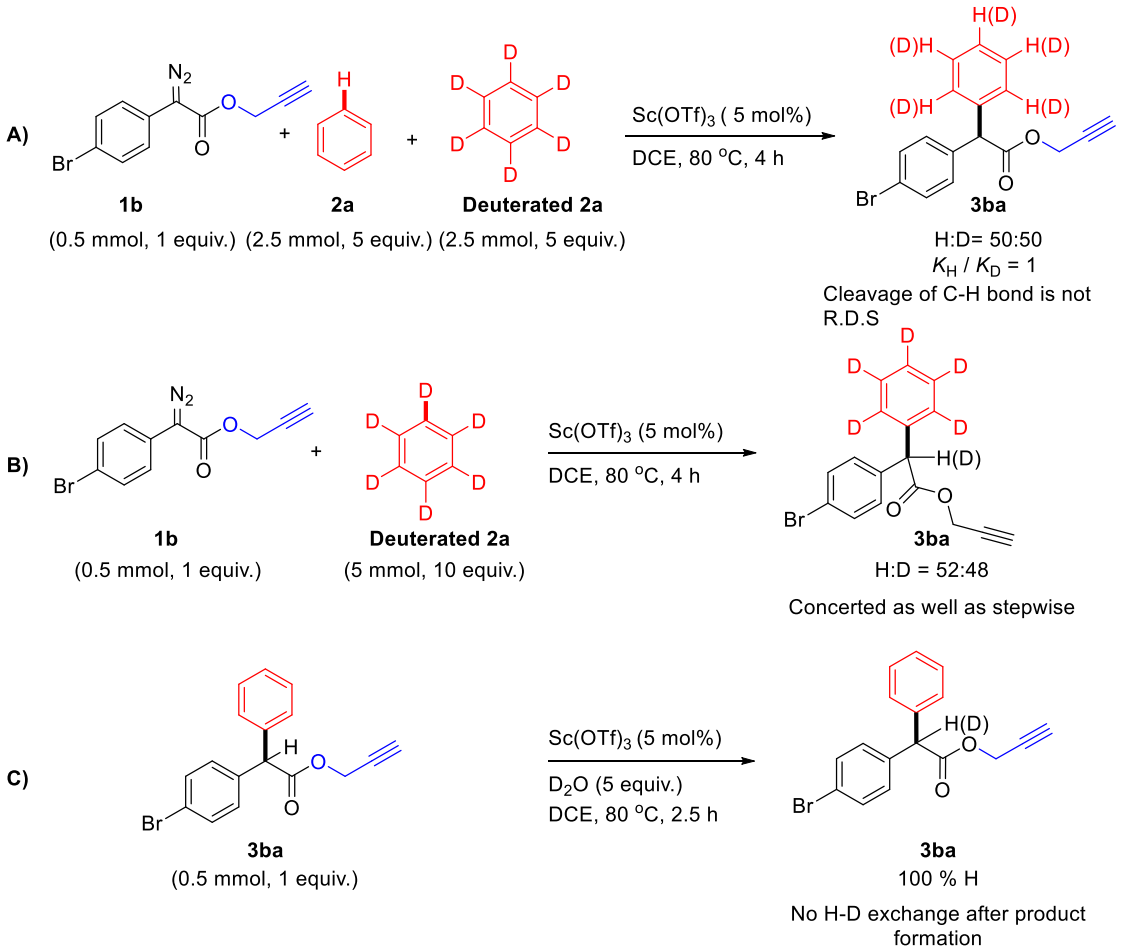
Further, in order to demonstrate the applicability of this protocol, we explored the synthesis of biologically active adiphenine **21** on a gram-scale. Adiphenine **21** is a nicotinic receptor inhibitor, used as an antispasmodic drug.[12] The C-H bond functionalization of benzene **2a** with propargyl *α*-phenyl-*α*-diazoacetate **1a** in the presence of catalytic amount of $Sc(OTf)_3$ (5 mol%) afforded the corresponding product **3aa**. This was further utilized for the synthesis of adiphenine **21** in two steps in good yield**.** The C-H bond functionalization of arene was utilized as a key step in this synthesis (Scheme 3A.15).



Scheme 3A.15 Gram-scale synthesis of Adiphenine-An antispasmodic drug

3A.2.2 Mechanistic studies

After successfully demonstrating the practicability of the protocol, we further planned to understand the reaction pathway. In order to understand whether or not the C-H bond cleavage of benzene is a rate-determining step in this reaction, we carried out kinetic isotope effect studies. The studies indicated that cleavage of the C-H bond of benzene was not a rate-determining step (K_H/K_D = 1, Scheme 3A.16 A). Further, to confirm whether or not the direct [1,2]-H shift from benzene takes place in this transformation, we carried out another controlled experiment (Scheme 3A.16 B). This result indicated that 48% of direct [1,2]-D shift from the deuterated benzene occurred in this transformation. The third controlled experiment in D_2O (5 equiv.) indicated that there was no direct proton exchange of **3ba** with D_2O under the optimized reaction conditions (Scheme 3A.16 C). Further mechanistic studies need to be explored in detail and are under progress to propose the most plausible mechanism.



Scheme 3A.16 Mechanistic studies

3A.3 Conclusions

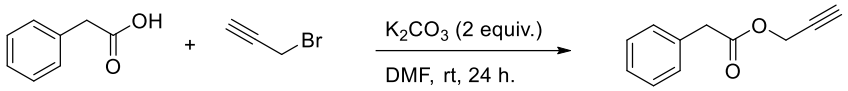
In conclusion, we have developed novel scandium catalyzed chemo highly- and regioselective C-H bond functionalization of unactivated arenes and mildly deactivated arenes with propargyl *α*-aryl-*α*-diazoacetates as a new reagent. The combination of catalyst-$Sc(OTf)_3$ and reagent-propargyl *α*-aryl-*α*-diazoacetate worked synergistically. The practicability of this protocol demonstrated on a gram-scale. The protocol has been successfully applied for the gram-scale synthesis of biologically active adiphenine- an antispasmodic drug.

3A.4 Experimental section

3A.4.1 General

Unless otherwise noted, all reactions were carried out with distilled and dried solvents using oven-dried glassware. All the reagents were purchased from commercial sources and used as received unless otherwise indicated. Thin-layer chromatography (TLC) was performed using silica gel 60 GF_{254} precoated aluminum backed plates (2.5 mm) with detection by UV light. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6. Chemical shifts in ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from tetramethylsilane with the solvent resonance as the internal standard or from the residual solvent peak as internal standard and *J* values are given in Hz. ^{13}C NMR spectra are reported as δ in ppm downfield from tetramethylsilane and relative to the signal of chloroform-d and DMSO-d_6. ^{13}C NMR spectra were recorded with complete proton decoupling. Mass samples were analyzed by high-resolution mass spectrometry (HRMS) using ESI TOF. FT-IR spectra were obtained using a FT-IR spectrophotometer as neat and reported in cm^{-1}. Melting points were measured in an open glass capillary and values are uncorrected.

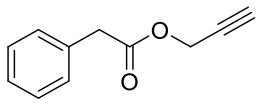
3A.4.2 General procedure A for the synthesis of propargyl esters



4a (1 equiv.) **5** (1.2 equiv.) **6a** (96%)

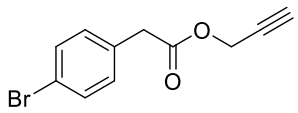
To the stirred solution of 2-phenylacetic acid **4a** (2.72 g, 20 mmol) in DMF (15 mL) was added propargyl bromide solution 80% in toluene (3.57 g, 24 mmol) and K_2CO_3 (5.53 g, 40 mmol). The reaction mixture was stirred at room temperature for 24 h. The progress of the reaction was monitored by TLC. The reaction mixture was filtered through celite, and the filtrate was diluted with water (30 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with cold water and brine solution. The extract was dried over anhydrous Na_2SO_4 and filtered. The filtrate was evaporated under vacuum and the crude product was purified using column chromatography over silica gel to afford product **6a** as colourless liquid (3.34 g, 96% yield).[15]

Prop-2-yn-1-yl 2-phenylacetate (6a):



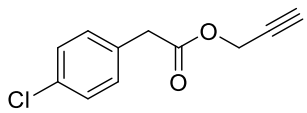
Compound **6a** was synthesized following the general procedure (A). The product was obtained as pale yellow liquid (3.34 g, 96% yield): R_f = 0.35 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3288, 2946, 2128, 1737, 1605, 1496, 1446, 1333, 1239, 1136, 999, 938, 760, 697; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.19 (m, 5H), 4.69 (d, *J* = 2.5 Hz, 2H), 3.68 (s, 2H), 2.47 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 133.5, 129.4, 128.8, 127.4, 77.6 , 75.2, 52.5, 41.1; HRMS (ESI TOF): Calculated for $C_{11}H_{10}NaO_2$ $(M + Na)^+$: 197.0578, Found: 197.0576.

Prop-2-yn-1-yl 2-(4-bromophenyl)acetate (6b):



Compound **6b** was synthesized following the general procedure (A). The product was obtained as white solid (4.657 g, 92% yield): R_f = 0.35 petroleum ether/EtOAc (95:5); m.p.: 41-43 ^{o}C; IR (neat) cm^{-1}: 3288, 3032, 2946, 2128, 1737, 1605, 1239, 1136, 831, 760, 697, 639; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 4.70 (d, *J* = 2.5 Hz, 2H), 3.63 (s, 2H), 2.48 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.4, 131.9, 131.2, 129.7, 121.5, 77.4, 75.3, 52.6, 40.4; HRMS (ESI TOF): Calculated for $C_{11}H_{10}BrO_2$ $(M + H)^+$: 252.9864, Found: 252.9871.

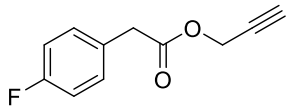
Prop-2-yn-1-yl 2-(4-chlorophenyl)acetate (6c):



Compound **6c** was synthesized following the general procedure (A). The product was obtained as viscous liquid (3.964 g, 95% yield): R_f = 0.3 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3293, 2948, 2129, 1738, 1597, 1492, 1371, 1143, 1091, 938, 807, 758, 676, 641; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.41 – 7.36 (m, 2H), 7.33 – 7.27 (m, 2H), 4.72 (d, *J* = 2.5 Hz, 2H), 3.75 (s, 2H), 3.55 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.1,

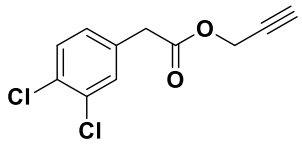
133.0, 131.6, 131.2, 128.2, 78.2, 77.7, 52.1, 39.0; HRMS (ESI TOF): Calculated for $C_{11}H_{10}ClO_2$ $(M + H)^+$: 209.0369, Found: 209.0365.

Prop-2-yn-1-yl 2-(4-fluorophenyl)acetate (6d):



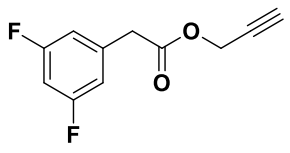
Compound **6d** was synthesized following the general procedure (A). The product was obtained as colourless liquid (3.611 g, 94% yield): R_f = 0.35 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3295, 2948, 2129, 1739, 1606, 1510, 1222, 1140, 937, 826, 785, 681, 643; ^1H NMR (400 MHz, DMSO-d_6): δ 7.38 – 7.28 (m, 2H), 7.20 – 7.11 (m, 2H), 4.71 (d, J = 2.5 Hz, 2H), 3.73 (s, 2H), 3.54 (t, J = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.3, 161.2 (d, J = 242.8 Hz), 131.3 (d, J = 8.1 Hz), 130.1 (d, J = 3.1 Hz), 115.0 (d, J = 21.3 Hz), 78.3, 77.7, 52.0, 38.8; HRMS (ESI TOF): Calculated for $C_{11}H_9FNaO_2$ $(M + Na)^+$: 215.0484, Found: 215.0490.

Prop-2-yn-1-yl 2-(3,4-dichlorophenyl)acetate (6e):



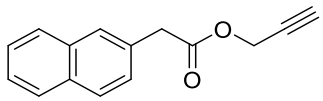
Compound **6e** was synthesized following the general procedure (A). The product was obtained as colourless liquid (4.473 g, 92% yield): R_f = 0.35 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3295, 2948, 2130, 1738, 1133, 1026, 998, 877, 820, 781, 743, 637; ^1H NMR (400 MHz, $CDCl_3$): δ 7.44 – 7.35 (m, 2H), 7.13 (dd, J = 8.3, 2.1 Hz, 1H), 4.71 (d, J = 2.5 Hz, 2H), 3.63 (s, 2H), 2.50 (t, J = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 133.5, 130.9, 129.8, 125.7, 125.4, 122.8, 77.4, 75.6, 52.6; HRMS (ESI TOF): Calculated for $C_{11}H_9Cl_2O_2$ $(M + H)^+$: 242.9980, Found: 242.9984.

Prop-2-yn-1-yl 2-(3,5-difluorophenyl)acetate (6f):



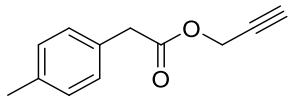
Compound **6f** was synthesized following the general procedure (A). The product was obtained as colourless liquid (3.909 g, 93% yield): R_f = 0.35 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3299, 3094, 2951, 2130, 1741, 1626, 1306, 1120, 994, 936, 850, 787, 667, 642; ^1H NMR (400 MHz, $CDCl_3$): δ 6.91 – 6.79 (m, 2H), 6.75 (m, 1H), 4.72 (d, *J* = 2.5 Hz, 2H), 3.65 (s, 2H), 2.50 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 163.1 (dd, *J* = 248.7, 12.9 Hz), 136.9 (t, *J* = 9.8 Hz), 113.5 – 111.6 (m), 103.1 (t, *J* = 25.2 Hz), 77.3, 75.4, 52.8, 40.6 (t, *J* = 2.0 Hz); HRMS (ESI TOF): Calculated for $C_{11}H_9FNaO_2$ $(M + Na)^+$: 215.0484, Found: 215.0490.

Prop-2-yn-1-yl 2-(naphthalen-2-yl)acetate (6g):



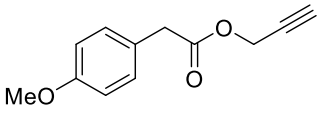
Compound **6g** was synthesized following the general procedure (A). The product was obtained as white solid (4.261 g, 95% yield): R_f = 0.3 petroleum ether/EtOAc (95:5); m.p.: 50-51°C; IR (neat) cm^{-1}: 3288, 3055, 2311, 2129, 1736, 1509, 1325, 1135, 946, 900, 857, 748, 679, 636; ^1H NMR (400 MHz, $CDCl_3$): δ 7.82-7.78 (m, 3H), 7.74 (s, 1H), 7.54 – 7.29 (m, 3H), 4.71 (d, *J* = 2.5 Hz, 2H), 3.83 (s, 2H), 2.47 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 133.6, 132.7, 131.0, 128.5, 128.2, 127.83, 127.80, 127.4, 126.3, 126.0, 77.7, 75.2, 52.5, 41.3; HRMS (ESI TOF): Calculated for $C_{13}H_{13}O_2$ $(M + H)^+$: 225.0916, Found: 225.0908.

Prop-2-yn-1-yl 2-(p-tolyl)acetate (6h):



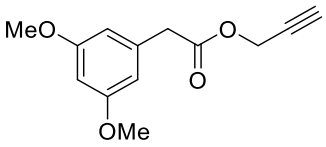
Compound **6h** was synthesized following the general procedure (A). The product was obtained as pale yellow liquid (3.539 g, 94% yield): R_f = 0.35 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3288, 2945, 2129, 1740, 1515, 1241, 1141, 1005, 938, 808, 774, 682, 644; ^1H NMR (400 MHz, $CDCl_3$): δ 7.17 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 4.68 (d, *J* = 2.5 Hz, 2H), 3.63 (s, 2H), 2.47 (t, *J* = 2.5 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 137.0, 130.5, 129.4, 129.3, 77.7, 75.1, 52.4, 40.7, 21.2; HRMS (ESI TOF): Calculated for $C_{12}H_{13}O_2$ $(M + H)^+$: 189.0916, Found: 189.0912.

Prop-2-yn-1-yl 2-(4-methoxyphenyl)acetate (6i):



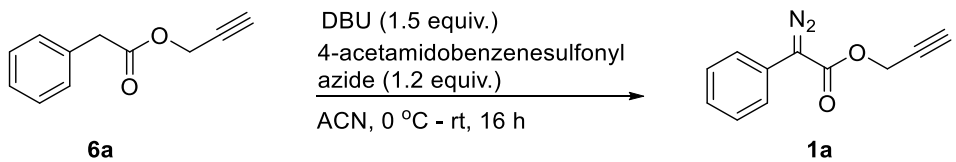
Compound **6i** was synthesized following the general procedure (A). The product was obtained as colourless liquid (3.88 g, 95% yield): R_f = 0.5 petroleum ether/EtOAc (80:20); IR (neat) cm^{-1}: 3285, 2948, 2128, 1736, 1511, 1242, 1138, 1025, 938, 819, 780, 682, 643; ^1H NMR (400 MHz, $CDCl_3$): δ 7.23 – 7.17 (m, 2H), 6.89 – 6.83 (m, 2H), 4.68 (d, J = 2.5 Hz, 2H), 3.79 (s, 3H), 3.61 (s, 2H), 2.47 (t, J = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 159.0, 130.4, 125.6, 114.2, 77.7, 75.1, 55.4, 52.4, 40.2; HRMS (ESI TOF): Calculated for $C_{12}H_{12}NaO_3$ $(M + Na)^+$: 227.0684, Found: 227.0685.

Prop-2-yn-1-yl 2-(3,5-dimethoxyphenyl)acetate (6j):



Compound **6j** was synthesized following the general procedure (A). The product was obtained as colourless liquid (4.263 g, 91% yield): R_f = 0.25 petroleum ether/EtOAc (90:10); IR (neat) cm^{-1}: 3282, 2946, 2127, 1739, 1597, 1201, 1142, 1061, 941, 835, 782, 683, 651; ^1H NMR (400 MHz, $CDCl_3$): δ 6.44 (d, J = 2.2 Hz, 2H), 6.37 (t, J = 2.2 Hz, 1H), 4.69 (d, J = 2.5 Hz, 2H), 3.77 (s, 6H), 3.60 (s, 2H), 2.48 (t, J = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 161.0, 135.5, 107.4, 99.5, 77.6, 75.1, 55.4, 52.4, 41.3; HRMS (ESI TOF): Calculated for $C_{13}H_{15}O_4$ $(M + H)^+$: 235.0970, Found: 235.0971.

3A.4.3 General procedure B for the synthesis of *α*-aryl-*α*-diazoacetates



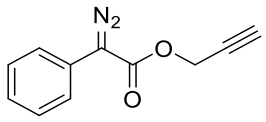
6a
(1 equiv.)

1a
(76%)

To the stirred solution propargyl 2-phenylacetate **6a** (1.74 g, 10 mmol) in 15 mL, acetonitrile was added 4-acetamidobenzenesulfonyl azide (2.88 g, 12 mmol) and DBU (2.24 mL, 15 mmol) at ambient temperature under inert atmosphere. The reaction mixture was

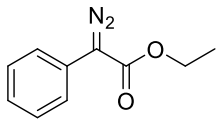
stirred for 16 h at room temperature. The reaction was quenched with saturated NH_4Cl, and the product was extracted with diethyl ether (30 mL x 3). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The extract was filtered, and the filtrate was evaporated under vacuum. The crude product was purified using column chromatography over silica gel to afford *α*-aryl-*α*-diazoacetates **1a** as orange solid (1.934 g, 84% yield).[16]

Prop-2-yn-1-yl 2-diazo-2-phenylacetate (1a):



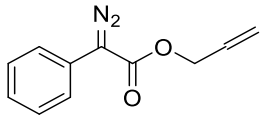
Compound **1a** was synthesized following the general procedure (B). The product was obtained as Orange solid (1.521 g, 76% yield): R_f = 0.4 petroleum ether/EtOAc (95:5); m.p.: 41-43 ^oC; IR (neat) cm^{-1}: 3295, 3062, 2948, 2085, 1696, 1597, 1497, 1240, 1143, 1017, 950, 752, 682, 637; ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 – 7.46 (m, 2H), 7.44 – 7.36 (m, 2H), 7.24 – 7.15 (m, 1H), 4.88 (d, *J* = 2.5 Hz, 2H), 2.52 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4, 129.1, 126.2, 125.1, 124.1, 77.7, 75.3, 52.3; HRMS (ESI TOF): Calculated for $C_{11}H_8N_2NaO_2$ $(M + Na)^+$: 223.0483, Found: 223.0478.

Ethyl 2-diazo-2-phenylacetate (1a′):



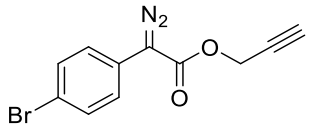
Compound **1a′** was synthesized following the general procedure (B). The product was obtained as orange liquid (1.522 g, 80% yield): R_f 0.35 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 2984, 2081, 1696, 1597, 1496, 1387, 1286, 1156, 1094, 979, 823, 688; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51 – 7.45 (m, 2H), 7.41 – 7.35 (m, 2H), 7.20 – 7.15 (m, 1H), 4.33 (q, *J* = 7.2 Hz, 2H), 1.34 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4, 129.0, 125.9, 125.8, 124.1, 61.1, 14.6; HRMS (ESI TOF): Calculated for $C_{10}H_{10}N_2NaO_2$ $(M + Na)^+$: 213.0639, Found: 213.0631.

Allyl 2-diazo-2-phenylacetate (1a′′):



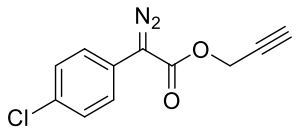
Compound **1a′′** was synthesized following the general procedure (B). The product was obtained as orange liquid (1.516 g, 75% yield): R_f = 0.35 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3028, 2952, 2085, 1700, 1598, 14971242, 1151, 1043, 1012, 929, 753, 694; ^1H NMR (400 MHz, $CDCl_3$): δ 7.50-7.47 (m, 2H), 7.41 – 7.34 (m, 2H), 7.21 – 7.15 (m, 1H), 5.98 (ddt, *J* = 17.2, 10.4, 5.6 Hz, 1H), 5.36 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.27 (ddd, *J* = 10.4, 2.6, 1.3 Hz, 1H), 4.84 – 4.70 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 132.3, 129.1, 126.0, 125.6, 124.2, 118.5, 65.6; HRMS (ESI TOF): Calculated for $C_{11}H_{10}N_2O_2$ $(M)^+$: 202.0742, Found: 202.0760.

Prop-2-yn-1-yl 2-(4-bromophenyl)-2-diazoacetate (1b):



Compound **1b** was synthesized following the general procedure (B). The product was obtained as orange solid (2.261 g, 81% yield): R_f = 0.45 petroleum ether/EtOAc (95:5); m.p.: 57-59 ºC; IR (neat) cm^{-1}: 3294, 2948, 2085, 1695, 1488, 1336, 1236, 1144, 1030, 999, 948, 813, 678, 632; ^1H NMR (400 MHz, $CDCl_3$): δ 7.54 – 7.47 (m, 2H), 7.38 – 7.33 (m, 2H), 4.87 (d, *J* = 2.3 Hz, 2H), 2.52 (t, *J* = 2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.0, 132.2, 125.5, 124.4, 119.7, 77.6, 75.5, 52.5; HRMS (ESI TOF): Calculated for $C_{11}H_7BrN_2NaO_2$ $(M + Na)^+$: 300.9589, Found: 300.9888.

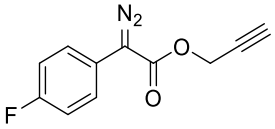
Prop-2-yn-1-yl 2-(4-chlorophenyl)-2-diazoacetate (1c):



Compound **1c** was synthesized following the general procedure (B). The product was obtained as orange solid (1.736 g, 74% yield). R_f = 0.35 petroleum ether/EtOAc (95:5); m.p.: 61-63 ºC; IR (neat) cm^{-1}: 3295, 2949, 2086, 1697, 1492, 1336, 1276, 1237, 1146, 1093, 1005,

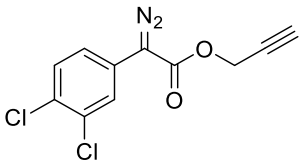
820, 734, 680, 637; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 – 7.39 (m, 2H), 7.38 – 7.33 (m, 2H), 4.87 (d, *J* = 2.5 Hz, 2H), 2.52 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 131.9, 129.3, 125.3, 123.8, 77.6, 75.4, 52.5; HRMS (ESI TOF): Calculated for $C_{11}H_7ClN_2NaO_2$ $(M + Na)^+$: 257.0094, Found: 257.0097.

Prop-2-yn-1-yl 2-diazo-2-(4-fluorophenyl)acetate (1d):



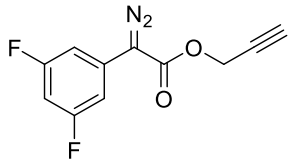
Compound **1d** was synthesized following the general procedure (B). The product was obtained as yellow solid (1.833 g, 84% yield). R_f = 0.3 petroleum ether/EtOAc (95:5); m.p.: 62-64 ^{o}C; IR (neat) cm^{-1}: 3298, 2950, 2086, 1696, 1508, 1339, 1286, 1233, 1145, 1033, 829, 683, 642; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 – 7.38 (m, 2H), 7.17 – 7.02 (m, 2H), 4.87 (d, *J* = 2.5 Hz, 2H), 2.52 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4, 161.3 (d, *J* = 246.7 Hz), 126.1 (d, *J* = 8.0 Hz), 120.9 (d, *J* = 3.2 Hz), 116.2 (d, *J* = 22.0 Hz), 77.7, 75.4, 52.4; HRMS (ESI TOF): Calculated for $C_{11}H_7FN_2NaO_2$ $(M + Na)^+$: 241.0389, Found: 241.0384.

Prop-2-yn-1-yl 2-diazo-2-(3,4-dichlorophenyl)acetate (1e):



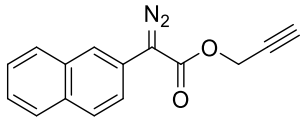
Compound **1e** was synthesized following the general procedure (B). The product was obtained as orange solid (2.206 g, 82% yield): R_f = 0.35 petroleum ether/EtOAc (95:5); m.p.: 52-54 ^{o}C; IR (neat) cm^{-1}: 3297, 2950, 2090, 1698, 1589,1475, 1274, 1149, 1039, 956, 884, 815, 736, 680, 640; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 2.3 Hz, 1H), 7.44 (d, *J* = 8.6 Hz, 1H), 7.28 (dd, *J* = 8.6, 2.4 Hz, 1H), 4.87 (d, *J* = 2.6 Hz, 2H), 2.53 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 133.5, 130.9, 129.8, 125.7, 125.4, 122.8, 77.4, 75.6, 52.6; HRMS (ESI TOF): Calculated for $C_{11}H_6Cl_2N_2NaO_2$ $(M + Na)^+$: 290.9704, Found: 290.9701.

Prop-2-yn-1-yl 2-diazo-2-(3,5-difluorophenyl)acetate (1f):



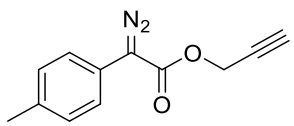
Compound **1f** was synthesized following the general procedure (B). The product was obtained as orange solid (1.842 g, 78% yield): R_f = 0.4 petroleum ether/EtOAc (95:5); m.p.: 36-38 ^oC; IR (neat) cm^{-1}: 3301, 3099, 2953, 2094, 1704, 1623, 1589, 1479, 1445, 1269, 1124, 1067, 987, 926, 839, 741, 669, 641; ^1H NMR (400 MHz, $CDCl_3$): δ 7.26 – 6.82 (m, 2H), 6.65-6.59 (m, 1H), 4.88 (d, *J* = 2.5 Hz, 2H), 2.54 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5 (dd, *J* = 247.8, 13.7 Hz), 163.3, 129.2 (t, *J* = 11.5 Hz), 106.7 – 106.2 (m), 101.2 (t, *J* = 25.5 Hz), 77.3, 75.6, 52.6; HRMS (ESI TOF): Calculated for $C_{11}H_6F_2N_2NaO_2$ $(M + Na)^+$: 259.0294, Found: 259.0281.

Prop-2-yn-1-yl 2-diazo-2-(naphthalen-2-yl)acetate (1g):



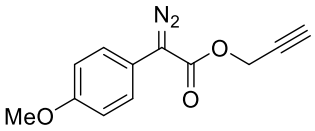
Compound **1g** was synthesized following the general procedure (B). The product was obtained as pale orange solid (1.927 g, 77% yield). R_f = 0.35 petroleum ether/EtOAc (95:5); m.p.: 82-84 ^oC; IR (neat) cm^{-1}: 3291, 3057, 2947, 2083, 1698, 1323, 1248, 1147, 1121, 1038, 895, 852, 812, 736, 680, 639; ^1H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 1.7 Hz, 1H), 7.92 – 7.69 (m, 3H), 7.58 – 7.37 (m, 3H), 4.91 (d, *J* = 2.5 Hz, 2H), 2.53 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 133.7, 131.7, 128.9, 127.8, 127.8, 126.8, 126.0, 122.8, 122.3, 121.9, 77.7, 75.4, 52.4; HRMS (ESI TOF): Calculated for $C_{15}H_{10}N_2NaO_2$ $(M + Na)^+$: 273.0640, Found: 273.0640.

Prop-2-yn-1-yl 2-diazo-2-(p-tolyl)acetate (1h):



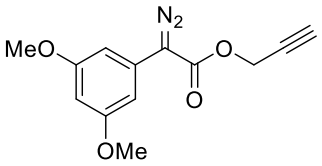
Compound **1h** was synthesized following the general procedure (B). The product was obtained as orange solid (1.392 g, 65% yield): R_f = 0.35 petroleum ether/EtOAc (95:5); m.p.: 52-54 ºC; IR (neat) cm^{-1}: 3293, 2947, 2084, 1699, 1567, 1514, 1242, 1154, 1037, 949, 811, 771, 735, 680, 640; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, *J* = 8.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 4.86 (d, *J* = 2.5 Hz, 2H), 2.51 (t, *J* = 2.5 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 136.1, 129.9, 124.3, 121.8, 77.8, 75.2, 52.3, 21.1; HRMS (ESI TOF): Calculated for $C_{12}H_{10}N_2NaO_2$ $(M + Na)^+$: 237.0640, Found: 237.0635.

Prop-2-yn-1-yl 2-diazo-2-(4-methoxyphenyl)acetate (1i):



Compound **1i** was synthesized following the general procedure (B). The product was obtained as dark orange solid (1.934 g, 84% yield): R_f = 0.3 petroleum ether/EtOAc (95:5); m.p.: 68-69 ºC; IR (neat) cm^{-1}: 3289, 2949, 2837, 2081, 1694, 1609, 1573, 1510, 1240, 1142, 1022, 949, 825, 735, 680, 640; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.30 (m, 2H), 7.09 – 6.81 (m, 2H), 4.86 (d, *J* = 2.4 Hz, 2H), 3.81 (s, 3H), 2.51 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 158.3, 126.2, 116.5, 114.8, 77.8, 75.2, 55.5, 52.3; HRMS (ESI TOF): Calculated for $C_{12}H_{10}N_2NaO_3$ $(M + Na)^+$: 253.0589, Found: 253.0584.

Prop-2-yn-1-yl 2-diazo-2-(3,5-dimethoxyphenyl)acetate (1j):



Compound **1j** was synthesized following the general procedure (B). The product was obtained as yellow solid (1.822 g, 70% yield): R_f = 0.25 petroleum ether/EtOAc (95:5); m.p.: 91-93 ºC; IR (neat) cm^{-1}: 3254, 2946, 2839, 2075, 1703, 1594, 1454, 1383, 1324, 1272, 1154, 1035, 954, 926, 830, 736, 672; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.67 (d, *J* = 2.2 Hz, 2H), 6.30 (t, *J* = 2.2 Hz, 1H), 4.86 (d, *J* = 2.5 Hz, 2H), 3.80 (s, 6H), 2.52 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 161.3, 127.3, 102.1, 98.4, 77.7, 75.3, 55.5, 52.3; HRMS (ESI TOF): Calculated for $C_{13}H_{12}N_2NaO_4$ $(M + Na)^+$: 283.0695, Found: 283.0695.

3A.4.4 General procedure C1 for catalyst screening

A mixture of 5 mol% of catalyst and 1.5 mL of benzene **2a** was stirred at room temperature in a dried 25 mL two-necked RB flask under an inert atmosphere for 5 minutes. Then *α*-aryl-*α*-diazoacetate **1** (0.5 mmol) in 1 mL of benzene was added to above reaction mixture dropwise over 5 minutes, and then the reaction mixture was stirred at room temperature or refluxed at 80 ^{o}C over 4-12 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The crude product obtained was purified by column chromatography over silica gel to furnish the product **3** (see Table 3A.1).

3A.4.5 General procedure C2 for solvent screening

In a dried 25 mL RB flask, $Sc(OTf)_3$ (2.5-5 mol%), propargyl *α*-phenyl-*α*-diazoacetate **1a** (0.1 g, 0.5 mmol) and benzene **2a** (0.45 mL, 5 mmol) was added in 2.5 mL of solvent at room temperature under inert atmosphere. Then the reaction mixture was refluxed at 72-80 ^{o}C over 4-12 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The crude product obtained was purified by column chromatography over silica gel to furnish the desired product **3aa** (see Table 3A.2).

3A.4.6 General procedure C3 for co-catalyst screening

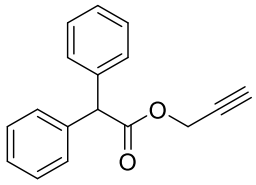
In a dried 25 mL RB flask, $Sc(OTf)_3$ (2.5-5 mol%), co-catalyst (0-5 mol%), propargyl *α*-phenyl-*α*-diazoacetate **1a** (0.1 g, 0.5 mmol) and benzene **2a** (0.45 mL, 5 mmol) was added in 2.5 mL of DCE at room temperature under inert atmosphere. Then the reaction mixture was refluxed at 80 ^{o}C over 2-12 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The crude product obtained was purified by column chromatography over silica gel to furnish the desired product **3aa** (see Table 3A.3).

3A.4.7 General procedure D for synthesis of *α*-diarylacetates

In a dried 25 mL RB flask, $Sc(OTf)_3$ (12.3mg, 5 mol%), propargyl *α*-phenyl-*α*-diazoacetate **1a** (0.1 g, 0.5 mmol) and benzene **2a** (0.45 mL, 5 mmol) was added in 2.5 mL of DCE at room temperature under inert atmosphere. Then the reaction mixture was refluxed at 80 ^{o}C over 4 h. The progress of the reaction was monitored by TLC. After completion of

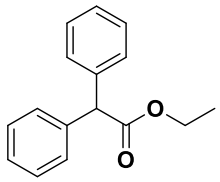
the reaction, the solvent was removed under reduced pressure. The crude product obtained was purified by column chromatography over silica gel to furnish the desired product **3aa** (0.09 g, 72% yield).

Prop-2-yn-1-yl 2,2-diphenylacetate (3aa):



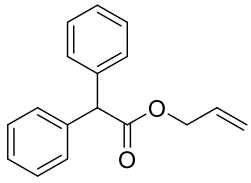
Compound **3aa** was synthesized following the general procedure (D). The product was obtained as white solid (0.09 g, 72% yield): R_f = 0.5 petroleum ether/EtOAc (95:5); m.p.: 46-48 ^oC; IR (neat) cm^{-1}: 3289, 3031, 2941, 2126, 1739, 1598, 1494, 1448, 1370, 1220, 1181, 1080, 997, 739, 694, 638, 564; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49 – 7.12 (m, 10H), 5.07 (s, 1H), 4.74 (d, J = 2.5 Hz, 2H), 2.46 (t, J = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 138.3, 128.8, 128.7, 127.5, 77.4, 75.3, 56.8, 52.7; HRMS (ESI TOF): Calculated for $C_{17}H_{14}NaO_2$ $(M + Na)^+$: 273.0891, Found: 273.0891.

Ethyl 2,2-diphenylacetate (3a′a):



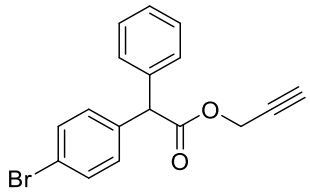
Compound **3a′a** was synthesized following the general procedure (D). The product was obtained as colourless liquid (0.037 g, 31% yield): R_f = 0.45 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3029, 2984, 1730, 1598, 1493, 1452, 1148, 1093, 1025, 961, 697, 633, 561; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.29 (m, 8H), 7.28 – 7.22 (m, 2H), 5.01 (s, 1H), 4.20 (q, J = 7.1 Hz, 2H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6, 138.9, 128.7, 128.7, 127.3, 61.3, 57.3, 14.3; HRMS (ESI TOF): Calculated for $C_{16}H_{16}NaO_2$ $(M + Na)^+$: 263.1048, Found: 263.1042.

Allyl 2,2-diphenylacetate (3a′′a):



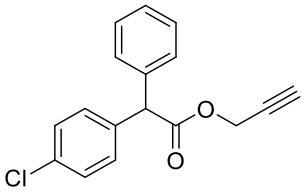
Compound **3a′′a** was synthesized following the general procedure (D). The product was obtained as colourless liquid (0.042 g, 33% yield): R_f = 0.6 petroleum ether/EtOAc (95:5); IR(neat) cm^{-1} : 3029, 2942, 2109, 1734, 1648, 1494, 1450, 1184, 1145, 1083, 989, 931, 740, 700, 624, 559; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.17 (m, 10H), 5.89 (ddt, J = 15.4, 10.4, 5.7 Hz, 1H), 5.22 (ddq, J = 15.4, 10.4, 1.4 Hz, 1H), 5.05 (s, 1H), 4.65 (dt, J = 5.7, 1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3, 138.8, 132.0, 128.8, 128.7, 127.4, 118.6, 65.9, 57.2; HRMS (ESI TOF): Calculated for $C_{17}H_{16}NaO_2$ $(M + Na)^+$: 275.1048, Found: 275.1044.

Prop-2-yn-1-yl 2-(4-bromophenyl)-2-phenylacetate (3ba):



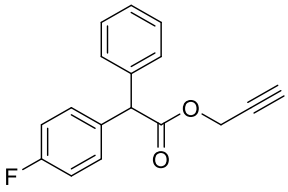
Compound **3ba** was synthesized following the general procedure (D). The product was obtained as white solid (0.122 g, 74% yield): R_f = 0.45 petroleum ether/EtOAc (95:5); m.p.: 104-106 ^{o}C; IR (neat) cm^{-1}: 3292, 3032, 2940, 2126, 1739, 1597, 1488, 1271, 1368, 1139, 1002, 810, 746, 694, 639, 579; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.43 (m, 2H), 7.36 – 7.25 (m, 5H), 7.22 – 7.17 (m, 2H), 5.02 (s, 1H), 4.85 – 4.62 (m, 2H), 2.48 (t, J = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 137.8, 137.3, 131.9, 130.5, 128.9, 128.6, 127.8, 121.7, 77.3, 75.5, 56.2, 52.9; HRMS (ESI TOF): Calculated for $C_{17}H_{14}$ $^{81}BrO_2$ $(M + H)^+$: 331.0157, Found: 331.0144.

Prop-2-yn-1-yl 2-(4-chlorophenyl)-2-phenylacetate (3ca):



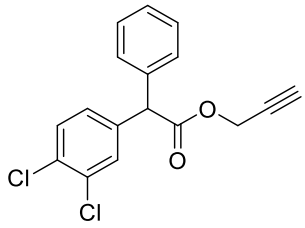
Compound **3ca** was synthesized following the general procedure (D). The product was obtained as white solid (0.114 g, 80% yield): R_f = 0.4 petroleum ether/EtOAc (95:5); m.p.: 83-85 ºC; IR (neat) cm^{-1}: 3293, 3033, 2127, 1739, 1598, 1490, 1272, 1222, 1138, 1001, 813, 751, 691, 636, 550; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.24 (m, 9H), 5.03 (s, 1H), 4.79 – 4.69 (m, 2H), 2.47 (t, J = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.0, 138.4, 137.7, 132.0, 130.4, 128.7, 128.5, 128.3, 127.3, 78.1 (for 2-C), 54.5, 52.6; HRMS (ESI TOF): Calculated for $C_{17}H_{13}ClNaO_2$ $(M + Na)^+$: 307.0502, Found: 307.0505.

Prop-2-yn-1-yl 2-(4-fluorophenyl)-2-phenylacetate (3da):



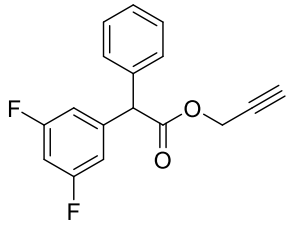
Compound **3da** was synthesized following the general procedure (D). The product was obtained as white solid (0.094 g, 70% yield): R_f = 0.4 petroleum ether/EtOAc (95:5); m.p.: 65-67 ºC; IR (neat) cm^{-1}: 3293, 3064, 2130, 1739, 1604, 1506, 1448, 1370, 1276, 1182, 1137, 996, 809, 732, 692, 636; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.25 (m, 7H), 7.09 – 6.92 (m, 2H), 5.05 (s, 1H), 4.78 – 4.67 (m, 2H), 2.47 (t, J = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 162.2 (d, J = 246.3 Hz), 138.2, 134.1(d, J = 3.3 Hz), 130.4 (d, J = 8.1 Hz), 128.9, 128.6, 127.7, 115.6 (d, J = 21.5 Hz), 77.4, 75.4, 56.0, 52.8; HRMS (ESI TOF): Calculated for $C_{17}H_{14}FO_2$ $(M + H)^+$: 269.0978, Found: 269.0980.

Prop-2-yn-1-yl 2-(3,4-dichlorophenyl)-2-phenylacetate (3ea):



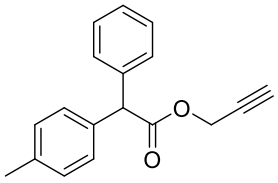
Compound **3ea** was synthesized following the general procedure (D). The product was obtained as colourless liquid (0.136 g, 85% yield): R_f = 0.35 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3295, 3071, 2948, 2124, 1743, 1596, 1470, 1269, 1145, 1028, 907, 772, 702; ^1H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, *J* = 2.2 Hz, 1H), 7.41 – 7.26 (m, 6H), 7.16 (dd, *J* = 8.3, 2.2 Hz, 1H), 5.00 (s, 1H), 4.80 – 4.69 (m, 2H), 2.49 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 138.4, 137.2, 132.8, 131.8, 130.7, 130.6, 129.1, 128.5, 128.2, 128.0, 75.6(for 2-C), 55.8, 53.0; HRMS (ESI TOF): Calculated for $C_{17}H_{12}Cl_2NaO_2$ $(M + Na)^+$: 341.0112, Found: 341.0099.

Prop-2-yn-1-yl 2-(3,5-difluorophenyl)-2-phenylacetate (3fa):



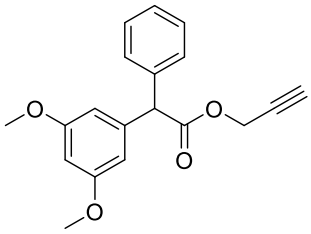
Compound **3fa** was synthesized following the general procedure (D). The product was obtained as colourless liquid (0.139 g, 97% yield): R_f = 0.45 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3297, 3091, 2130, 1742, 1623, 1597, 1495, 1450, 1302, 1219, 1146, 1119, 1026, 987, 848, 770, 697; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49 – 7.27 (m, 5H), 6.98 – 6.79 (m, 2H), 6.71 (tt, *J* = 8.8, 2.3 Hz, 1H), 5.01 (s, 1H), 4.92 – 4.48 (m, 2H), 2.49 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 163.1 (dd, *J* = 248.8, 12.8 Hz), 142.0 (t, *J* = 9.2 Hz), 137.0, 129.1, 128.6, 128.1, 112.11 – 111.55 (m), 103.1 (t, *J* = 25.3 Hz), 77.4, 75.6, 56.2 (t, *J* = 1.9 Hz), 53.0; HRMS (ESI TOF): Calculated for $C_{17}H_{13}F_2O_2$ $(M + H)^+$: 287.0884, Found: 287.0888.

Prop-2-yn-1-yl 2-phenyl-2-(*p*-tolyl)acetate (3ha):



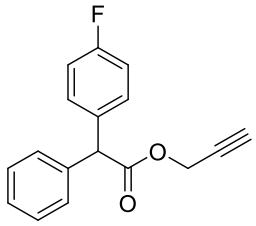
Compound **3ha** was synthesized following the general procedure (D). The product was obtained as white solid (0.02 g, 15% yield): R_f = 0.5 petroleum ether/EtOAc (95:5); m.p.: 88-90 ºC; IR (neat) cm^{-1}: 3290, 3028, 2927, 2128, 1742, 1509, 1448, 1370, 1221, 1182, 1141, 999, 731, 695; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 – 7.24 (m, 5H), 7.20 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 5.03 (s, 1H), 4.73 (d, *J* = 2.5 Hz, 2H), 2.45 (t, *J* = 2.5 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 138.5, 137.2, 135.4, 129.5, 128.7, 128.66 , 128.6, 127.4, 77.5, 75.3, 56.4, 52.7, 21.2; HRMS (ESI TOF): Calculated for $C_{18}H_{16}NaO_2$ $(M + Na)^+$: 287.1048, Found: 287.1040.

Prop-2-yn-1-yl 2-(3,5-dimethoxyphenyl)-2-phenylacetate (3ja):



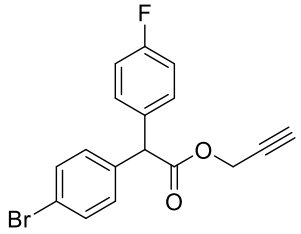
Compound **3ja** was synthesized following the general procedure (D). The product was obtained as colourless liquid (0.026 g, 17% yield): R_f = 0.5 petroleum ether/EtOAc (80:20); IR (neat) cm^{-1}: 3284, 2936, 2841, 2128, 1740, 1595, 1460, 1298, 1201, 1143, 1062, 999, 938, 834, 761; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.22 (m, 5H), 6.48 (d, *J* = 2.2 Hz, 2H), 6.37 (t, *J* = 2.2 Hz, 1H), 4.99 (s, 1H), 4.74 (d, *J* = 2.5 Hz, 2H), 3.75 (s, 6H), 2.46 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 161.0, 140.3, 138.0, 128.7, 128.7, 127.6, 107.0, 99.4, 77.5, 75.3, 56.9, 55.4, 52.7; HRMS (ESI TOF): Calculated for $C_{19}H_{19}O_4$ $(M + H)^+$: 311.1283, Found: 311.1287.

Prop-2-yn-1-yl 2-(4-fluorophenyl)-2-phenylacetate (3ab):



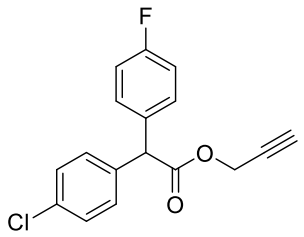
Compound **3ab** was synthesized following the general procedure (D). The product was obtained as a major product *para*-isomer (*p*:*o* = 91:9), *p*:*o* ratio determined by ^{1}H NMR. The product was obtained as viscous colourless liquid (0.054 g, 40% yield): R_f = 0.4 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3294, 3071, 2945, 2125, 1742, 1604, 1506, 1447, 1370, 1279, 1227, 1144, 1001, 816, 733, 695, 641, 560; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 – 7.18 (m, 7H), 7.13 – 6.85 (m, 2H), 5.05 (s, 1H), 4.73 (dd, *J* = 2.4, 1.0 Hz, 2H), 2.46 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 162.2 (d, *J* = 246.3 Hz), 138.1, 134.1 (d, *J* = 2.9 Hz), 130.4 (d, *J* = 8.0 Hz), 128.9, 128.5, 127.7, 115.6 (d, *J* = 21.3 Hz), 77.3, 75.4, 55.9, 52.8; HRMS (ESI TOF): Calculated for $C_{17}H_{14}FO_2$ $(M + H)^+$: 269.0978, Found: 269.0988.

Prop-2-yn-1-yl 2-(4-bromophenyl)-2-(4-fluorophenyl)acetate (3bb):



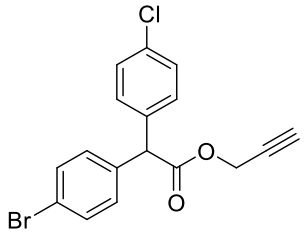
Compound **3bb** was synthesized following the general procedure (D). The product was obtained as a major product *para*-isomer (*p*:*o* = 91:9), *p*:*o* ratio determined by ^{1}H NMR. The product was obtained as semisolid (0.090 g, 52% yield): R_f = 0.45 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3295, 3060, 2130, 1741, 1603, 1504, 1438, 1369, 1273, 1227, 1144, 950, 822, 760, 683, 641; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 – 7.41 (m, 2H), 7.30 – 7.22 (m, 2H), 7.21 – 7.13 (m, 2H), 7.07 – 6.94 (m, 2H), 4.99 (s, 1H), 4.74 (dd, *J* = 3.8, 2.5 Hz, 2H), 2.48 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 162.3 (d, *J* = 246.9 Hz), 137.2, 133.6 (d, *J* = 3.3 Hz), 132.0, 130.3, 130.2, 121.8, 115.8 (d, *J* = 21.6 Hz), 77.2, 75.5, 55.4, 53.0; HRMS (ESI TOF): Calculated for $C_{17}H_{13}BrFO_2$ $(M + H)^+$: 347.0083, Found: 347.0092.

Prop-2-yn-1-yl 2-(4-chlorophenyl)-2-(4-fluorophenyl)acetate (3cb):



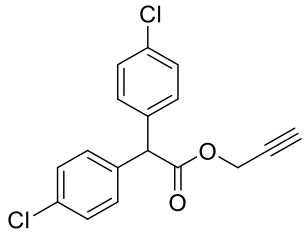
Compound **3cb** was synthesized following the general procedure (B). The product was obtained as a major product *para*-isomer (*p*:*o* = 91:9), *p*:*o* ratio determined by ^{1}H NMR. The product was obtained as colourless liquid (0.082 g, 54% yield). R_f = 0.45 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3297, 2947, 2130, 1741, 1602, 1439, 1270, 1227, 1143, 1093, 1005, 823, 762, 683, 641; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.16 (m, 6H), 7.15 – 6.90 (m, 2H), 5.01 (s, 1H), 4.73 (d, *J* = 2.5 Hz, 2H), 2.48 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 163.0 (d, *J* = 246.8 Hz), 136.6, 133.7, 133.6 (d, *J* = 3.3 Hz), 130.3 (d, *J* = 8.1 Hz), 129.9, 129.0, 115.8 (d, *J* = 21.6 Hz), 77.2, 75.5, 55.3, 52.9; HRMS (ESI TOF): Calculated for $C_{17}H_{13}ClFO_2$ $(M + H)^+$: 303.0588, Found: 303.0595.

Prop-2-yn-1-yl 2-(4-bromophenyl)-2-(4-chlorophenyl)acetate (3bc):



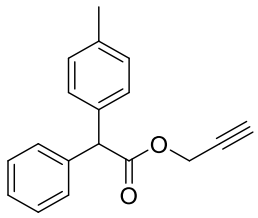
Compound **3bc** was synthesized following the general procedure (D). The product was obtained as a major product *para*-isomer (*p*:*o* = 90:10), *p*:*o* ratio determined by ^{1}H NMR. The product was obtained as viscous colourless liquid (0.091 g, 50% yield): R_f = 0.45 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3294, 2946, 2130, 1740, 1591, 1488, 1369, 1301, 1183, 1142, 1088, 1006, 954, 807, 761, 681, 638; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 – 7.43 (m, 2H), 7.34 – 7.14 (m, 6H), 4.98 (s, 1H), 4.74 (d, *J* = 2.5 Hz, 2H), 2.49 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 136.8, 136.2, 133.8, 132.0, 130.3, 130.0, 129.1, 121.9, 77.4, 75.6, 55.5, 53.0; HRMS (ESI TOF): Calculated for $C_{17}H_{13}BrClO_2$ $(M + H)^+$: 362.9787, Found: 362.9785.

Prop-2-yn-1-yl 2,2-bis(4-chlorophenyl)acetate (3cc):



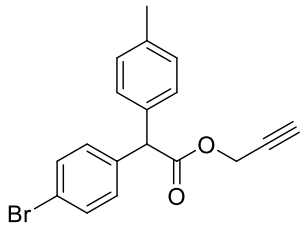
Compound **3cc** was synthesized following the general procedure (D). The product was obtained as a major product *para*-isomer (*p*:*o* = 89:11), *p*:*o* ratio determined by ^{1}H NMR. The product was obtained as colourless liquid (0.083 g, 52% yield): R_f = 0.4 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3295, 2947, 2130, 1740, 1594, 1489, 1369, 1268, 1141, 1090, 1003, 954, 905, 808, 762, 681, 637; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.28 (m, 4H), 7.25 – 7.18 (m, 4H), 5.00 (s, 1H), 4.74 (d, *J* = 2.5 Hz, 2H), 2.48 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 136.3, 133.8, 130.0, 129.1, 77.2, 75.6, 55.4, 53.0; HRMS (ESI TOF): Calculated for $C_{17}H_{13}Cl_2O_2$ $(M + H)^+$: 319.0293, Found: 319.0305.

Prop-2-yn-1-yl (S)-2-phenyl-2-(p-tolyl)acetate (3ad):



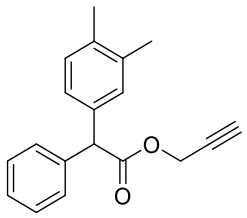
Compound **3ad** was synthesized following the general procedure (D). The product was obtained as a major product *para*-isomer (*p*:*o* = 80:20), *p*:*o* ratio determined by ^{1}H NMR. The product was obtained as viscous colourless liquid (0.111 g, 84% yield): R_f = 0.5 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3290, 2925, 2124, 1743, 1603, 1501, 1449, 1371, 1306, 1275, 1219, 1142, 999, 806, 732, 696, 640; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 – 6.99 (m, 9H), 5.03 (s, 1H), 4.73 (d, *J* = 2.4 Hz, 2H), 2.46 (t, *J* = 2.4 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 138.5, 137.2, 135.3, 129.5, 128.7, 128.7, 128.6, 127.5, 77.4, 75.3, 56.4, 52.7, 21.2; HRMS (ESI TOF): Calculated for $C_{18}H_{16}NaO_2$ $(M + Na)^+$: 287.1048, Found: 287.1054.

Prop-2-yn-1-yl 2-(4-bromophenyl)-2-(p-tolyl)acetate (3bd):



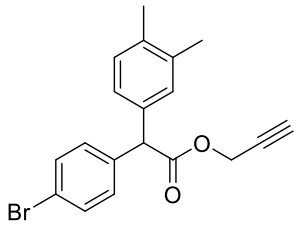
Compound **3bd** was synthesized following the general procedure (D). The product was obtained as a major product *para*-isomer (*p*:*o* = 78:22), *p*:*o* ratio determined by ^{1}H NMR. The product was obtained as colourless liquid (0.144 g, 84% yield): R_f = 0.45 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3291, 3025, 2945, 2130, 1739, 1592, 1487, 1441, 1369, 1270, 1219, 1073, 1002, 951, 809, 754, 680, 638; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 – 7.37 (m, 2H), 7.28 – 7.03 (m, 6H), 4.98 (s, 1H), 4.82 – 4.65 (m, 2H), 2.46 (t, *J* = 2.5 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 137.6 137.5, 134.8, 131.8, 130.4, 129.6, 128.4, 121.6, 77.4, 75.4, 55.8, 52.8, 21.2; HRMS (ESI TOF): Calculated for $C_{18}H_{16}BrO_2$ $(M + H)^+$: 343.0334, Found: 343.0330.

Prop-2-yn-1-yl 2-(3,4-dimethylphenyl)-2-phenylacetate (3ae):



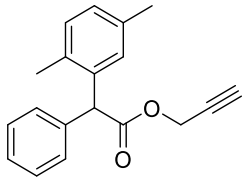
Compound **3ae** was synthesized following the general procedure (D). The product was obtained as a major product *para*-isomer (*p*:*o* = 84:16), *p*:*o* ratio determined by ^{1}H NMR. The product was obtained as white solid (0.124 g, 89% yield): R_f = 0.5 petroleum ether/EtOAc (95:5); m.p.: 88-90 ^{o}C; IR (neat) cm^{-1}: 3287, 3027, 2934, 2126, 1740, 1601, 1497, 1448, 1371, 1207, 1137, 1079, 997, 815, 695, 637, 573; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.21 (m, 5H), 7.11 – 7.02 (m, 3H), 5.01 (s, 1H), 4.79 – 4.68 (m, 2H), 2.46 (t, *J* = 2.5 Hz, 1H), 2.30 – 2.15 (m, 6H) (for 2-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 138.6, 137.0, 135.9, 135.7, 130.0, 129.9, 128.7, 128.7, 127.4, 126.0, 77.6, 75.2, 56.4, 52.7, 20.0, 19.5; HRMS (ESI TOF): Calculated for $C_{19}H_{19}O_2$ $(M + H)^+$: 279.1385, Found: 279.1387.

Prop-2-yn-1-yl 2-(4-bromophenyl)-2-(3,4-dimethylphenyl)acetate (3be):



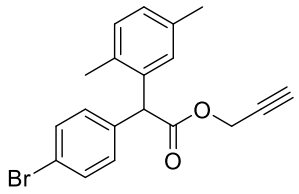
Compound **3be** was synthesized following the general procedure (D). The product was obtained as a major product *para*-isomer (*p*:*o* = 83:17), *p*:*o* ratio determined by ^{1}H NMR. The product was obtained as colourless liquid (0.161 g, 90% yield): R_f = 0.5 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3293, 2939, 2123, 1744, 1590, 1490, 1446, 1371, 1272, 1145, 1073, 1007, 949, 818, 762, 681, 641, 568; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.39 (m, 2H), 7.21 – 6.99 (m, 5H), 4.95 (s, 1H), 4.79 – 4.66 (m, 2H), 2.52 – 2.41 (m, 1H), 2.29 – 2.12 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 137.6, 137.2, 136.2, 135.2, 131.8, 130.4, 130.1, 129.7, 125.9, 121.5, 77.4, 75.4, 55.8, 52.8, 20.0, 19.5; HRMS (ESI TOF): Calculated for $C_{19}H_{18}BrO_2$ $(M + H)^+$: 357.0490, Found: 357.0487.

Prop-2-yn-1-yl 2-(2,5-dimethylphenyl)-2-phenylacetate (3af):



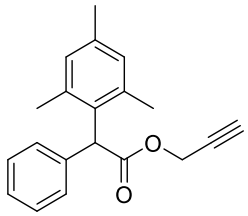
Compound **3af** was synthesized following the general procedure (D). The product was obtained as white solid (0.12 g, 86% yield): R_f = 0.5 petroleum ether/EtOAc (95:5); m.p.: 79-81 ^{o}C; IR (neat) cm^{-1}: 3289, 2929, 2126, 1740, 1606, 1498, 1447, 1370, 1273, 1213, 1141, 996, 946, 812, 736, 692, 637, 578; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 – 7.14 (m, 5H), 7.09 – 6.95 (m, 3H), 5.22 (s, 1H), 4.74 (d, *J* = 2.5 Hz, 2H), 2.46 (t, *J* = 2.5 Hz, 1H), 2.28 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 137.6, 136.3, 135.8, 133.4, 130.7, 129.1, 128.8, 128.7, 128.3, 127.4, 77.6, 75.2, 53.5, 52.7, 21.3, 19.5; HRMS (ESI TOF): Calculated for $C_{19}H_{18}NaO_2$ $(M + Na)^+$: 301.1204, Found: 301.1209.

Prop-2-yn-1-yl 2-(4-bromophenyl)-2-(2,5-dimethylphenyl)acetate (3bf):



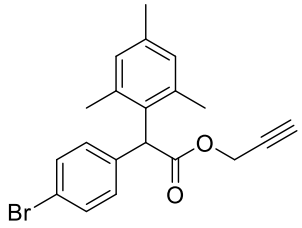
Compound **3bf** was synthesized following the general procedure (D). The product was obtained as white solid (0.168 g, 94% yield): R_f = 0.5 petroleum ether/EtOAc (95:5); m.p.: 115-117 ºC; IR (neat) cm^{-1}: 3292, 2930, 2123, 1743, 1613, 1491, 1445, 1370, 1315, 1213, 1149, 1074, 1007, 813, 761, 679, 641; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 – 7.33 (m, 2H), 7.19 – 6.94 (m, 5H), 5.16 (s, 1H), 4.90 – 4.64 (m, 2H), 2.48 (t, J = 2.5 Hz, 1H), 2.30 (s, 3H), 2.21 (s, 3H); ^{13}C NMR ((100 MHz, $CDCl_3$): δ 171.8, 136.7, 136.1, 135.8, 133.3, 131.8, 130.9, 130.8, 128.59 , 128.58 , 121.5, 77.4, 75.3, 53.0, 52.8, 21.2, 19.4; HRMS (ESI TOF): Calculated for $C_{19}H_{17}BrNaO_2$ $(M + Na)^+$: 379.0310, Found: 379.0305.

Prop-2-yn-1-yl 2-mesityl-2-phenylacetate (3ag):



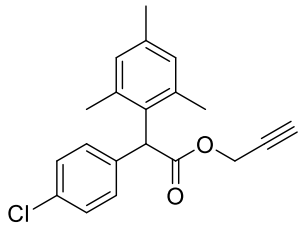
Compound **3ag** was synthesized following the general procedure (D). The product was obtained as colourless liquid (0.135 g, 92% yield): R_f = 0.5 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3286, 2922, 2125, 1742, 1608, 1489, 1448, 1371, 1271, 1154, 1000, 943, 853, 734, 693, 569; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.20 (m, 3H), 7.15 – 7.08 (m, 2H), 6.90 (s, 2H), 5.42 (s, 1H), 4.79-4.68 (m, 2H), 2.43 (t, J = 2.5 Hz, 1H), 2.29 (s, 3H), 2.18 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6, 137.6, 137.1, 136.5, 131.9, 130.1, 128.8, 128.3, 127.0, 77.8, 75.0, 52.5, 50.8, 21.0 (for two type of carbons); HRMS (ESI TOF): Calculated for $C_{20}H_{20}NaO_2$ $(M + Na)^+$: 315.1361, Found: 315.1365.

Prop-2-yn-1-yl 2-(4-bromophenyl)-2-mesitylacetate (3bg):



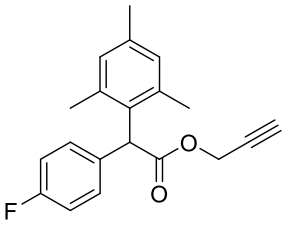
Compound **3bg** was synthesized following the general procedure (D). The product was obtained as colourless liquid (0.182 g, 98% yield): R_f = 0.45 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3292, 2949, 2120, 1743, 1611, 1486, 1447, 1159, 1075, 1005, 946, 878, 778, 679, 634; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 – 7.35 (m, 2H), 7.06 – 6.97 (m, 2H), 6.91 (s, 2H), 5.33 (s, 1H), 4.89 – 4.57 (m, 2H), 2.44 (t, J = 2.4 Hz, 1H), 2.30 (s, 3H), 2.16 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 137.5, 137.4, 135.5, 131.4, 131.4, 130.6, 130.1, 121.1, 77.6, 75.2, 52.6, 50.1, 21.0, 20.9; HRMS (ESI TOF): Calculated for $C_{20}H_{19}BrNaO_2$ $(M + Na)^+$: 393.0466, Found: 393.0452.

Prop-2-yn-1-yl 2-(4-chlorophenyl)-2-mesitylacetate (3cg):



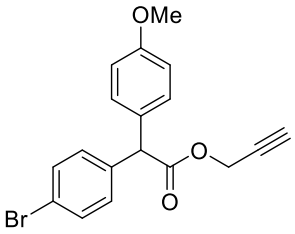
Compound **3cg** was synthesized following the general procedure (D). The product was obtained as colourless liquid (0.154 g, 94% yield): R_f = 0.4 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3293, 2923, 2123, 1742, 1610, 1489, 1448, 1268, 1159, 1093, 1008, 848, 775, 681, 635; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 – 7.21 (m, 2H), 7.10 – 7.03 (m, 2H), 6.91 (s, 2H), 5.35 (s, 1H), 4.78– 4.68(m, 2H), 2.43 (t, J = 2.5 Hz, 1H), 2.30 (s, 6H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 137.5, 137.3, 135.0, 132.9, 131.5, 130.2, 130.1, 128.5, 77.6, 75.1, 52.6, 50.1, 21.0, 20.9; HRMS (ESI TOF): Calculated for $C_{20}H_{19}ClNaO_2$ $(M + Na)^+$: 349.0971, Found: 349.0966.

Prop-2-yn-1-yl 2-(4-fluorophenyl)-2-mesitylacetate (3dg):



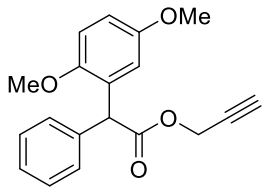
Compound **3dg** was synthesized following the general procedure (D). The product was obtained as colourless liquid (0.148 g, 95% yield): R_f = 0.45 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3293, 2924, 2122, 1743, 1606, 1509, 1452, 1372, 1273, 1227, 1158,1004, 847, 799, 681, 639; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 – 7.07 (m, 2H), 7.02 – 6.94 (m, 2H), 6.92 (s, 2H), 5.36 (s, 1H), 4.83 – 4.64 (m, 2H), 2.44 (t, *J* = 2.5 Hz, 1H), 2.31 (s, 3H), 2.18 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.5, 161.9 (d, *J* = 245.6 Hz), 137.5, 137.3, 132.1 (d, *J* = 3.2 Hz), 131.8, 130.4 (d, *J* = 7.9 Hz), 130.1, 115.1 (d, *J* = 21.4 Hz), 77.7, 75.1, 52.6, 50.0, 21.0, 20.9; HRMS (ESI TOF): Calculated for $C_{18}H_{19}FNaO_2$ $(M + Na)^+$: 333.1267, Found: 333.1268.

Prop-2-yn-1-yl 2-(4-bromophenyl)-2-(4-methoxyphenyl)acetate (3bh):



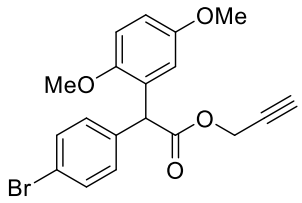
Compound **3bh** was synthesized following the general procedure (D). The product was obtained as a major product *para*-isomer (*p*:*o* = 74:26), *p*:*o* ratio determined by ^{1}H NMR. The product was obtained as (0.169 g, 94% yield). R_f = 0.3 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3290, 2946, 2838, 2309, 2126, 1899, 1739, 1504, 1368, 1297, 1147, 1007, 815, 681; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 – 7.38 (m, 2H), 7.31 – 7.12 (m, 4H), 6.94 – 6.80 (m, 2H), 4.96 (s, 1H), 4.78 – 4.65 (m, 2H), 3.78 (s, 3H), 2.46 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 159.1, 137.7, 131.8, 131.0, 130.3, 129.7, 121.6, 114.3, 77.4, 75.4, 55.4, 55.3, 52.8; HRMS (ESI TOF): Calculated for $C_{18}H_{16}BrO_3$ $(M + H)^+$: 359.0283, Found: 359.0275.

Prop-2-yn-1-yl 2-(2,5-dimethoxyphenyl)-2-phenylacetate (3ai):



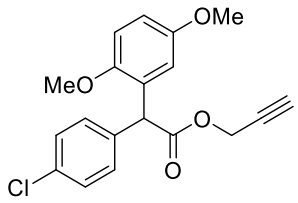
Compound **3ai** was synthesized following the general procedure (D). The product was obtained as white solid (0.149 g, 96% yield): R_f = 0.4 petroleum ether/EtOAc (80:20); m.p.: 74-76 ^oC; IR (neat) cm^{-1}: 3286, 2945, 2836, 2126, 1741, 1595, 1496, 1455, 1369, 1277, 1219, 1145, 1026, 947, 807, 699, 640; ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 – 7.24 (m, 5H), 6.82–6.74 (m, 2H), 6.61 (d, J = 2.9 Hz, 1H), 5.30 (s, 1H), 4.79– 4.66 (m, 2H), 3.78 (s, 3H), 3.68 (s, 3H), 2.44 (t, J = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 153.6, 151.3, 137.0, 129.2, 128.8, 128.6, 127.6, 116.2, 112.5, 111.4, 77.9, 74.9, 56.2, 55.7, 52.5, 51.0; HRMS (ESI TOF): Calculated for $C_{19}H_{19}O_4$ $(M + H)^+$: 311.1283, Found: 311.1277.

Prop-2-yn-1-yl 2-(4-bromophenyl)-2-(2,5-dimethoxyphenyl)acetate (3bi):



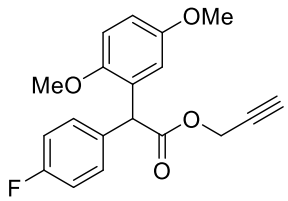
Compound **3bi** was synthesized following the general procedure (D). The product was obtained as white solid (0.175 g, 90% yield): R_f = 0.45 petroleum ether/EtOAc (80:20); m.p.: 97-99 ^oC; IR (neat) cm^{-1}: 3289, 2944, 2837, 2126, 1741, 1593, 1494, 1222, 1148, 1010, 945, 806, 712, 641, 537; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49 – 7.42 (m, 2H), 7.23 – 7.17 (m, 2H), 6.86 – 6.73 (m, 2H), 6.62 (d, J = 2.8 Hz, 1H), 5.25 (s, 1H), 4.78 – 4.67 (m, 2H), 3.77 (s, 3H), 3.70 (s, 3H), 2.45 (t, J = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 153.6, 151.1, 136.3, 131.9, 130.9, 128.0, 121.6, 115.9, 112.7, 111.5, 77.7, 75.1, 56.2, 55.8, 52.6, 50.4; HRMS (ESI TOF): Calculated for $C_{19}H_{17}BrO_4$ $(M)^+$: 388.0310, Found: 388.0305.

Prop-2-yn-1-yl 2-(4-chlorophenyl)-2-(2,5-dimethoxyphenyl)acetate (3ci):



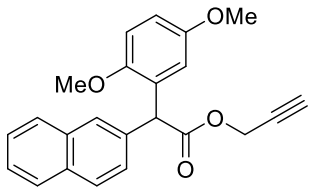
Compound **3ci** was synthesized following the general procedure (D). The product was obtained as white solid (0.159 g, 92% yield): R_f = 0.45 petroleum ether/EtOAc (80:20); m.p.: 98-99 ^oC; IR (neat) cm^{-1}: 3290, 2947, 2836, 2125, 1741, 1595, 1494, 1278, 1222, 1174, 1095, 1014, 806, 755, 709, 639, 539; ^1H NMR (400 MHz, $CDCl_3$): δ 7.33 – 7.28 (m, 2H), 7.27 – 7.22 (m, 2H), 6.85 – 6.74 (m, 2H), 6.62 (d, *J* = 2.8 Hz, 1H), 5.27 (s, 1H), 4.78 – 4.67 (m, 2H), 3.77 (s, 3H), 3.70 (s, 3H), 2.45 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 153.7, 151.2, 135.8, 133.5, 130.6, 128.9, 128.1, 115.9, 112.8, 111.6, 77.7, 75.0, 56.2, 55.8, 52.6, 50.3; HRMS (ESI TOF): Calculated for $C_{19}H_{17}ClNaO_4$ $(M + Na)^+$: 367.0713, Found: 367.0710.

Prop-2-yn-1-yl 2-(2,5-dimethoxyphenyl)-2-(4-fluorophenyl)acetate (3di):



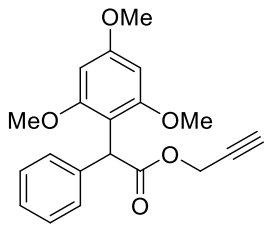
Compound **3di** was synthesized following the general procedure (D). The product was obtained as colourless liquid (0.156 g, 95% yield): R_f = 0.35 petroleum ether/EtOAc (85:15); IR (neat) cm^{-1}: 3291, 2948, 2838, 2122, 1744, 1603, 1503, 1457, 1369, 1280, 1226, 1153, 1040, 844, 808, 712, 642; ^1H NMR (400 MHz, $CDCl_3$): δ 7.34 – 7.25 (m, 2H), 7.07 – 6.96 (m, 2H), 6.78 (dt, *J* = 8.8, 5.8 Hz, 2H), 6.61 (d, *J* = 2.8 Hz, 1H), 5.27 (s, 1H), 4.78 – 4.66 (m, 2H), 3.77 (s, 3H), 3.69 (s, 3H), 2.45 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 162.2 (d, *J* = 245.8 Hz), 153.6, 151.1, 132.9 (d, *J* = 3.2 Hz), 130.8 (d, *J* = 8.2 Hz), 128.4, 115.8 (d, *J* = 18.1 Hz), 115.5, 112.6, 111.5, 77.7, 75.0, 56.1, 55.7, 52.5, 50.2; HRMS (ESI TOF): Calculated for $C_{19}H_{17}FNaO_4$ $(M + Na)^+$: 351.1009, Found: 351.1000.

Prop-2-yn-1-yl 2-(2,5-dimethoxyphenyl)-2-(naphthalen-2-yl)acetate (3gi):



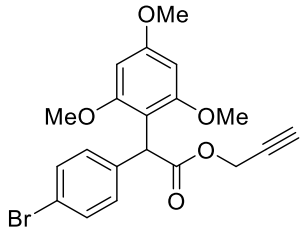
Compound **3gi** was synthesized following the general procedure (D). The product was obtained as white solid (0.151 g, 84% yield): R_f = 0.45 petroleum ether/EtOAc (80:20); m.p.: 91-93 ^{o}C; IR (neat) cm^{-1}: 3287, 2945, 2837, 2125, 1740, 1597, 1497, 1455, 1369, 1222, 1148, 1032, 863, 808, 750, 709, 644; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 – 7.73 (m, 4H), 7.52 – 7.40 (m, 3H), 6.84– 6.75 (m, 2H), 6.63 (d, J = 3.0 Hz, 1H), 5.47 (s, 1H), 4.82– 4.69 (m, 2H), 3.80 (s, 3H), 3.65 (s, 3H), 2.45 (t, J = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 153.6, 151.3, 134.5, 133.6, 132.8, 128.6, 128.5, 128.1, 128.0, 127.7, 127.3, 126.3, 126.1, 116.3, 112.6, 111.4, 77.9, 75.0, 56.2, 55.8, 52.6, 51.1; HRMS (ESI TOF): Calculated for $C_{23}H_{20}NaO_4$ $(M + Na)^+$: 383.1259, Found: 383.1262.

Prop-2-yn-1-yl 2-phenyl-2-(2,4,6-trimethoxyphenyl)acetate (3aj):



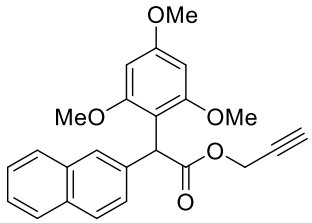
Compound **3aj** was synthesized following the general procedure (D). The product was obtained as white solid (0.157 g, 92% yield): R_f = 0.35 petroleum ether/EtOAc (80:20); m.p.: 121-123 ^{o}C; IR (neat) cm^{-1}: 3281, 2937, 2842, 2127, 1741, 1597, 1496, 1420, 1337, 1195, 1114, 1002, 949, 864, 814, 746, 696, 664; ^{1}H NMR ((400 MHz, $CDCl_3$)): δ 7.34 – 7.30 (m, 2H), 7.28 – 7.23 (m, 2H), 7.22 – 7.16 (m, 1H), 6.14 (s, 2H), 5.33 (s, 1H), 4.77 – 4.64 (m, 2H), 3.80 (s, 3H), 3.78 (s, 6H), 2.38 (t, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1, 160.7, 158.2, 138.7, 129.4, 128.1, 126.8, 109.2, 90.9, 78.5, 74.2, 55.9, 55.4, 52.0, 45.8; HRMS (ESI TOF): Calculated for $C_{20}H_{21}O_5$ $(M + H)^+$: 341.1389, Found: 341.1398.

Prop-2-yn-1-yl 2-(4-bromophenyl)-2-(2,4,6-trimethoxyphenyl)acetate (3bj):



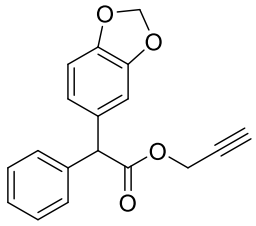
Compound **3bj** was synthesized following the general procedure (D). The product was obtained as colourless liquid (0.176 g, 84% yield): R_f = 0.3 petroleum ether/EtOAc (80:20); IR(neat) cm^{-1} : 3287, 2943, 2841, 2121, 1743, 1600, 1460, 1420, 1195, 1157, 1061, 1009, 950, 814, 759, 668, 634; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.33 (m, 2H), 7.26 – 7.17 (m, 2H), 6.13 (s, 2H), 5.27 (s, 1H), 4.75 – 4.64 (m, 2H), 3.79 (s, 3H), 3.77 (s, 6H), 2.39 (t, J = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6, 160.8, 158.1, 137.8, 131.2, 131.1, 120.7, 108.6, 90.9, 78.3, 74.4, 55.8, 55.4, 52.1, 45.2; HRMS (ESI TOF): Calculated for $C_{20}H_{20}BrO_5$ $(M + H)^+$: 419.0494, Found: 419.0494.

Prop-2-yn-1-yl 2-(naphthalen-2-yl)-2-(2,4,6-trimethoxyphenyl)acetate (3gj):



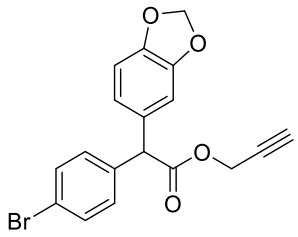
Compound **3gj** was synthesized following the general procedure (D). The product was obtained as white solid (0.166 g, 85% yield): R_f = 0.25 petroleum ether/EtOAc (80:20); m.p.: 99-101 ^{o}C; IR (neat) cm^{-1}: 3285, 2941, 2842, 2122, 1741, 1598, 1499, 1458, 1422, 1154, 1115, 1026, 950, 857, 812, 751, 662; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 – 7.72 (m, 3H), 7.67 (s, 1H), 7.55 (dd, J = 8.5, 1.8 Hz, 1H), 7.42 – 7.36 (m, 2H), 6.16 (s, 2H), 5.50 (s, 1H), 4.82 – 4.66 (m, 2H), 3.81 (s, 3H), 3.80 (s, 6H), 2.40 (t, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1, 160.8, 158.3, 136.3, 133.4, 132.6, 128.1, 128.0, 127.9, 127.6, 125.6, 125.5, 109.0, 91.0, 78.5, 77.4, 74.3, 55.9, 55.5, 52.1, 46.0; HRMS (ESI TOF): Calculated for $C_{24}H_{23}O_5$ $(M + H)^+$: 391.1545, Found: 391.1546.

Prop-2-yn-1-yl 2-(benzo[d][1,3]dioxol-5-yl)-2-phenylacetate (3ak):



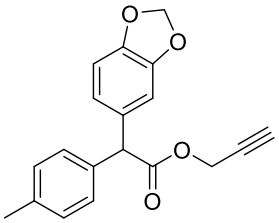
Compound **3ak** was synthesized following the general procedure (D). The product was obtained as a major product *para*-isomer (*p*:*o* = 90:10), *p*:*o* ratio determined by ^{1}H NMR. The product was obtained as colourless liquid (0.138 g, 94% yield): R_f = 0.55 petroleum ether/EtOAc (80:20); IR(neat) cm^{-1} : 3288, 3027, 2895, 2126, 1739, 1490, 1444, 1367, 1239, 1138, 1032, 997, 930, 807, 735, 694, 643; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.25 (m, 5H), 6.85 – 6.71 (m, 3H), 5.93 (d, *J* = 3.9 Hz, 2H), 4.98 (s, 1H), 4.73 (d, *J* = 2.6 Hz, 2H), 2.50 – 2.43 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 148.0, 147.1, 138.4, 132.1, 128.8, 128.5, 127.6, 122.1, 109.3, 108.4, 101.3, 77.4, 75.4, 56.3, 52.8; HRMS (ESI TOF): Calculated for $C_{18}H_{14}NaO_4$ $(M + Na)^+$: 317.0790, Found: 317.0778.

Prop-2-yn-1-yl 2-(benzo[d][1,3]dioxol-5-yl)-2-(4-bromophenyl)acetate (3bk):



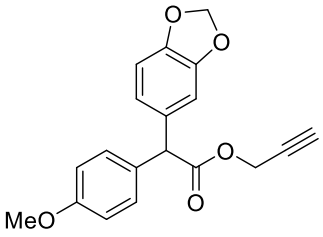
Compound **3bk** was synthesized following the general procedure (D). The product was obtained as a major product *para*-isomer (*p*:*o* = 92:8), *p*:*o* ratio determined by ^{1}H NMR. The product was obtained as colourless liquid (0.175 g, 94% yield): R_f = 0.6 petroleum ether/EtOAc (80:20); IR (neat) cm^{-1}: 3290, 2896, 2126, 1738, 1606, 1487, 1442, 1301, 1238, 1140, 1031, 1002, 931, 800, 760, 676, 640; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 – 7.39 (m, 2H), 7.24 – 7.13 (m, 2H), 6.82 – 6.69 (m, 3H), 5.94 (s, 2H), 4.92 (s, 1H), 4.78 – 4.68 (m, 2H), 2.48 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 148.1, 147.2, 137.4, 131.9, 131.5, 130.3, 122.0, 121.7, 109.1, 108.5, 101.4, 77.3, 75.5, 55.7, 52.9; HRMS (ESI TOF): Calculated for $C_{18}H_{13}BrNaO_4$ $(M + Na)^+$: 394.9895, Found: 394.9894.

Prop-2-yn-1-yl 2-(benzo[d][1,3]dioxol-5-yl)-2-(p-tolyl)acetate (3hk):



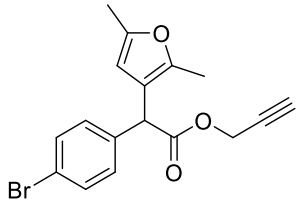
Compound **3hk** was synthesized following the general procedure (D). The product was obtained as a major product *para*-isomer (*p*:*o* = 98:2), *p*:*o* ratio determined by ^{1}H NMR. The product was obtained as white solid (0.094 g, 61% yield): R_f = 0.6 petroleum ether/EtOAc (80:20); m.p.: 59-61 ^{o}C; IR (neat) cm^{-1}: 3288, 2894, 2779, 2129, 1739, 1611, 1489, 1441, 1306, 1241, 1185, 1140, 1034, 997, 932, 808, 755, 681; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 – 7.16 (m, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.86 – 6.78 (m, 1H), 6.78 – 6.69 (m, 2H), 5.92 (s, 2H), 4.94 (s, 1H), 4.72 (d, *J* = 2.5 Hz, 2H), 2.46 (t, *J* = 2.5 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 148.0, 147.0, 137.3, 135.4, 132.3, 129.5, 128.4, 122.0, 109.2, 108.3, 101.2, 77.5, 75.3, 56.0, 52.7, 21.2; HRMS (ESI TOF): Calculated for $C_{19}H_{17}O_4$ $(M + H)^+$: 309.1127, Found: 309.1127.

Prop-2-yn-1-yl 2-(benzo[d][1,3]dioxol-5-yl)-2-(4-methoxyphenyl)acetate (3ik):



Compound **3ik** was synthesized following the general procedure (D). The product was obtained as a major product *para*-isomer (*p*:*o* = 99:1), *p*:*o* ratio determined by ^{1}H NMR. The product was obtained as colourless liquid (0.089 g, 55% yield): R_f = 0.5 petroleum ether/EtOAc (80:20); IR (neat) cm^{-1}: 3287, 2904, 2124, 1740, 1610, 1501, 1443, 1367, 1246, 1143, 1034, 933, 807, 760, 683, 637; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 – 7.19 (m, 2H), 6.88 – 6.82 (m, 2H), 6.80 (s, 1H), 6.77 – 6.70 (m, 2H), 5.91 (s, 2H), 4.93 (s, 1H), 4.72 (d, *J* = 2.5 Hz, 2H), 3.77 (s, 3H), 2.47 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 159.0, 148.0, 147.0, 132.5, 130.5, 129.6, 121.9, 114.2, 109.2, 108.3, 101.2, 77.5, 75.3, 55.5, 55.4, 52.7; HRMS (ESI TOF): Calculated for $C_{19}H_{17}O_5$ $(M + H)^+$: 325.1076, Found: 325.1092.

Prop-2-yn-1-yl 2-(4-bromophenyl)-2-(2,5-dimethylfuran-3-yl)acetate (3bl):

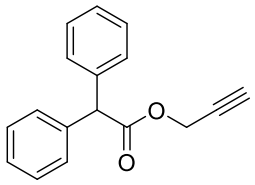


Compound **3bl** was synthesized following the general procedure (D). The product was obtained as colourless liquid (0.104 g, 60% yield): R_f = 0.5 petroleum ether/EtOAc (80:20); IR (neat) cm^{-1}: 3296, 2924, 2126, 1742, 1583, 1487, 1222, 1146, 1079, 1003, 935, 805, 762, 677, 640; ^1H NMR (400 MHz, $CDCl_3$): δ 7.44 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 5.98 (s, 1H), 4.75 (s, 1H), 4.71 (dd, *J* = 2.5, 1.9 Hz, 2H), 2.47 (t, *J* = 2.5 Hz, 1H), 2.21 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 150.1, 146.9, 137.3, 131.8, 129.9, 121.5, 116.4, 106.8, 77.3, 75.4, 52.8, 47.3, 13.6, 11.8; HRMS (ESI TOF): Calculated for $C_{17}H_{16}BrO_3$ $(M + H)^+$: 347.0283, Found: 347.0290.

3A.4.8 General procedure E for gram-scale synthrsis of *α*-diarylacetates

In a dried 100 mL RB flask, $Sc(OTf)_3$ (0.184 g, 5 mol%), propargyl *α*-phenyl-*α*-diazoacetate **1a** (1.5 g, 1 equiv.) and benzene **2a** (6.7 mL, 10 equiv.) was added in 25 mL of DCE at room temperature under inert atmosphere. Then the reaction mixture was refluxed at 80 ^oC over 4 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The crude product obtained was purified by column chromatography over silica gel to furnish the desired product **3aa** as white solid (1.31 g, 70% yield).

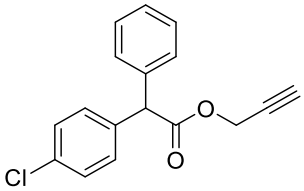
Prop-2-yn-1-yl 2,2-diphenylacetate (3aa):



Compound **3aa** was synthesized following the general procedure (E). The product was obtained as white solid (1.31 g, 70% yield): R_f = 0.5 petroleum ether/EtOAc (95:5); m.p.: 46-48 ^oC; IR (neat) cm^{-1}: 3289, 3031, 2941, 2126, 1739, 1598, 1494, 1448, 1370, 1220, 1181, 1080, 997, 739, 694, 638, 564; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49 – 7.12 (m, 10H), 5.07 (s,

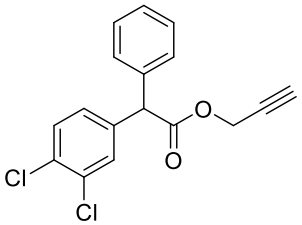
1H), 4.74 (d, *J* = 2.5 Hz, 2H), 2.46 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 138.3, 128.8, 128.7, 127.5, 77.4, 75.3, 56.8, 52.7; HRMS (ESI TOF): Calculated for $C_{17}H_{14}NaO_2$ $(M + Na)^+$: 273.0891, Found: 273.0891.

Prop-2-yn-1-yl 2-(4-chlorophenyl)-2-phenylacetate (3ca):



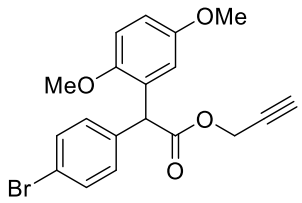
Compound **3ca** was synthesized following the general procedure (E). The product was obtained as white solid (1.31 g, 72% yield): R_f = 0.4 petroleum ether/EtOAc (95:5); m.p.: 83-85 ^oC; IR (neat) cm^{-1}: 3293, 3033, 2127, 1739, 1598, 1490, 1272, 1222, 1138, 1001, 813, 751, 691, 636, 550; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.24 (m, 9H), 5.03 (s, 1H), 4.79 – 4.69 (m, 2H), 2.47 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.0, 138.4, 137.7, 132.0, 130.4, 128.7, 128.5, 128.3, 127.3, 78.1 (for 2-C), 54.5, 52.6; HRMS (ESI TOF): Calculated for $C_{17}H_{13}ClNaO_2$ $(M + Na)^+$: 307.0502, Found: 307.0505.

Prop-2-yn-1-yl 2-(3,4-dichlorophenyl)-2-phenylacetate (3ea):



Compound **3ea** was synthesized following the general procedure (E). The product was obtained as colourless liquid (1.46 g, 82% yield): R_f = 0.35 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3295, 3071, 2948, 2124, 1743, 1596, 1470, 1269, 1145, 1028, 907, 772, 702; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, *J* = 2.2 Hz, 1H), 7.41 – 7.26 (m, 6H), 7.16 (dd, *J* = 8.3, 2.2 Hz, 1H), 5.00 (s, 1H), 4.80 – 4.69 (m, 2H), 2.49 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 138.4, 137.2, 132.8, 131.8, 130.7, 130.6, 129.1, 128.5, 128.2, 128.0, 75.6(for 2-C), 55.8, 53.0; HRMS (ESI TOF): Calculated for $C_{17}H_{12}Cl_2NaO_2$ $(M + Na)^+$: 341.0112, Found: 341.0099.

Prop-2-yn-1-yl 2-(4-bromophenyl)-2-(2,5-dimethoxyphenyl)acetate (3bi):

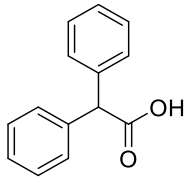


Compound **3bi** was synthesized following the general procedure (E). The product was obtained as white solid (1.84 g, 88% yield): R_f = 0.45 petroleum ether/EtOAc (80:20); m.p.: 97-99 ^oC; IR (neat) cm^{-1}: 3289, 2944, 2837, 2126, 1741, 1593, 1494, 1222, 1148, 1010, 945, 806, 712, 641, 537; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49 – 7.42 (m, 2H), 7.23 – 7.17 (m, 2H), 6.86 – 6.73 (m, 2H), 6.62 (d, *J* = 2.8 Hz, 1H), 5.25 (s, 1H), 4.78 – 4.67 (m, 2H), 3.77 (s, 3H), 3.70 (s, 3H), 2.45 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 153.6, 151.1, 136.3, 131.9, 130.9, 128.0, 121.6, 115.9, 112.7, 111.5, 77.7, 75.1, 56.2, 55.8, 52.6, 50.4; HRMS (ESI TOF): Calculated for $C_{19}H_{17}BrO_4$ $(M)^+$: 388.0310, Found: 388.0305.

3A.4.9 General procedure F for the deprotection of propargyl group

A mixture of diarylacetate **3aa** (1.25 g, 1 equiv.) and $LiOH.H_2O$ (0.524 g, 2.5 equiv.) was taken in 100 mL RB flask & 30 mL solvent (THF: MeOH: H_2O = 1:1:1) was added in above mixture under open atmosphere. The reaction mixture was stirred at room temperature over 1 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was acidified by using 3 N HCl and adjusted to pH 2-3. The crude product was extracted by using ethyl acetate. Solvent was removed under reduced pressure & crude product was purified by column chromatography over silica gel (100-200 mesh size) to furnish the product **4aa** as a white solid (1.01 g, 95% yield).

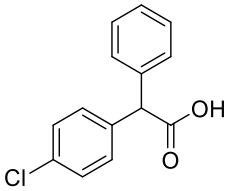
2,2-Diphenylacetic acid (4aa) :



Compound **4aa** was synthesized following the general procedure (F). The product was obtained as white solid (1.01 g, 95% yield). R_f = 0.5 petroleum ether/EtOAc (70:30); m.p.: 147-149 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ 7.45 – 7.16 (m, 10H), 5.04 (s, 1H); ^{13}C NMR

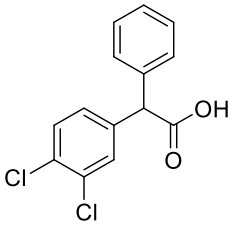
(100 MHz, $CDCl_3$): δ 178.9, 138.0, 128.8 (for two carbon), 127.6, 57.1; IR (neat) cm^{-1}: 3027, 2910, 1699, 1494, 1451, 1411, 1306, 1218, 1031, 934, 737, 698, 635; HRMS (ESI TOF): Calculated for $C_{14}H_{13}O_2$ $(M + H)^+$: 213.0916, Found: 213.0917.

2-(4-Chlorophenyl)-2-phenylacetic acid (4ca):



Compound 4ca was synthesized following the general procedure (F). The product was obtained as white solid (1.02 g, 94% yield). R_f = 0.25 petroleum ether/EtOAc (80:20); m.p.: 117-119 ^oC; IR (neat) cm^{-1}: 3029, 2695, 1704, 1599, 1491, 1452, 1408, 1280, 1213, 1091, 1015, 930, 812, 749, 700, 663; ^1H NMR ((400 MHz, $CDCl_3$): δ 7.39 – 7.20 (m, 9H), 5.01 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.6, 137.5, 136.4, 133.7, 130.2, 129.0 (for 2 Carbons), 128.7, 127.9, 56.4; HRMS (ESI TOF): Calculated for $C_{14}H_{11}ClNaO_2$ $(M + Na)^+$: 269.0345, Found: 269.0342.

2-(3,4-Dichlorophenyl)-2-phenylacetic acid (4ea):



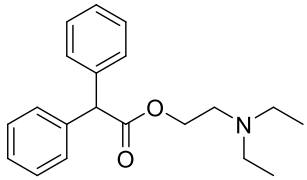
Compound **4ea** was synthesized following the general procedure (F). The product was obtained as white solid (1.06 g, 96% yield). R_f = 0.30 petroleum ether/EtOAc (75:25); m.p.: 118-121 ^oC; IR (neat) cm^{-1}: 3028, 1706, 1596, 1560, 1469, 1404, 1274, 1214, 1136, 1032, 917, 816, 755, 705; ^1H NMR (400 MHz, $CDCl_3$): δ 11.13 (bs, 1H), δ 7.45 – 7.29 (m, 7H), 7.18 (dd, J = 8.4, 2.1 Hz, 1H), 5.00 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.0, 138.0, 136.9, 132.9, 132.0, 130.8, 130.7, 129.1, 128.6, 128.2, 128.2, 56.1.

3A.4.10 Procedure for gram-scale synthesis of Adiphenine: antispasmodic drug

A mixture of 2,2-diphenylacetic acid **4aa** (0.9 g, 1 equiv.), sodium carbonate (2.25 g, 5 equiv.) and diethyl amine (8.8 mL, 20 equiv.) was stirred in 30 mL of DCE at room

temperature in 100 mL RB flask under inert atmosphere for 5 minutes. The reaction mixture was refluxed at 80 ºC over 16 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The residue was diluted with water (30 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with cold water and brine and dried over Na_2SO_4, filtered and the filtrate was evaporated under vacuum. The crude product obtained was purified by column chromatography over silica gel to furnish the desired product **21** obtained as colourless liquid (1.12 g, 85% yield).

2-(Diethylamino)ethyl 2,2-diphenylacetate (21):



The compound **21** was obtained as colourless liquid (1.12 g, 85% yield). R_f = 0.30 petroleum ether/EtOAc (75:25); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 – 7.20 (m, 10H), 5.03 (s, 1H), 4.22 (t, *J* = 6.2 Hz, 2H), 2.68 (t, *J* = 6.2 Hz, 2H), 2.50 (q, *J* = 7.2 Hz, 4H), 0.97 (t, *J* = 7.2 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6, 138.8, 128.8, 128.7, 127.3, 63.6, 57.3, 51.1, 47.7, 12.0; HRMS (ESI TOF): Calculated for $C_{20}H_{26}NO_2$ $(M + H)^+$: 312.1964, Found: 312.1969.

3A.5 Appendix II: ^{1}H, ^{13}C NMR spectral data of representative compounds

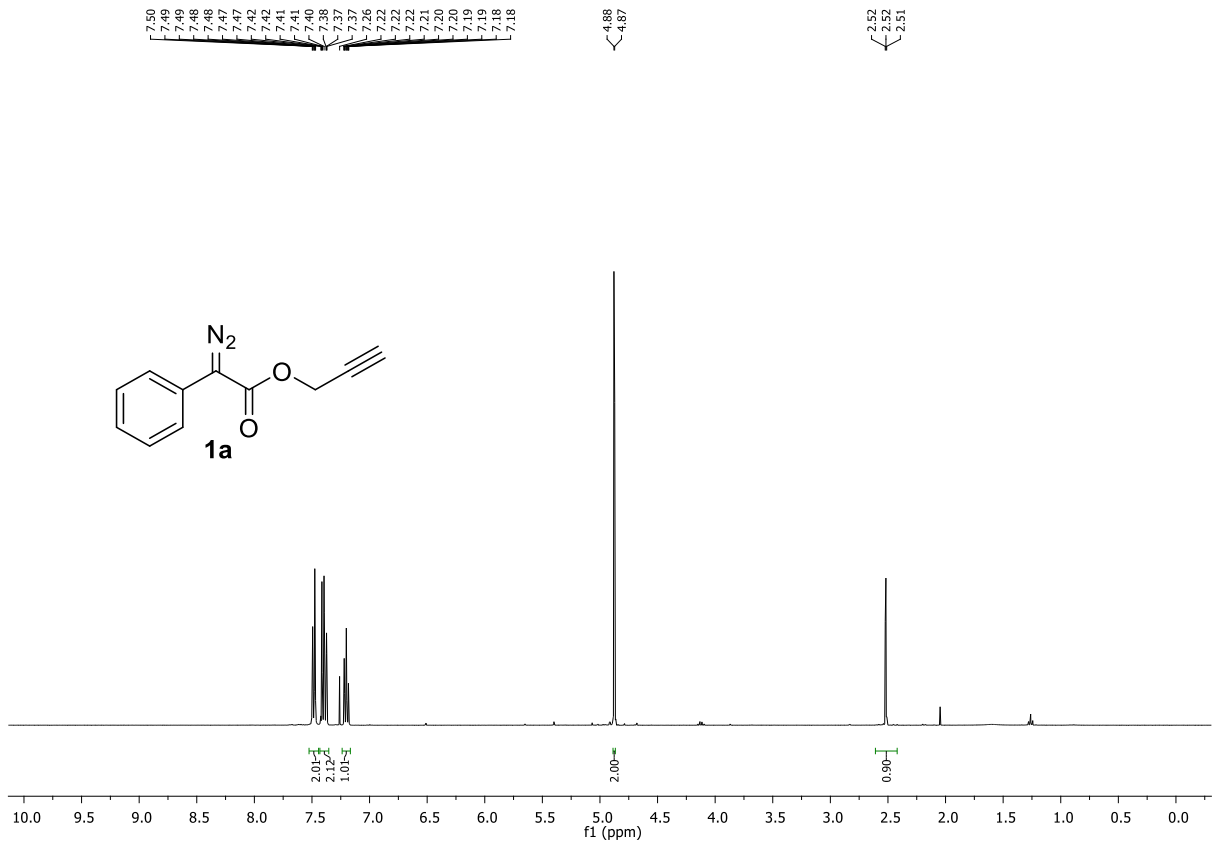


Figure IIIA.1: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **1a**

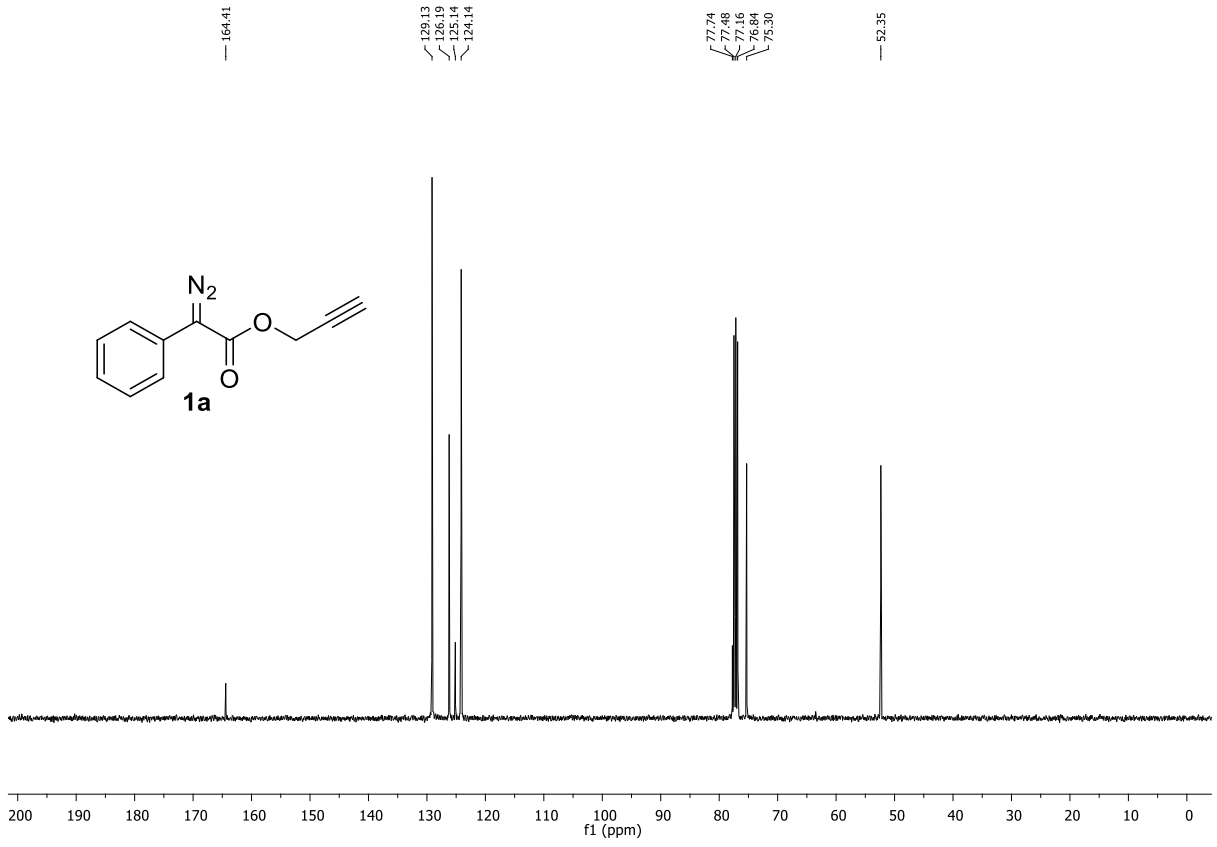


Figure IIIA.2: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **1a**

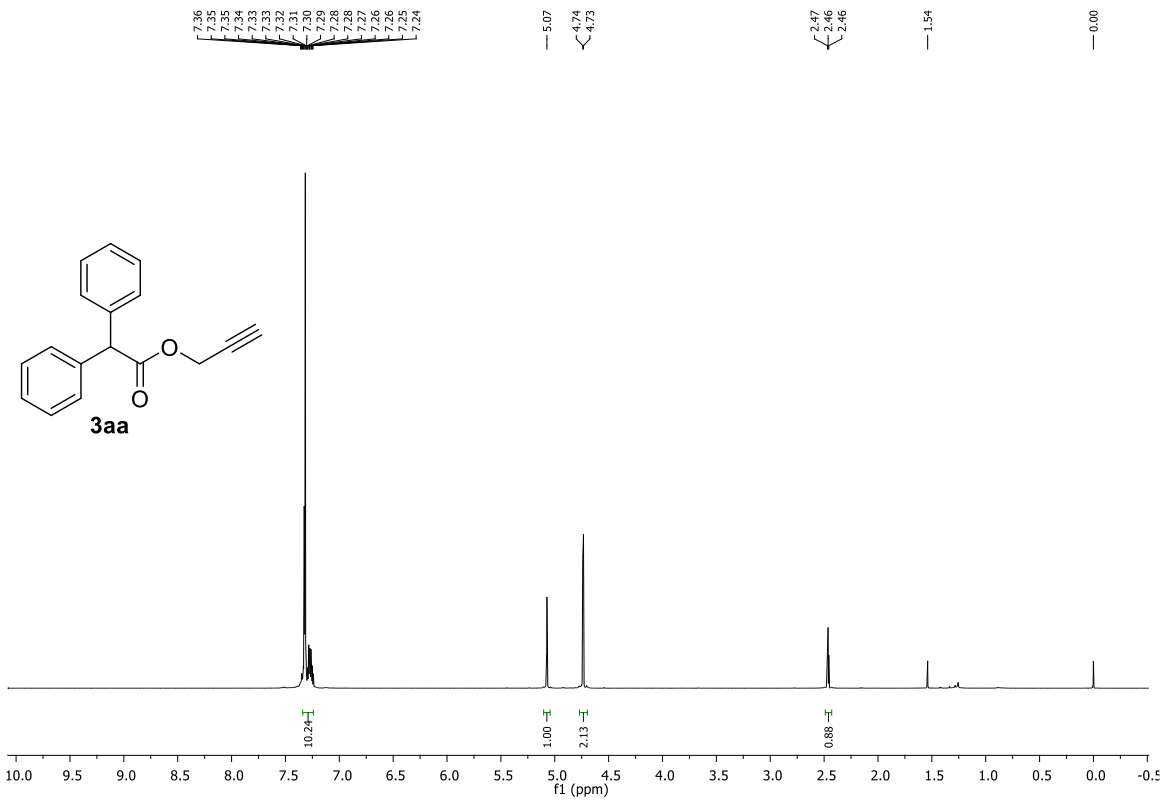


Figure IIIA.3: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3aa**

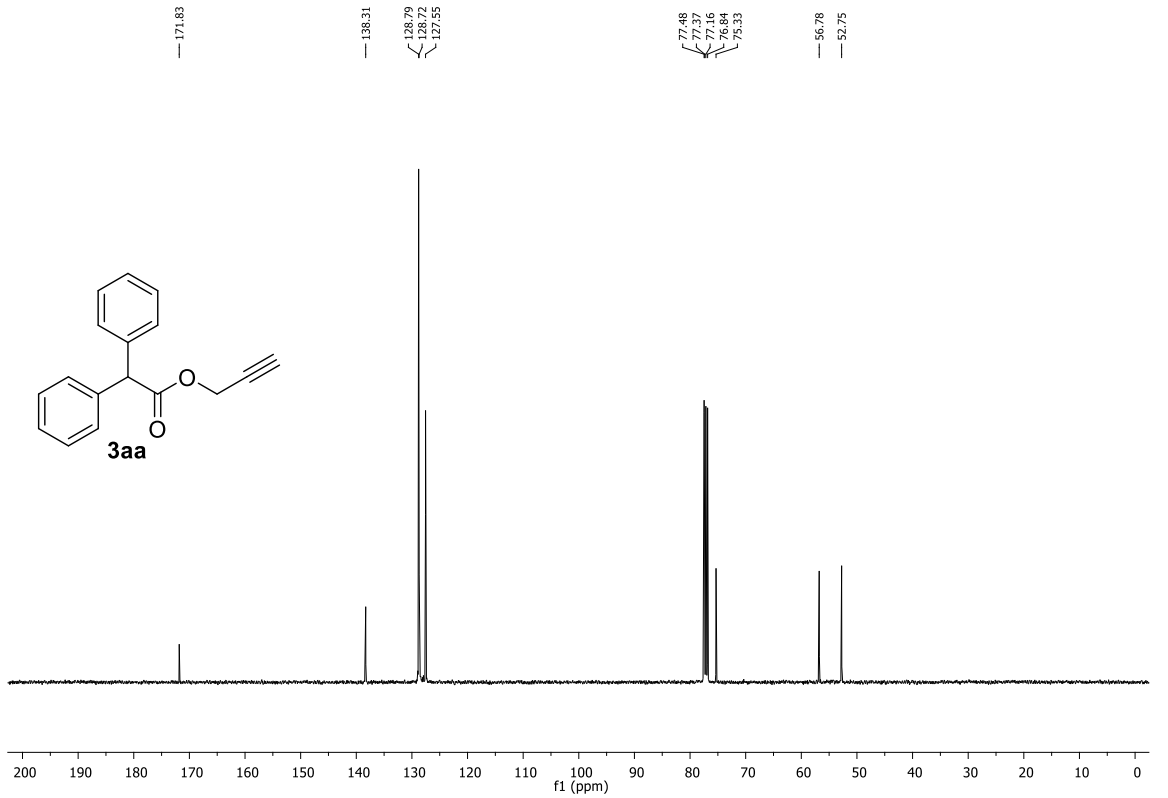


Figure IIIA.4: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3aa**

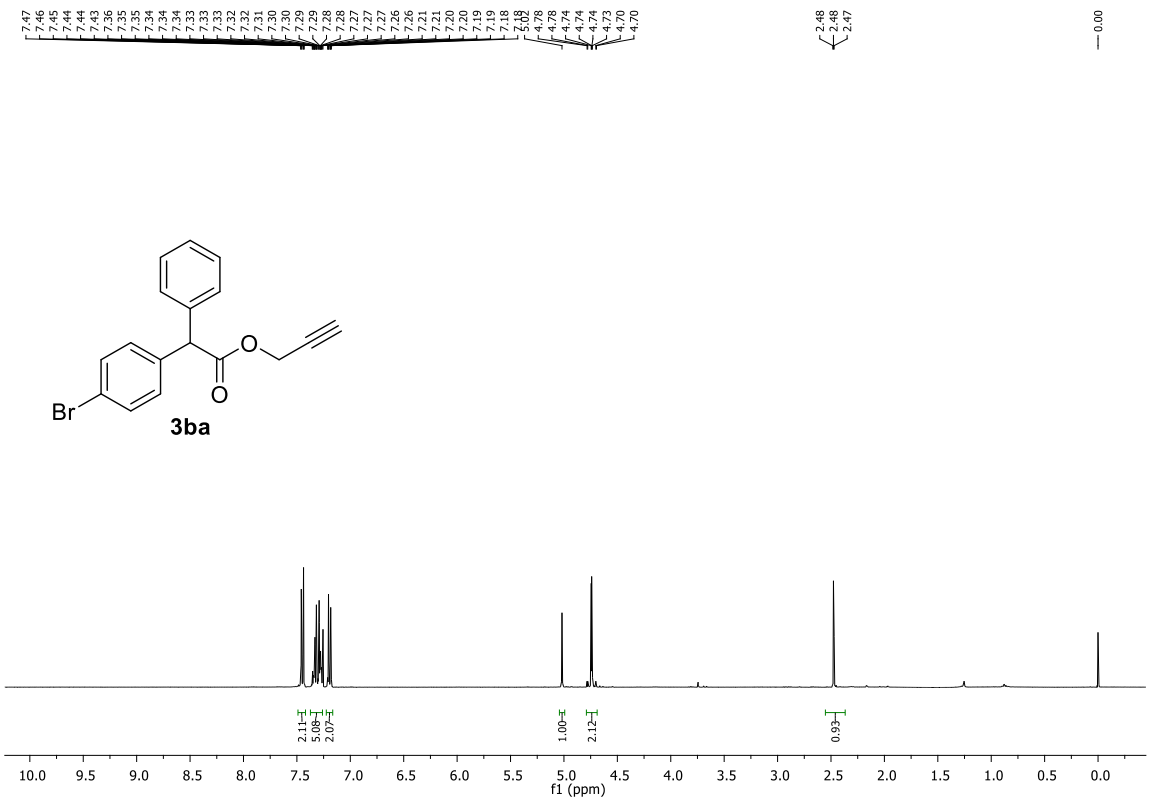


Figure IIIA.5: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3ba**

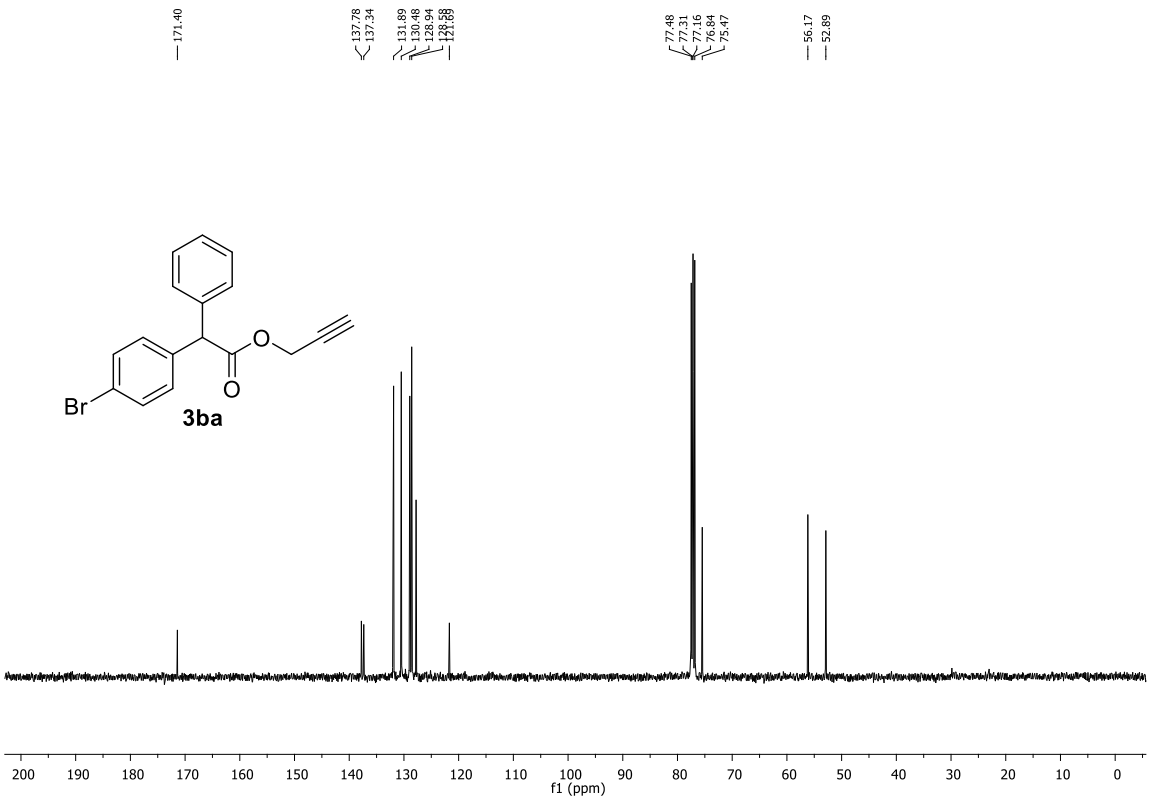


Figure IIIA.6: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3ba**

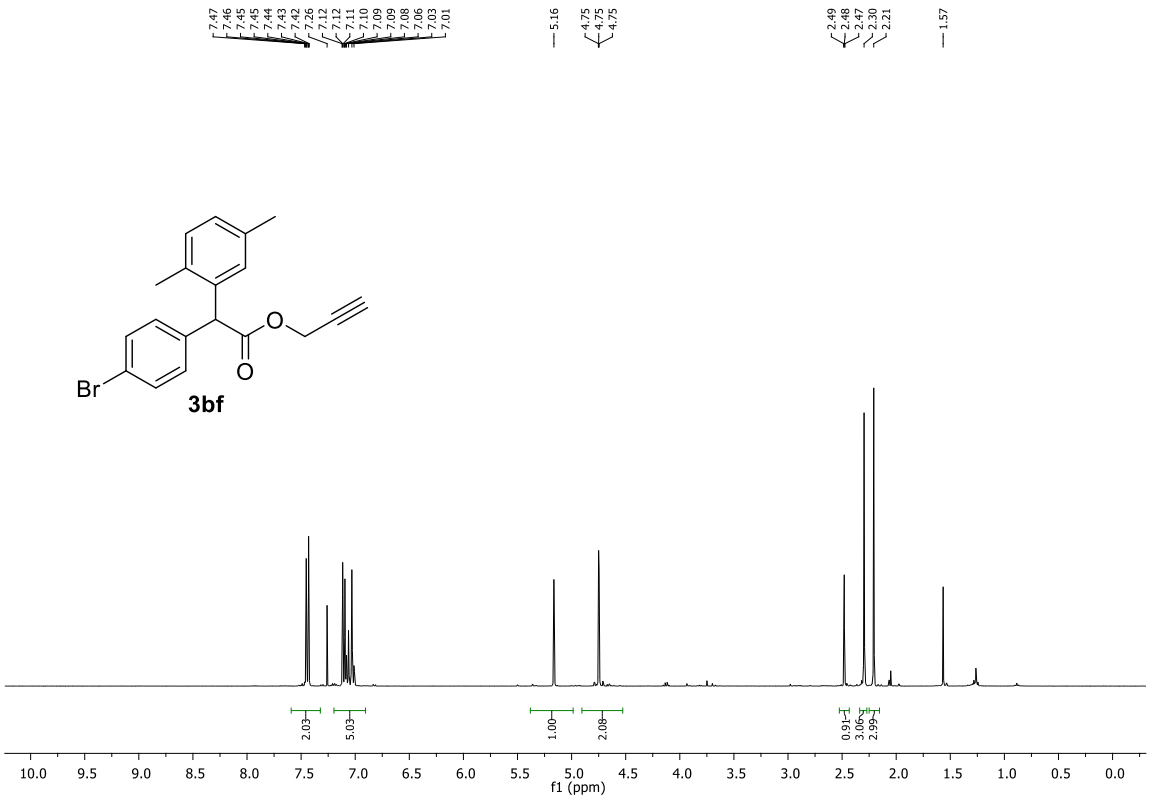


Figure IIIA.7: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3bf**

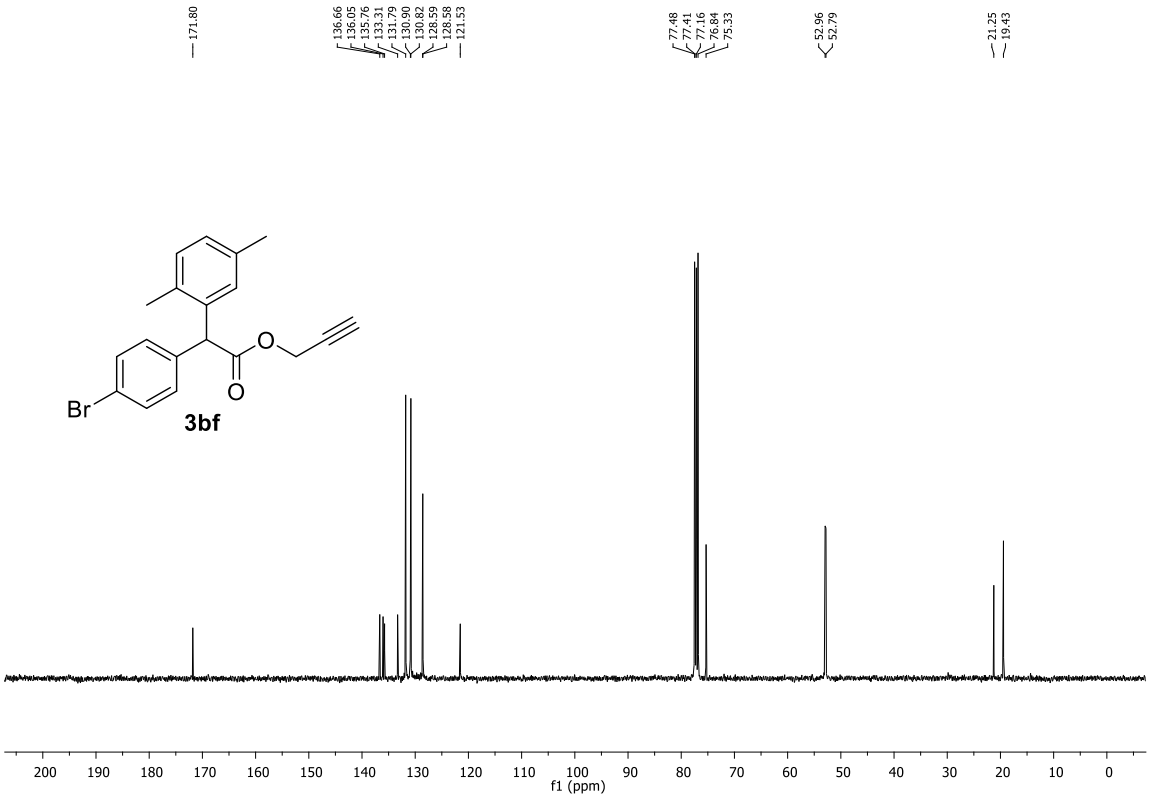


Figure IIIA.8: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3bf**

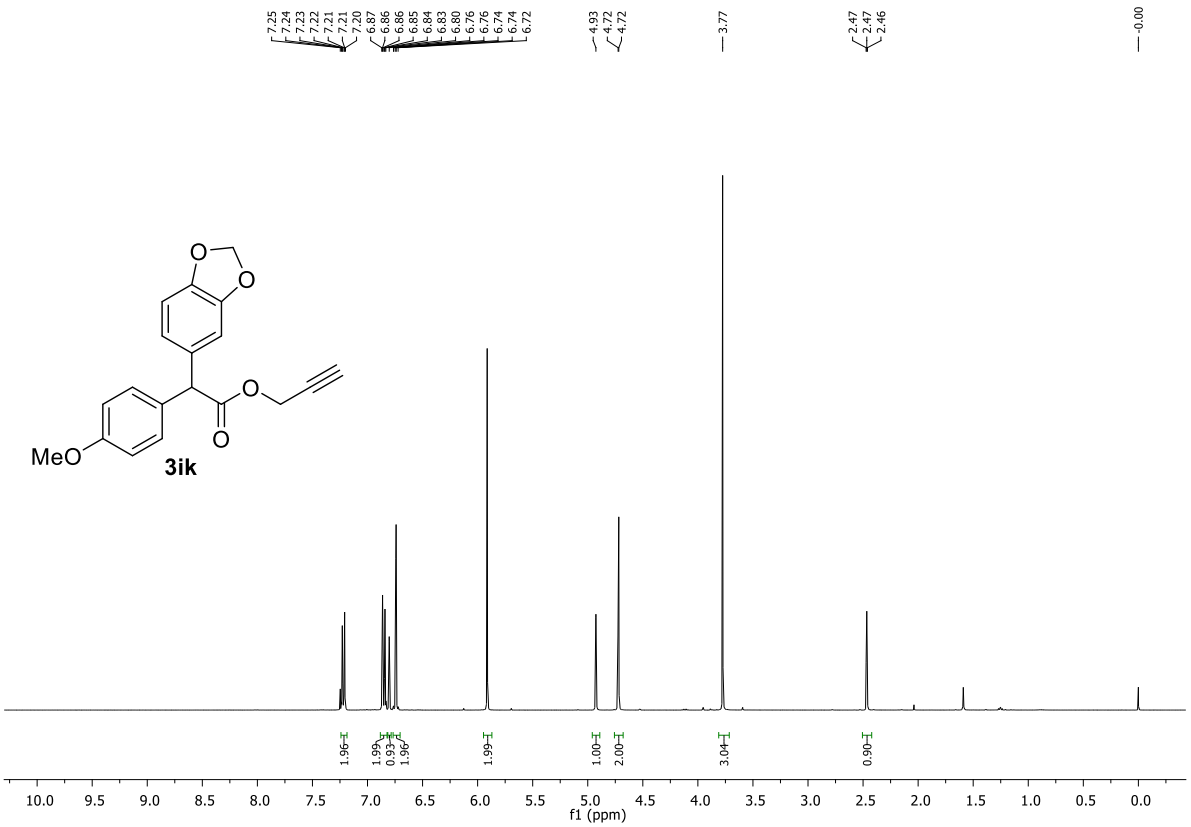


Figure IIIA.9: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3ik**

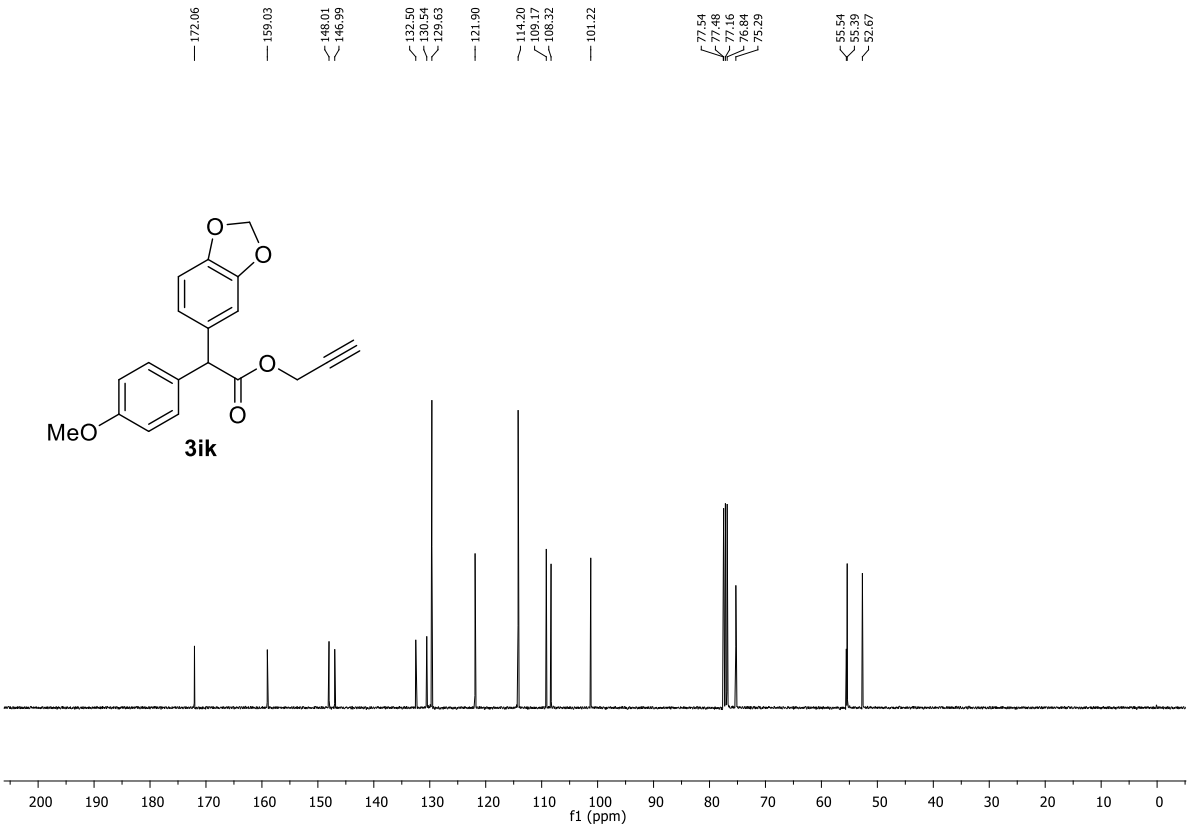


Figure IIIA.10: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3ik**

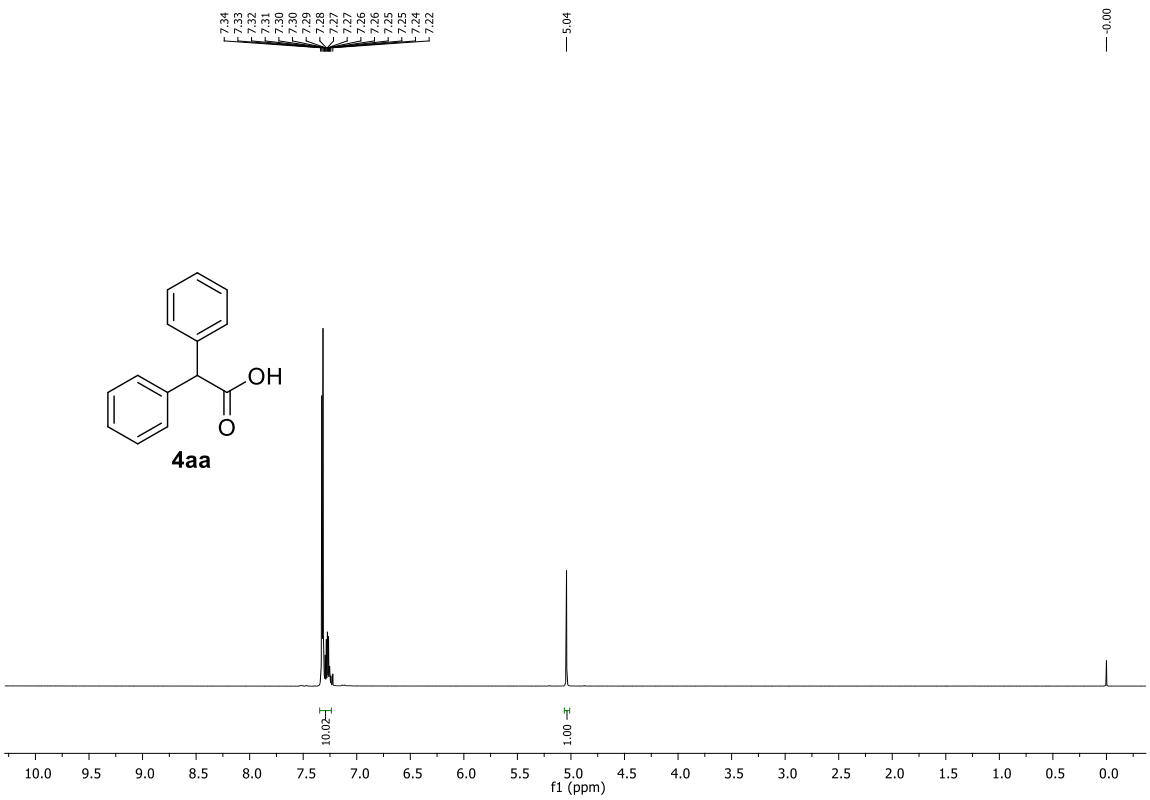


Figure IIIA.11: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **4aa**

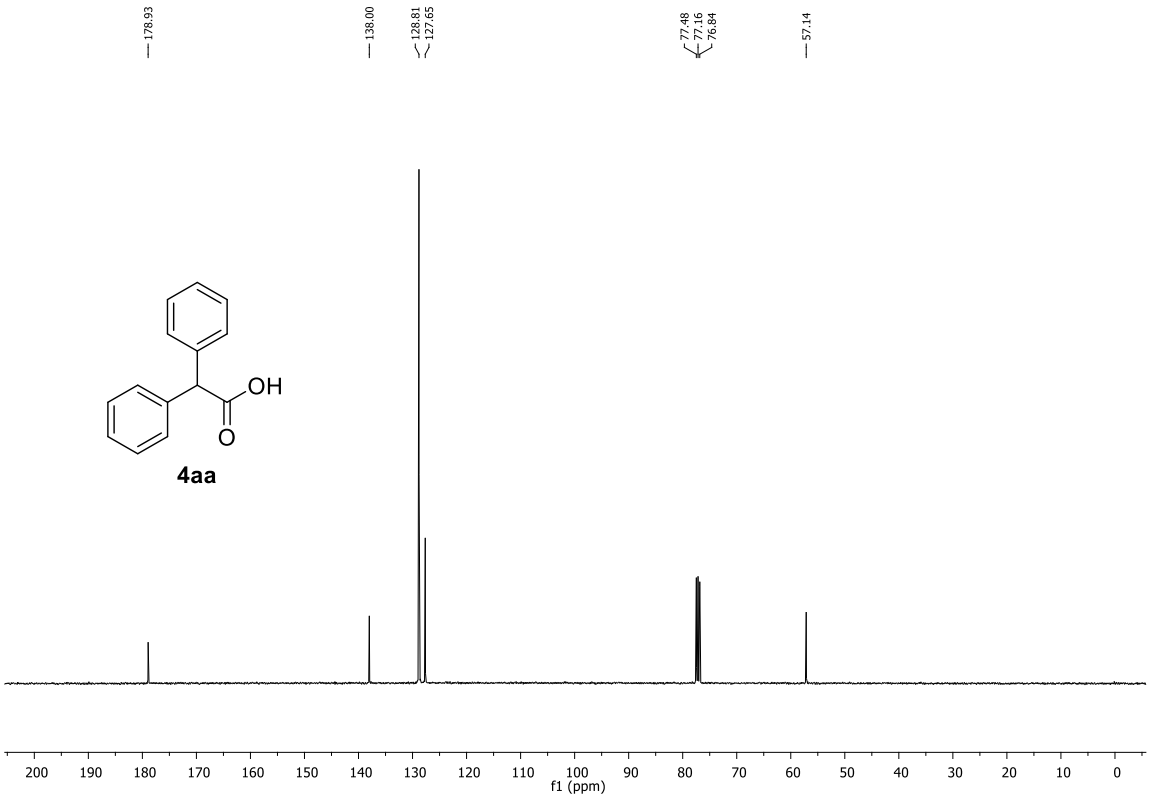


Figure IIIA.12: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **4aa**

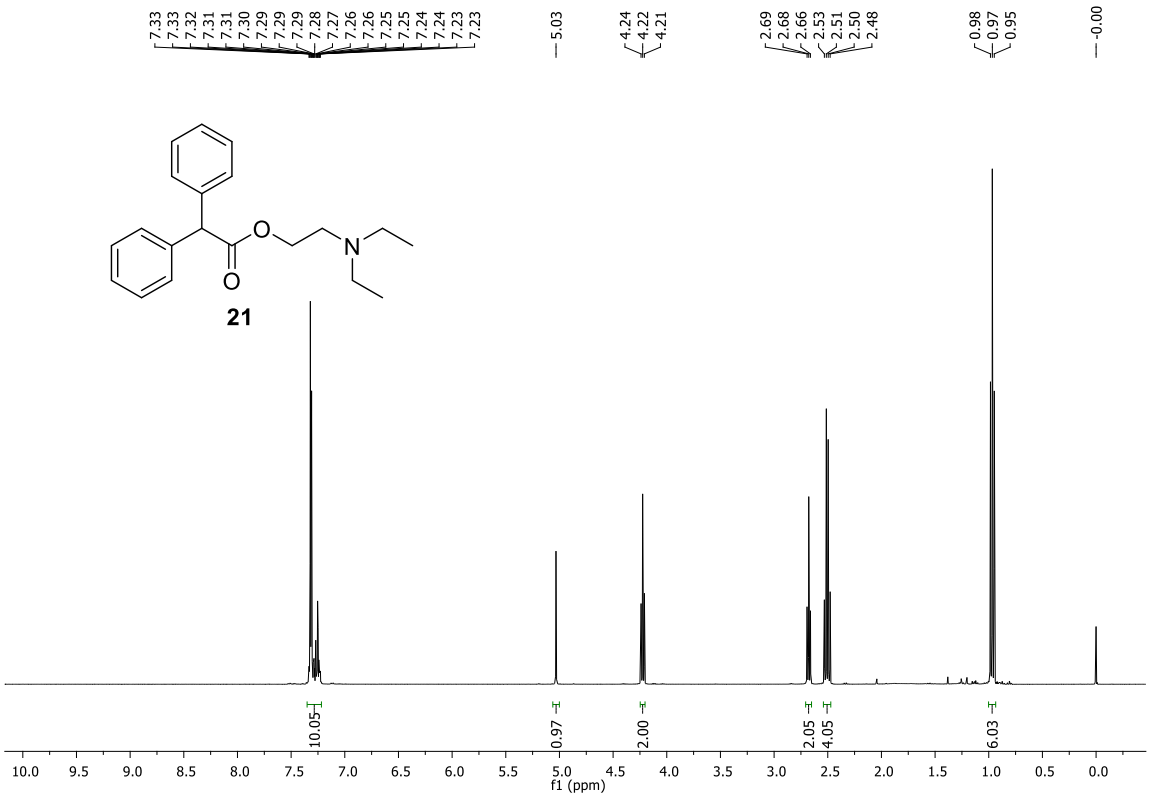


Figure IIIA.13: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **21**

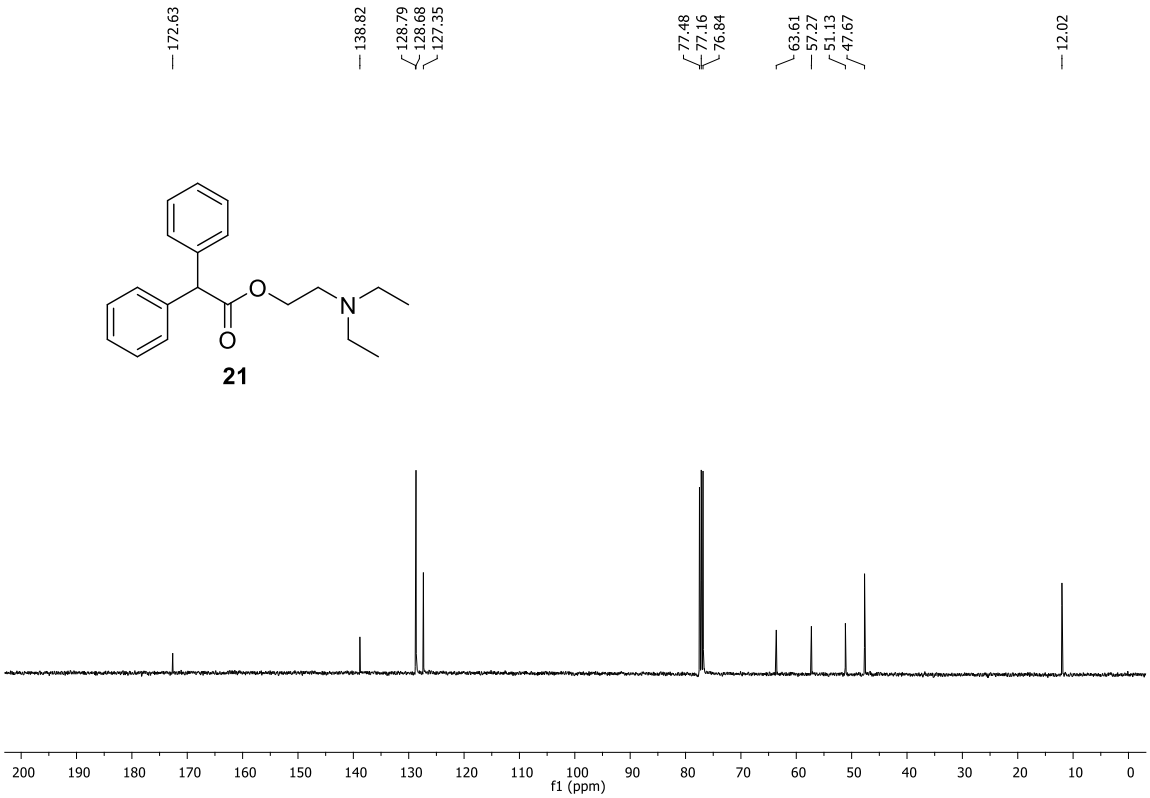
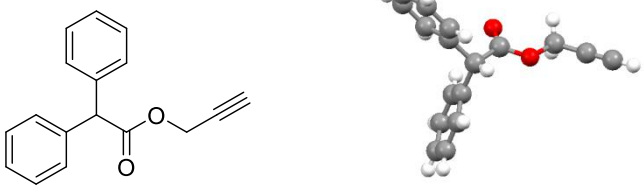


Figure IIIA.14: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **21**

3A.6 Crystal data of compound 3aa



Bond precision: C-C = 0.0025 A Wavelength=0.71073

Cell: a=6.234(3) b=24.681(9) c=9.003(3)
alpha=90 beta=95.074(10) gamma=90
Temperature: 150 K

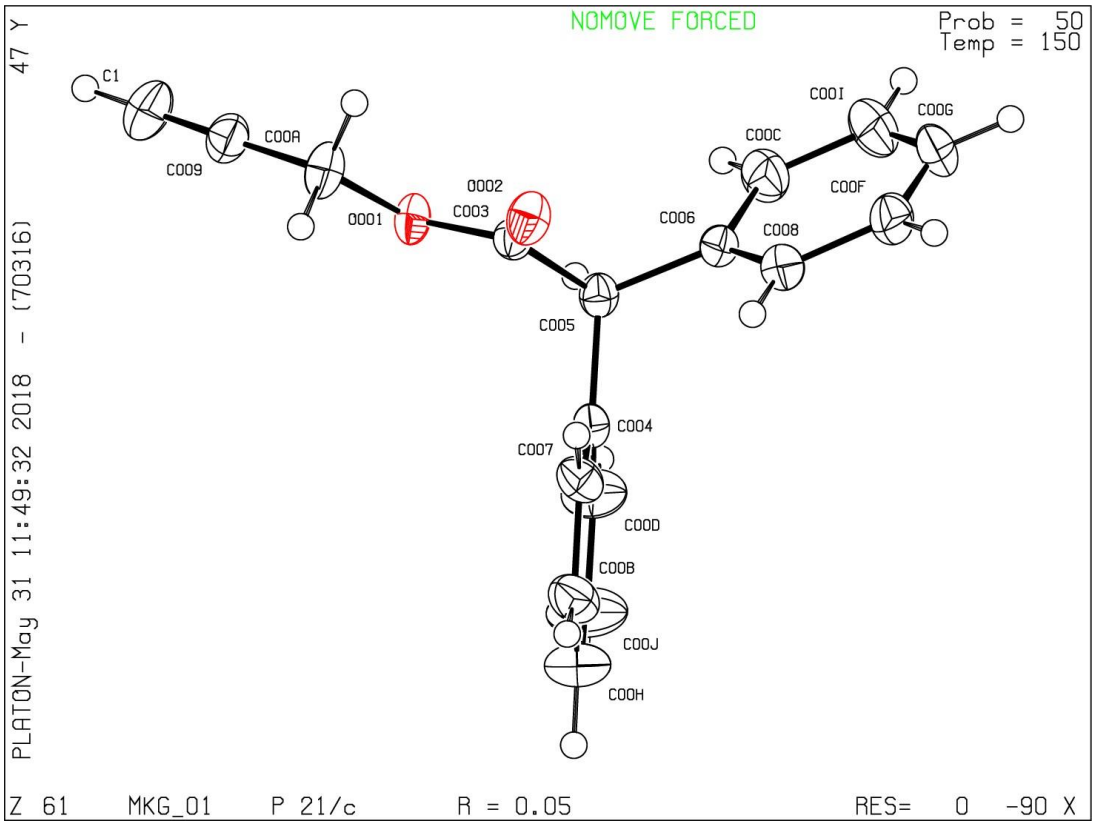
	Calculated	Reported
Volume	1379.8(10)	1379.8(9)
Space group	P 21/c	P 21/c
Hall group	-P 2ybc	-P 2ybc
Moiety formula	C17 H14 O2	?
Sum formula	C17 H14 O2	C17 H14 O2
Mr	250.28	250.28
Dx,g cm-3	1.205	1.205
Z	4	4
Mu (mm-1)	0.078	0.078
F000	528.0	528.0
F000'	528.25	
h,k,lmax	8,33,12	8,32,12
Nref	3527	3493
Tmin,Tmax	0.985,0.988	0.667,0.746
Tmin'	0.985	

Correction method= # Reported T Limits: Tmin=0.667
Tmax=0.746 AbsCorr = MULTI-SCAN

Data completeness= 0.990 Theta(max)= 28.575

R(reflections)= 0.0496(2311) wR2(reflections)= 0.1164(3493)

S = 1.005 Npar= 172


NOMOVE FORCED
Prob = 50
Temp = 150
47 Y
PLATON-May 31 11:49:32 2018 - (70316)
C1
C009
C00A
O001
O002
C003
C005
C006
C00C
C00I
C00G
C00F
C008
C004
C007
C00D
C00B
C00J
C00H
Z 61 MKG_01 P 21/c R = 0.05 RES= 0 -90 X

Section-B

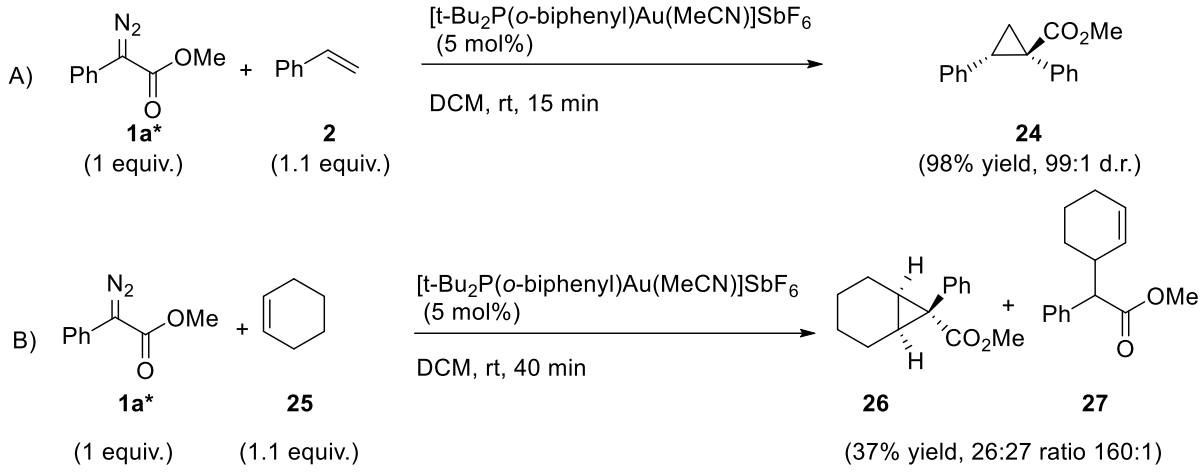
Chemoselective C-H Bond Functionalization of Arenes Bearing Olefin or Alkyne Functionality with Propargyl α-Aryl-α-diazoacetates via Scandium Catalysis

3B.1 Introduction

The C-H bond functionalization is one of the most important and greener methods for the direct synthesis of useful organic compounds.[1] Developing newer catalytic methods for chemoselective C-H bond functionalization is highly desirable but challenging task for the synthetic community due to the similar bond dissociation energies within the same molecule.[1d,17] α-Diazocarbonyl compounds are usually easily prepared from readily available starting materials. Thus the use of α-diazocarbonyl compounds in aromatic C-H bond functionalization has made steady progress for the past few years.[3-4,9] A lot of efforts have been made to develop newer catalysts, modify the diazo substrates, and reagents to make the methods more practical for chemoselective C-H bond functionalizations of arenes.[3]

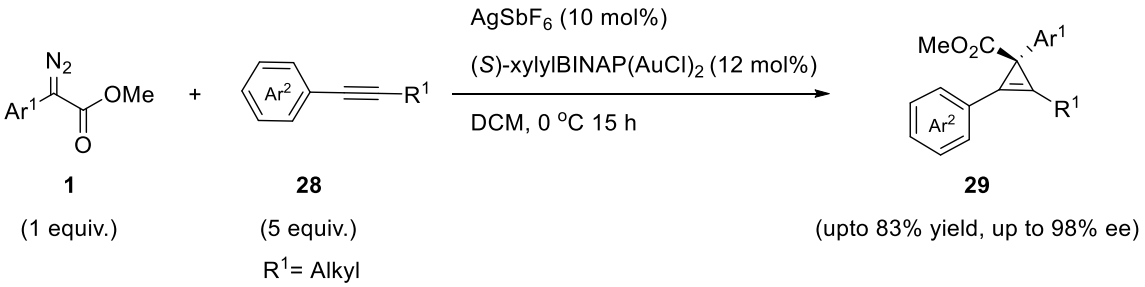
It is very important to note that arenes bearing olefin functionality usually undergo the cyclopropanation reaction with α-diazocarbonyl compounds in the presence of transition metal catalysts.[3,18] Also, the arenes bearing alkyne functionality undergo cyclopropenation reaction with α-diazocarbonyl compounds in the presence of transition metal catalysts.[18f] In this regard, developing a protocol for the chemoselective C-H bond functionalization of arenes containing alkene or alkyne moiety is a challenging task, and it is also less explored.[5d-5f] Some of the representative transition metal catalyzed protocols for the cyclopropanation reactions starting from arenes bearing alkene or alkyne moiety and α-diazocarbonyl compounds have been discussed here.

In 2009, Prieto and co-workers demonstrated the use of the gold catalyst in cyclopropanation reaction. In the presence of gold catalyst, styrene **2** selectively underwent the cyclopropanation reaction with α-phenyl-α-diazoacetate **1a*** to afford the cyclopropanation product **24** (Scheme 3B.1, eq. A). It is very important to note that the arene C-H bond functionalization product did not form in this transformation. Similarly, the reaction of cyclohexene **25** with α-phenyl-α-diazoacetate **1a*** in the presence of gold catalyst afforded the cyclopropanation product **26** and furnished only a trace amount of C-H functionalization product **27** (Scheme 3B.1, eq. B).[18b]



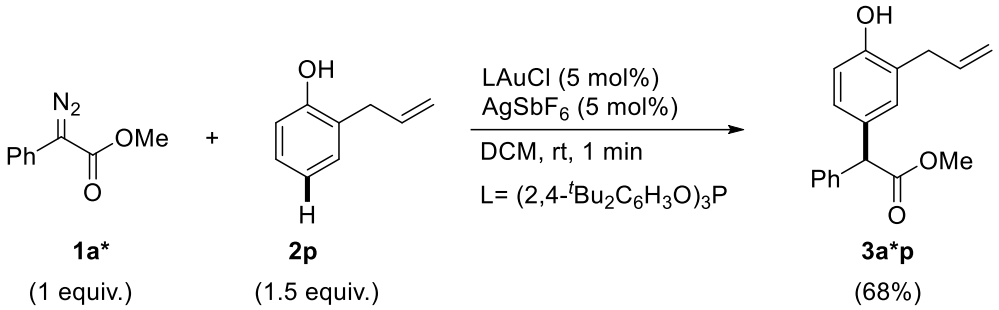
Scheme 3B.1 Gold-catalyzed cyclopropanation reactions

In 2012, Davies et al. reported a gold-catalyzed asymmetric cyclopropanation reaction of alkyne **28** with *α*-aryl-*α*-diazoacetates **1**. In this protocol arene **28** bearing alkyne functionality underwent exclusive cyclopropenation reaction with *α*-aryl-*α*-diazoacetates **1** and afforded the cyclic product **29** (Scheme 3B.2).[18f] This result indicated that the chemoselective C-H bond functionalization of arenes containing carbon-carbon triple bonds is a challenging approach.



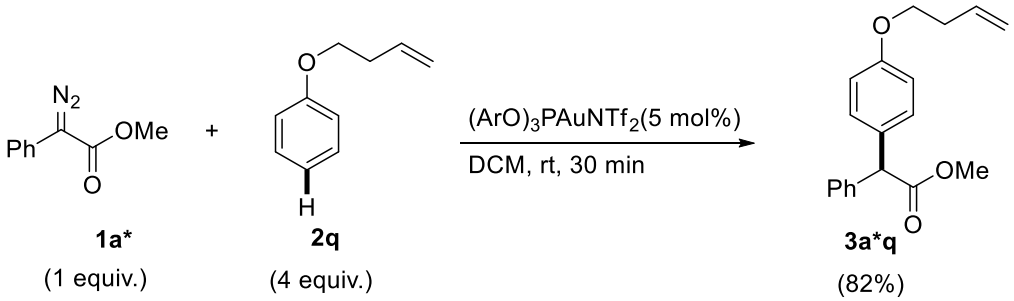
Scheme 3B.2 Gold-catalyzed cyclopropenation reaction of alkynes

In 2014, Zhang et al. explored the utility of gold catalyst for the chemoselective C-H bond functionalization of arene bearing olefin functionality using methyl *α*-phenyl-*α*-diazoacetate **1a***. Under the optimal reaction conditions, in the presence of gold catalyst phenol **2p** reacted methyl *α*-phenyl-*α*-diazoacetate **1a*** to furnish the desired C-H bond functionalization product **3a*p** in 68% yield (Scheme 3B.3). However, the protocol was limited to only electronically activated arenes such as phenols.[5d]



Scheme 3B.3 Chemoselective gold-catalyzed C-H bond functionalization of phenols

Xi and co-workers demonstrated the use of gold catalyst for the chemoselective aromatic C-H bond functionalization of aryl ether **2q** with methyl *α*-phenyl-*α*-diazoacetate **1a***. This protocol successfully avoided the cyclopropanation reaction of carbon-carbon double bond with *α*-phenyl-*α*-diazoacetate **1a*** to give the desired C-H bond functionalization product **3a*q** in good yield (82%, Scheme 3B.4).[5e]



Scheme 3B.4 Chemoselective gold-catalyzed C-H bond functionalization of arene bearing olefin functionality

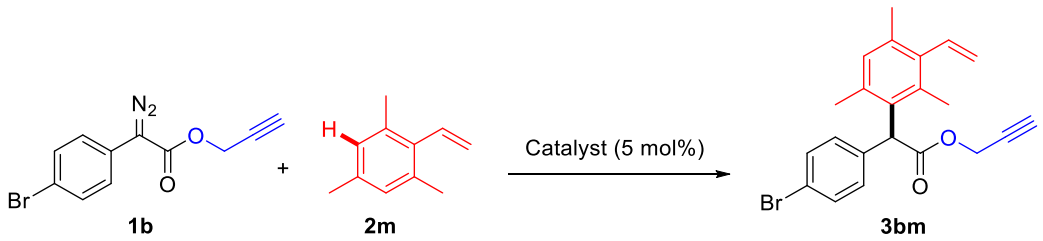
There are only a very few strategies available for the chemoselective C-H bond functionalization of arenes bearing olefin or alkyne substituents. Limited and available protocols require the use of expensive gold catalysts. Hence there is need to develop an alternative and new synthetic method for the chemoselective C-H bond functionalization of arenes having olefin or alkyne substituents using a *α*-diazocarbonyl compounds and easily and commercially available less expensive catalysts. Based on the our previous study, we were curious to study further the effect of $Sc(OTf)_3$ and propargyl *α*-aryl-*α*-diazoacetate on arene substrates bearing alkene and alkyne moieties.

3A.2 Results and discussion

In order to explore the feasibility of the idea, we planned to explore the reactivity of propargyl *α*-aryl-*α*-diazoacetates **1** with arenes **2** bearing olefin or alkyne moiety under scandium catalysis. In this regard, we commenced our study using propargyl *α*-(4-bromophenyl)-*α*-diazoacetate **1b** and arene bearing olefin functionality **2m** as the model substrates. Rhodium and copper catalysts found to be ineffective for the C-H bond functionalization of arene **2m** bearing olefin functionality at 80 ^{o}C (entry 1-2, Table 3B.1). The reaction of *α*-(4-bromophenyl)-*α*-diazoacetate **1b** with arene **2m** (1,3,5-trimethyl-2-vinylbenzene) in the presence of $Sc(OTf)_3$ (5 mol%) in DCE at room temperature did not work (entry 3, Table 3B.1).

Interestingly, the reaction of *α*-(4-bromophenyl)-*α*-diazoacetate **1b** with arene **2m** (1,3,5-trimethyl-2-vinylbenzene) in the presence of $Sc(OTf)_3$ (5 mol%) in DCE at 80 ^{o}C afforded the corresponding desired product **3bm** in moderate yield (50%, entry 4, Table 3B.1). We believed that the low yield of the desired product might be due to higher temperature of the reaction. Later, the treatment of propargyl *α*-(4-bromophenyl)-*α*-diazoacetate **1b** with arene **2m** (1,3,5-trimethyl-2-vinylbenzene) in the presence of $Sc(OTf)_3$ (5 mol%) in DCE at 72 ^{o}C afforded the desired product **3bm** in good yield (70%, entry 5, Table 3B.1). Later, we screened the different metal catalysts to optimize the reaction conditions. The attempted direct C-H bond functionalization of arene **2m** with propargyl *α*-(4-bromophenyl)-*α*-diazoacetate **1b** in presence of different metal catalysts at various reaction conditions afforded the desired product **3bm** in poor to moderate yields (entry 6-11, Table 3B.1). Further we screened different solvents to optimize the reaction condition. Solvents such as EtOAc, DMF, acetonitrile, and nitromethane proved to be inefficient and among all solvents dichoroethane-DCE proved to be the optimum solvent for the desired transformation (entry 12-15, Table 3B.1).The desired C-H bond functionalization did not work in the absence of any catalyst (entry 16, Table 3B.1). Based on the screening of various catalysts, solvents, and temperature, $Sc(OTf)_3$ (5 mol%), propargyl *α*-(4-bromophenyl)-*α*-diazoacetate **1b** (1 equiv.), arenes **2m** (10 equiv.) in DCE at 72 ^{o}C emerged as optimum reaction conditions.

Table 3B.1 Optimization of reaction conditions[a-c]

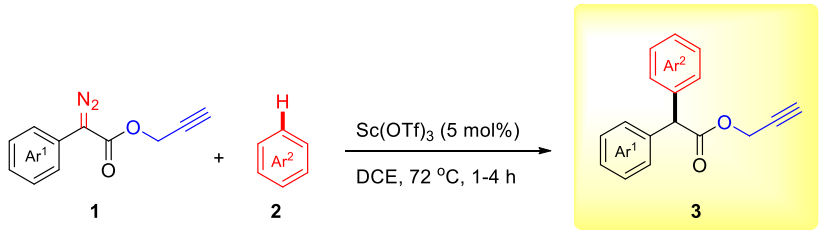


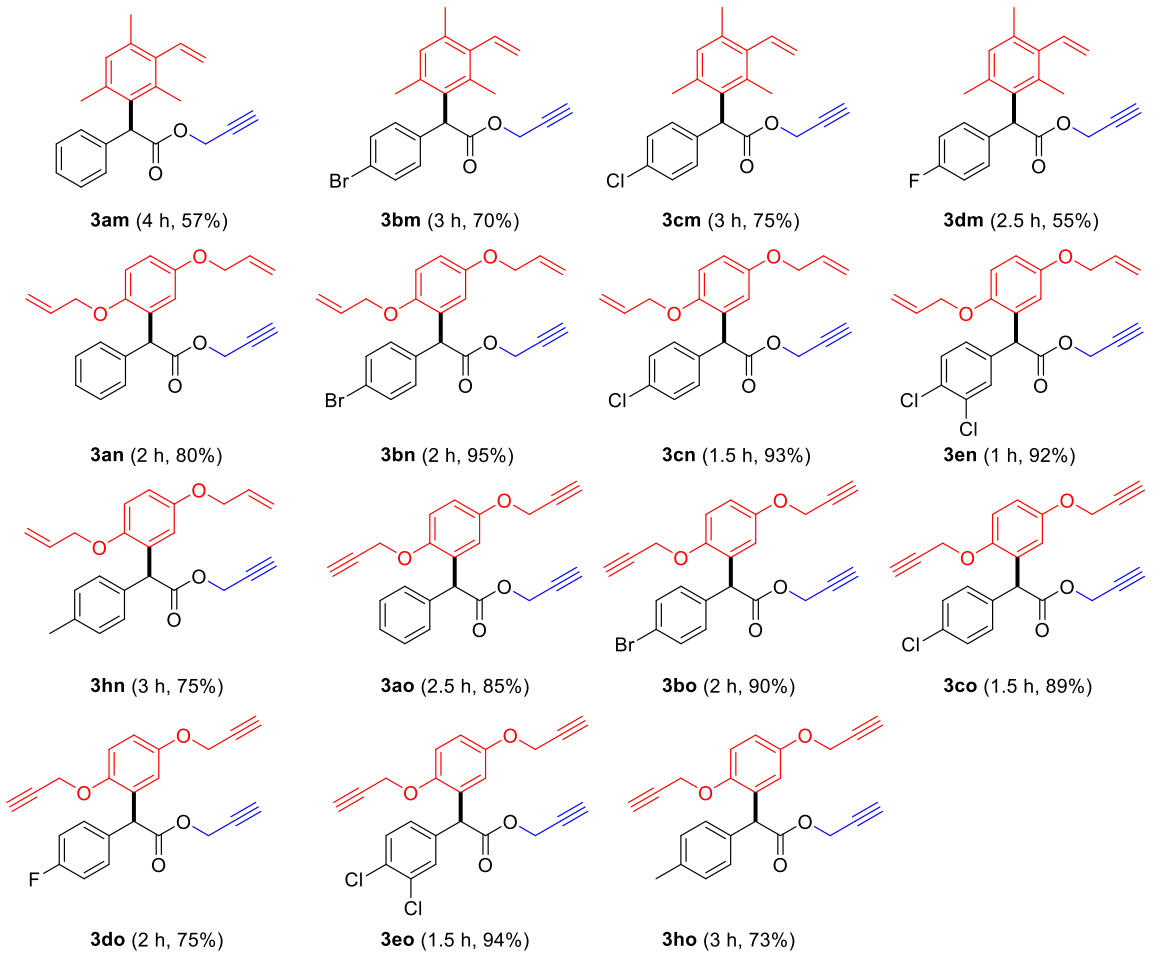
Entry	Catalyst	Solvent	Temp (°C)	Time (h)	Yield[b,c] (%)
1	$Cu(OTf)_3$	DCE	80	6	Trace
2	$Rh_2(OAc)_4$	DCE	80	6	Trace
3	$Sc(OTf)_3$	DCE	rt	3	NR
4	$Sc(OTf)_3$	DCE	80	3	50
5	**$Sc(OTf)_3$**	**DCE**	**72**	**3**	**70**
6	$Y(OTf)_3$	DCE	72	6	20
7	$Yb(OTf)_3$	DCE	72	6	15
8	$La(OTf)_3$	DCE	72	8	Trace
9	$Bi(OTf)_3$	DCE	72	10	08
10	$In(OTf)_3$	DCE	72	6	45
11	$FeCl_3.6H_2O$	DCE	72	8	13
12	$Sc(OTf)_3$	EtOAc	72	8	46
13	$Sc(OTf)_3$	DMF	72	12	NR
14	$Sc(OTf)_3$	Acetonitrile	72	12	NR
15	$Sc(OTf)_3$	Nitromethane	72	6	44
16	No catalyst	DCE	72	12	NR

[a]Reaction conditions: *α*-(4-bromophenyl)-*α*-diazoacetate **1b** (0.5 mmol, 1 equiv.), arene **2m** (5 mmol, 10 equiv.), and $Sc(OTf)_3$ (5 mol%) was added in solvent (2.5 mL) under inert atmosphere and reaction mixture was heated at 72-80 °C; the reaction was monitored by TLC. [b]Isolated yield after purification by column chromatography, [c]-NR- no reaction.

Encouraged by the initial interesting result, we planned to explore the wider substrate scope so as to generalize the protocol. In this regard, different propargyl *α*-aryl-*α*-diazoacetates (**1a-1d**) were treated with arene containing alkene moiety **2m** under the optimal reaction conditions to afford the corresponding desired products (**3am-3dm**) in moderate to good yields (up to 75%, Table 3B.2). 1,4-Bis(allyloxy)benzene **2n** also smoothly underwent the chemoselective C-H bond functionalization with different propargyl *α*-aryl-*α*-diazoacetates (**1a-1c, 1e, 1h**) under the optimized reaction conditions to furnish the

Table 3B.2 **C**-H bond functionalization of arenes bearing olefin and alkyne functionality[a,b]





[a]Reaction conditions: Propargyl *α*-aryl-*α*-diazoacetate **1** (0.5 mmol, 1 equiv.), arene **2** (5 mmol, 10 equiv.), and $Sc(OTf)_3$ (5 mol%) was added in DCE (2.5 mL) under inert atmosphere and reaction mixture was heated at 72 °C; the reaction was monitored by TLC. [b]Isolated yield after purification by column chromatography (Time and yields are given in parenthesis).

corresponding desired products (**3an-3cn, 3en, 3hn**) in good to excellent yields (up to 95%, Table 3B.2). The treatment of 1,4-bis(propargyloxy)benzene **2o** with different propargyl *α*-aryl-*α*-diazoacetates (**1a-1e, 1h**) furnished the corresponding C-H bond functionalization products (**3ao-3eo**, **3ho**) exclusively in good to excellent yields (up to 94% yield, Table 3B.2). During this transformations, we did not observe any isolable amount of

cyclopropanation by-product. The protocol afforded the C-H functionalized products exclusively. Unlike the previous procedures, protocol utilized the inexpensive reagents and catalysts. The combination $Sc(OTf)_3$ and propargyl α-aryl-α-diazoacetate as robust reagents proved to effective for the C-H bond functionalization of arenes bearing alkene and alkyne functionalities.

3A.3 Conclusions

We have successfully demonstrated novel and highly chemoselective C-H bond functionalization of arenes bearing olefin or alkyne functionality via scandium catalysis to afford α-diarylacetates. The propargyl α-aryl-α-diazoacetate proved to be robust reagents for the effective for the C-H bond functionalization. Using this protocol the C-H bond functionalization can be achieved exclusively there by avoiding the cyclopropanation product. The protocol proved to be practical, and it avoids the use of expensive catalysts and ligands.

3B.4 Experimental section

3B.4.1 General

Unless otherwise noted, all the reactions were carried out with distilled and dried solvents using oven-dried glassware. All reagents were purchased from commercial sources and used as received unless otherwise indicated. Thin-layer chromatography (TLC) was performed using silica gel 60 GF_{254} precoated aluminum backed plates (2.5 mm) with detection by UV light. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6. Chemical shifts in ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from tetramethylsilane with the solvent resonance as the internal standard or from the residual solvent peak as internal standard and J values are given in Hz. ^{13}C NMR spectra are reported as δ in ppm downfield from tetramethylsilane and relative to the signal of chloroform-d and DMSO-d_6. ^{13}C NMR spectra were recorded with complete proton decoupling. Mass samples were analyzed by high-resolution mass spectrometry (HRMS) using ESI TOF. FT-IR spectra were obtained using a FT-IR spectrophotometer as neat and reported in cm^{-1}. Melting points were measured in an open glass capillary and values are uncorrected.

3B.4.2 General procedure for the synthesis of *α*-aryl-*α*-diazoacetates

α-Aryl-*α*-diazoacetates were prepared according to previously reported procedure.[16] For more details and procedures-please see section 3A.4.3.

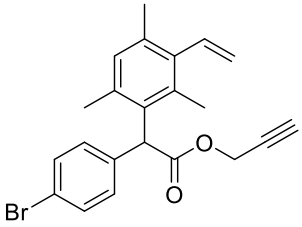
3B.4.3 General procedure E for optimization of reaction conditions

A mixture of 5 mol% of catalyst and arene **2m** (0.81 mL, 5 mmol) in 1.5 mL of solvent was stirred at room temperature in 25 mL two-necked RB flask under inert atmosphere for 5 minutes. Then propargyl *α*-(4-bromophenyl)-*α*-diazoacetate **1b** (0.5 mmol) in 1.5 mL of solvent was added dropwise over 5 minutes, and the reaction mixture was stirred at room temperature or heateded at 72 to 80 ^{o}C over 3-12 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The crude product obtained was purified by column chromatography over silica gel to furnish the product **3bm (**see Table 3B.1).

3B.4.4 General procedure F for the synthesis of *α*-diarylacetates

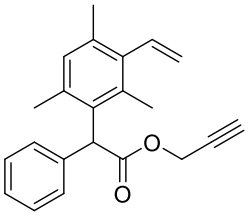
In a dried 25 mL RB flask, $Sc(OTf)_3$ (12.3 mg, 5 mol%), propargyl *α*-(4-bromophenyl)-*α*-diazoacetate **1b** (0.14 g, 0.5 mmol) and arene **2m** (0.81 mL, 5 mmol) was added in 2.5 mL of DCE at room temperature under inert atmosphere. Then the reaction mixture was heated at 72 ^oC over 4 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The crude product obtained was purified by column chromatography over silica gel to furnish the desired product **3bm** (0.139 g, 70% yield).

Prop-2-yn-1-yl 2-(4-bromophenyl)-2-(2,4,6-trimethyl-3-vinylphenyl)acetat (3bm):



Compound **3bm** was synthesized following the general procedure (F). The product was obtained as colourless liquid (0.139 g, 70 % yield): R_f = 0.6 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3296, 2957, 2139, 1739, 1629, 1485, 1449, 1156, 999, 800, 753, 673, 633; ^1H NMR (400 MHz, $CDCl_3$): δ 7.44 – 7.37 (m, 2H), 7.05 – 6.92 (m, 3H), 6.66 (dd, *J* = 17.9, 11.4 Hz, 1H), 5.54 (dd, *J* = 11.4, 2.1 Hz, 1H), 5.36 (s, 1H), 5.20 (dd, *J* = 17.9, 2.0 Hz, 1H), 4.73 (dd, *J* = 2.3, 0.6 Hz, 2H), 2.43 (t, *J* = 2.5 Hz, 1H), 2.29 (s, 3H), 2.18 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3, 137.5, 135.9, 135.8, 135.4, 132.1, 131.4, 130.8, 129.7, 128.5, 127.4, 121.1, 119.9, 77.6, 75.1, 52.6, 50.7, 21.1, 21.0, 18.4; HRMS (ESI TOF): Calculated for $C_{22}H_{22}BrO_2$ $(M + H)^+$: 397.0803, Found: 397.0793.

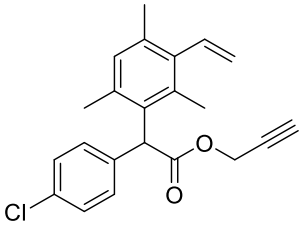
Prop-2-yn-1-yl 2-phenyl-2-(2,4,6-trimethyl-3-vinylphenyl)acetate (3am) :



Compound **3am** was synthesized following the general procedure (F). The product was obtained as colourless oil (0.091 g, 57% yield): R_f = 0.7 petroleum ether/EtOAc (95:5);

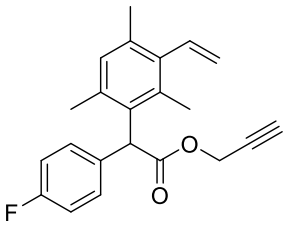
IR (neat) cm^{-1}: 3285, 2937, 1740, 1602, 1491, 1447, 1372, 1273, 1151, 996, 928, 867, 739, 692, 636; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.17 (m, 3H), 7.18 – 7.08 (m, 2H), 6.96 (s, 1H), 6.67 (dd, *J* = 18.0, 11.4 Hz, 1H), 5.53 (dd, *J* = 11.4, 1.9 Hz, 1H), 5.44 (s, 1H), 5.20 (dd, *J* = 18.0, 2.1 Hz, 1H), 4.74 (dd, *J* = 2.4, 1.0 Hz, 2H), 2.42 (t, *J* = 2.4 Hz, 1H), 2.28 (s, 3H), 2.20 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.7, 137.4, 136.4, 136.1, 136.0, 135.5, 135.1, 132.6, 130.7, 128.9, 128.3, 127.0, 119.7, 77.8, 75.0, 52.5, 51.3, 21.0 (for 2 Carbons), 18.5; HRMS (ESI TOF): Calculated for $C_{22}H_{23}O_2$ $(M + H)^+$: 319.1698, Found: 319.1696.

Prop-2-yn-1-yl 2-(4-chlorophenyl)-2-(2,4,6-trimethyl-3-vinylphenyl)acetate (3cm):



Compound **3cm** was synthesized following the general procedure (F). The product was obtained as colourless oil (0.133 g, 75 % yield): R_f = 0.6 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3294, 2950, 2128, 1740, 1490, 1371, 1156, 1092, 999, 930, 866, 804, 756, 677; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 – 7.20 (m, 2H), 7.12 – 7.02 (m, 2H), 6.96 (s, 1H), 6.66 (dd, *J* = 17.9, 11.4 Hz, 1H), 5.53 (dd, *J* = 11.4, 2.1 Hz, 1H), 5.38 (s, 1H), 5.20 (dd, *J* = 17.9, 2.1 Hz, 1H), 4.73 (dd, *J* = 2.4, 1.2 Hz, 2H), 2.43 (t, *J* = 2.5 Hz, 1H), 2.28 (s, 3H), 2.18 (s, 3H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4, 137.5, 135.9, 135.8, 135.4, 135.3, 134.9, 132.9, 132.2, 130.8, 130.4, 128.4, 119.8, 77.6, 75.1, 52.6, 50.6, 21.0, 21.0, 18.4; HRMS ((ESI TOF): Calculated for $C_{22}H_{22}ClO_2$ $(M + H)^+$: 353.1308, Found: 353.1295.

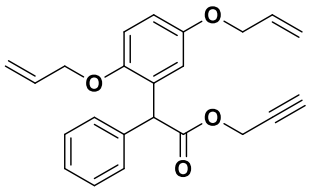
Prop-2-yn-1-yl 2-(4-fluorophenyl)-2-(2,4,6-trimethyl-3-vinylphenyl)acetate (3dm):



Compound **3dm** was synthesized following the general procedure (F). The product was obtained as colourless oil (0.0925 g, 55% yield): R_f = 0.6 petroleum ether/EtOAc (95:5);

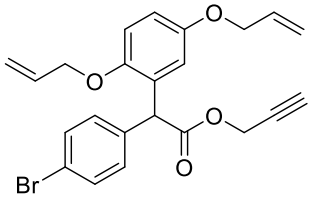
IR (neat) cm^{-1}: 3298, 2950, 2129, 1739, 1603, 1508, 1452, 1372, 1223, 1151, 1104, 996, 930, 849, 821, 805, 755, 677; ^1H NMR (400 MHz, $CDCl_3$): δ 7.13 – 7.06 (m, 2H), 7.02 – 6.91 (m, 3H), 6.67 (dd, *J* = 17.9, 11.5 Hz, 1H), 5.53 (dd, *J* = 11.4, 2.1 Hz, 1H), 5.38 (s, 1H), 5.20 (dd, *J* = 18.0, 2.0 Hz, 1H), 4.73 (d, *J* = 2.4 Hz, 2H), 2.43 (t, *J* = 2.5 Hz, 1H), 2.28 (s, 3H), 2.18 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.7, 161.9 (d, *J* = 245.7 Hz), 137.5, 136.0, 135.8, 135.3 (d, *J* = 10.4 Hz), 132.5, 132.0, 131.9, 130.6 (d, *J* = 7.9 Hz), 119.8, 115.1 (d, *J* = 21.5 Hz), 77.7, 75.0, 52.6, 50.5, 21.0, 20.9, 18.4; HRMS (ESI TOF): Calculated for $C_{22}H_{22}FO_2$ $(M + H)^+$: 337.1604, Found: 337.0604.

Prop-2-yn-1-yl 2-(2,5-bis(allyloxy)phenyl)-2-phenylacetate (3an):



Compound **3an** was synthesized following the general procedure (F). The product was obtained as colourless liquid (0.145 g, 80% yield): R_f = 0.42 petroleum ether/EtOAc (85:15); IR (neat) cm^{-1}: 3289, 3073, 3026, 2921, 2864, 2313, 2129, 1741, 1647, 1593, 1494, 1454, 1424, 1279, 1206, 1146, 1021, 996, 927, 876, 803, 734, 697, 641; ^1H NMR (400 MHz, $CDCl_3$): δ 7.40 – 7.27 (m, 5H), 6.82 – 6.72 (m, 2H), 6.62 (d, *J* = 2.8 Hz, 1H), 6.09 – 5.90 (m, 2H), 5.43 – 5.19 (m, 5H), 4.78 – 4.64 (m, 2H), 4.49 (dt, *J* = 5.4, 1.6 Hz, 2H), 4.39 (dt, *J* = 5.4, 1.6 Hz, 2H), 2.43 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 152.7, 150.3, 137.0, 133.6, 133.5, 129.3, 129.0, 128.8, 127.6, 117.8, 117.2, 116.9, 113.6, 112.7, 77.8, 75.0, 69.7, 69.5, 52.6, 51.1; HRMS (ESI TOF): Calculated for $C_{23}H_{23}O_4$ $(M + H)^+$: 363.1596, Found: 363.1592.

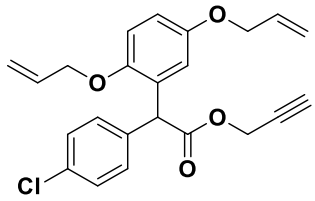
Prop-2-yn-1-yl 2-(2,5-bis(allyloxy)phenyl)-2-(4-bromophenyl)acetate (3bn):



Compound **3bn** was synthesized following the general procedure (F). The product was obtained as colourless liquid (0.21 g, 95% yield): R_f = 0.4 petroleum ether/EtOAc

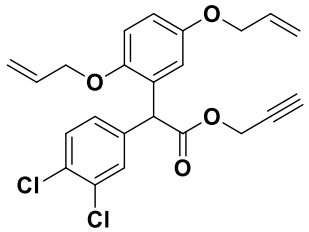
(86:15); IR (neat) cm^{-1}: 3292, 2921, 2864, 2129, 1742, 1493, 1455, 1423, 1209, 1150, 1073, 1000, 929, 805, 762, 678, 640; ^1H NMR (400 MHz, $CDCl_3$): δ 7.53 – 7.41 (m, 2H), 7.24 – 7.14 (m, 2H), 6.85 – 6.70 (m, 2H), 6.63 (d, *J* = 2.5 Hz, 1H), 6.07 – 5.93 (m, 2H), 5.48 – 5.13 (m, 5H), 4.71 (dd, *J* = 2.5, 0.9 Hz, 2H), 4.48 (dd, *J* = 5.4, 0.9 Hz, 2H), 4.41 (dt, *J* = 5.4, 1.5 Hz, 2H), 2.44 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 152.7, 150.2, 136.2, 133.5, 133.4, 131.9, 131.0, 128.3, 121.6, 117.9, 117.4, 116.7, 113.8, 112.8, 77.6, 75.2, 69.7, 69.5, 52.7, 50.5.

Prop-2-yn-1-yl 2-(2,5-bis(allyloxy)phenyl)-2-(4-chlorophenyl)acetate (3cn):



Compound **3cn** was synthesized following the general procedure (F). The product was obtained as colourless liquid (0.185 g, 93% yield): R_f = 0.38 petroleum ether/EtOAc (85:35); IR (neat) cm^{-1}: 3296, 2931, 2312, 2117, 1745, 1598, 1497, 1425, 1369, 1283, 1214, 1154, 1017, 931, 806, 680, 638; ^1H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.21 (m, 4H), 6.83 – 6.71 (m, 2H), 6.62 (d, *J* = 2.7 Hz, 1H), 6.06 – 5.91 (m, 2H), 5.42 – 5.19 (m, 5H), 4.71 (dd, *J* = 2.5, 1.0 Hz, 2H), 4.48 (dd, *J* = 5.4, 0.6 Hz, 2H), 4.40 (dt, *J* = 5.4, 1.4 Hz, 2H), 2.44 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 152.7, 150.2, 135.6, 133.5, 133.3, 130.6, 128.9, 128.4, 117.9, 117.4, 116.7, 113.8, 112.7, 77.6, 75.2, 69.7, 69.5, 52.7, 50.5; HRMS (ESI TOF): Calculated for $C_{23}H_{21}ClO_4$ $(M)^+$: 396.1128, Found: 396.1125.

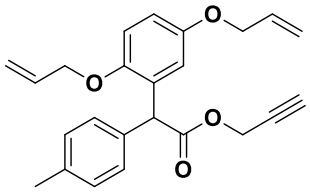
Prop-2-yn-1-yl 2-(2,5-bis(allyloxy)phenyl)-2-(3,4-dichlorophenyl)acetate (3en):



Compound **3en** was synthesized following the general procedure (F). The product was obtained as colourless liquid (0.198 g, 92% yield): R_f = 0.36 petroleum ether/EtOAc (85:15); IR (neat) cm^{-1}: 3294, 3084, 2927, 2867, 2124, 1743, 1646, 1594, 1496, 1279, 1209, 1153,

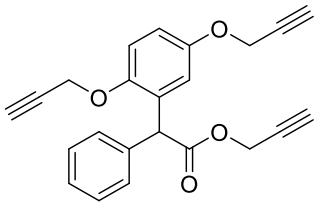
1023, 999, 927, 803, 758, 676, 638; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 – 7.35 (m, 2H), 7.17 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.84 – 6.74 (m, 2H), 6.73 – 6.60 (m, 1H), 6.10 – 5.90 (m, 2H), 5.35 (dq, *J* = 17.3, 1.6 Hz, 2H), 5.30 – 5.22 (m, 3H), 4.72 (d, *J* = 2.5 Hz, 2H), 4.47 (dtd, *J* = 4.0, 2.8, 1.6 Hz, 2H), 4.43 (dt, *J* = 5.4, 1.5 Hz, 2H), 2.46 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 152.8, 150.1, 137.5, 133.5, 133.2, 132.7, 131.7, 131.2, 130.6, 128.6, 127.7, 117.9, 117.6, 116.6, 114.1, 112.9, 75.3, 69.7, 69.6, 52.8, 50.2; HRMS (ESI TOF): Calculated for $C_{23}H_{20}Cl_2O_4$ $(M)^+$: 430.0739, Found: 430.0741.

Prop-2-yn-1-yl 2-(2,5-bis(allyloxy)phenyl)-2-(p-tolyl)acetate (3hn):



Compound **3hn** was synthesized following the general procedure (F). The product was obtained as colourless liquid (0.141 g, 75 % yield): R_f = 0.44 petroleum ether/EtOAc (85:15); IR (neat) cm^{-1}: 3289, 3016, 2926, 2867, 2123, 1742, 1594, 1496, 1425, 1369, 1280, 1209, 1147, 1001, 927, 803, 754, 679, 639; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (d, *J* = 8.1 Hz, 2H), 7.15 (d, *J* = 8.1 Hz, 2H), 6.80 – 6.70 (m, 2H), 6.62 (d, *J* = 2.8 Hz, 1H), 6.06 – 5.92 (m, 2H), 5.43 – 5.13 (m, 5H), 4.70 (qd, *J* = 15.6, 2.5 Hz, 2H), 4.49 (dt, *J* = 5.4, 1.6 Hz, 2H), 4.38 (dt, *J* = 5.4, 1.6 Hz, 2H), 2.42 (t, *J* = 2.5 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.2, 152.7, 150.3, 137.2, 133.9, 133.6, 133.5, 129.5, 129.2, 129.1, 117.8, 117.2, 117.0, 113.5, 112.6, 77.8, 74.9, 69.7, 69.5, 52.5, 50.8, 21.2; HRMS (ESI TOF): Calculated for $C_{24}H_{25}O_4$ $(M + H)^+$: 377.1753, Found: 377.1750.

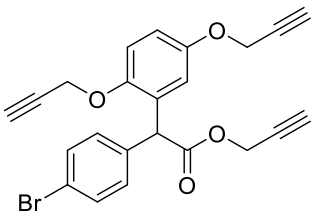
Prop-2-yn-1-yl 2-(2,5-bis(prop-2-yn-1-yloxy)phenyl)-2-phenylacetate (3ao):



Compound **3ao** was synthesized following the general procedure (F). The product was obtained as colourless liquid (0.152 g, 85% yield): R_f = 0.32 petroleum ether/EtOAc (75:25); IR (neat) cm^{-1}: 3287, 3061, 2928, 2868, 2124, 1739, 1597, 1493, 1445, 1202, 1151, 1023,

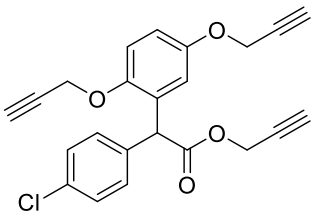
925, 687, 640; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 – 7.24 (m, 5H), 6.94 (d, *J* = 8.9 Hz, 1H), 6.85 (dd, *J* = 8.9, 3.0 Hz, 1H), 6.69 (d, *J* = 3.0 Hz, 1H), 5.32 (s, 1H), 4.73 (qd, *J* = 15.6, 2.5 Hz, 2H), 4.65 (d, *J* = 2.4 Hz, 2H), 4.54 (d, *J* = 2.4 Hz, 2H), 2.51 (t, *J* = 2.4 Hz, 1H), 2.45 (q (merged triplet), *J* = 2.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 152.3, 150.0, 136.7, 129.6, 129.2, 128.8, 127.6, 117.4, 113.9, 113.3, 78.8, 78.7, 77.8, 75.6, 75.5, 75.0, 57.0, 56.5, 52.6, 50.9; HRMS (ESI TOF): Calculated for $C_{23}H_{19}O_4$ $(M + H)^+$: 359.1283, Found: 359.1277.

Prop-2-yn-1-yl 2-(2,5-bis(prop-2-yn-1-yloxy)phenyl)-2-(4-bromophenyl)acetate (3bo):



Compound **3bo** was synthesized following the general procedure (F). The product was obtained as (0.197 g, 90% yield): R_f = 0.33 petroleum ether/EtOAc (75:25); IR (neat) cm^{-1}: 3289, 2921, 2868, 2125, 1740, 1594, 1492, 1370, 1205, 1154, 1015, 929, 807, 759, 679; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 – 7.43 (m, 2H), 7.24 – 7.18 (m, 2H), 6.94 (d, *J* = 8.9 Hz, 1H), 6.87 (dd, *J* = 8.9, 3.0 Hz, 1H), 6.71 (d, *J* = 3.0 Hz, 1H), 5.28 (s, 1H), 4.73 (dd, *J* = 4.8, 2.5 Hz, 2H), 4.64 (d, *J* = 2.4 Hz, 2H), 4.57 (d, *J* = 2.4 Hz, 2H), 2.51 (t, *J* = 2.4 Hz, 1H), 2.48 (t, *J* = 2.4 Hz, 1H), 2.46 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 152.3, 149.9, 135.9, 131.9, 131.0, 128.9, 121.7, 117.2, 114.1, 113.3, 78.7, 78.6, 77.6, 75.7, 75.6, 75.2, 57.0, 56.5, 52.8, 50.4; HRMS (ESI TOF): Calculated for $C_{23}H_{18}BrO_4$ $(M + H)^+$: 437.0388, Found: 437.0375.

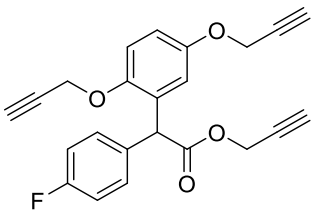
Prop-2-yn-1-yl 2-(2,5-bis(prop-2-yn-1-yloxy)phenyl)-2-(4-chlorophenyl)acetate (3co):



Compound **3co** was synthesized following the general procedure (F). The product was obtained as colourless liquid (0.175 g, 89% yield): R_f = 0.31 petroleum ether/EtOAc (75:25); IR (neat) cm^{-1}: 3290, 2927, 2866, 2124, 1741, 1493, 1444, 1370, 1280, 1204, 1154, 1023,

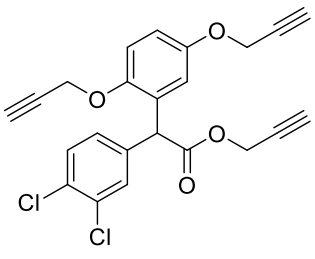
928, 758, 673; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.22 (m, 4H), 6.94 (d, *J* = 8.9 Hz, 1H), 6.86 (dd, *J* = 8.9, 3.0 Hz, 1H), 6.71 (d, *J* = 3.0 Hz, 1H), 5.29 (s, 1H), 4.82 – 4.66 (m, 2H), 4.64 (d, *J* = 2.4 Hz, 2H), 4.57 (d, *J* = 2.4 Hz, 2H), 2.50 (t, *J* = 2.4 Hz, 1H), 2.47 (t, *J* = 2.4 Hz, 1H), 2.45 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 152.3, 149.9, 135.4, 133.6, 130.6, 129.1, 129.0, 117.2, 114.1, 113.4, 78.7, 78.6, 77.6, 75.7, 75.6, 75.2, 57.0, 56.6, 52.8, 50.3; HRMS (ESI TOF): Calculated for $C_{23}H_{18}ClO_4$ $(M + H)^+$: 393.0894, Found: 393.0887.

Prop-2-yn-1-yl 2-(2,5-bis(prop-2-yn-1-yloxy)phenyl)-2-(4-fluorophenyl)acetate (3do):



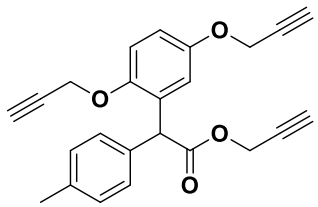
Compound **3do** was synthesized following the general procedure (F). The product was obtained as colourless liquid (0.141 g, 75% yield): R_f = 0.3 petroleum ether/EtOAc (75:25); IR (neat) cm^{-1}: 3290, 2924, 2867, 2313, 2125, 1741, 1499, 1207, 1154, 1107, 1028, 927, 844, 806, 757, 679, 641; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.27 (m, 2H), 7.07 – 6.99 (m, 2H), 6.94 (d, *J* = 8.9 Hz, 1H), 6.86 (dd, *J* = 8.9, 3.0 Hz, 1H), 6.70 (d, *J* = 3.0 Hz, 1H), 5.29 (s, 1H), 4.81 – 4.67 (m, 2H), 4.65 (d, *J* = 2.4 Hz, 2H), 4.57 (d, *J* = 2.4 Hz, 2H), 2.51 (t, *J* = 2.4 Hz, 1H), 2.47 (t, *J* = 2.4 Hz, 1H), 2.46 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 162.3 (d, *J* = 246.2 Hz), 152.3, 149.9, 132.6 (d, *J* = 3.2 Hz), 130.9 (d, *J* = 8.1 Hz), 129.4 , 117.2, 115.7 (d, *J* = 21.5 Hz), 114.0, 113.3, 78.7, 78.6, 77.7, 75.7, 75.6, 75.1, 57.0, 56.5, 52.7, 50.2; HRMS (ESI TOF): Calculated for $C_{23}H_{18}FO_4$ $(M + H)^+$: 377.1189, Found: 377.1172.

Prop-2-yn-1-yl 2-(2,5-bis(prop-2-yn-1-yloxy)phenyl)-2-(3,4-dichlorophenyl)acetate (3eo):



Compound **3eo** was synthesized following the general procedure (F). The product was obtained as colourless liquid (0.201 g, 94% yield): R_f = 0.28 petroleum ether/EtOAc (75:25); IR (neat) cm^{-1}: 3290, 2928, 2124, 1740, 1596, 1492, 1372, 1204, 1153, 1052, 807, 755, 640; ^1H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 2.1 Hz, 1H), 7.39 (d, *J* = 8.3 Hz, 1H), 7.18 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.94 (d, *J* = 8.9 Hz, 1H), 6.88 (dd, *J* = 8.9, 3.0 Hz, 1H), 6.76 (d, *J* = 2.9 Hz, 1H), 5.28 (s, 1H), 4.74 (d, *J* = 2.4 Hz, 2H), 4.64 (d, *J* = 2.4 Hz, 2H), 4.59 (d, *J* = 2.4 Hz, 2H), 2.51 (t, *J* = 2.4 Hz, 1H), 2.50 (t, *J* = 2.4 Hz, 1H), 2.48 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 152.3, 149.7, 137.3, 132.7, 131.8, 131.2, 130.6, 128.6, 128.3, 116.9, 114.5, 113.5, 78.6, 78.5, 77.4, 75.8, 75.8, 75.4, 56.9, 56.5, 52.9, 49.9; HRMS (ESI TOF): Calculated for $C_{23}H_{17}Cl_2O_4$ $(M + H)^+$: 427.0504, Found: 427.0498.

Prop-2-yn-1-yl 2-(2,5-bis(prop-2-yn-1-yloxy)phenyl)-2-(p-tolyl)acetate (3ho):



Compound **3ho** was synthesized following the general procedure (F). The product was obtained as colourless liquid (0.136 g, 73 % yield): R_f = 0.34 petroleum ether/EtOAc (75:25); IR (neat) cm^{-1}: 3287, 2925, 2868, 1739, 1599, 1494, 1443, 1371, 1278, 1202, 1150, 1024, 930, 805, 751, 639; ^1H NMR (400 MHz, $CDCl_3$): δ 7.21 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 1H), 6.84 (dd, *J* = 8.9, 3.0 Hz, 1H), 6.68 (d, *J* = 3.0 Hz, 1H), 5.27 (s, 1H), 4.72 (ddd, *J* = 20.4, 15.6, 2.5 Hz, 2H), 4.65 (d, *J* = 2.4 Hz, 2H), 4.54 (d, *J* = 2.4 Hz, 2H), 2.51 (t, *J* = 2.4 Hz, 1H), 2.46 (t, *J* = 2.4 Hz, 1H), 2.44 (t, *J* = 2.5 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 152.3, 150.0, 137.3, 133.6, 129.9, 129.6, 129.1, 117.5, 113.7, 113.2, 78.8, 78.8, 77.9, 75.6, 75.5, 75.0, 57.0, 56.5, 52.6, 50.6, 21.2; HRMS (ESI TOF): Calculated for $C_{24}H_{21}O_4$ $(M + H)^+$: 373.1440, Found: 373.1440.

3B.5 Appendix III: ^{1}H, ^{13}C NMR spectral data of representative compounds

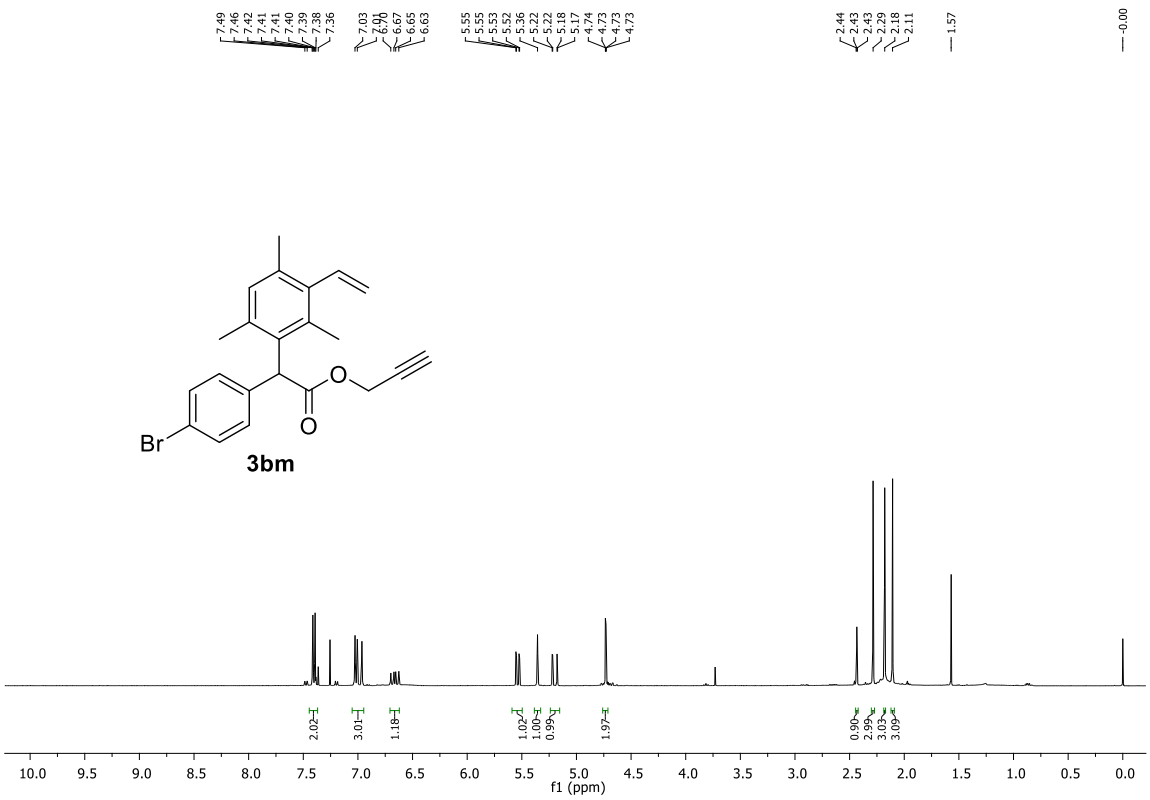


Figure IIIB.1: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3bm**

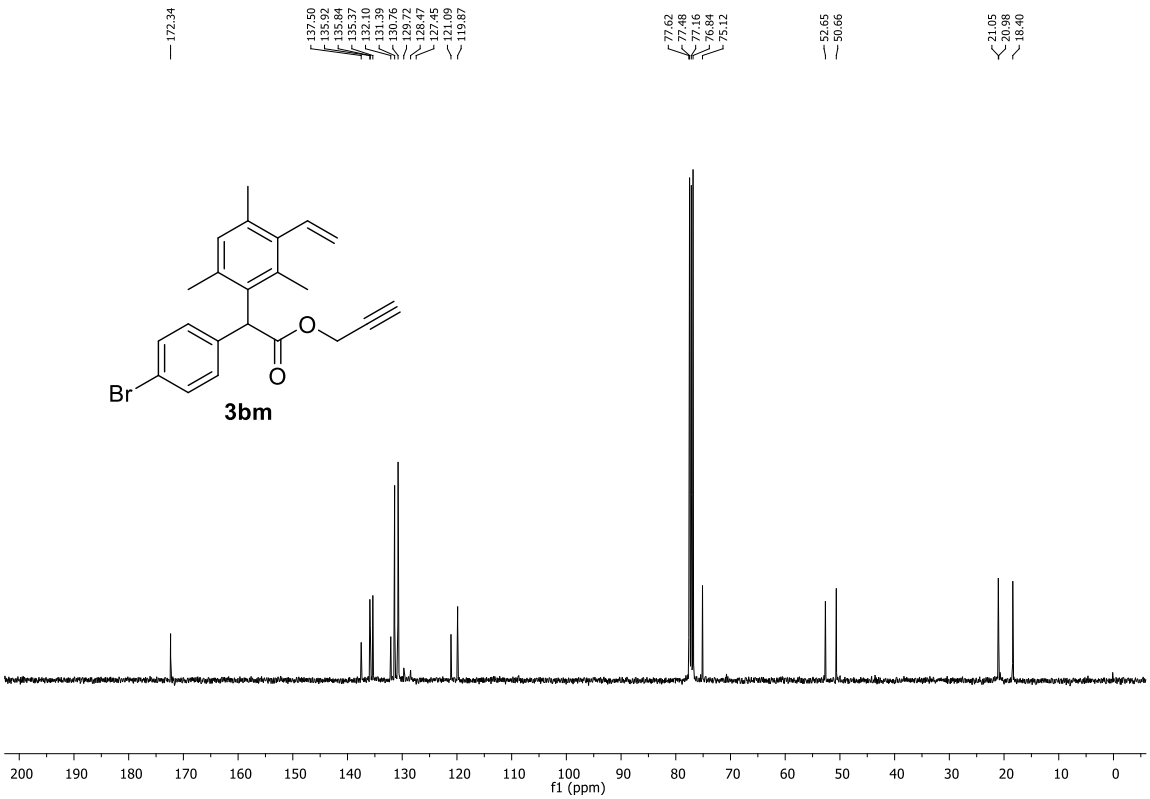


Figure IIIB.2: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3bm**

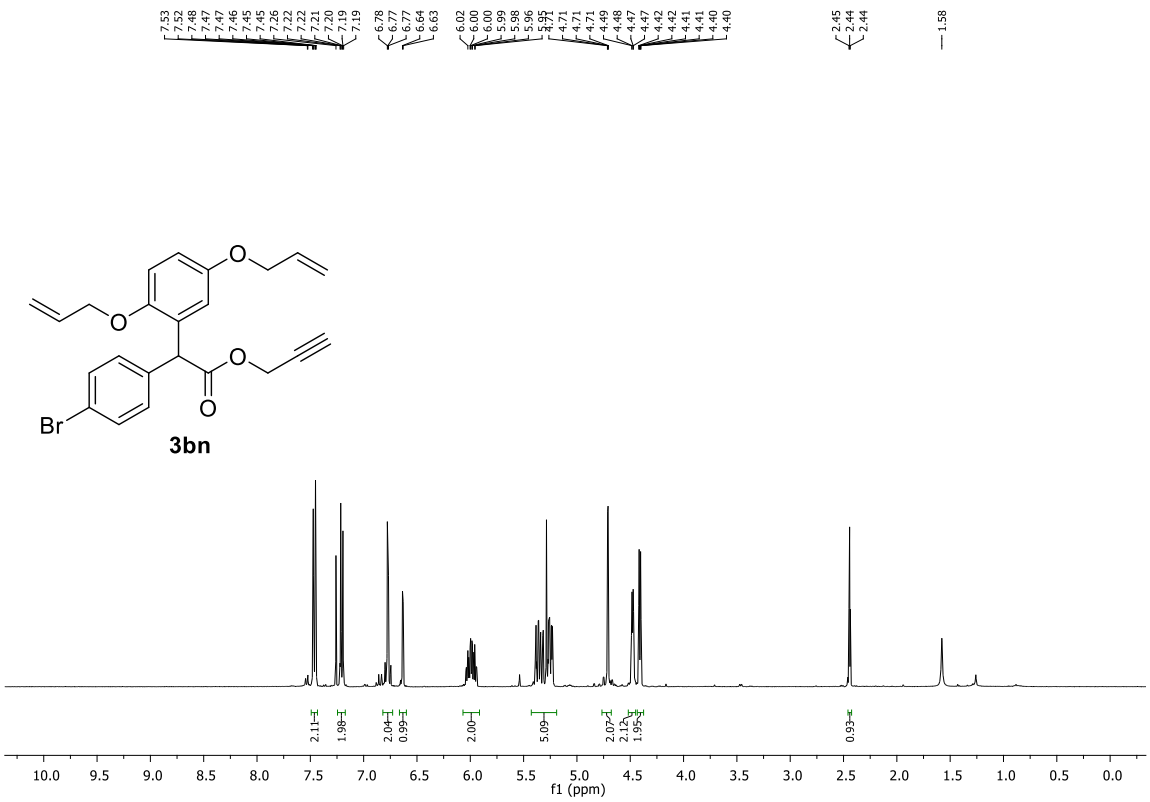


Figure IIIB.3: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3bn**

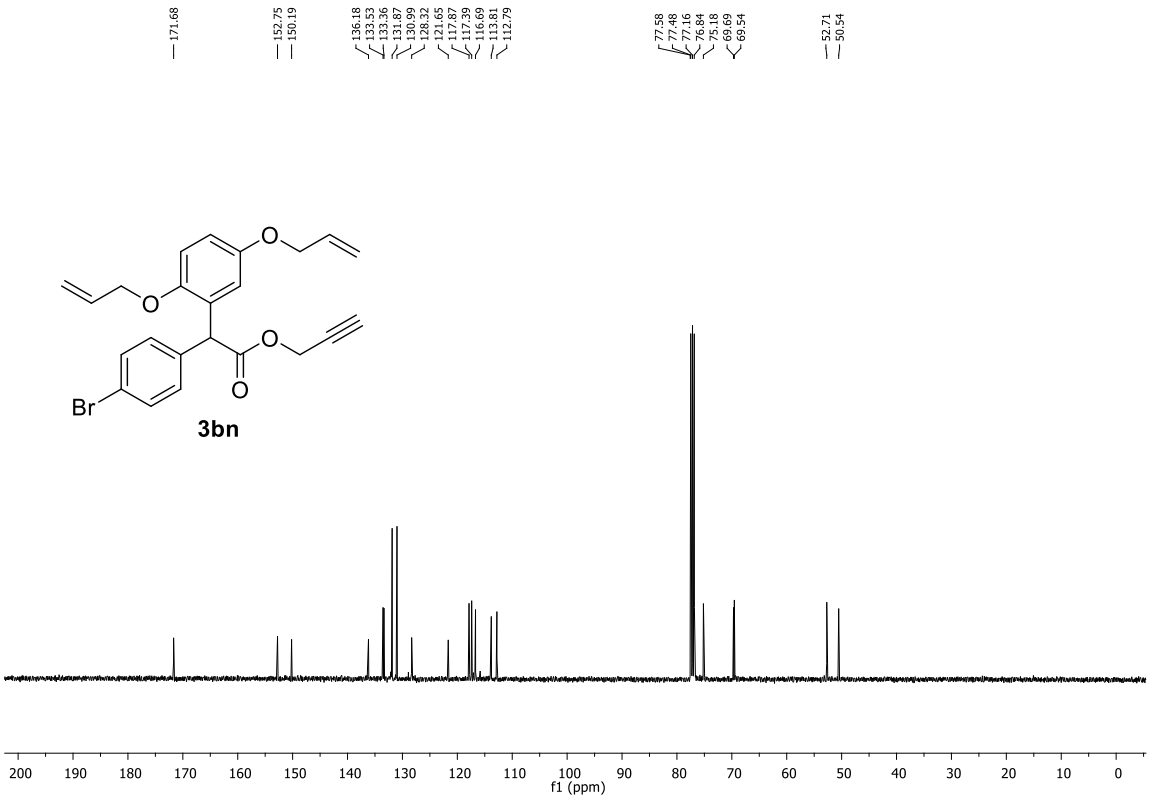


Figure IIIB.4: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3bn**

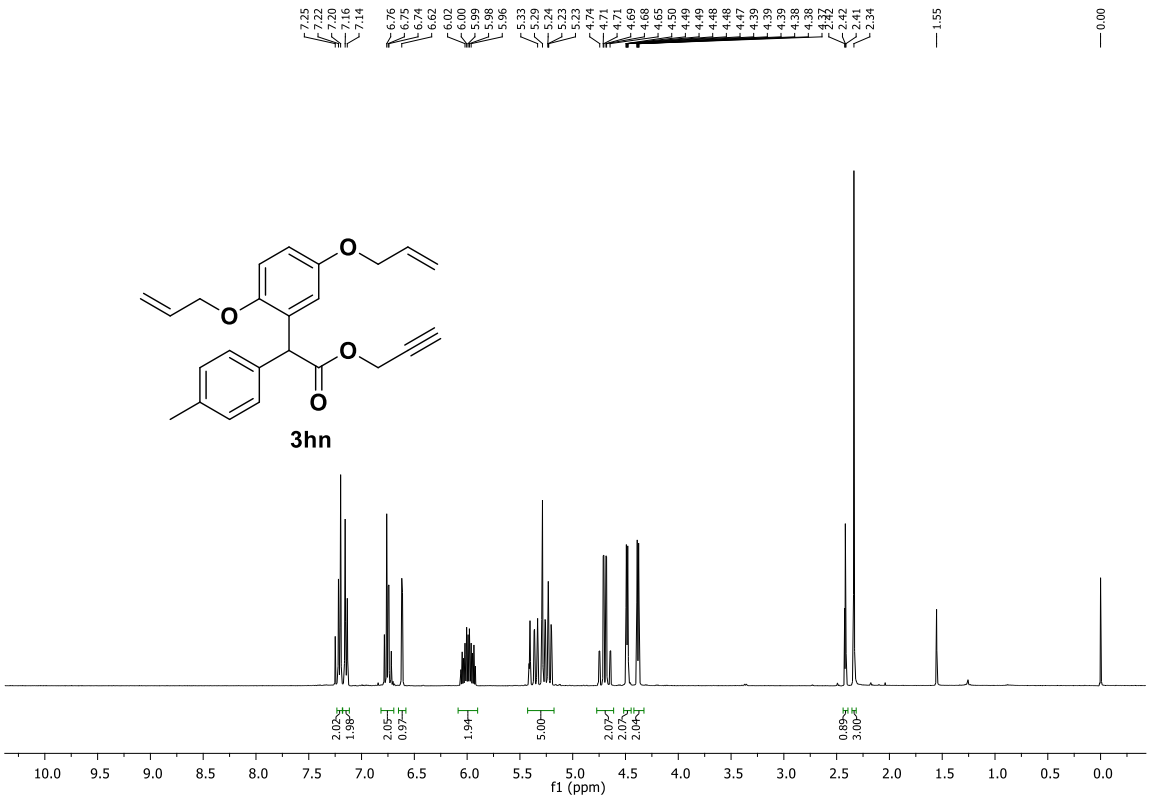


Figure IIIB.5: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3hn**

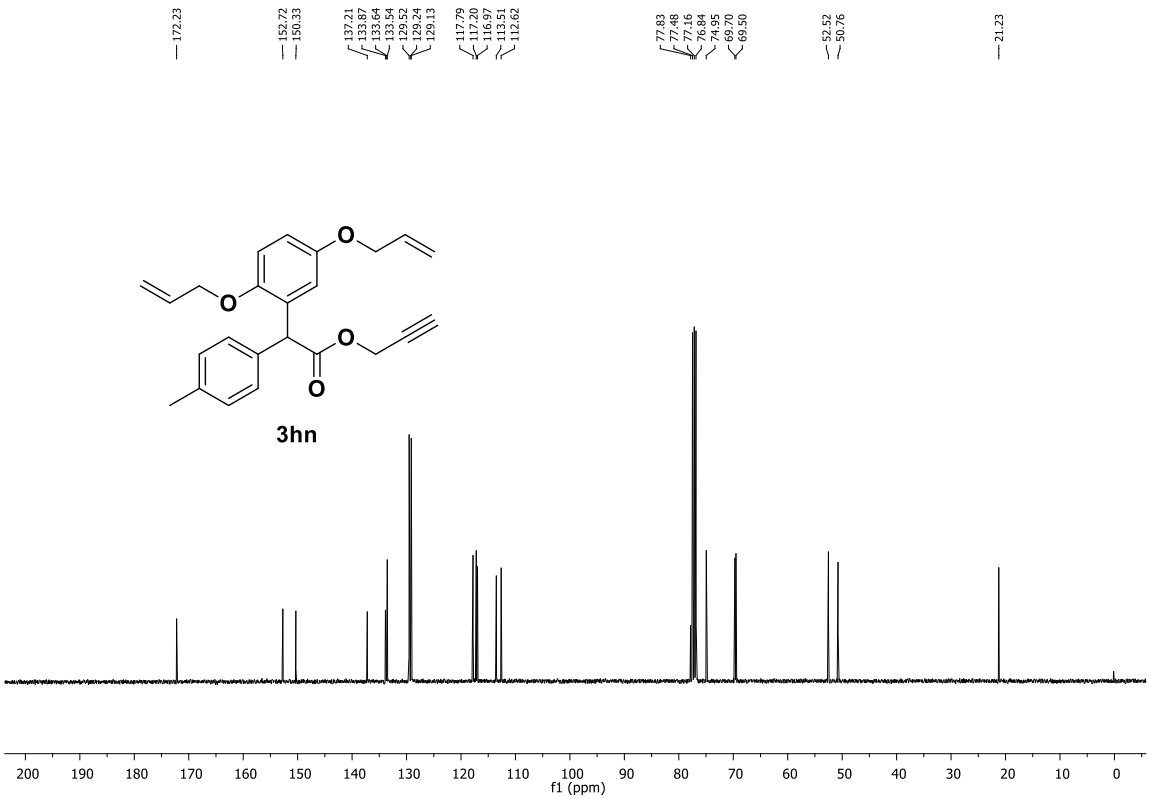


Figure IIIB.6: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3hn**

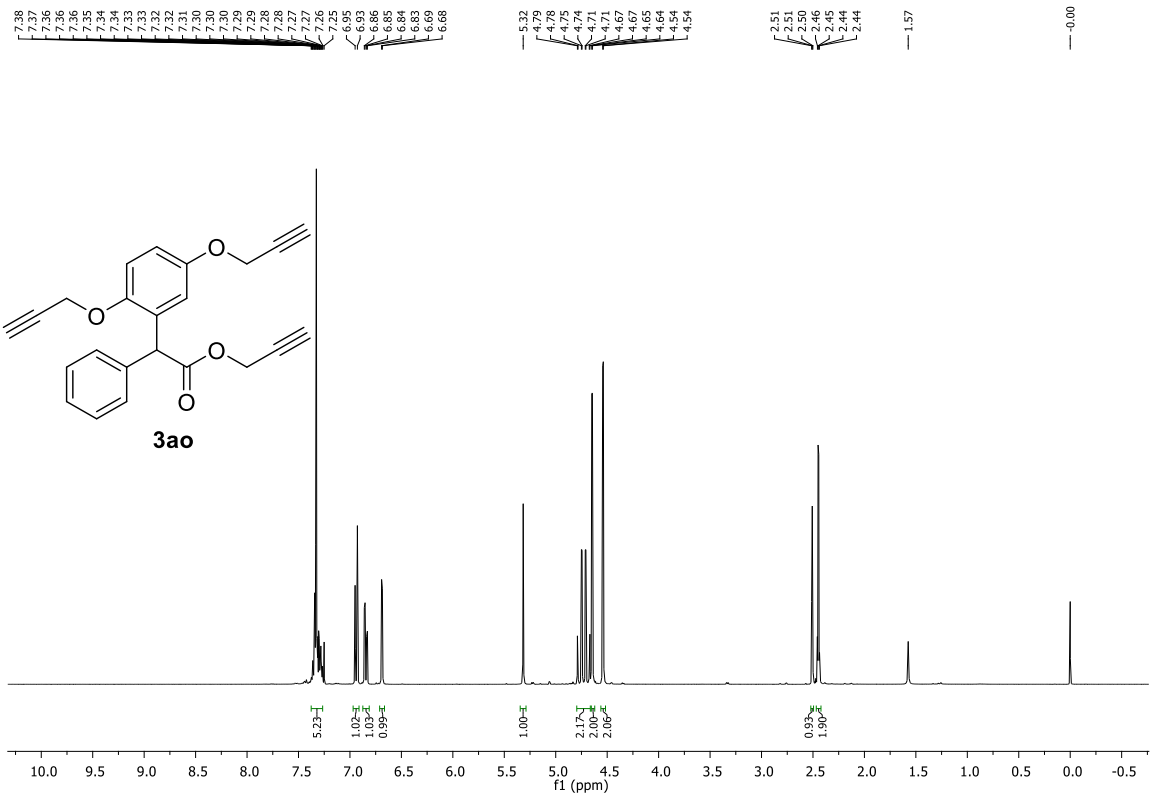


Figure IIIB.7: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3ao**

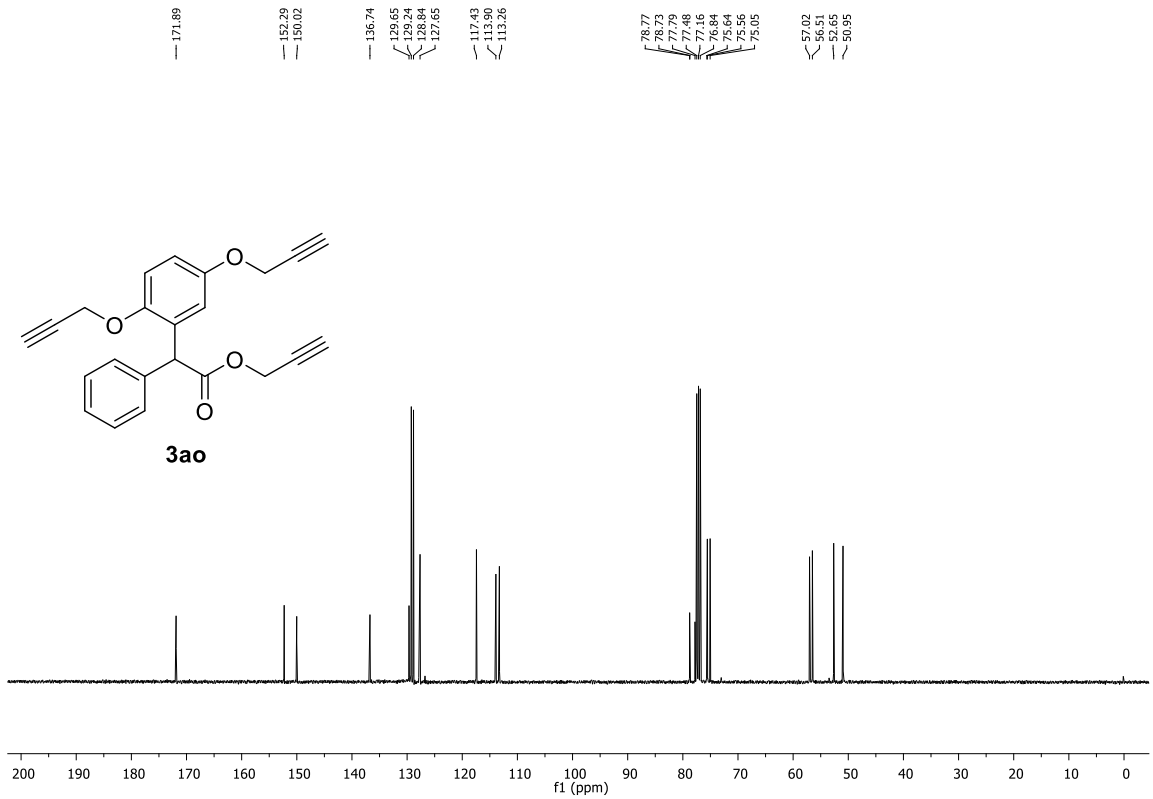


Figure IIIB.8: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3ao**

3AB References and notes

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14. CCDC number of compound **3aa** is 1848210. The number contains all crystallographic details of this publication and is available free of charge at https://www.ccdc.cam.ac.uk/structures/
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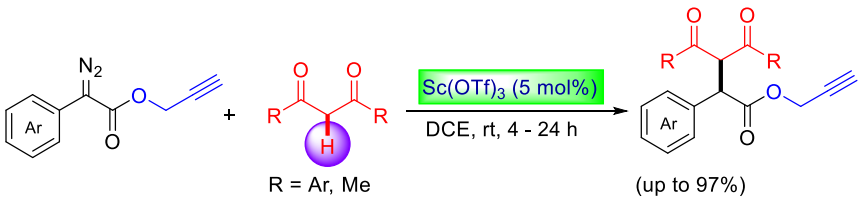
Chapter 4

Propargyl α-Aryl-α-diazoacetates as Robust Reagents for the Effective C-H Bond Functionalization of 1,3-Diketones via Scandium Catalysis



R = Ar, Me

(up to 97%)

- Propargyl α-aryl-α-diazoacetate-Robust reagent
- C-H functionalization at room temperature
- Works with deactivated substrates
- Less prone for side reactions
- Low Catalyst loading (5 mol%)
- Total of 22 examples and gram scale synthesis

F O U R

Propargyl α-Aryl-α-diazoaceates as Robust Reagents for the Effective C-H Bond Functionalization of 1,3-Diketones via Scandium Catalysis

4

Propargyl α-aryl-α-diazoacetate a new class of reagent is developed for the effective C-H bond functionalization of 1,3-diketones at room temperature. The combination of scandium triflate and propargyl α-aryl-α-diazoacetate proved to be an efficient catalyst-reagent system for the controlled C-H bond functionalization to afford 1,3-dicarbonyl alkylation. The protocol uses inexpensive $Sc(OTf)_3$ (5 mol%), and the reaction did not require the use of expensive catalysts or ligands and worked efficiently under room temperature. The practicality of the protocol has been demonstrated by the gram-scale synthesis.

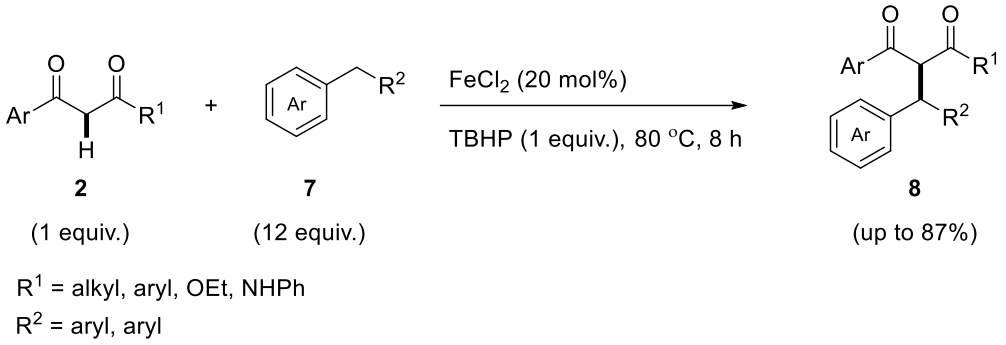
4.1 Introduction

Selective C-H bond functionalization for the construction of new C-C bonds presents an alternative and powerful strategy to the traditional methods in organic synthesis. The direct C-H bond functionalization has several advantages and has attracted great attention from the synthetic community.[1,2] The direct C-H bond functionalization reduces the number of synthetic steps, and the preactivation of starting materials could be avoided thereby increasing the overall atom-efficiency. It has rapidly become one of the powerful tools for the synthesis and modification of complex molecules.[3] Great progress has been made in this field using different transition metals.[4] However, identifying and developing a suitable combination of catalyst and reagent system for the selective C-H functionalization is always a challenging task. The diazo compounds have been established as versatile reagents for various metal-catalyzed reactions.[5] Davies is one of the pioneers who embarked on comprehensive investigations of the scope of intermolecular C-H functionalization.[6b,7]

The C-H bond insertion using α-diazo esters normally proceeds via transient metal-carbenoid species, which are usually formed by the reaction with transition-metal complexes.[6] The transition metals such as rhodium,[7] copper,[8] silver[9] and recently gold[10] have been successfully explored for the decomposition of α-diazo esters to achieve the C-H bond

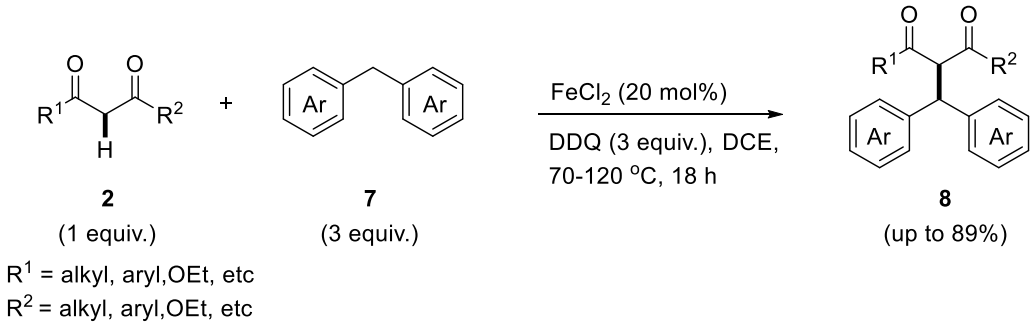
functionalization. Different carbon nucleophiles have been explored for the intermolecular C-H bond functionalization with donor/acceptor type α-diazoesters.[10d,11] The reactive 1,3-dicarbonyl compounds are very useful scaffolds, and they have been utilized for the transition-metal catalyzed oxidative C-H functionalization to access useful compounds.[12]

In 2007, Li and co-workers reported iron-catalyzed C-H bond functionalization of 1,3-dicarbonyl compounds **2** with benzylic C-H bonds for the construction of new C-C bond. In this protocol, Li and co-workers used an excess amount of benzylic compounds **7** to achieve the transformation. The reactions were carried out in the presence of $FeCl_2$ as a catalyst and TBHP as an oxidant at a higher temperature (Scheme 4.1).[12a]



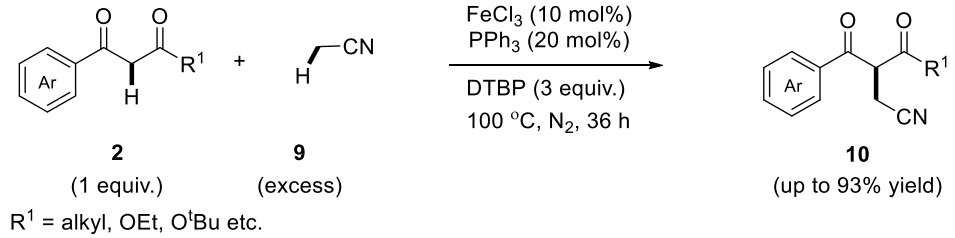
Scheme 4.1 Iron-catalyzed C-H bond functionalization of 1,3- dicarbonyl compounds

In 2015, Yang et al. reported the similar type of transformation in which iron catalyst was used along with DDQ as an oxidant for the C-H bond functionalization of various 1,3-dicarbonyl compounds **2** with diarylmethanes **7**. In this transformation, DDQ was used in excess to furnish the desired products **8**. The reactions were carried out at an elevated temperature (70 °C to 120 °C), depending on the substrates (Scheme 4.2).[12d]



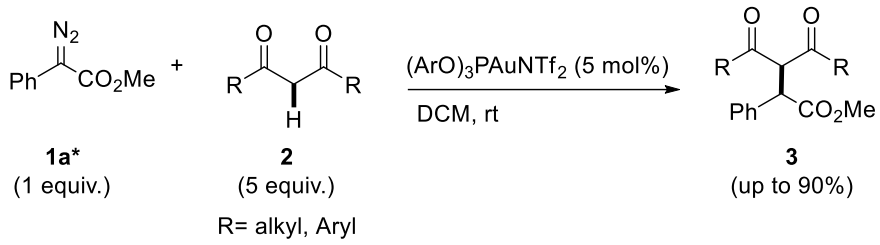
Scheme 4.2 C-H bond functionalization of 1,3-dicarbonyl compounds using an iron catalyst

In 2016, Wang et al. carried out the C-H bond functionalization of 1,3-dicarbonyl compounds **2** with acetonitrile **9** in the presence of ferric chloride as catalyst and triphenylphosphine as a ligand. The transformation required higher temperature and an excess amount of oxidant-DTBP (di-tert-butyl peroxide) to furnish the desired products **10** in good to excellent yields (Scheme 4.3).[12e]



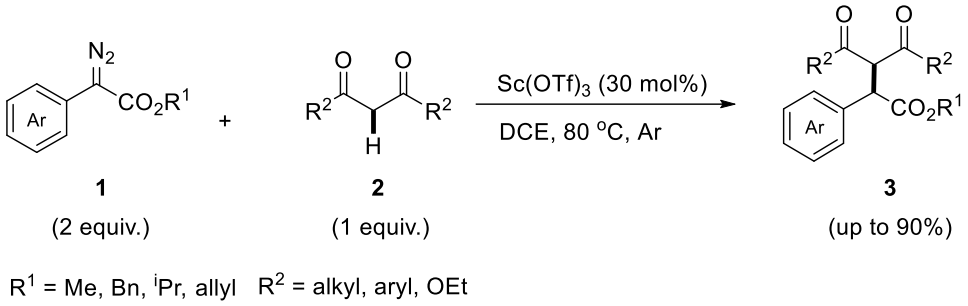
Scheme 4.3 Iron-catalyzed cross dehydrogenative coupling of 1,3-dicarbonyl compounds and acetonitrile

However, these useful protocols need oxidants, excess substrates and high temperature for the effective transformation. In the year 2014, Shi and co-workers elegantly presented the first gold-catalyzed C-H functionalization of 1,3-dicarbonyl compounds **2** with methyl *α*-phenyl-*α*-diazoacetate **1a***. It was demonstrated that the reaction followed the gold-catalyzed decomposition of methyl *α*-phenyl-*α*-diazoacetate **1a*** via the formation of a carbophilic carbocation. This transformation requires an excess amount of 1,3-dicarbonyl compounds **2** to furnish the desired products **3** in good yields (Scheme 4.4).[13]



Scheme 4.4 Gold-catalyzed C-H bond functionalization of 1,3- dicarbonyl compounds

Recently, Bi and co-workers reported the scandium catalyzed C-H bond functionalization of 1,3-dicarbonyl compounds **2** with *α*-aryl-*α*-diazoacetates **1**. This method used *α*-aryl-*α*-diazoester **1** in excess with a higher catalyst loading of the catalyst (30 mol%). Reactions were also carried out at a higher temperature to furnish the desired products **3**. The protocol proved to be less energy efficient regarding temperature and also less economical as it required an excess amount substrate and catalyst (Scheme 4.5).[9e]



Scheme 4.5 C-H bond functionalization via scandium catalysis

There is a great challenge to develop a new catalyst and reagent system that are easily available and less expensive. A lot more efforts are needed to avoid the use of any expensive catalysts, higher catalyst loadings and ligands, excess substrate to make the protocol simple and practical that work at room temperature under mild conditions. Although coinage metals and few of the heavy transitional-metals have been successfully explored for the C-H bond functionalization of *α*-diazoesters, alternative yet useful catalyst-reagent systems are desirable. Group 3 transition metals, e.g., scandium and lanthanides, have been used as environmentally friendly Lewis acid catalysts or promoters for a variety of chemical transformations.[14] Interestingly, early transition elements have been seldom explored in the literature due to its low reactivity. However, the synergistic combination of reagent and catalyst is very crucial for effective C-H bond functionalization. Scandium catalysis has been promising, and scandium triflate has been explored for the reactions of diazo compounds to achieve the successful C-H bond functionalization.[15] It would be very interesting to study the efficiency of scandium catalyst on the C-H bond functionalization of 1,3-dicarbonyl compounds with *α*-aryl-*α*-diazoacetates. The main challenges of this type of reaction are to avoid the formation of dimers (homocoupling of *α*-aryl-*α*-diazoacetates), *α*-oxoesters, azines and to minimize the catalytic amount of metal catalyst. It would also be a challenging task to have a catalyst control over insertion processes such as C-H insertion over O-H insertion. Our group has been independently pursuing the development of a catalyst-reagent system to expand the scope of C-H bond functionalization of *α*-diazoesters using early transition elements and lanthanides.[16] Despite many advances, still, there are numerous limitations such as high reaction temperature, high substrate-reagent ratio, excess catalyst amount, expensive catalysts, etc. Some of these limitations need to be overcome to make the protocols more practical and affordable. Herein, we report the discovery of propargyl *α*-aryl-*α*-diazoacetates as robust and useful new class of reagents for the C-H bond functionalization.

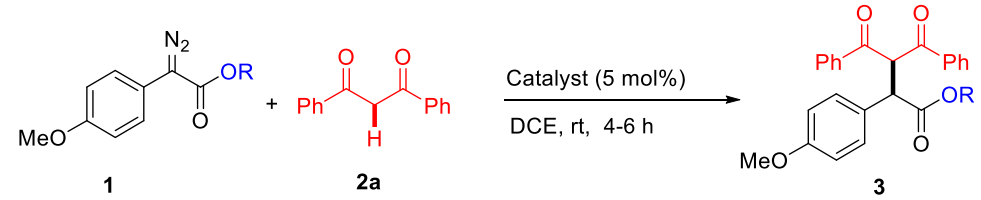
4.2 Results and discussion

At the outset, we began our investigation by choosing ethyl *α*-(4-methoxyphenyl)-*α*-diazoacetate **1i′** and 1,3-diphenylpropane-1,3-dione **2a** (1,3-diketone) as model substrates. The reaction of ethyl *α*-(4-methoxyphenyl)-*α*-diazoacetate **1i′** and 1,3-diketone **2a** in the presence of $Cu(OTf)_2$ (5 mol%) in DCE at room temperature afforded the corresponding desired C-H functionalized product **3i′a** in 52% yield in 6 h (Table 4.1, entry 1). While, the reaction in the presence of gold catalyst [$(ArO)_3PAuNTf_2$ (5 mol%)] afforded the **3i′a** in moderate yield 36%, (Table 4.1, entry 2). Interestingly, $Sc(OTf)_3$ (5 mol%) catalyzed the C-H bond functionalization reaction of ethyl *α*-(4-methoxyphenyl)-*α*-diazoacetate **1i′** (0.5 mmol) and 1,3-diketone **2a** (0.75 mmol) to afford the desired product **3i′a** in 51% yield in 6 h at room temperature (Table 4.1, entry 3). A slight excess of unreacted **2a** was isolated after the reaction during the purification. Likewise, allyl *α*-(4-methoxyphenyl)-*α*-diazoacetate **1i′′** (0.5 mmol) and 1,3-diketone **2a** (0.75 mmol) reacted in the presence of $Sc(OTf)_3$ (5 mol%) to afford the desired product **3i′′a** in 53% yield in 6 h at room temperature. It was very encouraging that desired reaction worked at room temperature under scandium catalysis. The reactions of allyl/propargyl *α*-(4-methoxyphenyl)-*α*-diazoacetate **1** and 1,3-diketone **2a** in the presence of gold catalyst [$(ArO)_3PAuNTf_2$ (5 mol%)] afforded the desired products in modest yields (entries, 5,6 Table 4.1). It is known in the literature that propargyl moiety is a weakly electron-withdrawing group[17] and in this regard, to increase the reactivity of *α*-aryl-*α*-diazoester, we planned to explore the effect of propargyl group in C-H bond functionalization of 1,3-dicarbonyl compounds**.** Propargyl *α*-(4-methoxyphenyl)-*α*-diazoacetate **1i** upon treatment with **2a** in the presence of $Sc(OTf)_3$ (5 mol%) in DCE at room temperature afforded the corresponding **3ia** in relatively shorter reaction time with an excellent yield (96%, Table 4.1, entry 7).

Later, we screened various catalysts to explore the reactivity of propargyl *α*-(4-methoxyphenyl)-*α*-diazoacetate **1i** in C-H bond functionalization of 1,3-diketone **2a** (Table 4.1, see entries 8-14). $Cu(OTf)_2$ catalyzed the desired reaction affording **3ia** in 71% yield in 6 h, whereas other catalysts found to be not useful. In order to confirm the catalytic efficiency of $Sc(OTf)_3$, and to rule out the possibility of the formation of trace amount of triflic acid in situ by the hydrolysis of $Sc(OTf)_3$ if any due to the moisture and its subsequent catalysis, we carried out the reaction of **1i** and **2a** in presence of catalytic amount triflic acid (see Table 4.1, entry 15). Interestingly, the reaction led to the decomposition of propargyl *α*-(4-

methoxyphenyl)-α-diazoacetate **1i** in the presence of triflic acid. The reaction did not work in the absence of any catalyst (Table 4.1, entry 16).

Table 4.1 Optimization of the reaction conditions for C-H bond functionalization[a-d]



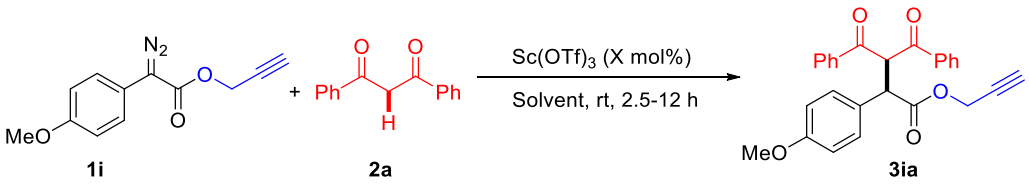
1i = R = propargyl
1i' = R = ethyl
1i'' = R = allyl

Entry	Catalyst	Substrate (1) R	Time (h)	Yield (%)
1	$Cu(OTf)_2$	Ethyl	6	52
2	$(ArO)_3PAuNTf_2$	Ethyl	4	36
3	$Sc(OTf)_3$	Ethyl	6	51
4	$Sc(OTf)_3$	Allyl	6	53
5	$(ArO)_3PAuNTf_2$	Allyl	6	39
6	$(ArO)_3PAuNTf_2$	Propargyl	4	37
7	**$Sc(OTf)_3$**	**Propargyl**	**4**	**96**
8	$Bi(OTf)_3$	Propargyl	6	trace
9	$Cu(OTf)_2$	Propargyl	6	71
10	Dichloro(*p*-cymene)ruthenium(II) dimer	Propargyl	6	DC[c]
11	$Y(OTf)_3$	Propargyl	6	18
12	$In(OTf)_3$	Propargyl	6	68
13	$Rh_2(OAc)_4$	Propargyl	4	DC[c]
14	$Yb(OTf)_3$	Propargyl	6	Trace
15	Triflic acid	Propargyl	6	DC[c]
16	No Catalyst	Propargyl	6	NR[d]

[a]Reaction conditions: Solution of α-aryl-α-diazoacetates **1** (0.5 mmol, 1 equiv.) in 1 mL DCE was added to the solution of catalyst (5 mol%) and 1,3-diketone **2a** (1.5 equiv., 0.75 mmol) in 2 mL DCE over 30 min at room temperature. [b]Isolated yield after purification by column chromatography. [c]DC- Decomposed, [d]NR- no reaction.

To optimize the reaction conditions further, we carried out the reaction of **1i** and **2a** in the presence of $Sc(OTf)_3$ in different solvents, and among all the solvents DCE proved to be the optimal solvent (see, Table 4.2, entry 6). The combination of propargyl *α*-aryl-*α*-diazoacetate and scandium triflate as reagent-catalyst system proved to be effective for the efficient C-H bond functionalization of 1,3-diketones. We observed that propargyl *α*-aryl-*α*-diazoesters and scandium catalyst worked synergistically to bring about desired C-H functionalization very efficiently at room temperature. Based on the exhaustive screening, propargyl *α*-aryl-*α*-diazoacetate **1** (0.5 mmol), 1,3-diketone **2** (0.75 mmol), $Sc(OTf)_3$ (5 mol%) in DCE at room temperature proved to be the optimum reaction condition.

Table 4.2 Screening of solvent for C-H bond functionalization[a,b]

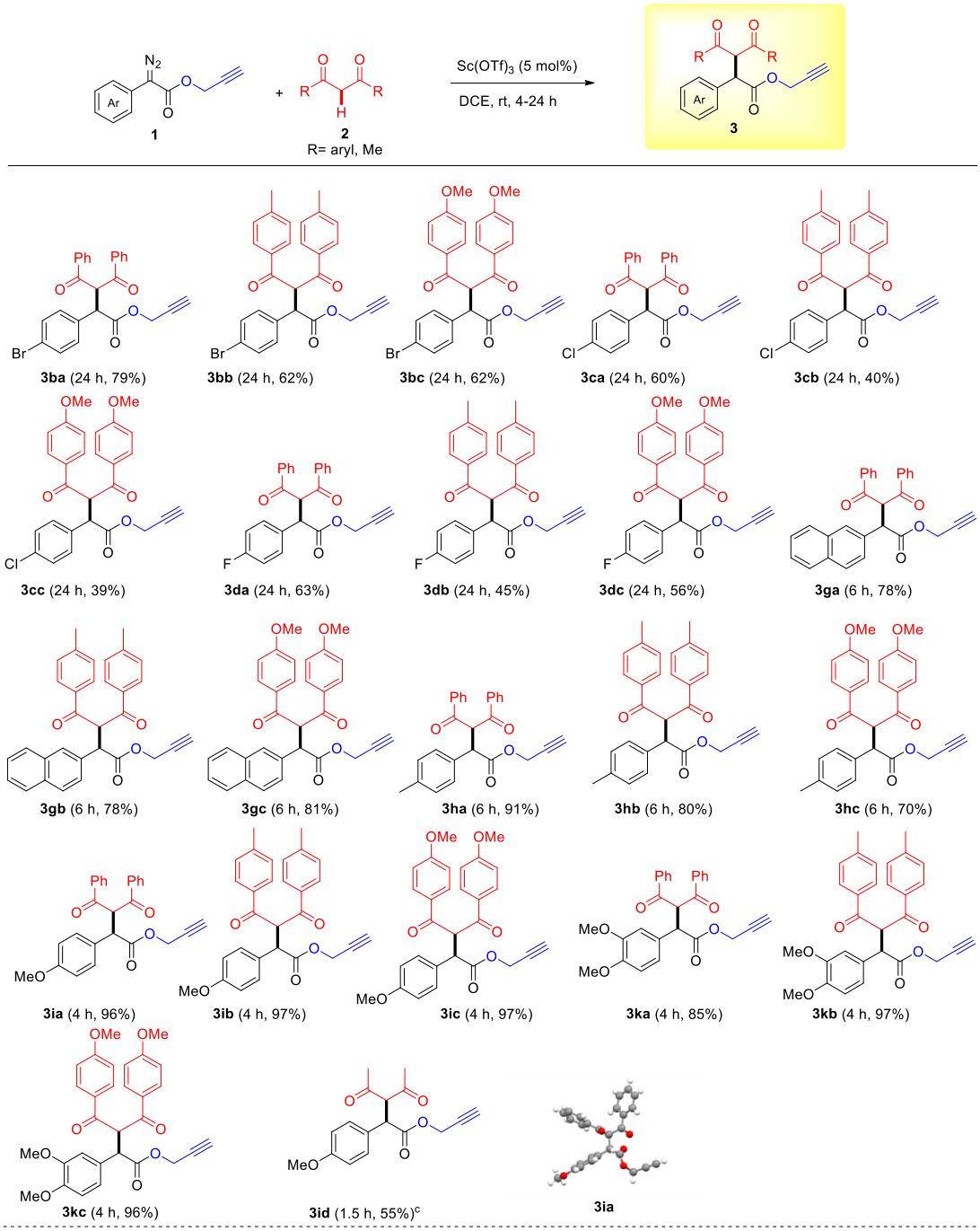


Entry	$Sc(OTf)_3$ (mol%)	1,3-diketone 2a (equiv.)	Solvent	Time (h)	Yield[b] (%)
1	5	1.5	DCM	8	71
2	5	1.5	MeCN	12	70
3	5	1.5	Chloroform	12	48
4	5	1.5	EtOAc	12	58
5	5	5	DCE	2.5	87
6	**5**	**1.5**	**DCE**	**4**	**96**
7	2.5	5	DCE	6	87
8	1	1.5	DCE	12	67
9	1	5	DCE	12	90

[a]Reaction conditions: Solution of *α*-(4-methoxyphenyl)-*α*-diazoacetates **1a** (0.5 mmol, 1 equiv.) in 1 mL DCE was added to the solution of $Sc(OTf)_3$ (1-5 mol%) and 1,3-diketone **2a** (1.5-5 equiv.) in 2 mL solvent over 30 min at room temperature. [b]Isolated yield after purification by column chromatography.

Encouraged by the initial success, we planned to explore the reactivity and scope of different propargyl *α*-aryl-*α*-diazoacetates (**1b-1d, 1g-1i, 1k**) for the effective C-H bond functionalization of 1,3-diketones (**2a-2d**). Mildly electron deactivated propargyl *α*-aryl-*α*-diazoacetates (**1b-1d**) reacted smoothly with different 1,3-diketones (**2a-2c**) under optimum

Table 4.3 C-H bond functionalization of 1,3-diketones[a,b]



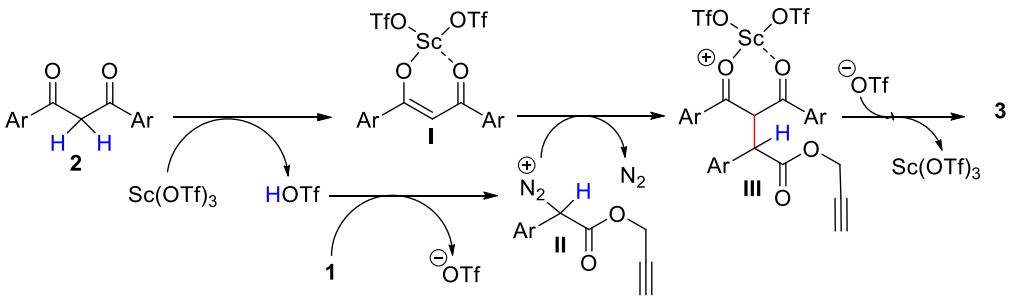
[a]Reaction conditions: Solution of *α*-aryl-*α*-diazoacetates **1** (0.5 mmol, 1 equiv.) in 1 mL DCE was added to the solution of $Sc(OTf)_3$ (5 mol%) and 1,3-diketone **2** (1.5 equiv., 0.75 mmol) in 2 mL DCE over 30 min at room temperature. [b]Isolated yield after purification by column chromatography (Time and yield are given in parenthesis), [c] the reaction was carried out at 50 °C.

reaction conditions to afford the corresponding desired products (**3ba-3dc**) in moderate to good yields (Table 4.3). While electronically neutral propargyl *α*-aryl-*α*-diazoacetate **1g**

reacted with various 1,3-diketones (**2a-2c**) under optimized reaction condition to afford the corresponding desired products (**3ga-3gc**) in good yields (Table 4.3). Electronically activated propargyl *α*-aryl-*α*-diazoacetates (**1h-1i, 1k**) also reacted smoothly with different 1, 3-diketones (**2a-2c**) under optimum reaction conditions to afford the corresponding desired products (**3ha-3ic, 3ka-3kc**) in good to excellent yields (Table 4.3). Further, the treatment of propargyl *α*-(4-methoxyphenyl)-*α*-diazoacetate **1i** with aliphatic 1,3-diketone **2d** afforded the desired product **3id** at a slightly elevated temperature in moderate yield (Table 4.3).

Both electron-rich and mildly electron deactivated propargyl *α*-aryl-*α*-diazoacetates tolerated the reaction conditions. Relatively electron rich propargyl *α*-aryl-*α*-diazoacetates **(1h, 1i, 1k)** showed better reactivity in terms of yields under optimum reaction conditions. We did not observe any side products such as carbene dimerization, *α*-oxoesters and azines during the C-H bond functionalization of 1,3-diketones under the optimal reaction conditions. To extend the scope the methodology, we carried out the reaction of propargyl *α*-(4-methoxyphenyl)-*α*-diazoacetate **1i** and 1,3-diketone **2a** on a gram scale under optimum reaction conditions. The protocol proved to be scalable and worked smoothly to afford the corresponding desired product **3ia** in 87% yield.

Further, the structure of the compound **3ia** was unambiguously confirmed by single crystal X-ray analysis.[18] The plausible reaction pathway is that 1,3-diketone **2** interacts with the $Sc(OTf)_3$ to form the scandium enolate **I** and triflic acid as a by-product. This eventually acts as a proton source to protonate the propargyl *α*-aryl-*α*-diazoacetate **1** to generate the intermediate diazonium ion **II**, which undergoes a facile nucleophilic attack by the scandium enolate **I** to afford the complex **III**.



Scheme 4.6 Plausible reaction pathway for the scandium-catalyzed C-H bond functionalization

Eventually, the reaction of triflate anion with complex **III** furnishes the desired product **3** by regenerating the catalyst. We believe that unlike electron donating power of ethyl/methyl group in ester, weak electron deactivating propargyl moiety played a significant role in enhancing the electrophilicity of the diazonium ion which eventually leads to the reactive carbocation towards the facile C-H insertion at room temperature.

4.3 Conclusions

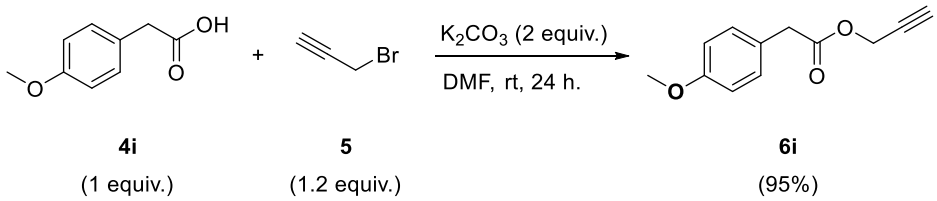
In conclusion, we have developed the new reagent-catalyst controlled effective C-H bond functionalization to afford 1,3-dicarbonyl alkylation via scandium catalysis. We have developed a new series of *α*-aryl-*α*-diazoacetates with propargyl ester as the robust acceptor group and employed them as reagents for the effective C-H functionalization at room temperature. The protocol avoids the use of excess, expensive catalysts, and ligands under practical conditions at room temperature. The practicality of the protocol has been demonstrated by the gram-scale synthesis. Further studies of C-H functionalization of neutral and deactivated arenes are under progress to explore the propargyl *α*-aryl-*α*-diazoacetates and scandium reagent-catalyst system is currently under progress.

4.4 Experimental section

4.4.1 General

Unless otherwise noted, all reactions were carried out with distilled and dried solvents using oven-dried glassware. All reagents were purchased from commercial sources and used as received unless otherwise indicated. Thin-layer chromatography (TLC) was performed using silica gel 60 GF254 precoated aluminum backed plates (2.5 mm) with detection by UV light. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6. Chemical shifts in ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from tetramethylsilane with the solvent resonance as the internal standard or from the residual solvent peak as internal standard and *J* values are given in Hz. ^{13}C NMR spectra are reported as δ in ppm downfield from tetramethylsilane and relative to the signal of chloroform-d and DMSO-d_6. ^{13}C NMR spectra were recorded with complete proton decoupling. Mass samples were analyzed by high-resolution mass spectrometry (HRMS) using ESI TOF. FT-IR spectra were obtained using a FT-IR spectrophotometer as neat and reported in cm^{-1}. Melting points were measured in an open glass capillary and values are uncorrected.

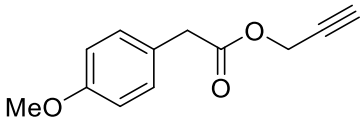
4.4.2 General procedure A for the synthesis of propargyl esters



4i (1 equiv.) + **5** (1.2 equiv.) → **6i** (95%)

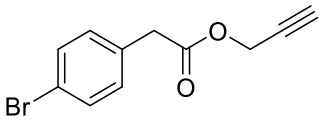
To the stirred solution of 2-(4-methoxyphenyl)acetic acid **4i** (3.32 g, 20 mmol) in DMF (15 mL) was added propargyl bromide solution 80% in toluene (3.57 g, 24 mmol) and K_2CO_3 (5.53 g, 40 mmol). The reaction mixture was stirred at room temperature for 24 h. The progress of the reaction was monitored by TLC. The reaction mixture was filtered through celite, and the filtrate was diluted with water (30 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with cold water and brine solution. The extract was dried over anhydrous Na_2SO_4 and filtered. The filtrate was evaporated under vacuum, and the crude product was purified using column chromatography over silica gel to afford product **6i** as colourless liquid (3.88 g, 95% yield).[19]

Prop-2-yn-1-yl 2-(4-methoxyphenyl)acetate (6i):



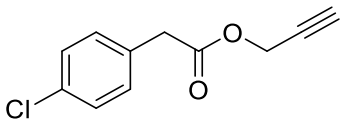
Compound **6i** was synthesized following the general procedure (A). The product was obtained as colourless liquid (3.88 g, 95% yield): R_f = 0.5 petroleum ether/EtOAc (80:20); IR (neat) cm^{-1}: 3285, 2948, 2128, 1736, 1511, 1242, 1138, 1025, 938, 819, 780, 682, 643; ^1H NMR (400 MHz, $CDCl_3$): δ 7.23 – 7.17 (m, 2H), 6.89 – 6.83 (m, 2H), 4.68 (d, J = 2.5 Hz, 2H), 3.79 (s, 3H), 3.61 (s, 2H), 2.47 (t, J = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 159.0, 130.4, 125.6, 114.2, 77.7, 75.1, 55.4, 52.4, 40.2; HRMS (ESI TOF): Calculated for $C_{12}H_{12}NaO_3$ $(M + Na)^+$: 227.0684, Found: 227.0685.

Prop-2-yn-1-yl 2-(4-bromophenyl)acetate (6b):



Compound **6b** was synthesized following the general procedure (A). The product was obtained as white solid (4.657 g, 92% yield): R_f = 0.35 petroleum ether/EtOAc (95:5); m.p.: 41-43 ^oC; IR (neat) cm^{-1}: 3288, 3032, 2946, 2128, 1737, 1605, 1239, 1136, 831, 760, 697, 639; ^1H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 4.70 (d, J = 2.5 Hz, 2H), 3.63 (s, 2H), 2.48 (t, J = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.4, 131.9, 131.2, 129.7, 121.5, 77.4, 75.3, 52.6, 40.4; HRMS (ESI TOF): Calculated for $C_{11}H_{10}BrO_2$ $(M + H)^+$: 252.9864, Found: 252.9871.

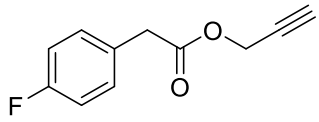
Prop-2-yn-1-yl 2-(4-chlorophenyl)acetate (6c):



Compound **6c** was synthesized following the general procedure (A). The product was obtained as viscous liquid (3.964 g, 95% yield): R_f = 0.3 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3293, 2948, 2129, 1738, 1597, 1492, 1371, 1143, 1091, 938, 807, 758, 676, 641; ^1H NMR (400 MHz, DMSO-d_6): δ 7.41 – 7.36 (m, 2H), 7.33 – 7.27 (m, 2H), 4.72 (d, J = 2.5

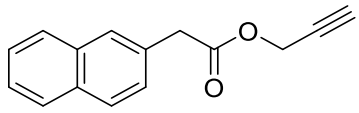
Hz, 2H), 3.75 (s, 2H), 3.55 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.1, 133.0, 131.6, 131.2, 128.2, 78.2, 77.7, 52.1, 39.0; HRMS (ESI TOF): Calculated for $C_{11}H_{10}ClO_2$ $(M + H)^+$: 209.0369, Found: 209.0365.

Prop-2-yn-1-yl 2-(4-fluorophenyl)acetate (6d):



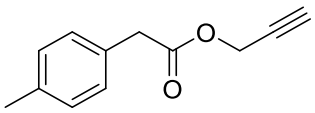
Compound **6d** was synthesized following the general procedure (A). The product was obtained as colourless liquid (3.611 g, 94% yield): R_f = 0.35 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3295, 2948, 2129, 1739, 1606, 1510, 1222, 1140, 937, 826, 785, 681, 643; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.38 – 7.28 (m, 2H), 7.20 – 7.11 (m, 2H), 4.71 (d, *J* = 2.5 Hz, 2H), 3.73 (s, 2H), 3.54 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.3, 161.2 (d, *J* = 242.8 Hz), 131.3 (d, *J* = 8.1 Hz), 130.1 (d, *J* = 3.1 Hz), 115.0 (d, *J* = 21.3 Hz), 78.3, 77.7, 52.0, 38.8; HRMS (ESI TOF): Calculated for $C_{11}H_9FNaO_2$ $(M + Na)^+$: 215.0484, Found: 215.0490.

Prop-2-yn-1-yl 2-(naphthalen-2-yl)acetate (6g):



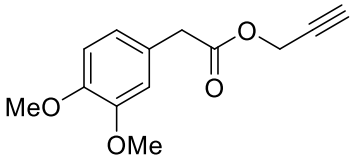
Compound **6g** was synthesized following the general procedure (A). The product was obtained as white solid (4.261 g, 95% yield): R_f = 0.3 petroleum ether/EtOAc (95:5); m.p.: 50-51^{o}C; IR (neat) cm^{-1}: 3288, 3055, 2311, 2129, 1736, 1509, 1325, 1135, 946, 900, 857, 748, 679, 636; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82-7.78 (m, 3H), 7.74 (s, 1H), 7.54 – 7.29 (m, 3H), 4.71 (d, *J* = 2.5 Hz, 2H), 3.83 (s, 2H), 2.47 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 133.6, 132.7, 131.0, 128.5, 128.2, 127.83, 127.80, 127.4, 126.3, 126.0, 77.7, 75.2, 52.5, 41.3; HRMS (ESI TOF): Calculated for $C_{13}H_{13}O_2$ $(M + H)^+$: 225.0916, Found: 225.0908.

Prop-2-yn-1-yl 2-(p-tolyl)acetate (6h):



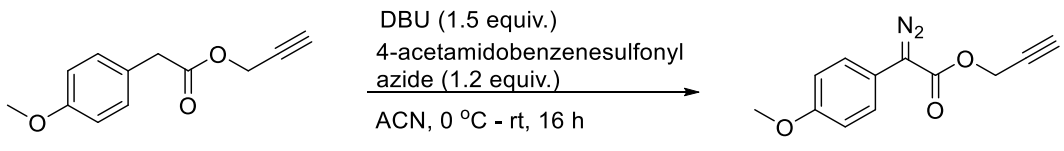
Compound **6h** was synthesized following the general procedure (A). The product was obtained as pale yellow liquid (3.539 g, 94% yield): R_f = 0.35 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 3288, 2945, 2129, 1740, 1515, 1241, 1141, 1005, 938, 808, 774, 682, 644; ^1H NMR (400 MHz, $CDCl_3$): δ 7.17 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 4.68 (d, *J* = 2.5 Hz, 2H), 3.63 (s, 2H), 2.47 (t, *J* = 2.5 Hz, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 137.0, 130.5, 129.4, 129.3, 77.7, 75.1, 52.4, 40.7, 21.2; HRMS (ESI TOF): Calculated for $C_{12}H_{13}O_2$ $(M + H)^+$: 189.0916, Found: 189.0912.

Prop-2-yn-1-yl 2-(3,4-dimethoxyphenyl)acetate (6k):



Compound **6k** was synthesized following the general procedure (A). The product was obtained as colourless liquid (3.98 g, 85% yield): R_f = 0.35 petroleum ether/EtOAc (70:30); IR (neat) cm^{-1}: 3276, 2944, 2836, 2126, 1737, 1593, 1513, 1456, 1370, 1259, 1133, 1021, 938, 808, 758; ^1H NMR (400 MHz, $CDCl_3$): δ 6.82 (s, 3H), 4.70 (d, *J* = 2.4 Hz, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.62 (s, 2H), 2.48 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 149.0, 148.3, 125.9, 121.5, 112.4, 111.3, 77.6, 75.1, 56.0, 55.9, 52.4, 40.6; HRMS (ESI TOF): Calculated for $C_{13}H_{14}NaO_4$ $(M + Na)^+$: 257.0790, Found: 257.0791.

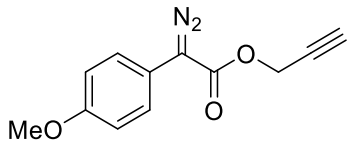
4.4.3 General procedure B for the synthesis of *α*-aryl-*α*-diazoacetates



To the stirred solution propargyl *α*-(4-methoxyphenyl)acetate **6i** (2.04 g, 10 mmol) in 15 mL acetonitrile was added 4-acetamidobenzenesulfonyl azide (2.88 g, 12 mmol) and DBU

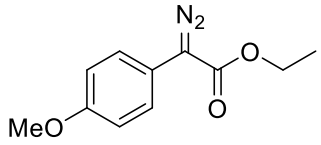
(2.24 mL, 15 mmol) at ambient temperature under inert atmosphere. The reaction mixture was stirred for 16 h at room temperature. The reaction was quenched with saturated NH_4Cl and the product was extracted with diethyl ether (30 mL x 3). The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. The extract was filtered and the filtrate was evaporated under vacuum. The crude product was purified using column chromatography over silica gel to afford propargyl *α*-(4-methoxyphenyl)-*α*-diazoacetate **1i** as orange solid (1.934 g, 84% yield).[20]

Prop-2-yn-1-yl 2-diazo-2-(4-methoxyphenyl)acetate (1i):



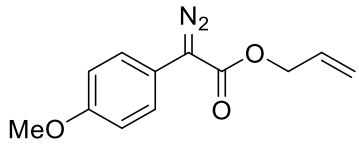
Compound **1i** was synthesized following the general procedure (B). The product was obtained as dark orange solid (1.934 g, 84% yield): R_f = 0.3 petroleum ether/EtOAc (95:5); m.p.: 68-69 ºC; IR (neat) cm^{-1}: 3289, 2949, 2837, 2081, 1694, 1609, 1573, 1510, 1240, 1142, 1022, 949, 825, 735, 680, 640; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.30 (m, 2H), 7.09 – 6.81 (m, 2H), 4.86 (d, *J* = 2.4 Hz, 2H), 3.81 (s, 3H), 2.51 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 158.3, 126.2, 116.5, 114.8, 77.8, 75.2, 55.5, 52.3; HRMS (ESI TOF): Calculated for $C_{12}H_{10}N_2NaO_3$ $(M + Na)^+$: 253.0589, Found: 253.0584.

Ethyl 2-diazo-2-(4-methoxyphenyl)acetate (1i′):



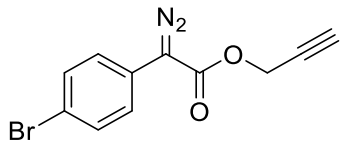
Compound **1i′** was synthesized following the general procedure (B). The product was obtained as orange liquid (1.65g, 75% yield): R_f = 0.5 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 2983, 2837, 2079, 1696, 1573, 1512, 1461, 1339, 1295, 1158, 1098, 987, 828; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.36 (m, 2H), 6.97 – 6.91 (m, 2H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 158.1, 126.1, 117.2, 114.7, 61.1, 55.5, 14.6; HRMS (ESI TOF): Calculated for $C_{11}H_{12}N_2NaO_3$ $(M + Na)^+$: 243.0746, Found: 243.0739.

Allyl 2-diazo-2-(4-methoxyphenyl)acetate (1i′′):



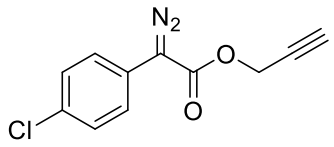
Compound **1i′′** was synthesized following the general procedure (B). The product was obtained as orange liquid (1.81 g, 78% yield): R_f = 0.5 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 2947, 2839, 2080, 1695, 1606, 1510, 1454, 1294, 1242, 1149, 1020, 930, 825, 738, 609; ^1H NMR (400 MHz, $CDCl_3$): δ 7.44 – 7.34 (m, 2H), 6.98 – 6.90 (m, 2H), 5.97 (ddt, *J* = 17.2, 10.5, 5.6 Hz, 1H), 5.38 – 5.32 (m, 1H), 5.28 – 5.25 (m, 1H), 4.76 (t, *J* = 1.4 Hz, 1H), 4.75 (t, *J* = 1.4 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4, 158.1, 132.2, 126.0, 118.3, 116.8, 114.6, 65.4, 55.4; HRMS (ESI TOF): Calculated for $C_{12}H_{12}N_2NaO_3$ $(M + Na)^+$: 255.0746, Found: 255.0739.

Prop-2-yn-1-yl 2-(4-bromophenyl)-2-diazoacetate (1b):



Compound **1b** was synthesized following the general procedure (B). The product was obtained as orange solid (2.261 g, 81% yield): R_f = 0.45 petroleum ether/EtOAc (95:5); m.p.: 57-59 °C; IR (neat) cm^{-1}: 3294, 2948, 2085, 1695, 1488, 1336, 1236, 1144, 1030, 999, 948, 813, 678, 632; ^1H NMR (400 MHz, $CDCl_3$): δ 7.54 – 7.47 (m, 2H), 7.38 – 7.33 (m, 2H), 4.87 (d, *J* = 2.3 Hz, 2H), 2.52 (t, *J* = 2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.0, 132.2, 125.5, 124.4, 119.7, 77.6, 75.5, 52.5; HRMS (ESI TOF): Calculated for $C_{11}H_7BrN_2NaO_2$ $(M + Na)^+$: 300.9589, Found: 300.9888.

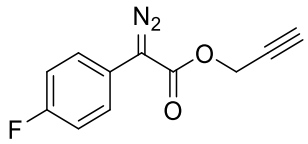
Prop-2-yn-1-yl 2-(4-chlorophenyl)-2-diazoacetate (1c):



Compound **1c** was synthesized following the general procedure (B). The product was obtained as orange solid (1.736 g, 74% yield). R_f = 0.35 petroleum ether/EtOAc (95:5); m.p.:

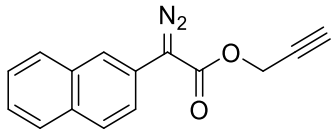
61-63 °C; IR (neat) cm^{-1}: 3295, 2949, 2086, 1697, 1492, 1336, 1276, 1237, 1146, 1093, 1005, 820, 734, 680, 637; ^1H NMR (400 MHz, $CDCl_3$): δ 7.45 – 7.39 (m, 2H), 7.38 – 7.33 (m, 2H), 4.87 (d, *J* = 2.5 Hz, 2H), 2.52 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 131.9, 129.3, 125.3, 123.8, 77.6, 75.4, 52.5; HRMS (ESI TOF): Calculated for $C_{11}H_7ClN_2NaO_2$ $(M + Na)^+$: 257.0094, Found: 257.0097

Prop-2-yn-1-yl 2-diazo-2-(4-fluorophenyl)acetate (1d):



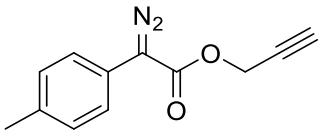
Compound **1d** was synthesized following the general procedure (B). The product was obtained as yellow solid (1.833 g, 84% yield). R_f = 0.3 petroleum ether/EtOAc (95:5); m.p.: 62-64 °C; IR (neat) cm^{-1}: 3298, 2950, 2086, 1696, 1508, 1339, 1286, 1233, 1145, 1033, 829, 683, 642; ^1H NMR (400 MHz, $CDCl_3$): δ 7.51 – 7.38 (m, 2H), 7.17 – 7.02 (m, 2H), 4.87 (d, *J* = 2.5 Hz, 2H), 2.52 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4, 161.3 (d, *J* = 246.7 Hz), 126.1 (d, *J* = 8.0 Hz), 120.9 (d, *J* = 3.2 Hz), 116.2 (d, *J* = 22.0 Hz), 77.7, 75.4, 52.4; HRMS (ESI TOF): Calculated for $C_{11}H_7FN_2NaO_2$ $(M + Na)^+$: 241.0389, Found: 241.0384.

Prop-2-yn-1-yl 2-diazo-2-(naphthalen-2-yl)acetate (1g):



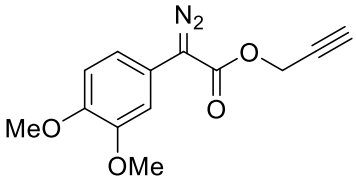
Compound **1g** was synthesized following the general procedure (B). The product was obtained as pale orange solid (1.927 g, 77% yield). R_f = 0.35 petroleum ether/EtOAc (95:5); m.p.: 82-84 °C; IR (neat) cm^{-1}: 3291, 3057, 2947, 2083, 1698, 1323, 1248, 1147, 1121, 1038, 895, 852, 812, 736, 680, 639; ^1H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 1.7 Hz, 1H), 7.92 – 7.69 (m, 3H), 7.58 – 7.37 (m, 3H), 4.91 (d, *J* = 2.5 Hz, 2H), 2.53 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 133.7, 131.7, 128.9, 127.8, 127.8, 126.8, 126.0, 122.8, 122.3, 121.9, 77.7, 75.4, 52.4; HRMS (ESI TOF): Calculated for $C_{15}H_{10}N_2NaO_2$ $(M + Na)^+$: 273.0640, Found: 273.0640.

Prop-2-yn-1-yl 2-diazo-2-(p-tolyl)acetate (1h):



Compound **1h** was synthesized following the general procedure (B). The product was obtained as orange solid (1.392 g, 65% yield): R_f = 0.35 petroleum ether/EtOAc (95:5); m.p.: 52-54 ^oC; IR (neat) cm^{-1}: 3293, 2947, 2084, 1699, 1567, 1514, 1242, 1154, 1037, 949, 811, 771, 735, 680, 640; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 4.86 (d, J = 2.5 Hz, 2H), 2.51 (t, J = 2.5 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 136.1, 129.9, 124.3, 121.8, 77.8, 75.2, 52.3, 21.1; HRMS (ESI TOF): Calculated for $C_{12}H_{10}N_2NaO_2$ $(M + Na)^+$: 237.0640, Found: 237.0635.

Prop-2-yn-1-yl 2-diazo-2-(3,4-dimethoxyphenyl)acetate (1k):



Compound **1k** was synthesized following the general procedure (B). The product was obtained as pale yellow liquid (1.69 g, 65% yield): R_f = 0.3 petroleum ether/EtOAc (90:10); IR (neat) cm^{-1}: 3230, 2939, 2840, 2087, 1678, 1581, 1517, 1455, 1385, 1233, 1139, 1051, 951, 866, 793, 732; ^1H NMR (400 MHz, $CDCl_3$): δ 7.19 (d, J = 1.9 Hz, 1H), 7.00 – 6.79 (m, 2H), 4.87 (d, J = 2.5 Hz, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 2.52 (t, J = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 149.6, 147.6, 117.0, 116.6, 111.8, 108.5, 77.8, 75.3, 56.1, 56.0, 52.3; HRMS (ESI TOF): Calculated for $C_{13}H_{13}N_2O_4$ $(M + Na)^+$: 261.0875, Found: 261.0875.

4.4.4 General Procedure C1 for optimization of reaction conditions

A mixture of 5 mol% of catalyst and 1,3-diphenylpropane-1,3-dione (1,3-diketone) **2a** was stirred in 2 mL DCE at room temperature in 25 mL two necked RB flask under inert atmosphere for 5 minutes. Then *α*-aryl-*α*-diazoacetate **1** (0.5 mmol) in 1 mL of DCE was added to above reaction mixture drop wise over 30 minutes. Then the reaction mixture was stirred at room temperature over 4-6 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The crude

product obtained was purified by column chromatography over silica gel to afford the corresponding desired product **3** (see Table 4.1).

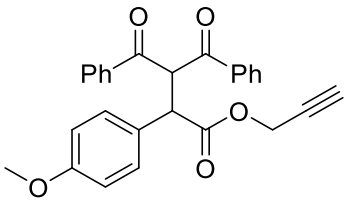
4.4.5 General Procedure C2 for the screening of solvents

A mixture of $Sc(OTf)_3$ (1 to 5 mol%) and 1,3-diphenylpropane-1,3-dione **2a** (1.5 to 5 equiv.) was stirred in 2 mL solvent at room temperature in 25mL two-necked RB flask under inert atmosphere for 5 minutes. Then propargyl 2-diazo-2-(4-methoxyphenyl)acetate **1i** (0.115 g, 0.5 mmol) in 1 mL of solvent was added to above reaction mixture dropwise over 30 minutes. Then the reaction mixture was stirred at room temperature over 2.5-12 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The crude product obtained was purified by column chromatography over silica gel to furnish the desired product **3ia** (see Table 4.2).

4.4.6 General procedure D for C-H bond functionalization of 1,3-diketones

A mixture of $Sc(OTf)_3$ (12.3 mg, 5 mol%) and 1,3-diphenylpropane-1,3-dione **2a** (0.168 g, 0.75 mmol) was stirred in 2 mL DCE at room temperature in 25 mL two-necked RB flask under inert atmosphere for 5 minutes. Then propargyl *α*-(4-methoxyphenyl)-*α*-diazoacetate **1i** (0.115 g, 0.5 mmol) in 1 mL of DCE was added to the reaction mixture dropwise over 30 minutes, and then the reaction mixture was stirred at room temperature over 4 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The crude product obtained was purified by column chromatography over silica gel to furnish the desired product **3ia** (0.205 g, 96% yield). The slightly excess 1,3-diketone **2a** was recovered during the purification.

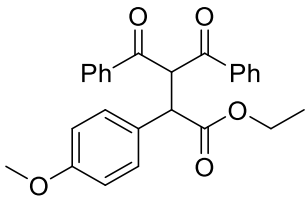
Prop-2-yn-1-yl 3-benzoyl-2-(4-methoxyphenyl)-4-oxo-4-phenylbutanoate (3ia):



Compound **3ia** was synthesized following the general procedure (D). The product was obtained as a white solid (0.205 g, 96% yield): R_f = 0.3 petroleum ether/EtOAc (80:20); m.p.: 171-173 ^oC; IR (neat) cm^{-1}: 3289, 2949, 2122, 1737, 1692, 1599, 1511, 1448, 1373,

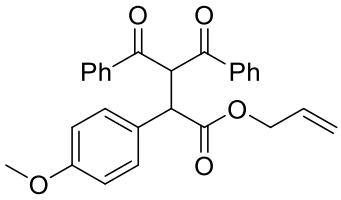
1260, 1162, 831, 762, 689; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 – 7.90 (m, 2H), 7.66 (dd, *J* = 5.2, 3.3 Hz, 2H), 7.52 – 7.41 (m, 2H), 7.37 – 7.25 (m, 4H), 7.19 – 7.14 (m, 2H), 6.74 – 6.64 (m, 2H), 6.05 (d, *J* = 11.1 Hz, 1H), 4.81 (d, *J* = 11.1 Hz, 1H), 4.72 – 4.60 (m, 2H), 3.67 (s, 3H), 2.40 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.6, 194.3, 172.2, 159.4, 136.7, 136.3, 133.6, 133.5, 129.8, 128.9, 128.8, 128.7, 126.5, 114.4, 77.3, 75.3, 61.2, 55.3, 53.0, 51.4; HRMS (ESI TOF): Calculated for $C_{27}H_{22}NaO_5$ $(M + Na)^+$: 449.1365, Found: 449.1360.

Ethyl 3-benzoyl-2-(4-methoxyphenyl)-4-oxo-4-phenylbutanoate (3i′a):



Compound **3i′a** was synthesized following the general procedure (D). The product was obtained as white solid (0.158 g, 76% yield): R_f = 0.4 petroleum ether/EtOAc (80:20); m.p.: 175-177 ^{o}C; IR (neat) cm^{-1}: 2968, 2109, 1689, 1596, 1511, 1449, 1260, 1172, 1028, 980, 831, 759, 690; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (dt, *J* = 8.5, 1.6 Hz, 2H), 7.68 (dt, *J* = 8.5, 1.6 Hz, 2H), 7.51 – 7.41 (m, 2H), 7.38 – 7.32 (m, 2H), 7.28 (ddd, *J* = 8.5, 3.1, 1.3 Hz, 2H), 7.21 – 7.15 (m, 2H), 6.75 – 6.64 (m, 2H), 6.07 (d, *J* = 11.2 Hz, 1H), 4.76 (d, *J* = 11.2 Hz, 1H), 4.24 – 4.01 (m, 2H), 3.68 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.8, 194.5, 173.0, 159.2, 136.7, 136.4, 133.6, 133.4, 129.7, 128.9, 128.8, 128.8, 128.6, 127.3, 114.3, 61.5, 61.2, 55.3, 51.8, 14.1; HRMS (ESI TOF): Calculated for $C_{26}H_{25}O_5$ $(M + H)^+$: 417.1702, Found: 417.1708.

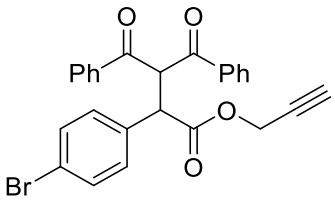
Allyl 3-benzoyl-2-(4-methoxyphenyl)-4-oxo-4-phenylbutanoate (3i′′a):



Compound **3i′′a** was synthesized following the general procedure (D). The product was obtained as white solid (0.167 g, 78% yield): R_f = 0.4 petroleum ether/EtOAc (80:20); m.p.: 175-177 ^{o}C; IR (neat) cm^{-1}: 2943, 2841, 2110, 1729, 1692, 1599, 1511, 1449, 1258,

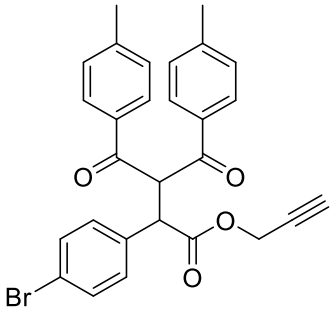
1168, 1029, 991, 832, 763, 691; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 – 7.90 (m, 2H), 7.72 – 7.64 (m, 2H), 7.51 – 7.40 (m, 2H), 7.38 – 7.32 (m, 2H), 7.31 – 7.25 (m, 2H), 7.20 – 7.14 (m, 2H), 6.72 – 6.66 (m, 2H), 6.08 (d, *J* = 11.2 Hz, 1H), 5.87 – 5.73 (m, 1H), 5.21-5.12 (m, 2H), 4.81 (d, *J* = 11.2 Hz, 1H), 4.57 (qdt, *J* = 13.4, 5.7, 1.5 Hz, 2H), 3.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.7, 194.4, 172.7, 159.3, 136.7, 136.4, 133.6, 133.4, 131.9, 129.8, 128.9, 128.8, 128.8, 128.6, 127.1, 118.2, 114.3, 65.9, 61.2, 55.3, 51.7; HRMS (ESI TOF): Calculated for $C_{27}H_{24}NaO_5$ $(M + Na)^+$: 451.1521, Found: 451.1530.

Prop-2-yn-1-yl 3-benzoyl-2-(4-bromophenyl)-4-oxo-4-phenylbutanoate (3ba):



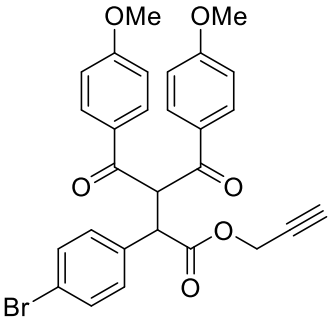
Compound **3ba** was synthesized following the general procedure (D). The product was obtained as white solid (0.188 g, 79% yield): R_f = 0.5 petroleum ether/EtOAc (80:20); m.p.: 111-113 ºC; IR(neat) cm^{-1}: 3292, 3065, 2946, 2125, 1739, 1691, 1592, 1487, 1445, 1371, 1274, 1164, 1077, 1003, 819, 763, 688; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (dt, *J* = 8.5, 1.5 Hz, 2H), 7.67 (dt, *J* = 8.5, 1.5 Hz, 2H), 7.49 (dddt, *J* = 11.1, 9.6, 7.1, 1.3 Hz, 2H), 7.39 – 7.28 (m, 6H), 7.17 – 7.10 (m, 2H), 6.04 (d, *J* = 11.2 Hz, 1H), 4.83 (d, *J* = 11.2 Hz, 1H), 4.73 – 4.61 (m, 2H), 2.42 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.1, 193.9, 171.6, 136.4, 136.1, 133.8, 133.8, 133.7, 132.1, 130.4, 128.9, 128.9, 128.8, 128.8, 122.4, 77.0, 75.4, 60.8, 53.2, 51.6; HRMS (ESI TOF): Calculated for $C_{26}H_{19}BrNaO_4$ $(M + Na)^+$: 497.0364, Found: 497.0355.

Prop-2-yn-1-yl 2-(4-bromophenyl)-3-(4-methylbenzoyl)-4-oxo-4-(p-tolyl)butanoate (3bb):



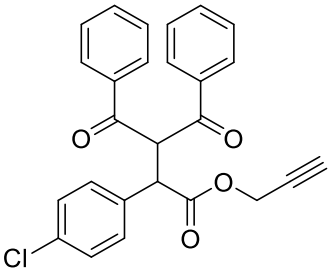
Compound **3bb** was synthesized following the general procedure (D). The product was obtained as white solid (0.156 g, 62% yield): R_f = 0.55 petroleum ether/EtOAc (80:20); m.p.: 152-154 ^oC; IR(neat) cm^{-1}: 3292, 2942, 2843, 2121, 1738, 1680, 1595, 1504, 1259, 1161, 1020, 834, 753; ^1H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.3 Hz, 2H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.33 – 7.27 (m, 2H), 7.13 (dt, *J* = 11.3, 7.9 Hz, 6H), 5.97 (d, *J* = 11.2 Hz, 1H), 4.81 (d, *J* = 11.2 Hz, 1H), 4.71 – 4.60 (m, 2H), 2.41 (t, *J* = 2.4 Hz, 1H), 2.34 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.7, 193.6, 171.7, 144.9, 144.8, 133.9, 133.8, 133.6, 132.1, 130.4, 129.5, 129.1, 129.0, 122.3, 77.4, 75.4, 60.6, 53.1, 51.6, 21.8; HRMS (ESI TOF): Calculated for $C_{28}H_{23}BrNaO_4$ $(M + Na)^+$: 525.0677, Found: 525.0681.

Prop-2-yn-1-yl 2-(4-bromophenyl)-3-(4-methoxybenzoyl)-4-(4-methoxyphenyl)-4-oxobutanoate (3bc):



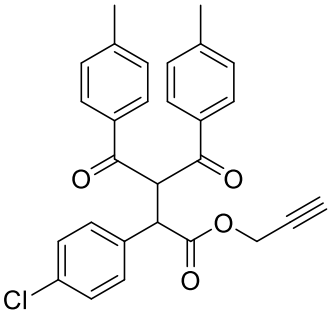
Compound **3bc** was synthesized following the general procedure (D). The product was obtained as white solid (0.166 g, 62% yield): R_f = 0.3 petroleum ether/EtOAc (70:30); m.p.: 111-113 ^oC; IR(neat) cm^{-1}: 3291, 3016, 2840, 2119, 1735, 1680, 1502, 1258, 1163, 832, 753, 674, 639; ^1H NMR (400 MHz, $CDCl_3$): δ 7.97 – 7.91 (m, 2H), 7.74 – 7.66 (m, 2H), 7.30 (t, *J* = 5.4 Hz, 2H), 7.17 – 7.10 (m, 2H), 6.89 – 6.74 (m, 4H), 5.89 (d, *J* = 11.3 Hz, 1H), 4.80 (d, *J* = 11.3 Hz, 1H), 4.73 – 4.60 (m, 2H), 3.82 (s, 3H), 3.80 (s, 3H), 2.41 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.5, 171.7, 164.0, 164.0, 133.9, 132.0, 131.3, 131.3, 130.4, 129.3, 129.0, 122.2, 114.0, 77.1, 75.4, 60.5, 55.6, 55.6, 53.1, 51.6; HRMS (ESI TOF): Calculated for $C_{28}H_{24}BrO_6$ $(M + H)^+$: 535.756, Found: 535.0750.

Prop-2-yn-1-yl 3-benzoyl-2-(4-chlorophenyl)-4-oxo-4-phenylbutanoate (3ca):



Compound **3ca** was synthesized following the general procedure (D). The product was obtained as white solid (0.129 g, 60% yield): R_f = 0.55 petroleum ether/EtOAc (80:20); m.p.: 116-118 ^oC; IR (neat) cm^{-1}: 3295, 3065, 2125, 1738, 1690, 1592, 1491, 1446, 1371, 1272, 1159, 1090, 1002, 824, 759, 688; ^1H NMR (400 MHz, $CDCl_3$): δ 7.93 (dt, *J* = 8.5, 1.6 Hz, 2H), 7.70 – 7.64 (m, 2H), 7.55 – 7.43 (m, 2H), 7.40 – 7.29 (m, 4H), 7.23 – 7.12 (m, 4H), 6.04 (d, *J* = 11.2 Hz, 1H), 4.84 (d, *J* = 11.2 Hz, 1H), 4.73 – 4.59 (m, 2H), 2.42 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.1, 194.0, 171.7, 136.4, 136.1, 134.2, 133.8, 133.8, 133.1, 130.1, 129.2, 128.9, 128.9, 128.8, 128.8, 77.0, 75.4, 60.8, 53.2, 51.5; HRMS (ESI TOF): Calculated for $C_{26}H_{19}ClNaO_4$ $(M + Na)^+$: 453.0870, Found: 453.0870.

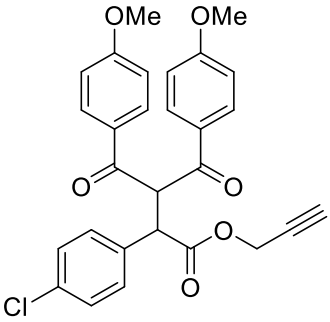
Prop-2-yn-1-yl 2-(4-chlorophenyl)-3-(4-methylbenzoyl)-4-oxo-4-(p-tolyl)butanoate (3cb):



Compound **3cb** was synthesized following the general procedure (D). The product was obtained as white solid (0.092 g, 40% yield): R_f = 0.55 petroleum ether/EtOAc (80:20); m.p.: 145-147 ^oC; IR(neat) cm^{-1}: 3295, 3035, 2938, 2124, 1738, 1688, 1605, 1491, 1443, 1276, 1161, 1091, 1006, 914, 821, 756, 677, 639; ^1H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.3 Hz, 2H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.23 – 7.17 (m, 2H), 7.17 – 7.07 (m, 6H), 5.98 (d, *J* = 11.2 Hz, 1H), 4.82 (d, *J* = 11.2 Hz, 1H), 4.72 – 4.59 (m, 2H), 2.41 (t, *J* = 2.5 Hz, 1H), 2.33 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.7, 193.6, 171.7, 144.9, 144.7, 134.1,

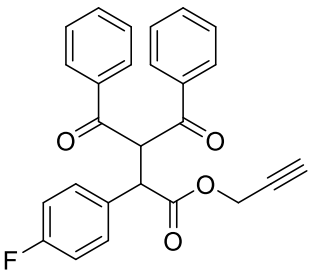
133.9, 133.6, 133.3, 130.1, 129.5, 129.1, 129.1, 129.0, 77.1, 75.4, 60.6, 53.1, 51.5, 21.8; HRMS (ESI TOF): Calculated for $C_{28}H_{24}ClO_4$ $(M + H)^+$: 459.1363, Found: 459.1370.

Prop-2-yn-1-yl 2-(4-chlorophenyl)-3-(4-methoxybenzoyl)-4-(4-methoxyphenyl)-4-oxobutanoate (3cc):



Compound **3cc** was synthesized following the general procedure (D). The product was obtained as white solid (0.096 g, 39% yield). R_f = 0.3 petroleum ether/EtOAc (80:20); m.p.: 96-98 ^oC; IR (neat) cm^{-1}: 3293, 2931, 2846, 2122, 1738, 1680, 1596, 1505, 1457, 1422, 1259, 1611, 1092, 1022, 912, 834, 754, 679, 639; ^1H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 8.8 Hz, 2H), 7.70 (d, *J* = 8.8 Hz, 2H), 7.17 (q, *J* = 8.5 Hz, 4H), 6.81 (dd, *J* = 19.2, 8.8 Hz, 4H), 5.89 (d, *J* = 11.2 Hz, 1H), 4.81 (d, *J* = 11.2 Hz, 1H), 4.74 – 4.59 (m, 2H), 3.82 (s, 3H), 3.80 (s, 3H), 2.41 (t, *J* = 2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.5, 171.8, 164.0, 164.0, 134.0, 133.4, 131.3, 131.3, 130.0, 129.4, 129.1, 114.0, 77.4, 75.3, 60.6, 55.6, 55.6, 53.1, 51.5; HRMS (ESI TOF): Calculated for $C_{28}H_{24}ClO_6$ $(M + H)^+$: 491.1261, Found: 491.1257.

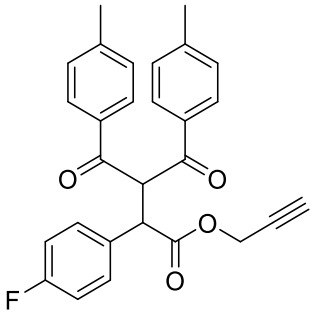
Prop-2-yn-1-yl 3-benzoyl-2-(4-fluorophenyl)-4-oxo-4-phenylbutanoate (3da):



Compound **3da** was synthesized following the general procedure (D). The product was obtained as white solid (0.131 g, 63% yield). R_f = 0.5 petroleum ether/EtOAc (80:20); m.p.: 92-94 ^oC; IR (neat) cm^{-1}: 3296, 3068, 2934, 1736, 1690, 1597, 1508, 1444, 1372, 1274, 1227, 1160, 1083, 997, 834, 760, 687; ^1H NMR (400 MHz, $CDCl_3$): δ 7.97 – 7.89 (m, 2H),

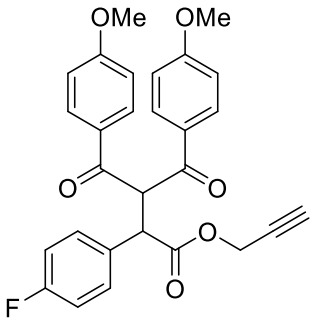
7.71 – 7.63 (m, 2H), 7.47 (dddd, *J* = 10.3, 8.6, 2.4, 1.2 Hz, 2H), 7.38 – 7.20 (m, 6H), 6.89 – 6.81 (m, 2H), 6.06 (d, *J* = 11.2 Hz, 1H), 4.84 (d, *J* = 11.2 Hz, 1H), 4.73 – 4.61 (m, 2H), 2.41 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.3, 194.0, 171.8, 162.5 (d, *J* = 247.4 Hz), 136.5, 136.2, 133.7, 133.7, 130.4 (d, *J* = 8.2 Hz), δ 130.4 (d, *J* = 3.5 Hz), 128.9, 128.8, 128.7, 115.9 (d, *J* = 21.6 Hz), 77.1, 75.3, 61.0, 53.1, 51.4; HRMS (ESI TOF): Calculated for $C_{26}H_{19}FNaO_4$ $(M + Na)^+$: 437.1165, Found: 437.1169.

Prop-2-yn-1-yl 2-(4-fluorophenyl)-3-(4-methylbenzoyl)-4-oxo-4-(p-tolyl)butanoate (3db):



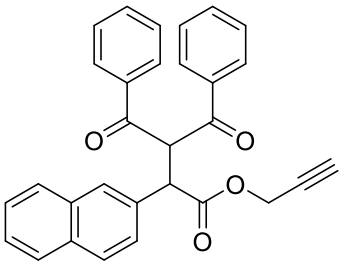
Compound **3db** was synthesized following the general procedure (D). The product was obtained as white solid (0.1 g, 45% yield): R_f = 0.5 petroleum ether/EtOAc (80:20); m.p.: 126-128 ^{o}C; IR (neat) cm^{-1}: 3296, 3031, 1737, 1686, 1604, 1490, 1412, 1372, 1273, 1158, 1090, 1005, 913, 820, 752, 674, 639; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.3 Hz, 2H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.25 – 7.19 (m, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 6.90 – 6.81 (m, 2H), 5.98 (d, *J* = 11.2 Hz, 1H), 4.82 (d, *J* = 11.2 Hz, 1H), 4.73 – 4.61 (m, 2H), 2.40 (t, *J* = 2.5 Hz, 1H), 2.33 (s, 6H); ^{13}C NMR (400 MHz, $CDCl_3$): δ 193.8, 193.6, 171.9, 162.5 (d, *J* = 247.1 Hz), 144.8, 144.7, 134.1, 133.7, 130.6 (d, *J* = 3.3 Hz), 130.4 (d, *J* = 8.2 Hz), 129.5, 129.5, 129.1, 129.0, 115.9 (d, *J* = 21.6 Hz), 77.2, 75.3, 60.8, 53.0, 51.5, 21.7; HRMS (ESI TOF): Calculated for $C_{28}H_{24}FO_4$ $(M + H)^+$: 443.1659, Found: 443.1660.

Prop-2-yn-1-yl 2-(4-fluorophenyl)-3-(4-methoxybenzoyl)-4-(4-methoxyphenyl)-4-oxobutanoate (3dc):



Compound **3dc** was synthesized following the general procedure (D). The product was obtained as white solid (0.133 g, 56% yield): R_f = 0.3 petroleum ether/EtOAc (70:30); m.p.: 85-87 ^oC; IR (neat) cm^{-1}: 3294, 2944, 2843, 2122, 1738, 1681, 1598, 1509, 1458, 1424, 1312, 1262, 1163, 911, 838, 755, 643; ^1H NMR (400 MHz, $CDCl_3$): δ 8.00 – 7.87 (m, 2H), 7.76 – 7.63 (m, 2H), 7.26 – 7.18 (m, 2H), 6.91 – 6.73 (m, 6H), 5.90 (d, *J* = 11.2 Hz, 1H), 4.81 (d, *J* = 11.2 Hz, 1H), 4.72 – 4.60 (m, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 2.41 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.7, 192.6, 172.0, 164.0, 164.0, 162.5 (d, *J* = 247.0 Hz), 131.3 (d, *J* = 2.9 Hz), 130.7 (d, *J* = 3.3 Hz), 130.4, 130.3, 129.5, 129.2, 115.9, 115.7, 114.0 (d, *J* = 4.8 Hz), 77.2, 75.3, 60.8, 55.6, 55.6, 53.0, 51.4; HRMS (ESI TOF): Calculated for $C_{28}H_{24}FO_6$ $(M + H)^+$: 475.1557, Found: 475.1561.

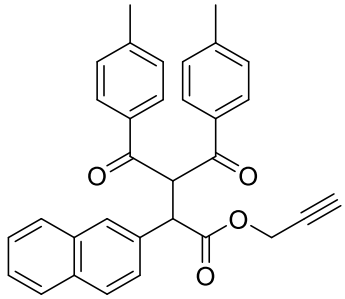
Prop-2-yn-1-yl 3-benzoyl-2-(naphthalen-2-yl)-4-oxo-4-phenylbutanoate (3ga):



Compound **3ga** was synthesized following the general procedure (D). The product was obtained as white solid (0.174 g, 78% yield). R_f = 0.5 petroleum ether/EtOAc (80:20); m.p.: 158-160 ^oC; IR (neat) cm^{-1}: 3295, 3031, 2953, 2124, 1737, 1687, 1604, 1442, 1271, 1159, 1086, 1000, 963, 815, 750, 647; ^1H NMR (400 MHz, $CDCl_3$): δ 8.03 – 7.92 (m, 2H), 7.75 – 7.58 (m, 6H), 7.53 – 7.45 (m, 1H), 7.44 – 7.27 (m, 6H), 7.19 – 7.11 (m, 2H), 6.20 (d, *J* = 11.2 Hz, 1H), 5.04 (d, *J* = 11.2 Hz, 1H), 4.74 – 4.60 (m, 2H), 2.38 (t, *J* = 2.5 Hz, 1H); ^{13}C

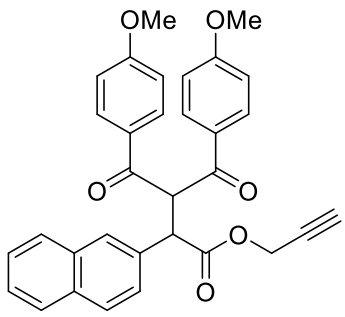
NMR (100 MHz, $CDCl_3$): δ 194.3, 194.2, 172.0, 136.6, 136.4, 133.7, 133.4, 133.4, 132.9, 132.0, 129.0, 128.9, 128.8, 128.7, 128.5, 128.3, 128.0, 127.7, 126.4, 126.3, 126.0, 77.2, 75.3, 61.2, 53.1, 52.4; HRMS (ESI TOF): Calculated for $C_{30}H_{22}NaO_4$ $(M + Na)^+$: 469.1416, Found: 469.1407.

Prop-2-yn-1-yl 3-(4-methylbenzoyl)-2-(naphthalen-2-yl)-4-oxo-4-(p-tolyl)butanoate (3gb):



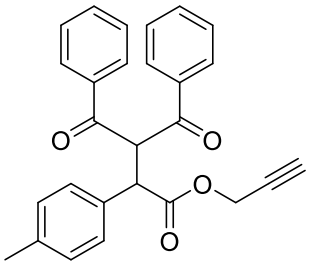
Compound **3gb** was synthesized following the general procedure (D). The product was obtained as white solid (0.185 g, 78% yield): R_f = 0.55 petroleum ether/EtOAc (80:20); m.p.: 157-159 ^oC; IR(neat) cm^{-1}: 3294, 3031, 2928, 2123, 1737, 1686, 1604, 1271, 1160, 1086, 1001, 964, 915, 749, 646; ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 8.2 Hz, 2H), 7.74 – 7.64 (m, 4H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.45 – 7.35 (m, 3H), 7.16 (d, *J* = 8.4 Hz, 2H), 6.96 (d, *J* = 8.2 Hz, 2H), 6.14 (d, *J* = 11.2 Hz, 1H), 5.02 (d, *J* = 11.2 Hz, 1H), 4.73 – 4.61 (m, 2H), 2.38 (t, *J* = 2.5 Hz, 1H), 2.33 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.9, 193.8, 172.1, 144.6, 144.5, 134.1, 133.8, 133.3, 132.9, 132.2, 129.5, 129.3, 129.1, 128.9, 128.8, 128.3, 128.0, 127.6, 126.3, 126.2, 126.0, 77.2, 75.3, 60.9, 53.0, 52.3, 21.8, 21.6; HRMS (ESI TOF): Calculated for $C_{32}H_{26}NaO_4$ $(M + Na)^+$: 497.1729, Found: 497.1731.

Prop-2-yn-1-yl 3-(4-methoxybenzoyl)-4-(4-methoxyphenyl)-2-(naphthalen-2-yl)-4-oxobutanoate (3gc):



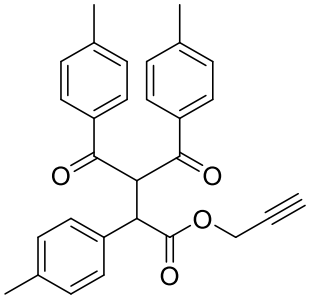
Compound **3gc** was synthesized following the general procedure (D). The product was obtained as white solid (0.205 g, 81% yield): R_f = 0.3 petroleum ether/EtOAc (70:30); m.p.: 72-74 °C; IR(neat) cm^{-1}: 3293, 3017, 2938, 2843, 2121, 1737, 1682, 1597, 1510, 1457, 1423, 1371, 1260, 1161, 1086, 1025, 838, 751, 641; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.8 Hz, 2H), 7.68 (dd, *J* = 13.5, 6.9 Hz, 6H), 7.47 – 7.34 (m, 3H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.64 (d, *J* = 8.8 Hz, 2H), 6.05 (d, *J* = 11.2 Hz, 1H), 5.01 (d, *J* = 11.2 Hz, 1H), 4.74 – 4.58 (m, 2H), 3.80 (s, 3H), 3.71 (s, 3H), 2.37 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.8, 192.7, 172.2, 164.0, 163.7, 133.4, 132.9, 132.3, 131.4, 131.2, 129.6, 129.3, 128.7, 128.2, 128.0, 127.7, 126.3, 126.2, 126.1, 114.0, 113.8, 77.3, 75.2, 60.9, 55.6, 55.5, 53.0, 52.3; HRMS (ESI TOF): Calculated for $C_{32}H_{27}O_6$ $(M + H)^+$: 507.1808, Found: 507.1807.

Prop-2-yn-1-yl 3-benzoyl-4-oxo-4-phenyl-2-(p-tolyl)butanoate (3ha):



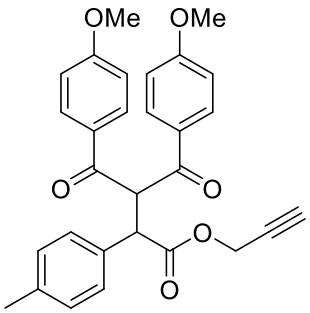
Compound **3ha** was synthesized following the general procedure (D). The product was obtained as white solid (0.187 g, 91% yield): R_f = 0.35 petroleum ether/EtOAc (70:30); m.p.: 180-182 °C; IR (neat) cm^{-1}: 3291, 3059, 2928, 2123, 1734, 1690, 1591, 1511, 1445, 1372, 1274, 1158, 1083, 990, 812, 760, 686, 648; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 – 7.89 (m, 2H), 7.70 – 7.61 (m, 2H), 7.53 – 7.40 (m, 2H), 7.34 (dd, *J* = 10.7, 4.9 Hz, 2H), 7.27 (dd, *J* = 10.3, 5.3 Hz, 2H), 7.13 (d, *J* = 8.1 Hz, 2H), 6.97 (d, *J* = 7.9 Hz, 2H), 6.06 (d, *J* = 11.2 Hz, 1H), 4.82 (d, *J* = 11.2 Hz, 1H), 4.71 – 4.60 (m, 2H), 2.40 (t, *J* = 2.5 Hz, 1H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.5, 194.3, 172.2, 137.9, 136.7, 136.4, 133.6, 133.4, 131.5, 129.6, 128.9, 128.8, 128.8, 128.6, 128.6, 77.3, 75.2, 61.3, 53.0, 51.9, 21.1; HRMS (ESI TOF): Calculated for $C_{27}H_{23}O_4$ $(M + H)^+$: 411.1596, Found: 411.1596.

Prop-2-yn-1-yl 3-(4-methylbenzoyl)-4-oxo-2,4-di-p-tolylbutanoate (3hb):



Compound **3hb** was synthesized following the general procedure (D). The product was obtained as white solid (0.175 g, 80% yield): R_f = 0.5 petroleum ether/EtOAc (80:20); m.p.: 148-150 ^{o}C; IR (neat) cm^{-1}: 3290, 3031, 2926, 2125, 1737, 1687, 1605, 1512, 1274, 1160, 1084, 994, 816, 751, 675, 642; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.3 Hz, 2H), 7.58 (d, *J* = 8.3 Hz, 2H), 7.13 (d, *J* = 8.1 Hz, 4H), 7.07 (d, *J* = 8.1 Hz, 2H), 6.97 (d, *J* = 7.9 Hz, 2H), 5.99 (d, *J* = 11.2 Hz, 1H), 4.81 (d, *J* = 11.2 Hz, 1H), 4.71 – 4.58 (m, 2H), 2.39 (t, *J* = 2.4 Hz, 1H), 2.32 (s, 3H), 2.31 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.0, 193.9, 172.2, 144.5, 144.4, 137.7, 134.3, 133.9, 131.7, 129.6, 129.4, 129.3, 129.1, 129.0, 128.5, 77.4, 75.2, 61.1, 52.9, 51.9, 21.7, 21.7, 21.1; HRMS (ESI TOF): Calculated for $C_{29}H_{26}NaO_4$ $(M + Na)^+$: 461.1729, Found: 461.1740.

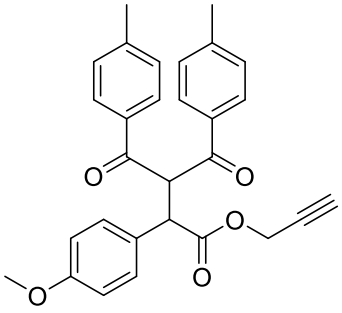
Prop-2-yn-1-yl 3-(4-methoxybenzoyl)-4-(4-methoxyphenyl)-4-oxo-2-(p-tolyl)butanoate (3hc):



Compound **3hc** was synthesized following the general procedure (D). The product was obtained as white solid (0.165 g, 70% yield). R_f = 0.3 petroleum ether/EtOAc (70:30); m.p.: 137-139 ^{o}C; IR (neat) cm^{-1}: 3291, 3016, 2940, 2122, 1737, 1681, 1597, 1510, 1456, 1424, 1259, 1160, 1024, 910, 834, 753,640; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 – 7.90 (m, 2H), 7.73 – 7.65 (m, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 6.97 (d, *J* = 8.0 Hz, 2H), 6.85 – 6.79 (m, 2H), 6.79 – 6.71 (m, 2H), 5.90 (d, *J* = 11.3 Hz, 1H), 4.80 (d, *J* = 11.3 Hz, 1H), 4.71 – 4.59

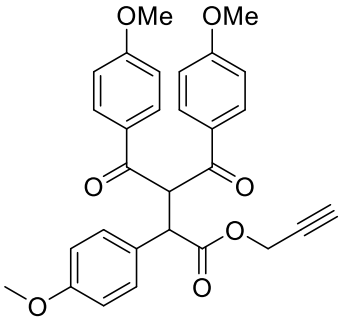
(m, 2H), 3.80 (s, 3H), 3.80 (s, 3H), 2.40 (t, *J* = 2.5 Hz, 1H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.9, 172.3, 163.9, 163.8, 137.7, 131.8, 131.3, 129.8, 129.6, 129.4, 128.5, 114.0, 113.9, 77.4, 75.1, 61.1, 55.6, 52.9, 51.8, 21.1; HRMS (ESI TOF): Calculated for $C_{29}H_{26}NaO_6$ $(M + Na)^+$: 493.1627, Found: 493.1622.

Prop-2-yn-1-yl 2-(4-methoxyphenyl)-3-(4-methylbenzoyl)-4-oxo-4-(p-tolyl)butanoate (3ib):



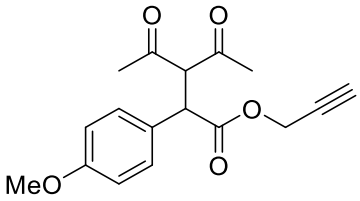
Compound **3ib** was synthesized following the general procedure (D). The product was obtained as white solid (0.22 g, 97% yield): R_f = 0.35 petroleum ether/EtOAc (80:20); m.p.: 140-142 ^{o}C; IR (neat) cm^{-1}: 3290, 3030, 2946, 2122, 1736, 1687, 1605, 1511, 1448, 1372, 1257, 1160, 1083, 1028, 823, 753, 641; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.3 Hz, 2H), 7.59 (d, *J* = 8.3 Hz, 2H), 7.20 – 7.11 (m, 4H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.73 – 6.66 (m, 2H), 5.98 (d, *J* = 11.2 Hz, 1H), 4.79 (d, *J* = 11.2 Hz, 1H), 4.65 (dd, *J* = 2.5, 1.1 Hz, 2H), 3.68 (s, 3H), 2.39 (t, *J* = 2.5 Hz, 1H), 2.32 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.1, 193.9, 172.3, 159.3, 144.5, 144.4, 134.3, 133.9, 129.8, 129.5, 129.4, 129.1, 129.0, 126.7, 114.4, 77.4, 75.2, 61.1, 55.3, 52.9, 51.4, 21.7; HRMS (ESI TOF): Calculated for $C_{29}H_{26}NaO_5$ $(M + Na)^+$: 477.1678, Found: 477.1681.

Prop-2-yn-1-yl 3-(4-methoxybenzoyl)-2,4-bis(4-methoxyphenyl)-4-oxobutanoate(3ic):



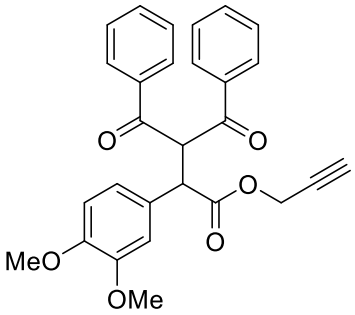
Compound **3ic** was synthesized following the general procedure (D). The product was obtained as white solid (0.236 g, 97% yield): R_f = 0.45 petroleum ether/EtOAc (60:40); m.p.: 131-133 ^oC; IR (neat) cm^{-1}: 3289, 2942, 2842, 2122, 1736, 1680, 1595, 1510, 1457, 1253, 1158, 1024, 911, 834, 753, 642; ^1H NMR (400 MHz, $CDCl_3$): δ 7.97 – 7.90 (m, 2H), 7.74 – 7.66 (m, 2H), 7.20 – 7.13 (m, 2H), 6.85 – 6.80 (m, 2H), 6.79 – 6.74 (m, 2H), 6.73 – 6.67 (m, 2H), 5.89 (d, *J* = 11.3 Hz, 1H), 4.78 (d, *J* = 11.3 Hz, 1H), 4.66 (dd, *J* = 2.5, 0.8 Hz, 2H), 3.81 (s, 3H), 3.79 (s, 3H), 3.69 (s, 3H), 2.40 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.9, 192.9, 172.3, 163.9, 163.8, 159.3, 131.3, 129.8, 129.4, 126.8, 114.3, 114.0, 113.9, 77.4, 75.1, 61.1, 55.6, 55.3, 52.9, 51.4; HRMS (ESI TOF): Calculated for $C_{29}H_{26}NaO_7$ $(M + Na)^+$: 509.1576, Found: 509.1573.

Prop-2-yn-1-yl 3-acetyl-2-(4-methoxyphenyl)-4-oxopentanoate (3id):



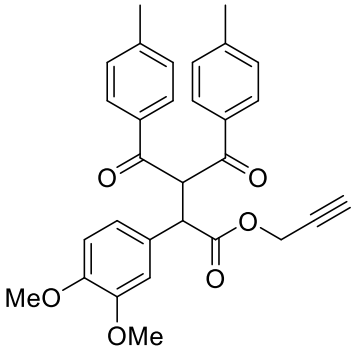
Compound **3id** was synthesized following the general procedure (D). The product was obtained as colourless liquid (0.083 g, 55% yield): R_f = 0.45 petroleum ether/EtOAc (80:20); IR (neat) cm^{-1}: 3288, 2951, 2120, 1735, 1695, 1599, 1513, 1450, 1374, 1270, 1160, 830, 766, 686; ^1H NMR (400 MHz, $CDCl_3$): δ 7.25 – 7.09 (m, 2H), 6.95 – 6.73 (m, 2H), 4.80 – 4.48 (m, 3H), 4.38 (d, *J* = 11.8 Hz, 1H), 3.78 (s, 3H), 2.42 (t, *J* = 2.5 Hz, 1H), 2.28 (s, 3H), 1.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.8, 201.5, 171.7, 159.6, 129.6, 126.4, 114.7, 75.3, 71.3, 55.4, 53.0, 49.7, 30.5, 30.0; HRMS (ESI TOF): Calculated for $C_{17}H_{18}NaO_5$ $(M + Na)^+$: 325.1052, Found: 325.1054.

Prop-2-yn-1-yl 3-benzoyl-2-(3,4-dimethoxyphenyl)-4-oxo-4-phenylbutanoate (3ka):



Compound **3ka** was synthesized following the general procedure (D). The product was obtained as white solid (0.194 g, 85% yield): R_f = 0.2 petroleum ether/EtOAc (70:30); m.p.: 140-142 ^oC; IR (neat) cm^{-1}: 3289, 3016, 2948, 2839, 2123, 1736, 1691, 1592, 1514, 1450, 1253, 1153, 1024, 808, 757, 689, 639; ^1H NMR (400 MHz, $CDCl_3$): δ 8.00 – 7.89 (m, 2H), 7.74 – 7.65 (m, 2H), 7.54 – 7.41 (m, 2H), 7.40 – 7.24 (m, 4H), 6.80 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.69 (d, *J* = 2.1 Hz, 1H), 6.65 (d, *J* = 8.3 Hz, 1H), 6.05 (d, *J* = 11.2 Hz, 1H), 4.79 (d, *J* = 11.2 Hz, 1H), 4.69 (d, *J* = 2.5 Hz, 2H), 3.75 (s, 3H), 3.75 (s, 3H), 2.41 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.6, 194.2, 172.1, 149.2, 148.9, 136.7, 136.3, 133.6, 133.6, 128.9, 128.8, 128.8, 128.7, 126.8, 121.1, 111.9, 111.5, 77.3, 75.2, 61.2, 56.0, 55.9, 53.0, 51.8; HRMS (ESI TOF): Calculated for $C_{28}H_{25}O_6$ $(M + H)^+$: 457.1651, Found: 457.1655.

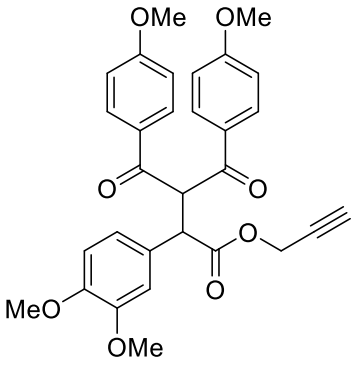
Prop-2-yn-1-yl 2-(3,4-dimethoxyphenyl)-3-(4-methylbenzoyl)-4-oxo-4-(p-tolyl)butanoate (3kb):



Compound **3kb** was synthesized following the general procedure (D). The product was obtained as white solid (0.235 g, 97% yield). R_f = 0.25 petroleum ether/EtOAc (70:30); m.p.: 130-132 ^oC; IR (neat) cm^{-1}: 3289, 3021, 2946, 2839, 2123, 1736, 1687, 1603, 1514, 1454, 1372, 1255, 1153, 1082, 1025, 814, 754, 638; ^1H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.3 Hz, 2H), 7.61 (d, *J* = 8.3 Hz, 2H), 7.14 (d, *J* = 8.1 Hz, 2H), 7.09 (d, *J* = 8.1 Hz, 2H),

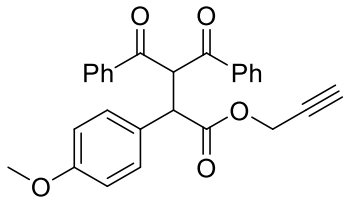
6.80 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.71 (d, *J* = 2.1 Hz, 1H), 6.65 (d, *J* = 8.3 Hz, 1H), 5.99 (d, *J* = 11.2 Hz, 1H), 4.77 (d, *J* = 11.2 Hz, 1H), 4.68 (d, *J* = 2.5 Hz, 2H), 3.76 (s, 3H), 3.75 (s, 3H), 2.41 (t, *J* = 2.4 Hz, 1H), 2.32 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.2, 193.9, 172.2, 149.1, 148.8, 144.5, 134.3, 133.8, 129.5, 129.4, 129.0, 129.0, 127.0, 121.1, 111.9, 111.5, 77.4, 75.2, 60.9, 56.0, 55.9, 52.9, 51.8, 21.7; HRMS (ESI TOF): Calculated for $C_{30}H_{26}NaO_6$ $(M + Na)^+$: 507.1784, Found: 507.1784.

Prop-2-yn-1-yl 2-(3,4-dimethoxyphenyl)-3-(4-methoxybenzoyl)-4-(4-methoxyphenyl)-4-oxobutanoate (3kc):



Compound **3kc** was synthesized following the general procedure (D). The product was obtained as white solid (0.248 g, 96% yield): R_f = 0.4 petroleum ether/EtOAc (60:40); m.p.: 123-125 ^oC; IR (neat) cm^{-1}: 3283, 3011, 2945, 2840, 2120, 1736, 1680, 1596, 1512, 1457, 1256, 1158, 1024, 839, 753, 633; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 8.9 Hz, 2H), 7.72 (d, *J* = 8.9 Hz, 2H), 6.88 – 6.74 (m, 5H), 6.71 (d, *J* = 1.9 Hz, 1H), 6.66 (d, *J* = 8.3 Hz, 1H), 5.89 (d, *J* = 11.2 Hz, 1H), 4.77 (d, *J* = 11.2 Hz, 1H), 4.68 (d, *J* = 2.4 Hz, 2H), 3.81 (s, 3H), 3.80 (s, 3H), 3.76 (s, 6H), 2.41 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.0, 192.8, 172.2, 164.0, 163.8, 149.1, 148.8, 131.3, 131.2, 129.8, 129.3, 127.2, 121.0, 114.0, 113.9, 111.9, 111.5, 77.4, 75.1, 60.9, 56.0, 55.9, 55.6, 55.5, 52.9, 51.8; HRMS (ESI TOF): Calculated for $C_{30}H_{28}NaO_8$ $(M + Na)^+$: 539.1682, Found: 539.1686.

4.4.7 Gram-scale synthesis of 3ia



A mixture of $Sc(OTf)_3$ (0.134 g, 5 mol%) and 1,3-diketone **2a** (1.83 g, 1.5 equiv.) was stirred in 20 mL DCE at room temperature in 100 mL two-necked RB flask under inert atmosphere for 5 minutes. Then propargyl α-(4-methoxyphenyl)- α-diazoacetate **1i** (1.25 g, 1 equiv.) in 10 mL of DCE was added to the reaction mixture dropwise over 30 minutes. Then the reaction mixture was stirred at room temperature over 6 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The crude product was purified by column chromatography over silica gel to furnish the desired product **3ia** (2.01 g, 87% yield). Slightly excess amount of 1,3-diketone **2a** was recovered during the purification.

4.5 Appendix IV: ^{1}H, ^{13}C NMR spectral data of representative compounds

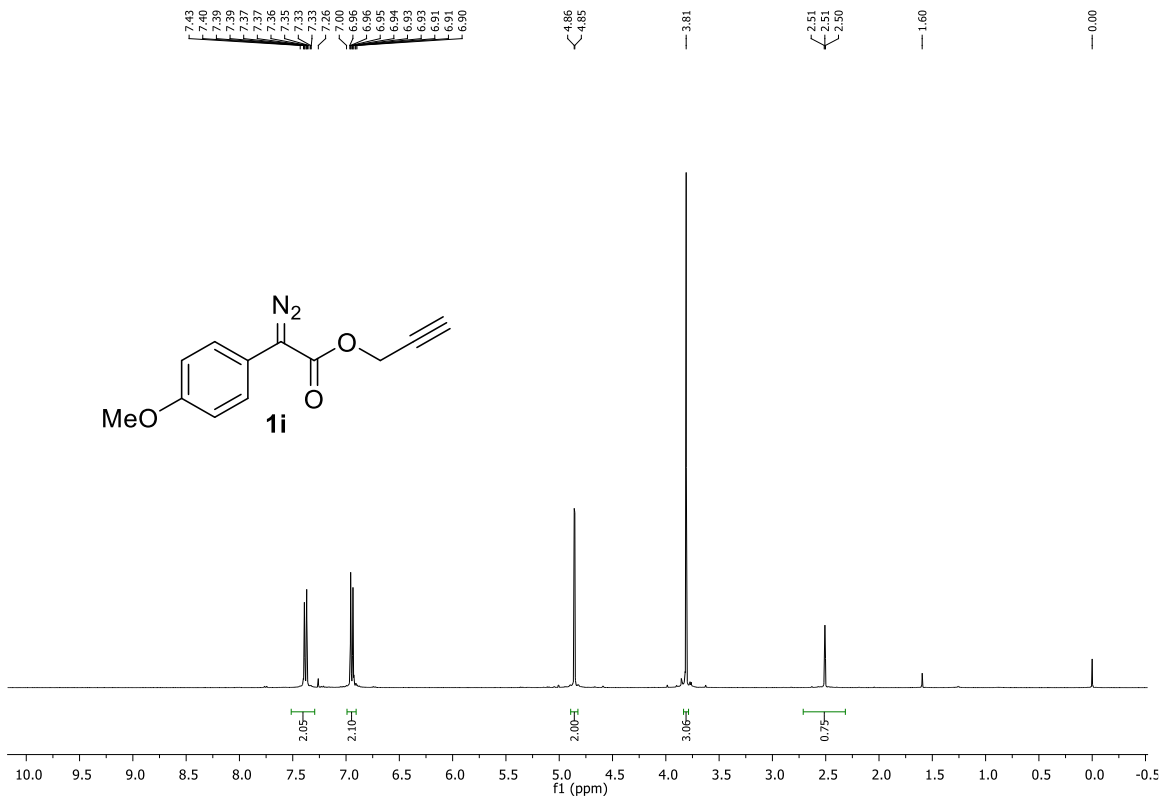


Figure IV.1: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **1i**

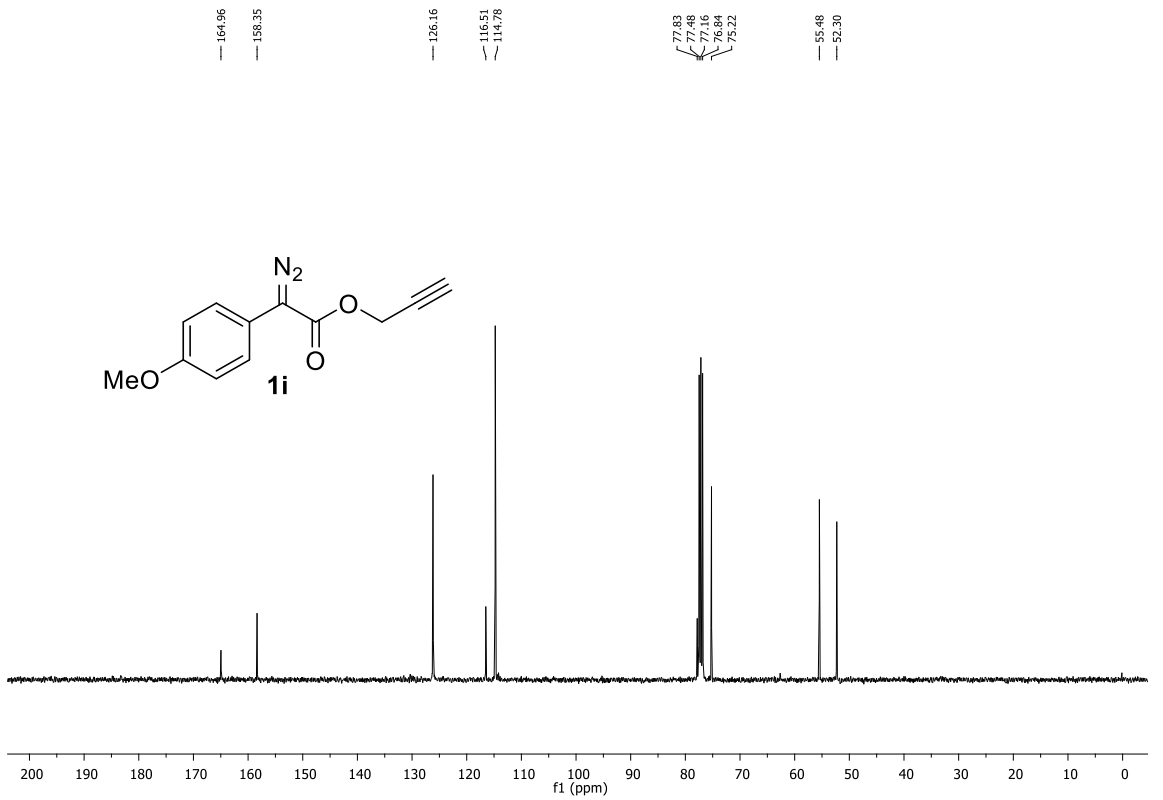


Figure IV.2: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **1i**

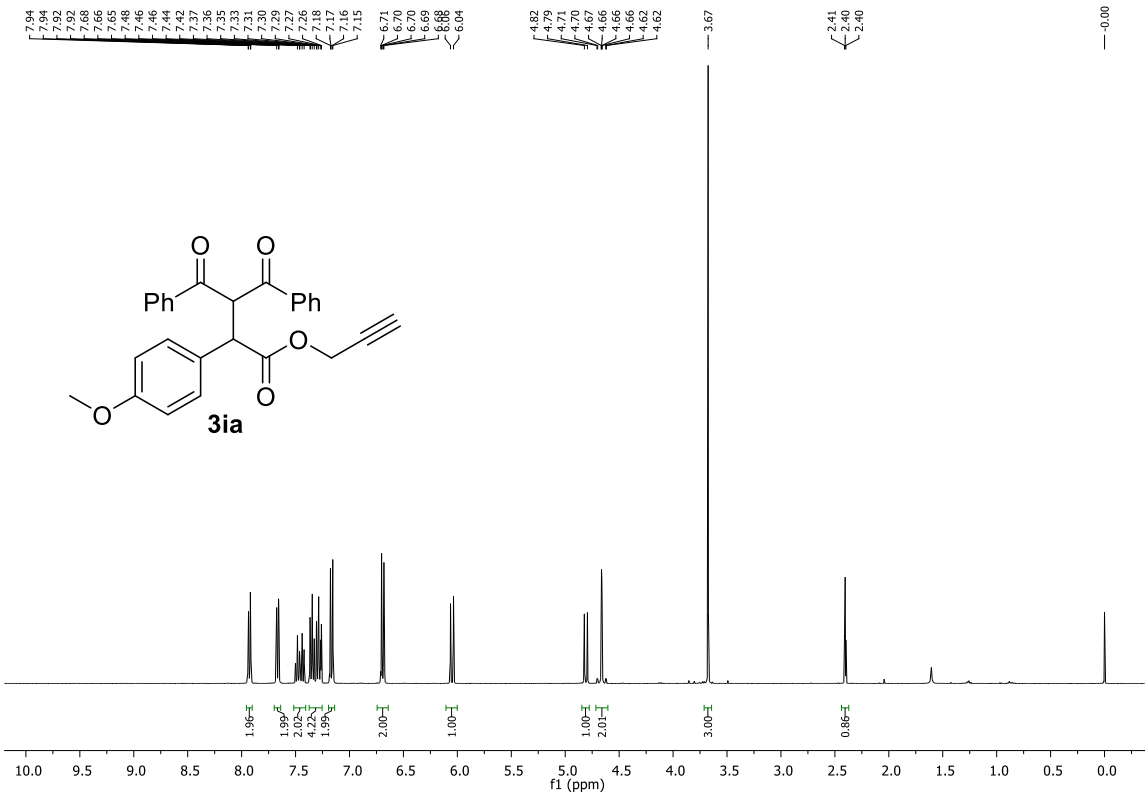


Figure IV.3: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3ia**

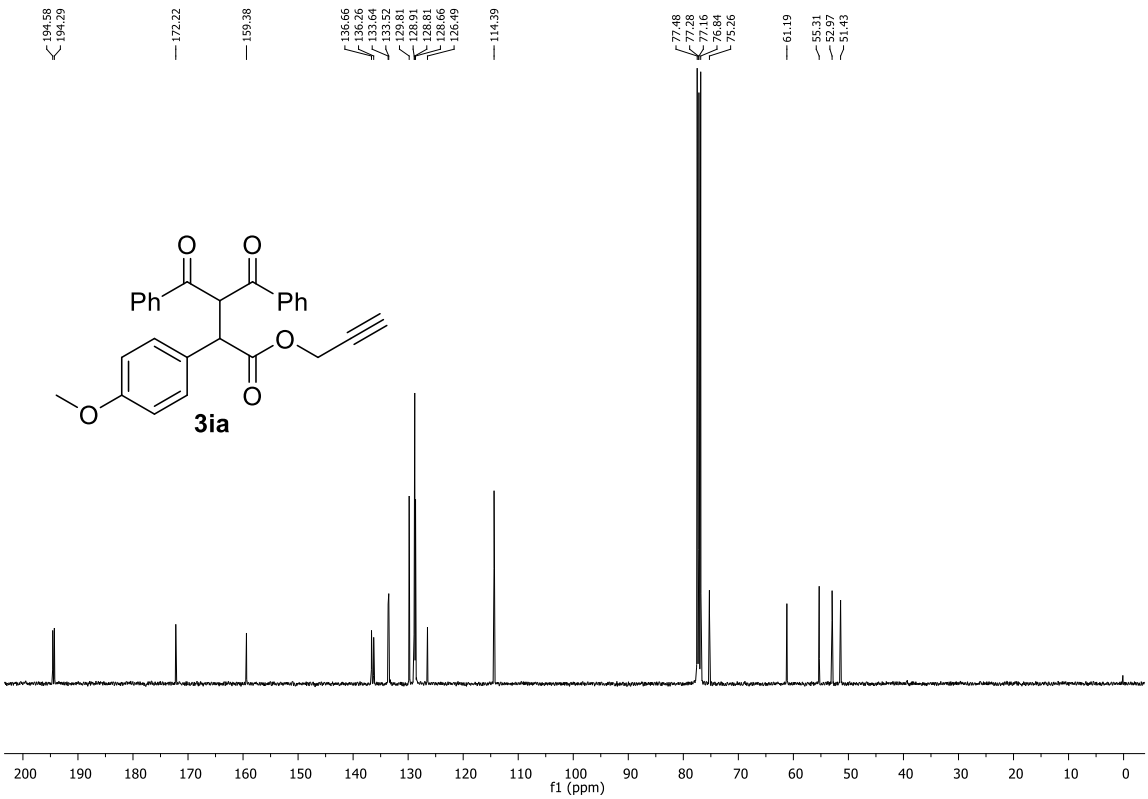


Figure IV.4: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3ia**

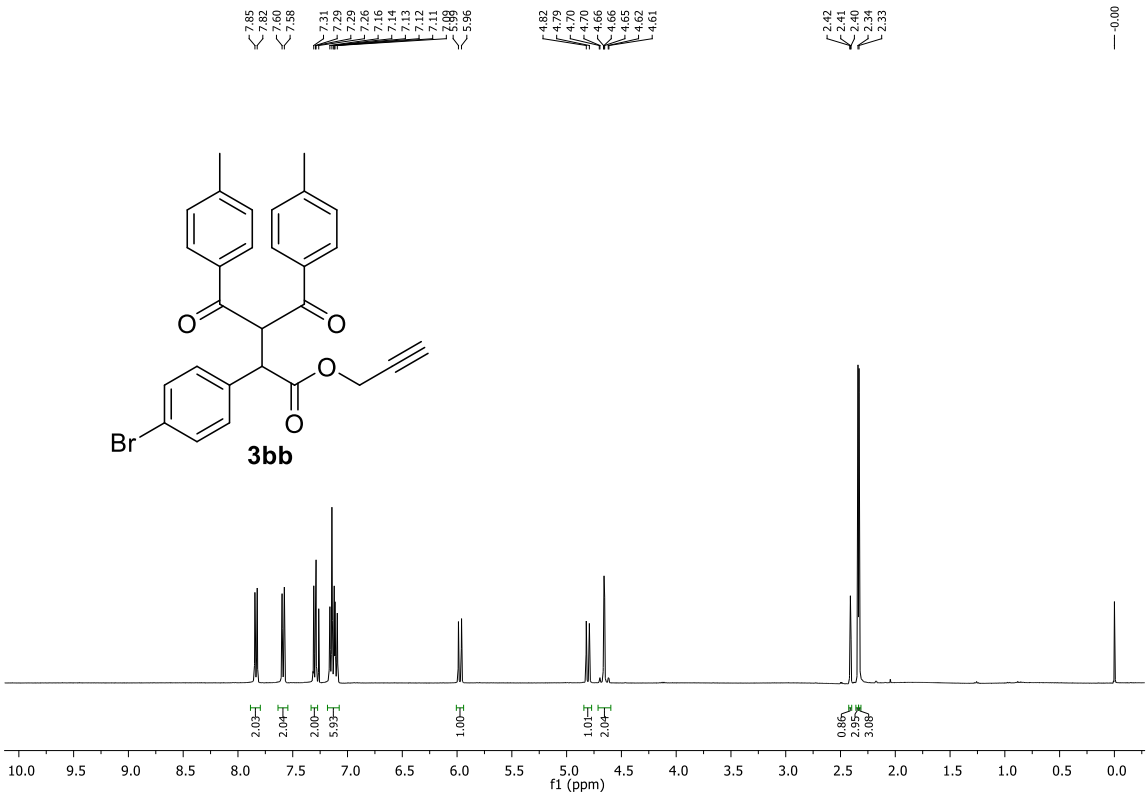


Figure IV.5: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3bb**

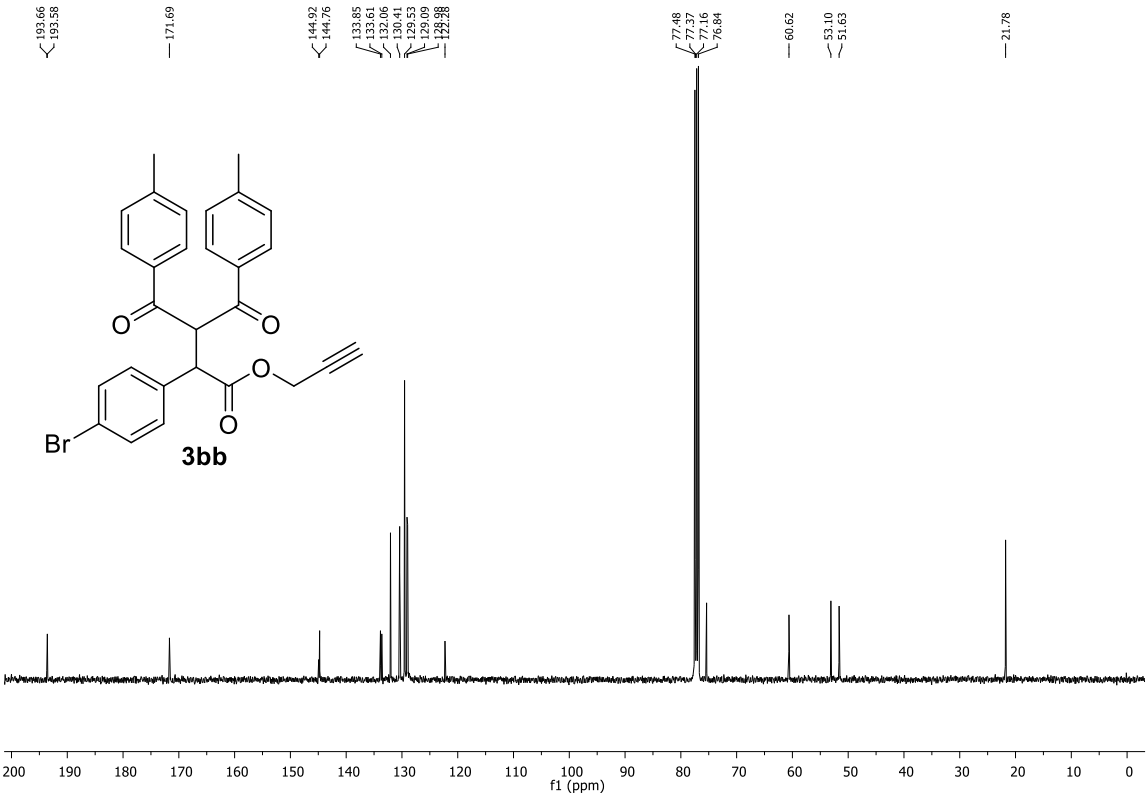


Figure IV.6: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3bb**

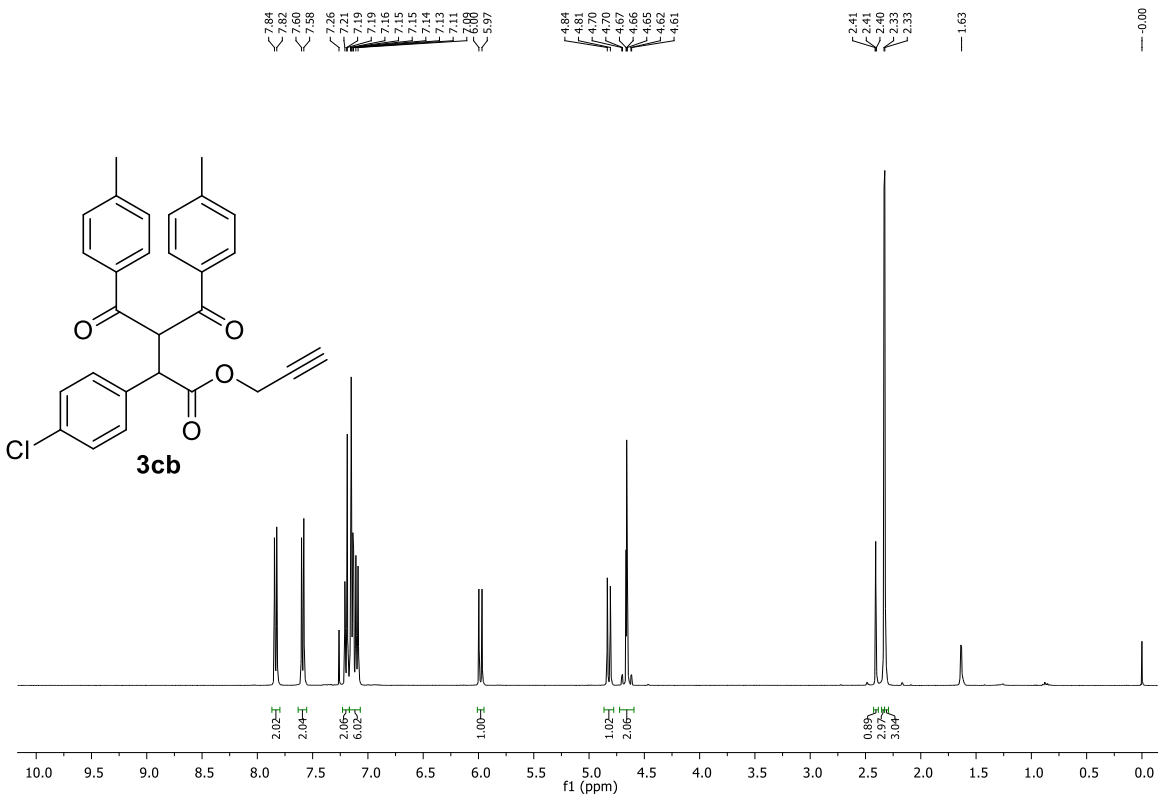


Figure IV.7: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3cb**

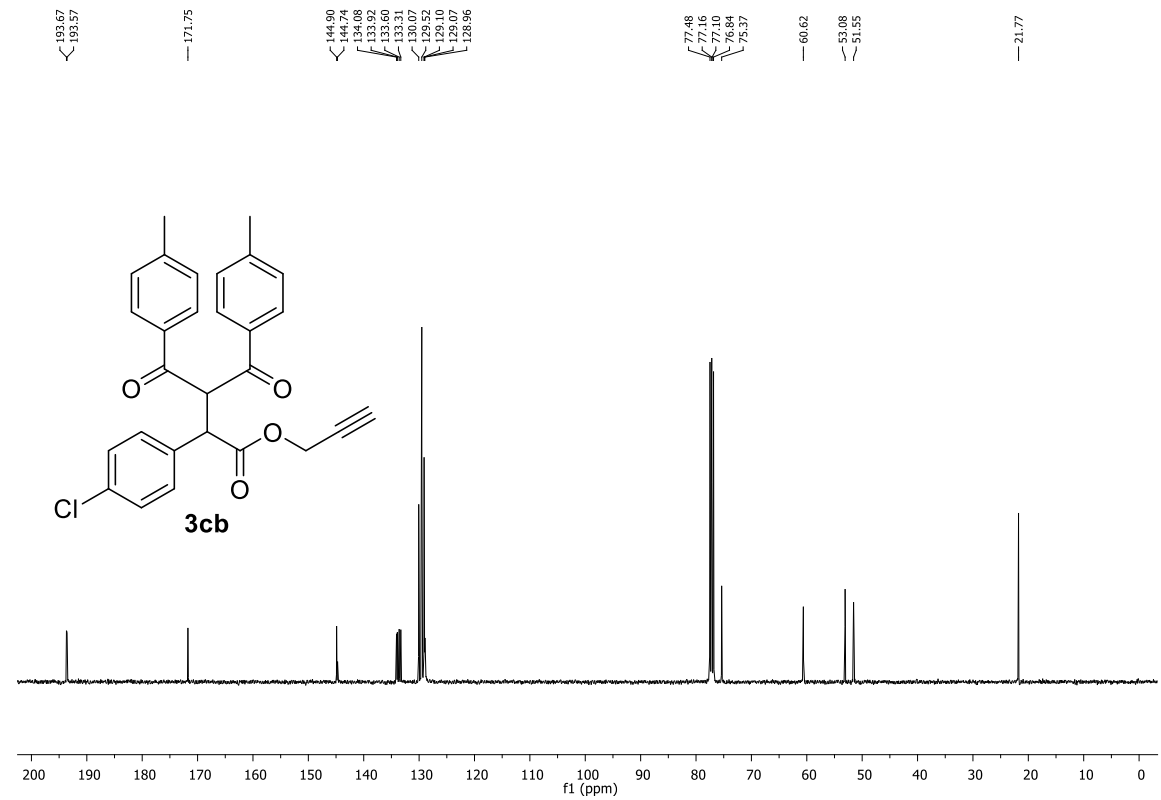


Figure IV.8: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3cb**

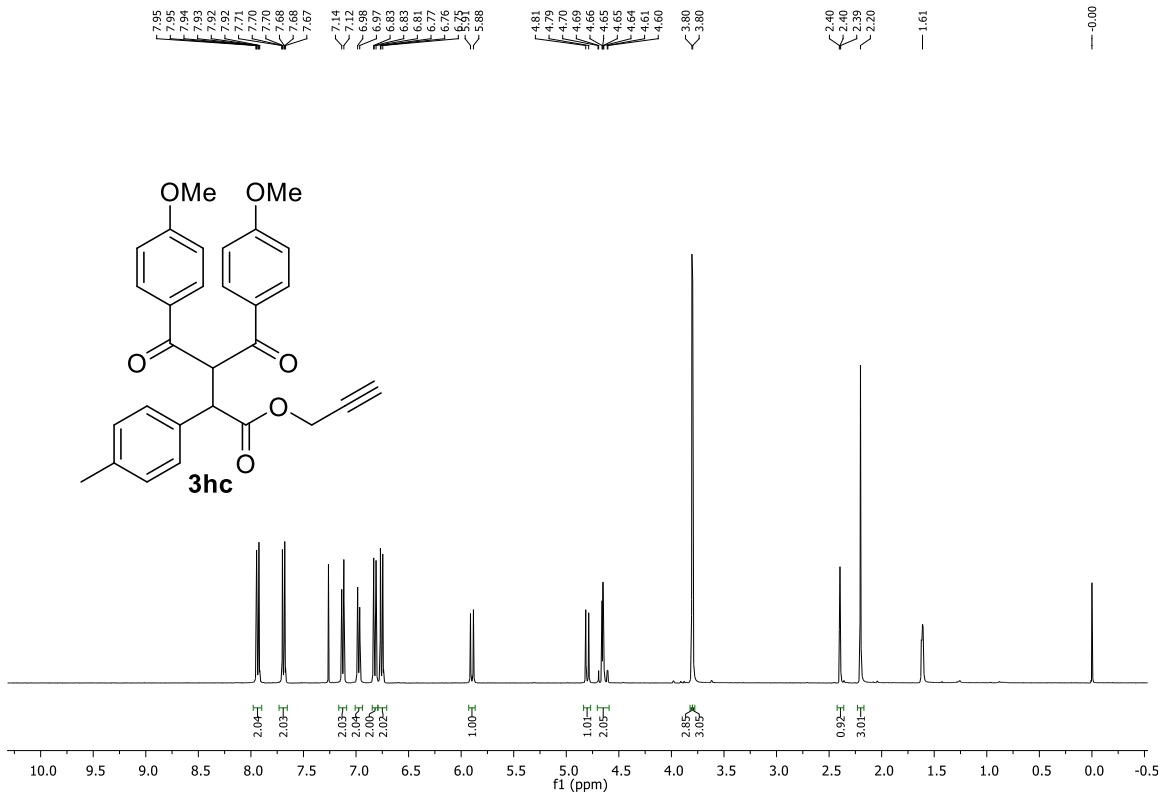


Figure IV.9: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3hc**

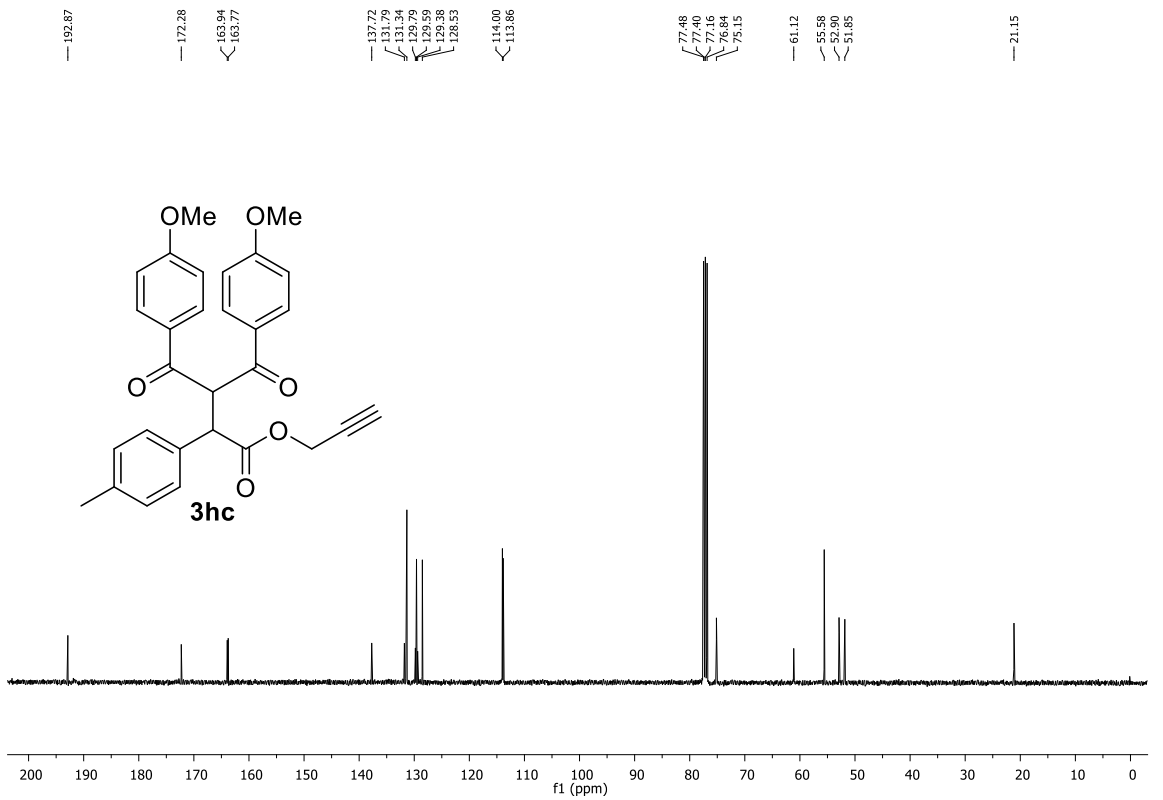


Figure IV.10: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3hc**

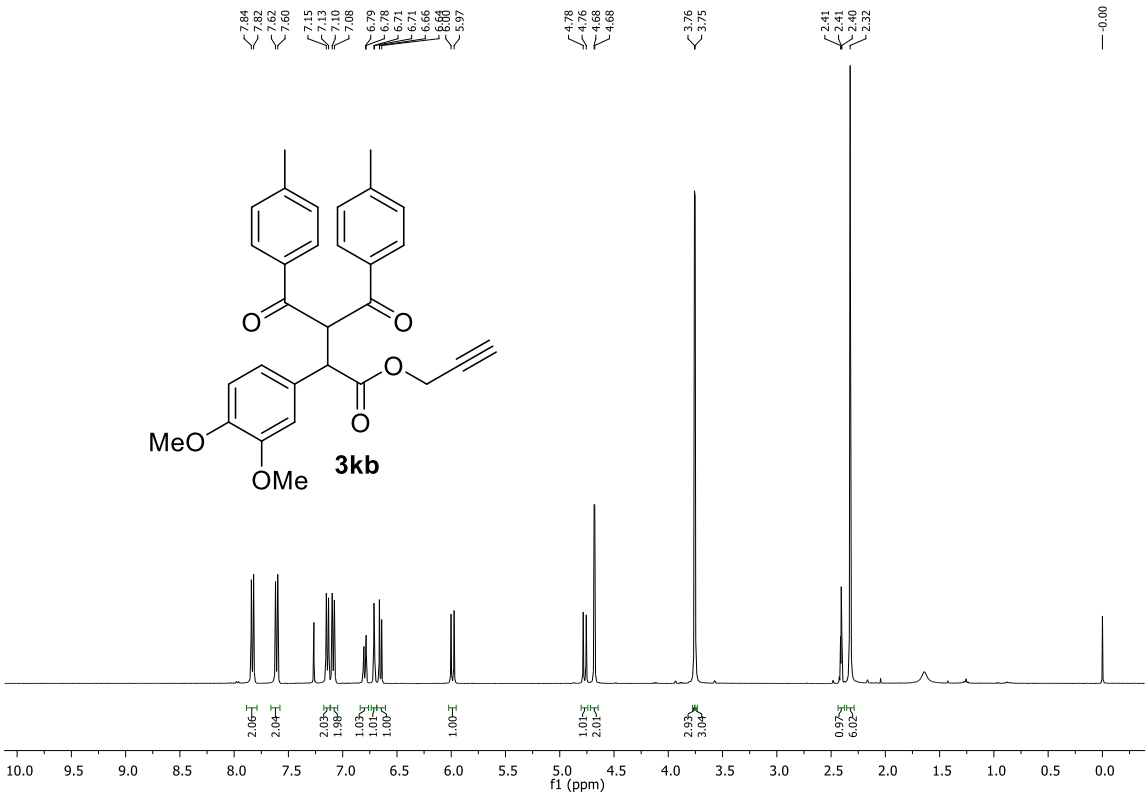


Figure IV.11: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3kb**

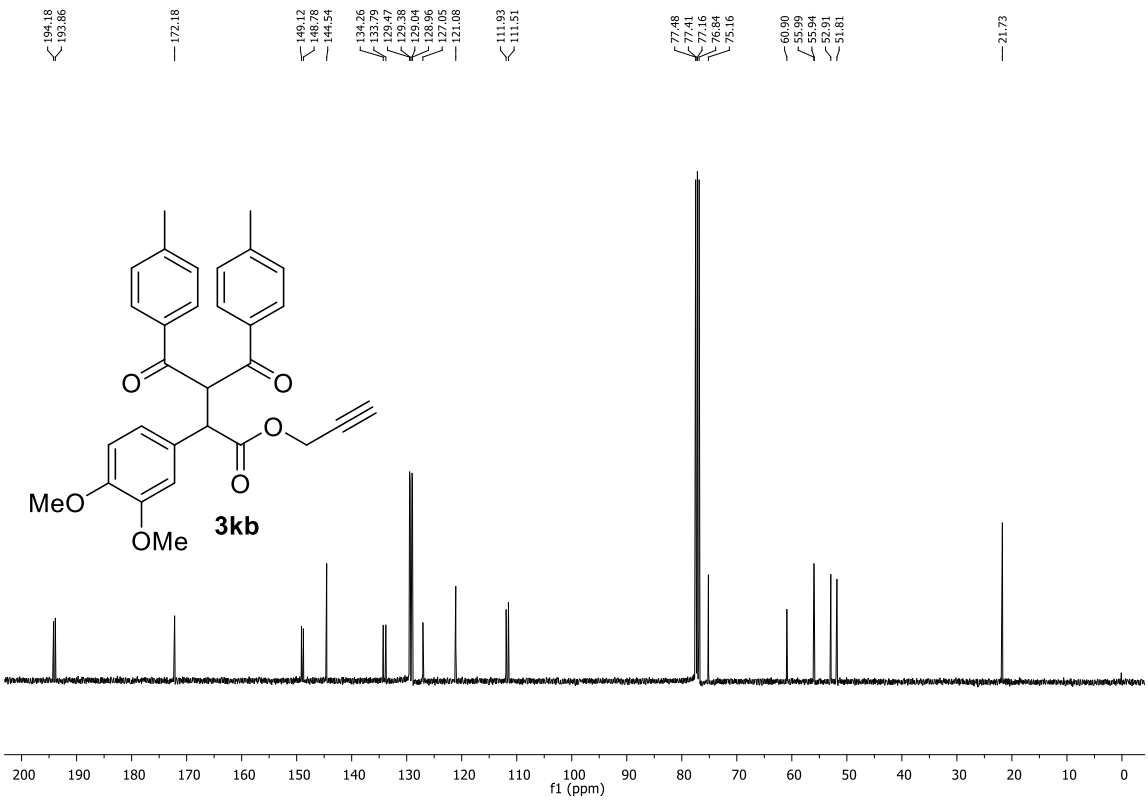


Figure IV.12: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3kb**

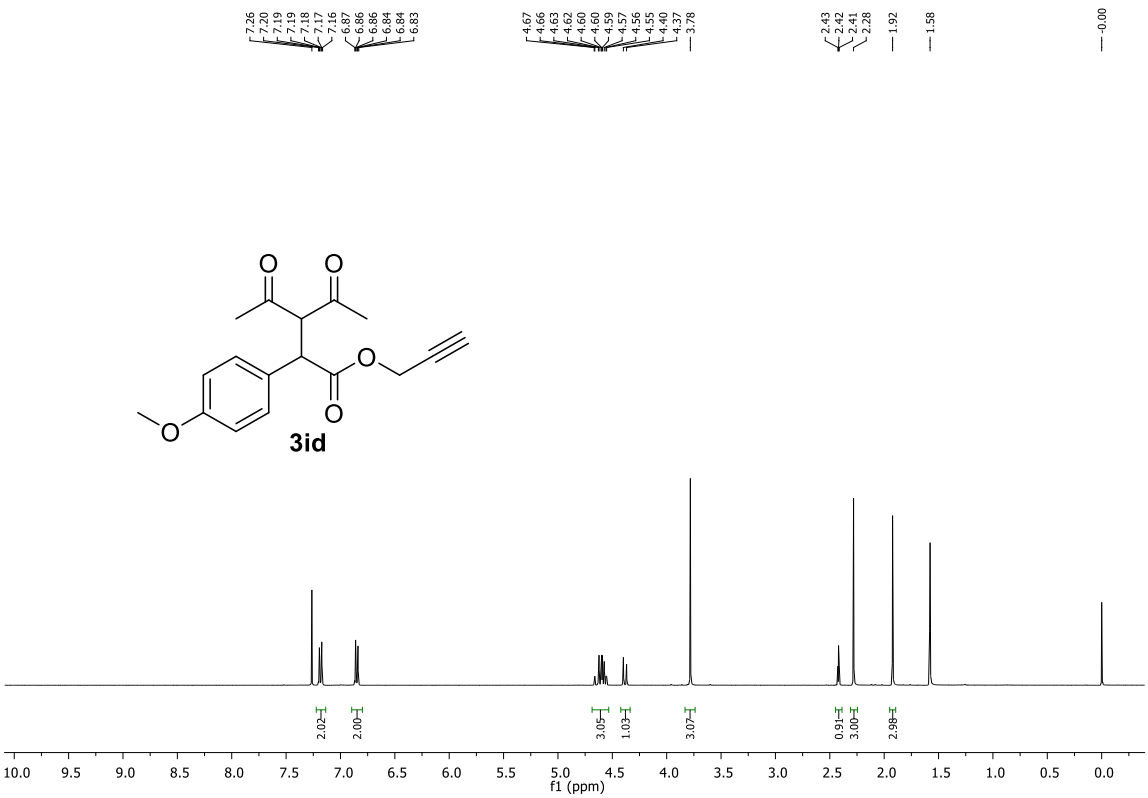
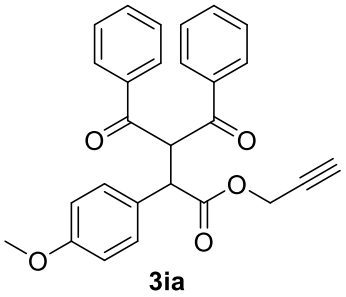


Figure IV.13: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3id**

Figure IV.14: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3id**

4.6 Crystal data of compound 3ia



3ia

Bond precision:	C-C = 0.0022 A	Wavelength=0.71073	
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	alpha=90	beta=100.516(7)	gamma=90
Temperature:	150 K		
	Calculated	Reported	
Volume	2197.6(11)	2197.4(10)	
Space group	P 21/n	P 21/n	
Hall group	-P 2yn	-P 2yn	
Moiety formula	C27 H22 O5	?	
Sum formula	C27 H22 O5	C27 H22 O5	
Mr	426.45	426.44	
Dx,g cm-3	1.289	1.289	
Z	4	4	
Mu (mm-1)	0.089	0.089	
F000	896.0	896.0	
F000'	896.47		
h,k,lmax	13,20,19	13,20,18	
Nref	5539	5482	
Tmin,Tmax	0.984,0.988	0.701,0.746	
Tmin'	0.984		

Correction method= # Reported T Limits: Tmin=0.701 Tmax=0.746
AbsCorr = MULTI-SCAN
Data completeness= 0.990 Theta(max)= 28.419
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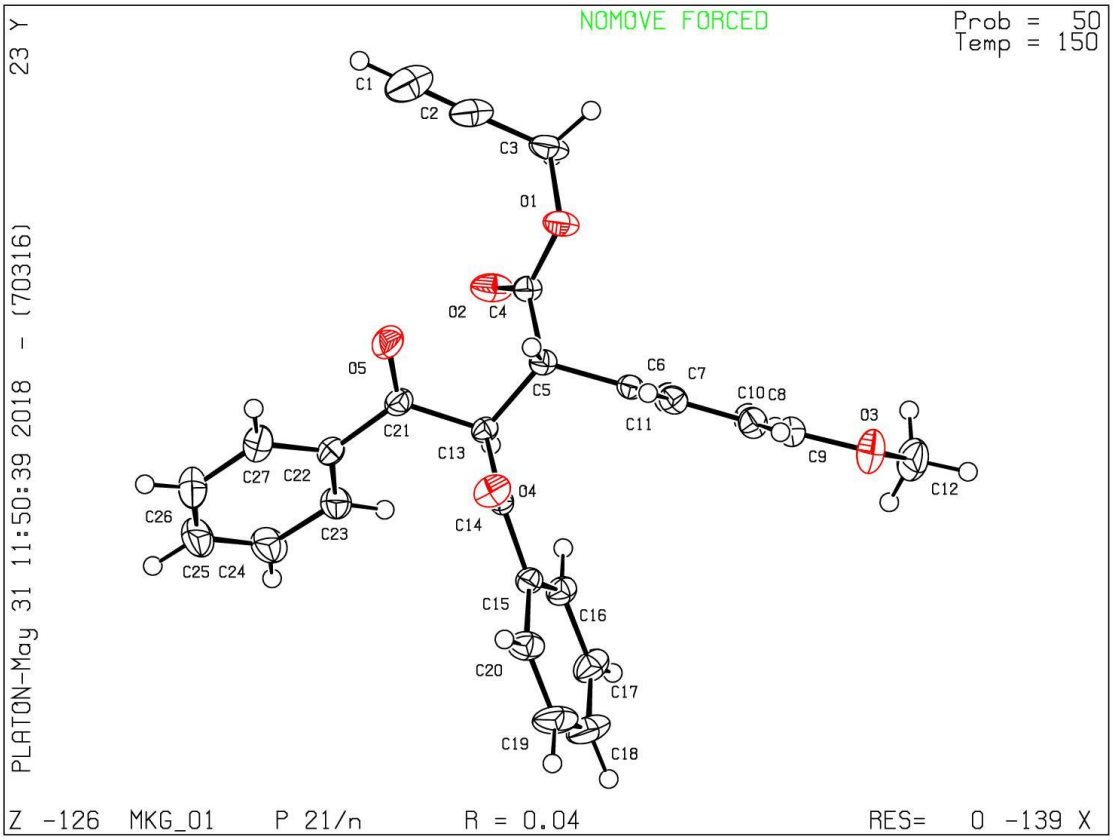
NOMOVE FORCED
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PLATON-May 31 11:50:39 2018 - (70316)
23 Y
C1
C2
C3
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O2
C4
O5
C5
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C7
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C11
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C12
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C25
C24
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C19
C18
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4.7 References and notes

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16. We have been pursuing scandium triflate catalyzed C-H bond functionalizations under the sanctioned research project-*Site-selective direct C-H bond functionalization by early transition metal-carbenoid insertion and its applications*- EMR/2015/000909, SERB-DST Govt. of India
17. It is speculated that in addition to being weakly electron-withdrawing, the propargyl moiety may also play a previously undescribed role that accelerates aminolysis. From the transition-state calculations it is revealed that the hydrogen on the propargyl moiety appears to be better positioned and oriented to hydrogen bond with the ester oxygen, potentially stabilizing the transition state. (See King, K.; Vong, H.; Maeda, S.; Tanaka, K. *Chem. Eur. J.* **2016**, *22*, 18865.)
18. CCDC number of **3aa** is 1848209 The number contains all crystallographic details of this publication and is available free of charge at http://www.ccdc.cam.ac.uk/conts/retrieving.html.
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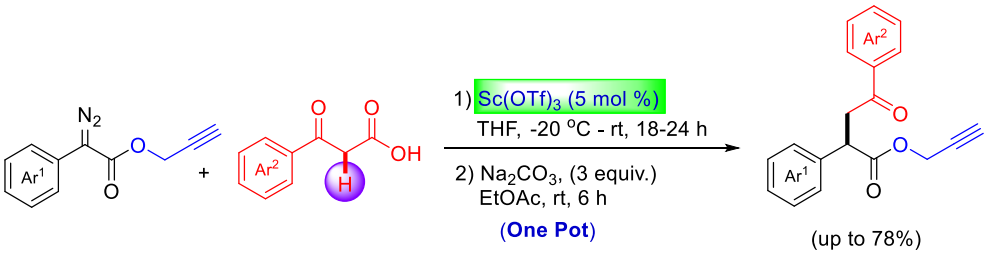
Chapter 5

Scandium(III) Triflate-Catalyzed One-Pot Synthesis of γ-Keto Esters from ß-Keto Acids and Propargyl α-Aryl-α-diazoacetates



(up to 78%)

- C-H functionalization at room temperature
- Less prone for side reactions
- Low Catalyst loading (5 mol%)
- Total of 15 examples and gram scale synthesis

F I V E

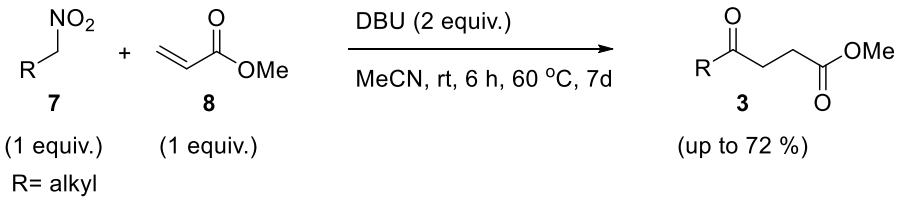
Scandium(III) Triflate-Catalyzed One-Pot Synthesis of γ-Keto Esters from ß-Keto Acids and Propargyl α-Aryl-α-diazoacetates

5

A one pot synthesis of α-substituted γ-keto esters is developed via decarboxylative C-H bond functionalization of ß-keto acids with α-aryl-α-diazoacetates in the presence of scandium catalyst. This protocol utilized the combination of $Sc(OTf)_3$ as a catalyst and α-aryl-α-diazoacetates as a reagent for the effective transformation. In this protocol, the C-H bond functionalization and decarboxylation takes place in one pot to furnish the synthetically important α-substituted γ-keto esters. Application of this protocol is also demonstrated on a gram scale.

5.1 Introduction

γ-Keto esters are the essential building blocks for the synthesis of biologically active compounds and natural products.[1] They are also utilized in the synthesis of various heterocyclic and carbocyclic compounds.[2] Due to the synthetic utility of γ-keto esters; various methods have been developed by researchers to synthesize them. Some of the important and selected methods have been presented here. The Michael addition is one of the very important reactions in synthetic transformation. The different nucleophiles have utilized with

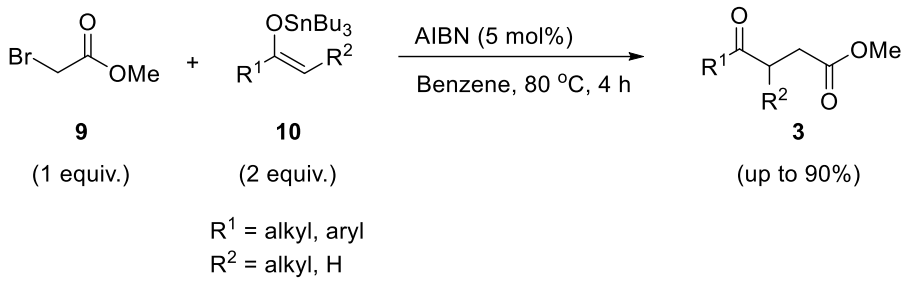


Scheme 5.1 Synthesis of γ-keto esters via Michael addition reaction

various Michael acceptors to synthesize γ-keto esters.[3] In 2002, Fiorini and co-workers reported the synthesis of γ-keto esters **3** by using Michael addition reaction between α,ß-

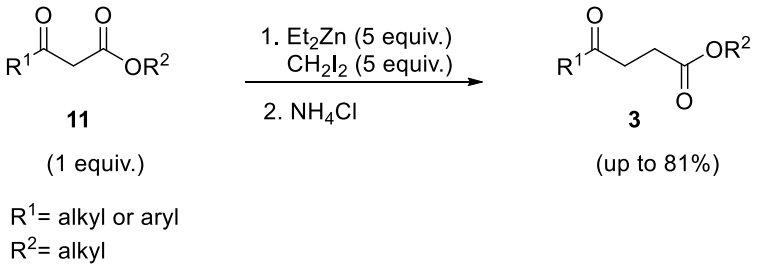
unsaturated ester **8** and primary nitroalkanes **7** in the presence of an excess amount of DBU (Scheme 5.1).[3c]

The nucleophilic substitution reaction of *α*-haloesters is another interesting approach to synthesize *γ*-keto esters.[4] In 2001, Miura et al. carried out the synthesis of *γ*-keto esters **3** by using radical mediated *ß*-ketoalkylation of *α*-haloester **9** with the tributylstannyl enolates **10** in the presence of catalytic amount of AIBN. The desired product **3** was obtained in very good yield (Scheme 5.2).[4b]



Scheme 5.2 Synthesis of *γ*-keto esters using α-haloesters

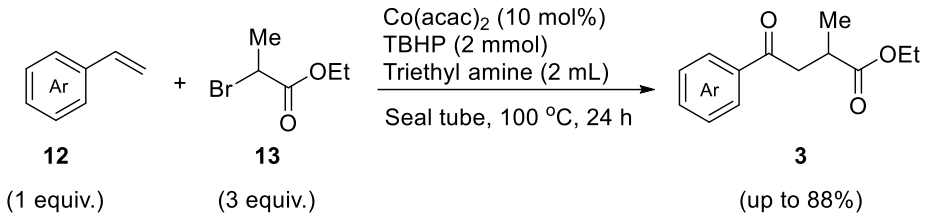
The chain extension and ring expansion reactions of 1,3-dicarbonyl compounds **11** is also very important approach for the synthesis of *γ*-keto esters **3**.[5] In 1997, Zercher and co-workers reported the synthesis of *γ*-keto esters **3** via zinc-carbenoid mediated homologation reaction of *ß*-keto esters **11** with diethylzinc and diiodomethane. This method gave rapid access to *γ*-keto esters **3** starting from *ß*-keto esters in good yield (Scheme 5.3).[5b]



Scheme 5.3 Homologation of *ß*-ketoesters

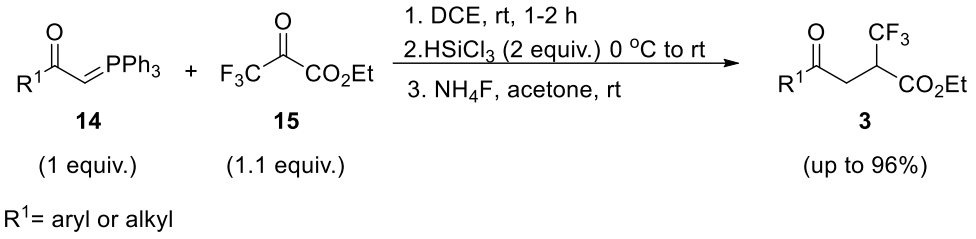
The oxidative coupling reactions between styrenes **12** and *α*-bromoester **13** is another interesting approach to synthesize *γ*-keto esters **3**.[6] Recently, Wan and co-workers developed cobalt catalyzed oxidative coupling reaction between styrenes **12** and *α*-bromoester **13** to access *γ*-keto esters **3**. In this reaction, they utilized TBHP as an oxidant for the required

transformation. *α*-Substituted *γ*-keto esters **3** were easily accessed by this method in moderate to good yields (Scheme 5.4).[6b]



Scheme 5.4 Cobalt-catalyzed synthesis of *γ*-keto esters

In 2013, Chen et al. reported the one-pot synthesis of *γ*-keto esters **3**, by tandem Wittig–conjugate transformation phosphorus ylides **14** underwent Wittig reaction with ethyl trifluoropyruvate **15** to afford the *α,ß*-unsaturated esters and Ph_3PO. Though the Witting reaction is a useful reduction reaction. In this reaction, however, it is not economical as Ph_3PO (high molecular weight) is generated as a by-product. Interestingly, the by-product generated mediates the conjugate reduction reaction in the presence of $HSiCl_3$ to afford the desired product *γ*-keto esters **3** (Scheme 5.5).[1c]

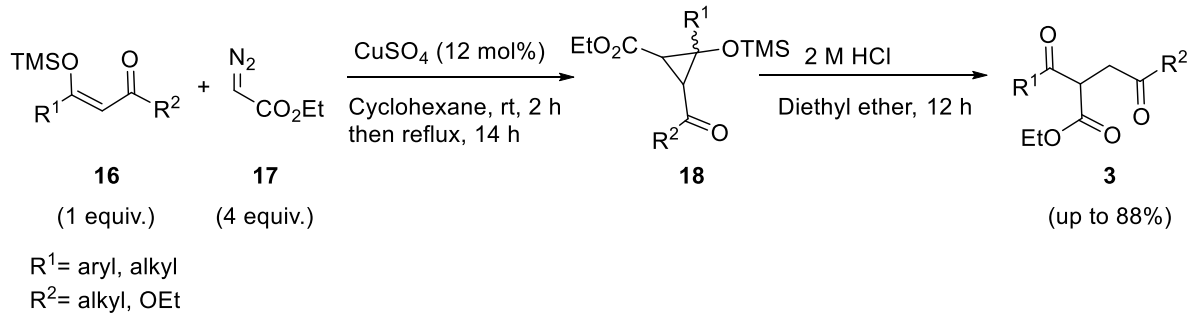


Scheme 5.5 One-pot synthesis of *γ*-keto esters

Despite the above available methods, the synthesis of *γ*-keto esters starting from diazocarbonyl compounds is an interesting and alternative approach available in the literature. The diazocarbonyl compounds are the important building blocks in the synthesis of organic compounds and are easily prepared from readily available starting materials.[7] Some of the important and selected methods for synthesis of *γ*-keto esters starting from *α*-diazocarbonyl compounds have been presented here.

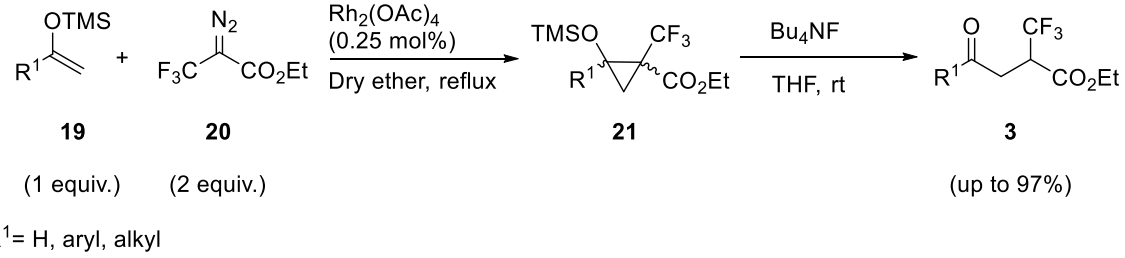
In 1984, Saigo et al. reported the copper-catalyzed the synthesis of *γ*-keto esters **3** by using silyl enol ethers **16** and ethyl diazoacetate **17**. The cyclopropanation intermediate **18** was believed to form initially, which upon treatment with 2 M HCl, undergoes a ring opening

reaction to afford the desired product *γ*-keto esters **3** in good to excellent yields. The overall transformation was carried out in two steps (Scheme 5.6).[8]



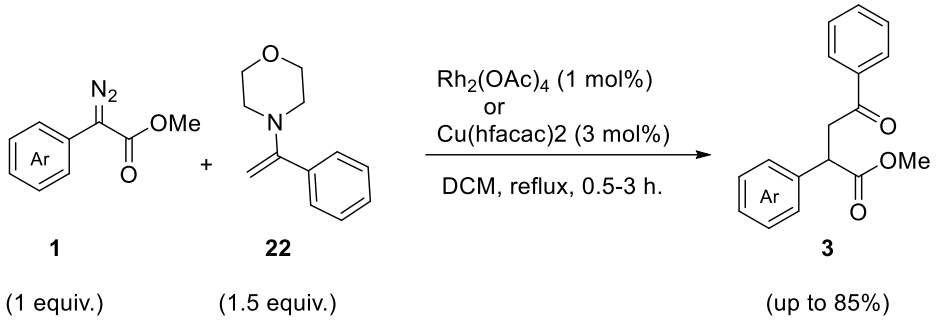
Scheme 5.6 Copper-catalyzed synthesis of *γ*-keto esters

In 1990, Xu and co-workers carried out the rhodium catalyzed synthesis of *γ*-keto esters **3** by using silyl enol ethers **19** and *α*-diazoester **20**.[9] In this transformation, silyl enol ethers **19** reacted with ethyl 3,3,3-Trifluoro-2-diazopropionate **20** in the presence of catalytic amount of $Rh_2(OAc)_4$ to give the corresponding cyclopropane product **21**. This upon treatment with with Bu_4NF in THF furnished the desired product *γ*-keto esters **3**. All the steps were carried out in one pot to afford the desired product **3** (Scheme 5.7).



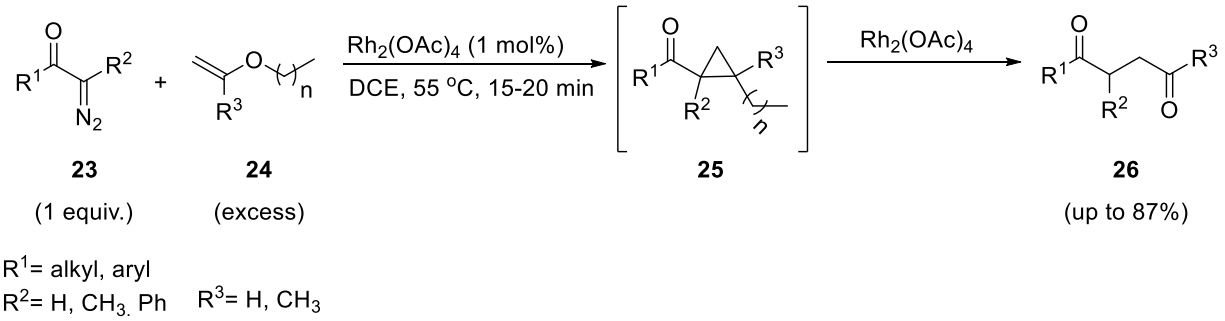
Scheme 5.7 Synthesis of *γ*-keto esters from silyl enol ethers

In 2005, Ji and co-workers reported rhodium or copper-catalyzed synthesis of *γ*-keto esters by starting from enamines **22** and *α*-aryl-*α*-diazoacetates **1.** It was proposed that the nucleophilic attack of enamines **22** on metal carbene species formed by **1** affords the required product **3**. The desired product *γ*-keto esters **3** were obtained in good yields by using this method (Scheme 5.8).[10]



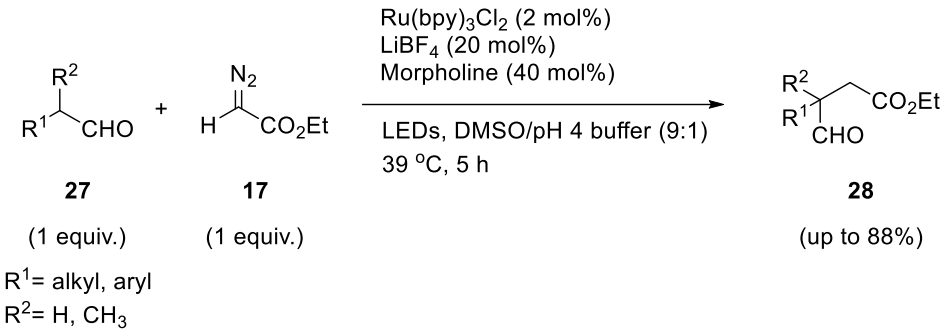
Scheme 5.8 Synthesis of *γ*-keto esters using enamines

In 2006, Muthusamy and co-workers carried out the synthesis of 1,4-dicarbonyl compounds **26** using *α*-diazo ketones **23** and vinyl ethers **24** in the presence of rhodium catalyst. It was proposed that initially formed oxycyclopropane intermediate **25** undergoes a subsequent ring opening in the presence of rhodium catalyst to afford the desired product **26**. (Scheme 5.9).[11]



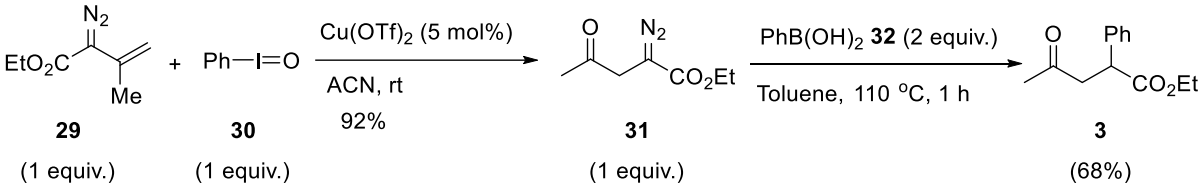
Scheme 5.9 Synthesis of *γ*-keto esters using vinyl ethers

Recently, Gryko and co-workers described the synthesis of 1,4-dicarbonyl compounds using aldehydes **27** and ethyl diazoacetate **17** in the presence of morpholine as an organocatalyst along with the $Ru(bpy)_3Cl_2$ as a photoredox catalyst. In this transformation, the combination of organocatalyst and the photoredox catalyst was explored to furnish the desired product 1,4-dicarbonyl compounds **28** in good yields. They explored the use of visible light for the effective transformation (Scheme 5.10).[12]



Scheme 5.10 Synthesis of *γ*-keto esters using aldehydes

In 2011, Barluenga and co-workers reported the synthesis of *α*-substituted *γ*-keto esters **3** in two steps. In this transformation alkenyldiazo compound **29** was treated with iodosylbenzene **30** in the presence of a copper catalyst to afford *β*-oxodiazo derivatives **31** at room temperature. *β*-oxodiazo derivatives reacted with phenylboronic acid **32** in toluene at refluxing condition to give the *α*-substituted *γ*-keto ester **3** (Scheme 5.11).[13]



Scheme 5.11 Synthesis of *γ*-keto esters using alkenyldiazo compound

Although various methods are available for the synthesis of *γ*-keto esters, yet novel catalytic methods are still in demand to widen the substrate scope. The easy availability of starting materials and cost-effective strategies make the protocols useful and practical. The C-H bond functionalization reactions afford the desired products in a minimum number of steps. As a part of our ongoing efforts to explore the *α*-diazocarbonyl compounds in C-H bond functionalization reactions, herein, we report the scandium catalyzed synthesis of *γ*-keto esters by using *ß*-keto acids and *α*-aryl-*α*-diazoacetates at room temperature. To the best of our knowledge, this is the first protocol for the synthesis of *α*-substituted *γ*-keto esters starting from *ß*-keto acids and *α*-aryl-*α*-diazoacetates in the presence of scandium catalyst. The C-H bond functionalization and decarboxylation have been carried out in one pot to access the

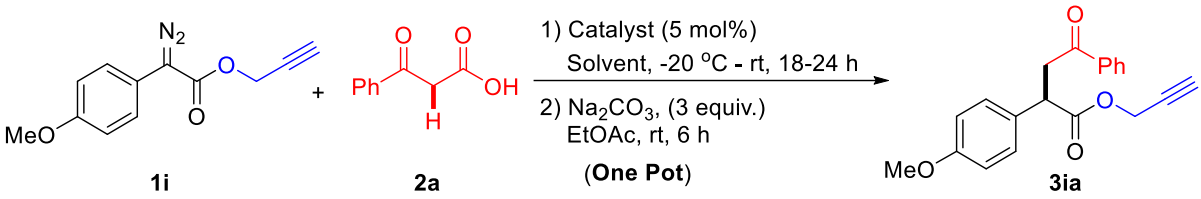
desired product. The protocol proved to be highly chemoselective for the synthesis of *α*-substituted *γ*-keto esters.

5.2 Results and discussion

Based on the previous experience, we planned to explore the efficiency of scandium triflate-propargyl *α*-aryl-*α*-diazoacetate as a catalyst-reagent system to synthesize the *γ*-keto esters. To explore the feasibility of the reaction, we chose propargyl *α*-(4-methoxyphenyl)-*α*-diazoacetate **1i** and *ß*-keto acid **2a** as model substrates. As shown in table 5.1, a variety of metal catalysts were screened in different solvents at various temperature. In our preliminary studies, we observed that the reaction of propargyl *α*-(4-methoxyphenyl)-*α*-diazoacetate **1i** (1 equiv.) and *ß*-keto acid **2a** (2.5 equiv.) and $Sc(OTf)_3$ (5 mol%) in dichloroethane at varying temperature ranging from -20 ^oC to room temperature followed by the treatment with the Na_2CO_3 (3 equiv.) afforded the desired product *α*-substituted *γ*-keto ester **3ia** in lower yields (entries 1-3, Table 5.1). Other catalysts such as rhodium and gold catalysts found to be not suitable for this transformation (entries 4-5, Table 5.1).

Later, when we carried out the model reaction in tetrahydrofuran in the presence of $Sc(OTf)_3$ (5 mol%) at room temperature followed the treatment with Na_2CO_3 afforded the desired product **3ia** in slightly improved yield 34% in 24 h (entry 6, Table 5.1). Later, the dropwise addition (in 45 min) of *α*-(4-methoxyphenyl)-*α*-diazoacetate **1i** to the mixture of *ß*-keto acid **2a** and $Sc(OTf)_3$ (5 mol%) in THF at 0 ^oC was carried out. The reaction mixture was allowed to slowly warm to room temperature and stirred for 18 h. The subsequent addition of Na_2CO_3 afforded the desired product in 48% yield (entry 7, Table 5.1). Further, the propargyl *α*-(4-methoxyphenyl)-*α*-diazoacetate **1i** was added dropwise to the reaction mixture of $Sc(OTf)_3$, and **2a**.at lower temperature (at -20 ^oC, over 45 min). The reaction mixture was allowed to slowly warm to room temperature and stirred for 18 h, and subsequently, Na_2CO_3 was added to afford the desired product **3ia** in 76% yield (entry 8, Table 5.1). Based on the experimental observations, slow addition at a relatively lower temperature (-20 ^oC) proved to beneficial for the desired transformation.

Table 5.1 Optimization of reaction conditions[a-c]



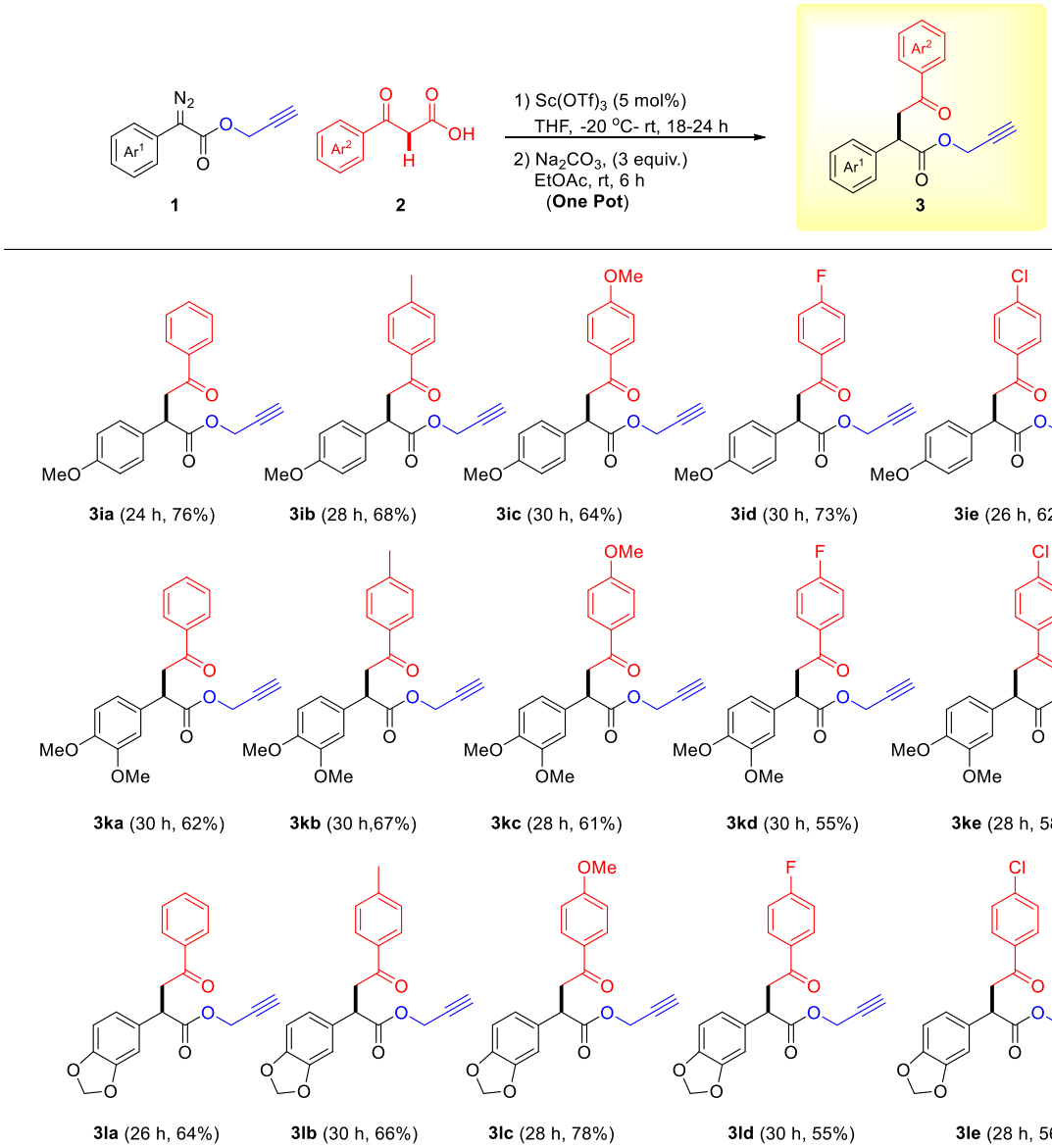
Entry	Catalyst	Ketoacid 2a (x equiv.)	Solvent	Time (h)	Temp. (ºC)	Yield[b] (%)
1	$Sc(OTf)_3$	2.5	DCE	30	rt	12
2	$Sc(OTf)_3$	2.5	DCE	30	0 to rt	18
3	$Sc(OTf)_3$	2.5	DCE	30	-20 to rt	26
4	$Rh_2(OAc)_4$	2.5	DCE	30	-20 to rt	trace.
5	$Cu(OTf)_2$	2.5	DCE	30	-20 to rt	trace
6	$Sc(OTf)_3$	2.5	THF	24	rt	34
7	$Sc(OTf)_3$	2.5	THF	24	0 to rt	48
8	**$Sc(OTf)_3$**	**2.5**	**THF**	**24**	**-20 to rt**	**76**
9	$(ArO)_3PAuNTf_2$	2.5	DCE	30	-20 to rt	trace
10	$(ArO)_3PAuNTf_2$	2.5	THF	30	-20 to rt	trace
11	$Sc(OTf)_3$	1.5	THF	30	-20 to rt	36
12	$Sc(OTf)_3$	5	THF	24	-20 to rt	67
13	$Cu(OTf)_2$	2.5	THF	30	-20 to rt	trace
14	$In(OTf)_3$	2.5	THF	30	-20 to rt	35
15	$In(OTf)_3$	2.5	DCE	30	-20 to rt	21
16	$Y(OTf)_3$	2.5	THF	30	-20 to rt	18
17	Triflic acid	2.5	THF	30	-20 to rt	00
18	No Catalyst	2.5	THF	30	-20 to rt	NR[c]

[a]Reaction conditions: 1) Solution of *α*-(4-methoxyphenyl)-*α*-diazoacetates **1i** (0.5 mmol, 1 equiv.) in 1.5 mL solvent was added to the solution of catalyst (1-5 mol%) and *ß*-keto acid **2a** (1.5-5 equiv.) in 2 mL solvent over 45 min under inert atmosphere; the reaction was monitored by TLC. 2) Na_2CO_3 (3 equiv.), EtOAc (4 mL) open atmosphere, 6 h. [b]Isolated yield after purification by column chromatography, [c]NR= No reaction.

Interestingly, gold catalyst [$(ArO)_3PAuNTf_2$, 5 mol%] found to be ineffective for this transformation (entries 9-10, Table 5.1). Lowering the amount of *ß*-keto acid **2a** (1.5 equiv.) resulted in a lower yield of **3ia** (36%, entry 11, Table 5.1). The excess amount of *ß*-keto acid **2a** (5 equiv.) did not enhance the yield of the product **3ia** and proved to be not beneficial (entry 12, Table 5.1). Some of the other metal catalysts were found to be not effective in the desired transformation as they afforded the desired product **3ia** in poor yield and some in cases reaction did not work (entries 13-16, Table 5.1). The model reaction in the presence of triflic acid as a catalyst (5 mol%) did not afford the desired product (entry 17, Table 5.1). The reaction did not work in the absence of any catalyst (entry 18, Table 5.1). Based on the exhaustive screening of catalysts, solvents, and varying temperature, propargyl *α*-(4-methoxyphenyl)-*α*-diazoacetate **1i** (1 equiv.), *ß*-keto acid **2a** (2.5 equiv.), $Sc(OTf)_3$ (5 mol%) in THF at -20 ^oC to room temperature followed by the treatment with Na_2CO_3 (3 equiv.) emerged as optimum reaction condition (entry 8, Table 5.1).

Encouraged by the initial success and having optimized reaction conditions in hand, we focused our attention on exploring the substrate scope for this protocol. Under optimal reaction conditions, the propargyl *α*-aryl-*α*-diazoesters (**1i, 1k-1l**) reacted with various aromatic *ß*-keto acids (**2a-2e**) to give the desired products: *α*-substituted *γ*-keto esters (**3ia-3ie**, **3ka-3ke**, **3la-3le**) in moderate to good yields (see, Table 5.2).

Table 5.2 Substrate scope for the scandium-catalyzed synthesis of γ-keto esters[a,b]

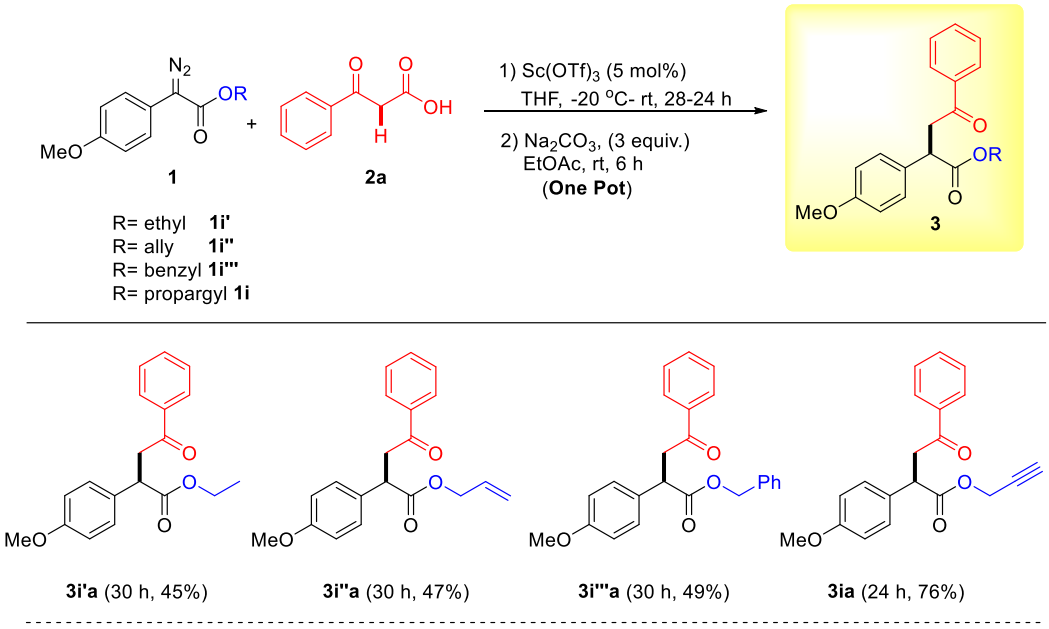


[a]Reaction conditions: 1) Solution of α-aryl-α-diazoacetates **1** (0.5 mmol, 1 equiv.) in 1.5 mL THF was added to the solution of $Sc(OTf)_3$ (5 mol%) and ß-keto acid **2** (2.5 equiv.) in 2 mL THF over 45 min under inert atmosphere; the reaction was monitored by TLC. 2) Na_2CO_3 (3 equiv.), EtOAc (4 mL) open atmosphere, [b]Isolated yield after purification by column chromatography (Time and yields are given in parenthesis).

After the initial success with propargyl α-aryl-α-diazoacetates as reactive reagents, we planned to explored and compare reactivity of different α-aryl-α-diazoacetates such as ethyl, allyl, benzyl and propargyl α-aryl-α-diazoacetates (**1i′, 1i″, 1i‴ and 1i**). The treatment of various α-aryl-α-diazoacetates **(1i′, 1i″, 1i‴, and 1i)** with ß-keto acids **2a** under optimum

reaction conditions afforded the corresponding desired products (**3i′a, 3i′′a, 3i′′′a, and 3i**) in moderate to good yields (Table 5.3).

Table 5.3 Comparitive reactivity of various *α*-aryl-*α*-diazoacetates[a,b]

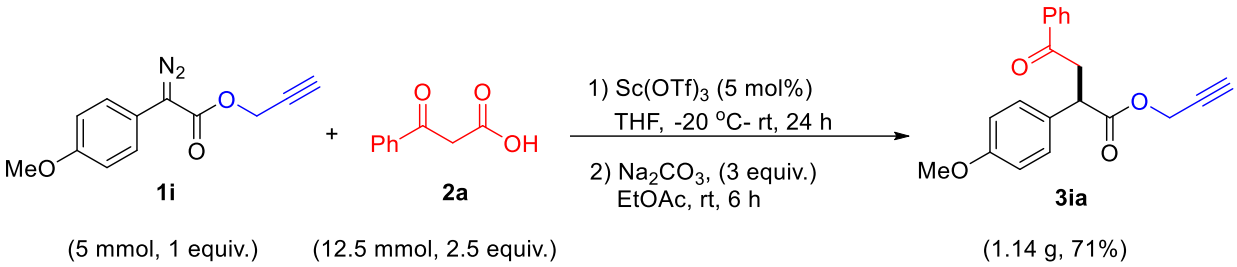


[a]Reaction conditions: 1) *α*-aryl-*α*-diazoester **1** (0.5 mmol, 1 equiv.), *ß*-keto acid **2a** (2.5 equiv.), THF (3 mL) nitrogen atmosphere; reaction was monitored by TLC. 2) Na_2CO_3 (3 equiv.), EtOAc (4 mL) open atmosphere, [b]Isolated yield after purification by column chromatography (Time and yields are given in parenthesis).

The results indicated that propargyl *α*-aryl-*α*-diazoacetates are more reactive and efficient dizo reagents for the desired C-H bond functionalization. This indicated that weakly electron withdrawing[14] propargyl group in *α*-aryl-*α*-diazoacetates is necessary for enhancing the reactivity of *α*-aryl-*α*-diazoacetates. Propargyl *α*-aryl-*α*-diazoacetates and scandium catalyst worked synergistically to afford desired products in good yields.

5.2.1 Gram-scale synthesis of *α*-substituted *γ*-keto ester

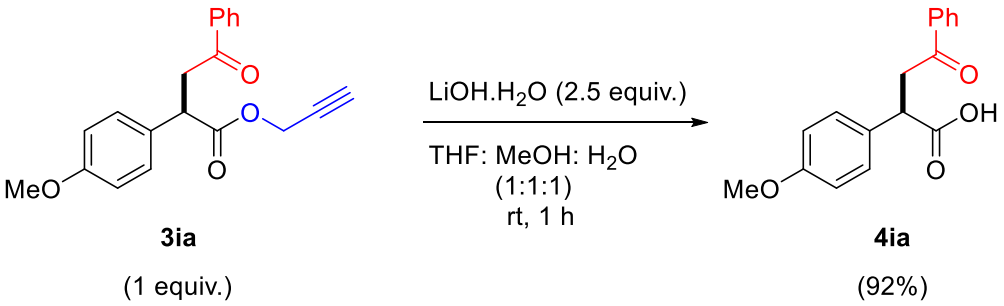
In order to demonstrate the practicability of the protocol, we explored this protocol on a gram-scale synthesis of the *α*-substituted *γ*-keto ester **3ia**. The treatment of propargyl *α*-aryl-*α*-diazoacetate **1i** (5 mmol, 1 equiv.) with 3-oxo-3-phenylpropanoic acid **2a** (12.5 mmol, 2.5 equiv.) in the presence of $Sc(OTf)_3$ (5 mol%) in THF followed by treatment with mild base (Na_2CO_3) afforded the desired product: *α*-substituted *γ*-keto ester **3ia** in 71% yield (Scheme 5.12). The protocol worked efficiently on gram-scale and proved to be reproducible. We did not observe any traceable side product O-H insertion of *ß*-keto acids.



Scheme 5.12 Gram-scale synthesis of *α*-substituted *γ*-keto ester

5.2.2 Hydrolysis of *α*-substituted *γ*-keto esters

Finally, the hydrolysis of propargyl ester of *α*-substituted *γ*-keto ester **3ia** was carried out using $LiOH.H_2O$ (2.5 equiv.) in ethanol- tetrahydrofuran-water (1:1:1) mixture at room temperature in 1 h, to furnish the corresponding product **4ia** in excellent yields (up to 92% yield, Scheme 5.13). The easy removal of propargyl ester under mild condition proved to be useful for the further synthetic transformations.



Scheme 5.13 Hydrolysis of α-substituted γ-keto esters

5.3 Conclusions

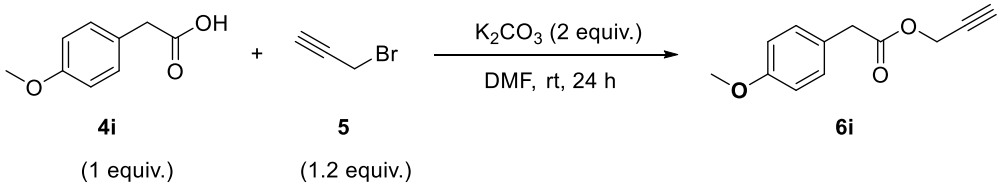
In conclusion, we have successfully developed $Sc(OTf)_3$ catalyzed the highly chemoselective one-pot synthesis of the *α*-substituted *γ*-keto ester using propargyl *α*-aryl-*α*-diazoacetate and *ß*-keto acids. Various *α*-substituted *γ*-keto esters were prepared in moderate to good yields by using this novel protocol. The C-H bond functionalization and decarboxylation of *ß*-keto acids took place in one pot to afford the desired product. We did not observe any O-H insertion of *ß*-keto acids. It is noteworthy that we have successfully avoided the use of additives and co-catalyst for this transformation. This protocol is highly practical, economical and environmentally friendly.

5.4 Experimental section

5.4.1 General

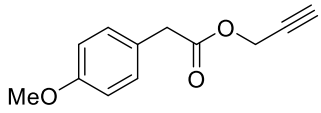
Unless otherwise noted, all reactions were carried out with distilled and dried solvents using oven-dried glassware. All reagents were purchased from commercial sources and used as received unless otherwise indicated. *ß*-Keto acids were prepared following known procedures.[17] Thin-layer chromatography (TLC) was performed using silica gel 60 GF_{254} precoated aluminum backed plates (2.5 mm) with detection by UV light. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6. Chemical shifts in ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from tetramethylsilane with the solvent resonance as the internal standard or from the residual solvent peak as internal standard and *J* values are given in Hz. ^{13}C NMR spectra are reported as δ in ppm downfield from tetramethylsilane and relative to the signal of chloroform-d and DMSO-d_6. ^{13}C NMR spectra were recorded with complete proton decoupling. Mass samples were analyzed by high-resolution mass spectrometry (HRMS) using ESI TOF. FT-IR spectra were obtained using a FT-IR spectrophotometer as neat and reported in cm^{-1}. Melting points were measured in an open glass capillary and values are uncorrected.

5.4.2 General procedure A for the synthesis of propargyl esters



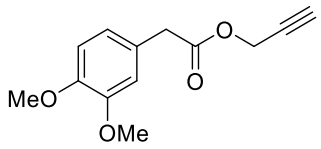
To the stirred solution of 2-(4-methoxyphenyl)acetic acid **4i** (3.320 g, 20 mmol) in DMF (15 mL) was added propargyl bromide solution 80% in toluene (3.570 g, 24 mmol) and K_2CO_3 (5.530 g, 40 mmol). The reaction mixture was stirred at room temperature for 24 h. The progress of the reaction was monitored by TLC. The reaction mixture was filtered through celite, and the filtrate was diluted with water (30 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with cold water and brine and dried over Na_2SO_4, filtered and the filtrate was evaporated under vacuum. The crude product was purified using column chromatography over silica gel to afford product **6i** as colourless liquid (3.880 g, 95% yield).[15]

Prop-2-yn-1-yl 2-(4-methoxyphenyl)acetate (6i):



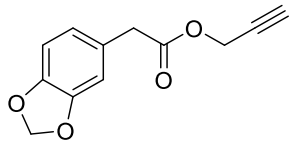
Compound **6i** was synthesized following the general procedure (A). The product was obtained as colourless liquid (3.880 g, 95% yield): R_f = 0.5 petroleum ether/EtOAc (80:20); IR (neat) cm^{-1}: 3285, 2948, 2128, 1736, 1511, 1242, 1138, 1025, 938, 819, 780, 682, 643; ^1H NMR (400 MHz, $CDCl_3$): δ 7.23 – 7.17 (m, 2H), 6.89 – 6.83 (m, 2H), 4.68 (d, J = 2.5 Hz, 2H), 3.79 (s, 3H), 3.61 (s, 2H), 2.47 (t, J = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 159.0, 130.4, 125.6, 114.2, 77.7, 75.1, 55.4, 52.4, 40.2; HRMS (ESI TOF): Calculated for $C_{12}H_{12}NaO_3$ $(M + Na)^+$: 227.0684, Found: 227.0685.

Prop-2-yn-1-yl 2-(3,4-dimethoxyphenyl)acetate (6k):



Compound **6k** was synthesized following the general procedure (A). The product was obtained as colourless liquid (3.98 g, 85% yield): R_f = 0.35 petroleum ether/EtOAc (70:30); IR (neat) cm^{-1}: 3276, 2944, 2836, 2126, 1737, 1593, 1513, 1456, 1370, 1259, 1133, 1021, 938, 808, 758; ^1H NMR (400 MHz, $CDCl_3$): δ 6.82 (s, 3H), 4.70 (d, J = 2.4 Hz, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.62 (s, 2H), 2.48 (t, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 149.0, 148.3, 125.9, 121.5, 112.4, 111.3, 77.6, 75.1, 56.0, 55.9, 52.4, 40.6; HRMS (ESI TOF): Calculated for $C_{13}H_{14}NaO_4$ $(M + Na)^+$: 257.0790, Found: 257.0791.

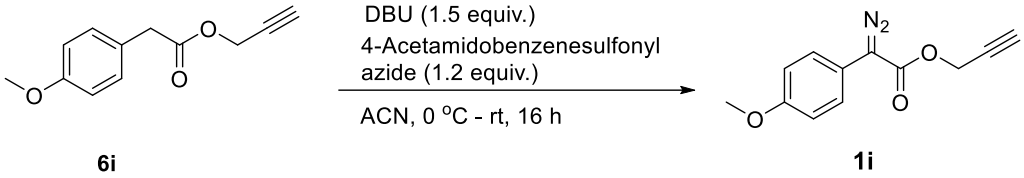
Prop-2-yn-1-yl 2-(benzo[d][1,3]dioxol-5-yl)acetate (6l):



Compound **6l** was synthesized following the general procedure (A). The product was obtained as colourless liquid (3.930 g, 90% yield): R_f = 0.4 petroleum ether/EtOAc (80:20); IR (neat) cm^{-1}: 3287, 2896, 2780, 2128, 1736, 1673, 1611, 1493, 1442, 1367, 1325, 1242, 1188, 1137, 1032, 1001, 927, 867, 790, 747, 639; ^1H NMR (400 MHz, $CDCl_3$): δ 6.79-6.75

(m, 2H), 6.73-6.70 (m, 1H), 5.94 (s, 2H), 4.69 (d, *J* = 2.5 Hz, 2H), 3.58 (s, 2H), 2.48 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 147.9, 146.9, 127.0, 122.6, 109.8, 108.4, 101.2, 77.6, 75.2, 52.5, 40.6; HRMS (ESI TOF): Calculated for $C_{12}H_{11}O_4$ $(M + H)^+$: 219.0657, Found: 219.0648.

5.4.3 General procedure B for the synthesis of *α*-aryl-*α*-diazoacetates



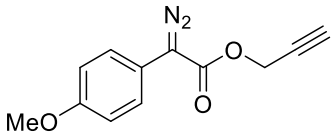
6i

(1 equiv.)

1i

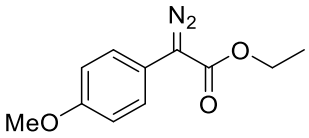
To the stirred solution prop-2-yn-1-yl 2-(4-methoxyphenyl)acetate **6i** (2.040 g, 10 mmol) in 15 ml acetonitrile was added 4-acetamidobenzenesulfonyl azide (2.880 g, 12 mmol) and DBU (2.24 mL, 15 mmol) at ambient temperature under inert atmosphere. The reaction mixture was stirred for 16 h at room temperature. The reaction was quenched with saturated NH_4Cl and the product was extracted with diethyl ether. The combined organic layers were washed with brine and dried over Na_2SO_4, filtered and the filtrate was evaporated under vacuum. The crude product was purified using column chromatography over silica gel to afford *α*-aryl-*α*-diazoacetates **1i** as orange solid (1.934 g, 84% yield).[16]

Prop-2-yn-1-yl 2-diazo-2-(4-methoxyphenyl)acetate (1i):



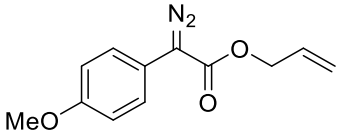
Compound **1i** was synthesized following the general procedure (B). The product was obtained as dark orange solid (1.934 g, 84% yield): R_f = 0.3 petroleum ether/EtOAc (95:5); m.p.: 68-69 °C; IR (neat) cm^{-1}: 3289, 2949, 2837, 2081, 1694, 1609, 1573, 1510, 1240, 1142, 1022, 949, 825, 735, 680, 640; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 – 7.30 (m, 2H), 7.09 – 6.81 (m, 2H), 4.86 (d, *J* = 2.4 Hz, 2H), 3.81 (s, 3H), 2.51 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.0, 158.3, 126.2, 116.5, 114.8, 77.8, 75.2, 55.5, 52.3; HRMS (ESI TOF): Calculated for $C_{12}H_{10}N_2NaO_3$ $(M + Na)^+$: 253.0589, Found: 253.0584.

Ethyl 2-diazo-2-(4-methoxyphenyl)acetate (1i′):



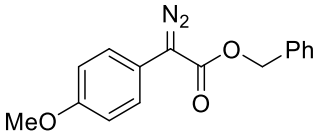
Compound **1i′** was synthesized following the general procedure (B). The product was obtained as orange liquid (1.650 g, 75% yield): R_f = 0.5 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 2983, 2837, 2079, 1696, 1573, 1512, 1461, 1339, 1295, 1158, 1098, 987, 828; ^1H NMR (400 MHz, $CDCl_3$): δ 7.41 – 7.36 (m, 2H), 6.97 – 6.91 (m, 2H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 158.1, 126.1, 117.2, 114.7, 61.1, 55.5, 14.6; HRMS (ESI TOF): Calculated for $C_{11}H_{12}N_2NaO_3$ $(M + Na)^+$: 243.0746, Found: 243.0739.

Allyl 2-diazo-2-(4-methoxyphenyl)acetate (1i′′):



Compound **1i′′** was synthesized following the general procedure (B). The product was obtained as orange liquid (1.810 g, 78% yield): R_f = 0.5 petroleum ether/EtOAc (95:5); IR (neat) cm^{-1}: 2947, 2839, 2080, 1695, 1606, 1510, 1454, 1294, 1242, 1149, 1020, 930, 825, 738, 609; ^1H NMR (400 MHz, $CDCl_3$): δ 7.44 – 7.34 (m, 2H), 6.98 – 6.90 (m, 2H), 5.97 (ddt, *J* = 17.2, 10.5, 5.6 Hz, 1H), 5.38 – 5.32 (m, 1H), 5.28 – 5.25 (m, 1H), 4.76 (t, *J* = 1.4 Hz, 1H), 4.75 (t, *J* = 1.4 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.4, 158.1, 132.2, 126.0, 118.3, 116.8, 114.6, 65.4, 55.4; HRMS (ESI TOF): Calculated for $C_{12}H_{12}N_2NaO_3$ $(M + Na)^+$: 255.0746, Found: 255.0739.

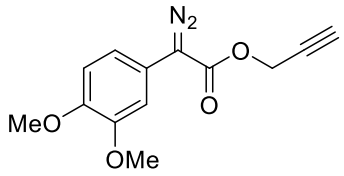
Benzyl 2-diazo-2-(4-methoxyphenyl)acetate (1i′′′):



Compound **1i′′′** was synthesized following the general procedure (B). The product was obtained as orange solid (1.980 g, 70% yield): R_f = 0.7 petroleum ether/EtOAc (80:20);

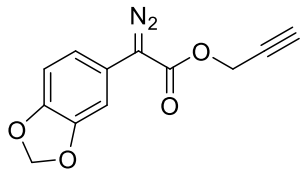
m.p.: 31-33 °C; IR (neat) cm^{-1}: 2949, 2837, 2079, 1691, 1608, 1509, 1455, 1381, 1339, 1295, 1242, 1146, 1015, 911, 825, 738, 696, 605; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 – 7.31 (m, 7H), 6.94 (d, *J* = 9.0 Hz, 2H), 5.30 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 158.3, 136.1, 128.7, 128.4, 128.3, 126.1, 117.0, 114.8, 66.6, 55.5; HRMS (ESI TOF): Calculated for $C_{16}H_{14}N_2NaO_3$ $(M + Na)^+$: 305.0902, Found: 305.0905.

Prop-2-yn-1-yl 2-diazo-2-(3,4-dimethoxyphenyl)acetate (1k):



Compound **1k** was synthesized following the general procedure (B). The product was obtained as pale yellow liquid (1.690 g, 65% yield): R_f = 0.3 petroleum ether/EtOAc (90:10); IR (neat) cm^{-1}: 3230, 2939, 2840, 2087, 1678, 1581, 1517, 1455, 1385, 1233, 1139, 1051, 951, 866, 793, 732; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (d, *J* = 1.9 Hz, 1H), 7.00 – 6.79 (m, 2H), 4.87 (d, *J* = 2.5 Hz, 2H), 3.90 (s, 3H), 3.89 (s, 3H), 2.52 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 149.6, 147.6, 117.0, 116.6, 111.8, 108.5, 77.8, 75.3, 56.1, 56.0, 52.3; HRMS (ESI TOF): Calculated for $C_{13}H_{13}N_2O_4$ $(M + Na)^+$: 261.0875, Found: 261.0875.

Prop-2-yn-1-yl 2-(benzo[d][1,3]dioxol-5-yl)-2-diazoacetate (1l):



Compound **1l** was synthesized following the general procedure (B). The product was obtained as dark orange solid (1.700 g, 70% yield): R_f = 0.4 petroleum ether/EtOAc (80:20); m.p.: 87-89 °C; IR (neat) cm^{-1}: 3290, 2896, 2781, 2383, 1695, 1610, 1494, 1445, 1376, 1325, 1279, 1233, 168, 1130, 1100, 1030, 931, 864, 808, 733, 678; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05 (d, *J* = 1.1 Hz, 1H), 6.94 – 6.74 (m, 2H), 5.97 (s, 2H), 4.85 (d, *J* = 2.5 Hz, 2H), 2.51 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 148.5, 146.4, 118.2, 118.1, 109.0, 106.0, 101.4, 77.8, 75.3, 52.4; HRMS (ESI TOF): Calculated for $C_{12}H_8N_2NaO_4$ $(M + Na)^+$: 267.0382, Found: 267.0381.

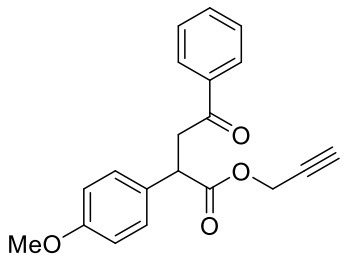
5.4.4 General Procedure C for the screening of catalyst

A mixture of 5 mol% of Lewis acid catalyst and *ß*-keto acid **2a** was stirred in 1.5 mL solvent ranging from -20 ^{o}C to room temperature in a two-necked RB flask under inert atmosphere. Then propargyl *α*-aryl-*α*-diazoacetate **1i** (0.115 g, 0.5 mmol) in 1.5 mL of solvent was added dropwise to above reaction mixture over 45 min, and then the reaction mixture was allowed to warm to room temperature and stirred for 18-24 h. The progress of the reaction was monitored by TLC. Later, the reaction mixture was diluted with 4 mL ethyl acetate & solid Na_2CO_3 (0.159 g, 1.5 mmol) was added in the reaction mixture. The reaction mixture again stirred at room temperature over 6 h. The reaction mixture was filtered through a sintered funnel, and the filtrate was evaporated under reduced pressure. The crude product was purified by column chromatography over silica gel to furnish the product *α*-substituted *γ*-keto ester **3ia** (see Table 5.1).

5.4.5 General Procedure D for preparation of *α*-substituted *γ*-keto esters

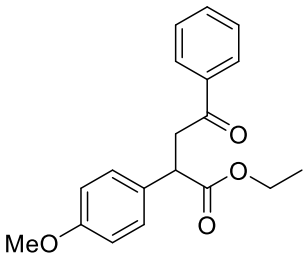
A mixture of $Sc(OTf)_3$ (12.3 mg, 5 mol%) and *ß*-keto acid **2a** (0.205 g, 1.25 mmol) was stirred in 2 mL THF at -20 ^{o}C in a two-necked RB flask under inert atmosphere. Then *α*-aryl-*α*-diazoacetate **1i** (0.115 g, 0.5 mmol) dissolved in 1.5 mL of THF was added to the reaction mixture dropwise over 45 min. Then the reaction mixture was allowed to warm to room temperature & stirred over 18 h. The progress of the reaction was monitored by TLC. Then, the reaction mixture was diluted with 5 mL ethyl acetate and solid Na_2CO_3 (0.159 g, 1.5 mmol) was added in the reaction mixture. The reaction mixture again stirred at room temperature over 6 h. The reaction mixture filtered through a sintered funnel and the filtrate was evaporated under reduced pressure. The crude product was purified by column chromatography over silica gel to furnish the product *α*-substituted *γ*-keto ester **3ia** as a colourless liquid (0.123 g, 76% yield).

Prop-2-yn-1-yl 2-(4-methoxyphenyl)-4-oxo-4-phenylbutanoate (3ia):



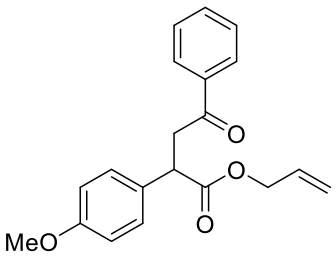
Compound **3ia** was synthesized following the general procedure (D). The product was obtained as colourless liquid (0.123 g, 76% yield): R_f = 0.25 petroleum ether/EtOAc (85:15); IR (neat) cm^{-1}: 3284, 2945, 2839, 2124, 1738, 1683, 1603, 1511, 1449, 1250, 1155, 1027, 990, 835, 758, 685; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 – 7.93 (m, 2H), 7.58 – 7.52 (m, 1H), 7.48 – 7.41 (m, 2H), 7.31 – 7.25 (m, 2H), 6.91 – 6.85 (m, 2H), 4.75 – 4.61 (m, 2H), 4.27 (dd, *J* = 10.1, 4.3 Hz, 1H), 3.90 (dd, *J* = 18.0, 10.1 Hz, 1H), 3.79 (s, 3H), 3.29 (dd, *J* = 18.0, 4.3 Hz, 1H), 2.42 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.6, 172.9, 159.2, 136.5, 133.4, 129.9, 129.0, 128.7, 128.2, 114.4, 77.6, 75.1, 55.4, 52.7, 45.5, 43.0; HRMS (ESI TOF): Calculated for $C_{20}H_{18}NaO_4$ $(M + Na)^+$: 345.1103, Found: 345.1101.

Ethyl 2-(4-methoxyphenyl)-4-oxo-4-phenylbutanoate (3i′a):



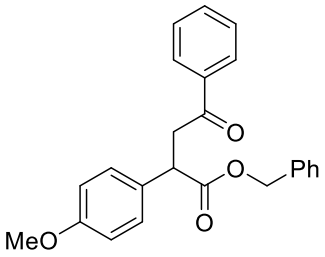
Compound **3i′a** was synthesized following the general procedure (D). The product was obtained as colourless liquid (0.070 g, 45% yield): R_f = 0.3 petroleum ether/EtOAc (85:15); IR (neat) cm^{-1}: 2984, 2839, 2311, 2110, 1730, 1686, 1607, 1513, 1454, 1365, 1304, 1252, 1171, 1096, 1031, 992, 837, 761, 691; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (dt, *J* = 8.4, 1.6 Hz, 2H), 7.59 – 7.52 (m, 1H), 7.48 – 7.42 (m, 2H), 7.30 – 7.25 (m, 2H), 6.91 – 6.84 (m, 2H), 4.24 – 4.17 (m, 2H), 4.15 – 4.06 (m, 1H), 3.91 (dd, *J* = 17.9, 10.2 Hz, 1H), 3.80 (s, 3H), 3.24 (dd, *J* = 17.9, 4.2 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.9, 173.7, 159.0, 136.6, 133.4, 130.6, 129.0, 128.7, 128.2, 114.3, 61.2, 55.4, 45.8, 43.0, 14.2; HRMS (ESI TOF): Calculated for $C_{19}H_{20}NaO_4$ $(M + Na)^+$: 335.1259, Found: 335.1259.

Allyl 2-(4-methoxyphenyl)-4-oxo-4-phenylbutanoate (3i′′a):



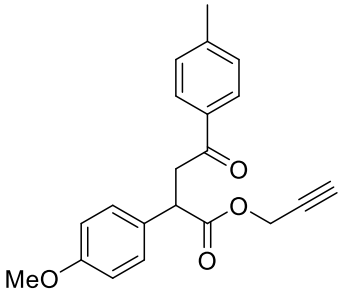
Compound **3i′′a** was synthesized following the general procedure (D). The product was obtained as colourless liquid (0.076 g, 47% yield): R_f = 0.3 petroleum ether/EtOAc (85:15); IR (neat) cm^{-1}: 2983, 2841, 2110, 1731, 1683, 1603, 1510, 1450, 1359, 1305, 1247, 1158, 1089, 1030, 990, 834, 759; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 – 7.94 (m, 2H), 7.58 – 7.52 (m, 1H), 7.48 – 7.41 (m, 2H), 7.31 – 7.26 (m, 2H), 6.91 – 6.85 (m, 2H), 5.92 – 5.78 (m, 1H), 5.24 – 5.13 (m, 2H), 4.65 – 4.54 (m, 2H), 4.27 (dd, *J* = 10.2, 4.2 Hz, 1H), 3.92 (dd, *J* = 18.0, 10.2 Hz, 1H), 3.79 (s, 3H), 3.26 (dd, *J* = 18.0, 4.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.8, 173.4, 159.1, 136.5, 133.4, 132.1, 130.4, 129.0, 128.7, 128.2, 118.0, 114.4, 65.6, 55.4, 45.7, 42.9; HRMS (ESI TOF): Calculated for $C_{20}H_{21}O_4$ $(M + H)^+$: 325.1440, Found: 325.1444.

Benzyl 2-(4-methoxyphenyl)-4-oxo-4-phenylbutanoate (3i′′′a):



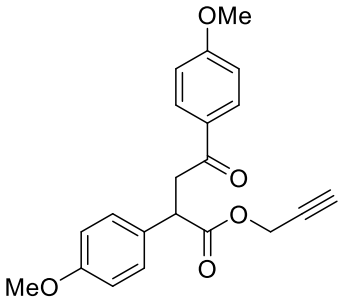
Compound **3i′′′a** was synthesized following the general procedure (D). The product was obtained as colourless liquid (0.092 g, 49% yield): R_f = 0.3 petroleum ether/EtOAc (85:15); IR (neat) cm^{-1}: 3060, 2923, 2845, 2109, 1730, 1683, 1604, 1509, 1452, 1304, 1248, 1155, 1083, 1031, 994, 910, 834, 750, 692; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (dt, *J* = 8.5, 1.7 Hz, 2H), 7.58 – 7.52 (m, 1H), 7.47 – 7.41 (m, 2H), 7.32 – 7.20 (m, 7H), 6.88 – 6.83 (m, 2H), 5.13 (q, *J* = 12.6 Hz, 2H), 4.31 (dd, *J* = 10.2, 4.3 Hz, 1H), 3.92 (dd, *J* = 18.0, 10.2 Hz, 1H), 3.79 (s, 3H), 3.27 (dd, *J* = 18.0, 4.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.8, 173.5, 159.1, 136.5, 136.0, 133.4, 130.3, 129.1, 128.7, 128.5, 128.2, 128.1, 127.9, 114.3, 66.7, 55.4, 45.7, 42.8; HRMS (ESI TOF): Calculated for $C_{24}H_{23}O_4$ $(M + H)^+$: 375.1596, Found: 375.1599.

Prop-2-yn-1-yl 2-(4-methoxyphenyl)-4-oxo-4-(p-tolyl)butanoate (3ib):



Compound **3ib** was synthesized following the general procedure (D). The product was obtained as colourless liquid (0.114 g, 68% yield): R_f = 0.25 petroleum ether/EtOAc (85:15); IR (neat) cm^{-1}: 3284, 2946, 2841, 2378, 2123, 1738, 1679, 1608, 1511, 1450, 1405, 1304, 1251, 1155, 1084, 1028, 988, 811, 762, 678; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J* = 8.2 Hz, 2H), 7.28 – 7.22 (m, 4H), 6.90 – 6.83 (m, 2H), 4.67 (qd, *J* = 15.6, 2.5 Hz, 2H), 4.26 (dd, *J* = 10.1, 4.3 Hz, 1H), 3.90 – 3.82 (m, 1H), 3.78 (s, 3H), 3.26 (dd, *J* = 18.0, 4.3 Hz, 1H), 2.42 (t, *J* = 2.5 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.1, 173.0, 159.1, 144.2, 134.0, 129.9, 129.4, 129.0, 128.3, 114.4, 77.6, 75.0, 55.3, 52.6, 45.5, 42.8, 21.7. HRMS (ESI TOF): Calculated for $C_{21}H_{21}O_4$ $(M + H)^+$: 337.1440, Found: 337.1439.

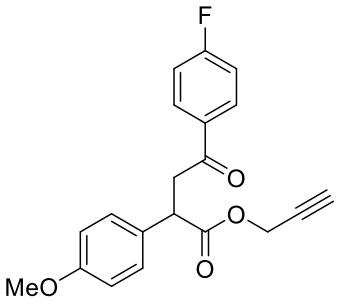
Prop-2-yn-1-yl 2,4-bis(4-methoxyphenyl)-4-oxobutanoate (3ic):



Compound **3ic** was synthesized following the general procedure (D). The product was obtained as colourless liquid (0.113 g, 64% yield): R_f = 0.15 petroleum ether/EtOAc (85:15); IR (neat) cm^{-1}: 3284, 2945, 2840, 2125, 1737, 1673, 1600, 1510, 1457, 1361, 1311, 1251, 1157, 1082, 1027, 987, 829, 757, 680; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 – 7.90 (m, 2H), 7.31 – 7.24 (m, 2H), 6.95 – 6.84 (m, 4H), 4.75 – 4.61 (m, 2H), 4.26 (dd, *J* = 10.1, 4.3 Hz, 1H), 3.88 – 3.80 (m, 1H), 3.86 (s, 3H), 3.79 (s, 3H), 3.24 (dd, *J* = 17.8, 4.3 Hz, 1H), 2.42 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.1, 173.1, 163.8, 159.1, 130.5, 130.0,

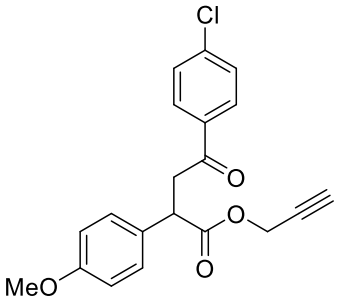
129.6, 129.0, 114.4, 113.9, 77.6, 75.0, 55.6, 55.4, 52.6, 45.6, 42.6; HRMS (ESI TOF): Calculated for $C_{21}H_{21}O_5$ $(M + H)^+$: 353.1389, Found: 353.1394.

Prop-2-yn-1-yl 4-(4-fluorophenyl)-2-(4-methoxyphenyl)-4-oxobutanoate (3id):



Compound **3id** was synthesized following the general procedure (D). The product was obtained as colourless liquid (0.124 g, 73% yield): R_f = 0.25 petroleum ether/EtOAc (85:15); IR (neat) cm^{-1}: 3287, 2949, 2839, 2310, 2125, 1737, 1683, 1597, 1509, 1453, 1408, 1304, 1238, 1150, 1087, 1027, 990, 828, 757, 678; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 – 7.95 (m, 2H), 7.30 – 7.24 (m, 2H), 7.15 – 7.07 (m, 2H), 6.91 – 6.84 (m, 2H), 4.68 (qd, *J* = 15.6, 2.5 Hz, 2H), 4.26 (dd, *J* = 10.2, 4.2 Hz, 1H), 3.91 – 3.82 (m, 1H), 3.79 (s, 3H), 3.24 (dd, *J* = 18.0, 4.2 Hz, 1H), 2.43 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.0, 172.9, 166.0 (d, *J* = 255.1 Hz), 159.2, 132.9 (d, *J* = 3.0 Hz), 130.8 (d, *J* = 9.3 Hz), 129.7, 129.0, 115.8 (d, *J* = 21.9 Hz), 114.4, 77.5, 75.1, 55.4, 52.7, 45.5, 42.8; HRMS (ESI TOF): Calculated for $C_{20}H_{18}FO_4$ $(M + H)^+$: 341.1189, Found: 341.1194.

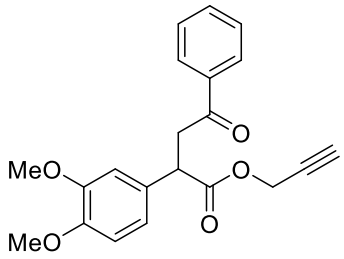
Prop-2-yn-1-yl 4-(4-chlorophenyl)-2-(4-methoxyphenyl)-4-oxobutanoate (3ie):



Compound **3ie** was synthesized following the general procedure (D). The product was obtained as colourless liquid (0.111 g, 62% yield): R_f = 0.25 petroleum ether/EtOAc (85:15); IR (neat) cm^{-1}: 3288, 2933, 2841, 2376, 2123, 1738, 1684, 1590, 1511, 1450, 1398, 1303, 1251, 1155, 1088, 1026, 990, 823, 679, 640; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 – 7.86 (m,

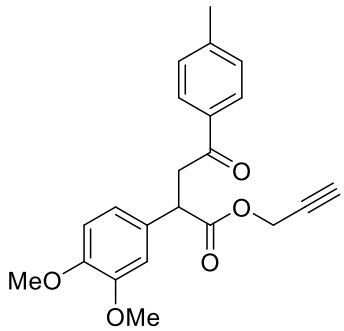
2H), 7.45 – 7.39 (m, 2H), 7.29 – 7.23 (m, 2H), 6.91 – 6.84 (m, 2H), 4.75 – 4.60 (m, 2H), 4.26 (dd, *J* = 10.2, 4.2 Hz, 1H), 3.86 (dd, *J* = 18.0, 10.2 Hz, 1H), 3.79 (s, 3H), 3.24 (dd, *J* = 18.0, 4.2 Hz, 1H), 2.43 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.4, 172.9, 159.2, 139.9, 134.7, 129.6, 129.6, 129.0, 129.0, 114.4, 77.3, 75.1, 55.4, 52.7, 45.4, 42.9; HRMS (ESI TOF): Calculated for $C_{20}H_{18}ClO_4$ $(M + H)^+$: 357.0894, Found: 357.0899.

Prop-2-yn-1-yl 2-(3,4-dimethoxyphenyl)-4-oxo-4-phenylbutanoate (3ka):



Compound **3ka** was synthesized following the general procedure (D). The product was obtained as colourless liquid (0.109 g, 62% yield): R_f = 0.25 petroleum ether/EtOAc (75:25); IR (neat) cm^{-1}: 3278, 2943, 2838, 2124, 1738, 1683, 1593, 1514, 1453, 1331, 1251, 1150, 1025, 932, 860, 813, 761, 689, 640; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 – 7.94 (m, 2H), 7.61 – 7.53 (m, 1H), 7.50 – 7.42 (m, 2H), 6.93 – 6.81 (m, 3H), 4.77 – 4.64 (m, 2H), 4.27 (dd, *J* = 10.2, 4.2 Hz, 1H), 3.98 – 3.91 (m, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.31 (dd, *J* = 18.0, 4.2 Hz, 1H), 2.43 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.6, 172.8, 149.3, 148.6, 136.4, 133.5, 130.3, 128.7, 128.2, 120.1, 111.5, 111.0, 77.6, 75.1, 56.0, 56.0, 52.7, 45.9, 43.1; HRMS (ESI TOF): Calculated for $C_{21}H_{21}O_5$ $(M + H)^+$: 353.1389, Found: 353.1392.

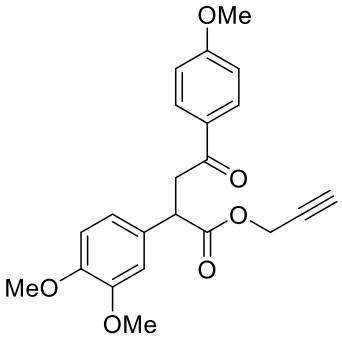
Prop-2-yn-1-yl 2-(3,4-dimethoxyphenyl)-4-oxo-4-(p-tolyl)butanoate (3kb):



Compound **3kb** was synthesized following the general procedure (D). The product was obtained as white solid (0.123 g, 67% yield): R_f = 0.27 petroleum ether/EtOAc (75:25);

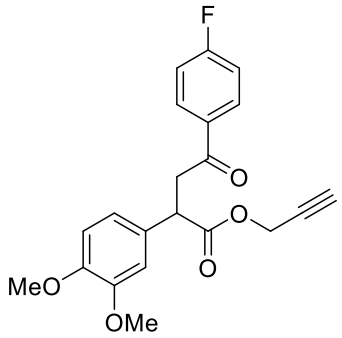
m.p.: 111-113 ^{o}C; IR (neat) cm^{-1}: 3277, 2944, 2839, 2123, 1737, 1679, 1602, 1514, 1455, 1332, 1250, 1149, 1086, 1024, 858, 810, 759, 678; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.2 Hz, 2H), 7.27 – 7.22 (m, 2H), 6.91 – 6.82 (m, 3H), 4.77 – 4.64 (m, 2H), 4.26 (dd, *J* = 10.2, 4.2 Hz, 1H), 3.98 – 3.89 (m, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.29 (dd, *J* = 18.0, 4.2 Hz, 1H), 2.42 (t, *J* = 2.5 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.2, 172.9, 149.3, 148.6, 144.3, 134.0, 130.4, 129.4, 128.3, 120.1, 111.5, 111.0, 77.6, 75.0, 56.0, 56.0, 52.7, 46.0, 42.9, 21.8; HRMS (ESI TOF): Calculated for $C_{22}H_{23}O_5$ $(M + H)^+$: 367.1545, Found: 367.1546.

Prop-2-yn-1-yl 2-(3,4-dimethoxyphenyl)-4-(4-methoxyphenyl)-4-oxobutanoate (3kc):



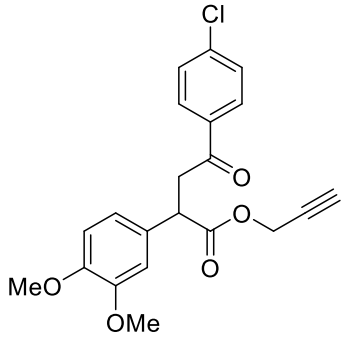
Compound **3kc** was synthesized following the general procedure (D). The product was obtained as colourless liquid (0.123 g, 67% yield): R_f = 0.25 petroleum ether/EtOAc (75:25); IR (neat) cm^{-1}: 3278, 3008, 2942, 2840, 2122 1737, 1673, 1598, 1513, 1457, 1322, 1251, 1152, 1086, 1024, 826, 754, 634; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 – 7.91 (m, 2H), 6.96 – 6.86 (m, 4H), 6.83 (d, *J* = 8.2 Hz, 1H), 4.76 – 4.63 (m, 2H), 4.25 (dd, *J* = 10.2, 4.2 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.85 (s, 3H), 3.83 (d, *J* = 10.2 Hz, 1H), 3.26 (dd, *J* = 17.8, 4.2 Hz, 1H), 2.43 (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.0, 172.9, 163.7, 149.2, 148.5, 130.4, 130.4, 129.5, 120.0, 113.8, 111.4, 110.9, 77.6, 75.0, 56.0, 55.6, 55.5, 52.6, 45.9, 42.6; HRMS (ESI TOF): Calculated for $C_{22}H_{23}O_6$ $(M + H)^+$: 383.1495, Found: 383.1495.

Prop-2-yn-1-yl 2-(3,4-dimethoxyphenyl)-4-(4-fluorophenyl)-4-oxobutanoate (3kd):



Compound **3kd** was synthesized following the general procedure (D). The product was obtained as white solid (0.102 g, 55% yield): R_f = 0.3 petroleum ether/EtOAc (70:30); m.p.: 83-85 ^oC; IR (neat) cm^{-1}: 3273, 2932,2842, 2121, 1738, 1682, 1596, 1513, 1457, 1415, 1332, 1240, 1151, 1092, 1023, 834, 759, 678, 639; ^1H NMR (400 MHz, $CDCl_3$): δ 8.03 – 7.97 (m, 2H), 7.16 – 7.09 (m, 2H), 6.91 – 6.83 (m, 3H), 4.76 – 4.64 (m, 2H), 4.26 (dd, *J* = 10.3, 4.1 Hz, 1H), 3.99 – 3.89 (m, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.27 (dd, *J* = 18.0, 4.1 Hz, 1H), 2.44 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.0, 172.8, 166.0 (d, *J* = 255.0 Hz), 149.3, 148.6, 132.8 (d, *J* = 2.6 Hz), 130.9 (d, *J* = 9.4 Hz), 130.1, 120.0, 115.9 (d, *J* = 21.9 Hz), 111.5, 110.9, 77.4, 75.1, 56.0 (for two carbon), 52.7, 45.9, 43.0; HRMS (ESI TOF): Calculated for $C_{21}H_{20}FO_5$ $(M + H)^+$: 371.1295, Found: 371.1299.

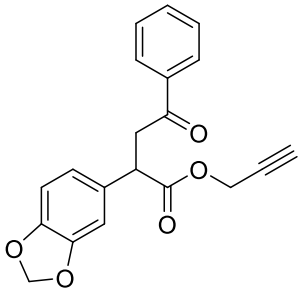
Prop-2-yn-1-yl 4-(4-chlorophenyl)-2-(3,4-dimethoxyphenyl)-4-oxobutanoate (3ke):



Compound **3ke** was synthesized following the general procedure (D). The product was obtained as colourless liquid (0.112 g, 58% yield): R_f = 0.35 petroleum ether/EtOAc (70:30); IR (neat) cm^{-1}: 3287, 2924, 2851, 2122, 1737, 1684, 1590, 1514, 1456, 1401, 1332, 1250, 1150, 1089, 1023, 818, 757, 675; ^1H NMR (400 MHz, $CDCl_3$): δ 7.94 – 7.88 (m, 2H), 7.46 – 7.41 (m, 2H), 6.90 – 6.83 (m, 3H), 4.76 – 4.64 (m, 2H), 4.25 (dd, *J* = 10.3, 4.1 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.90 – 3.83 (m, 1H), 3.26 (dd, *J* = 18.1, 4.1 Hz, 1H), 2.43 (t, *J*

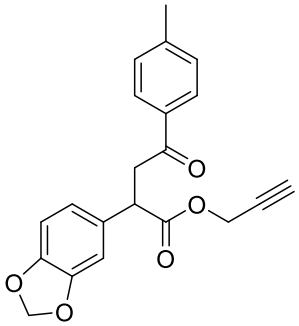
= 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.4, 172.8, 149.3, 148.7, 140.0, 134.7, 130.1, 129.6, 129.1, 120.1, 111.5, 110.9, 77.5, 75.1, 56.1, 56.0, 52.8, 45.9, 43.0; HRMS (ESI TOF): Calculated for $C_{21}H_{20}ClO_5$ $(M + H)^+$: 387.0999, Found: 387.1001.

Prop-2-yn-1-yl 2-(benzo[*d*][1,3]dioxol-5-yl)-4-oxo-4-phenylbutanoate (3la):



Compound **3la** was synthesized following the general procedure (D). The product was obtained as colourless liquid (0.108 g, 64% yield): R_f = 0.3 petroleum ether/EtOAc (80:20); IR (neat) cm^{-1}: 3289, 2905, 2783, 2125, 1737, 1682, 1600, 1492, 1443, 1363, 1329, 1238, 1155, 1099, 1035, 992, 930, 863, 814, 755, 685, 635; ^{1}H NMR (400 MHz, $CDCl_3$): 7.97 – 7.94 (m, 2H), 7.61 – 7.51 (m, 1H), 7.48 – 7.40 (m, 2H), 6.92 – 6.70 (m, 3H), 5.94 (s, 2H), 4.69 (qd, *J* = 15.6, 2.5 Hz, 2H), 4.24 (dd, *J* = 10.1, 4.3 Hz, 1H), 3.87 (dd, *J* = 18.0, 10.1 Hz, 1H), 3.28 (dd, *J* = 18.0, 4.3 Hz, 1H), 2.44 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.4, 172.7, 148.1, 147.2, 136.4, 133.5, 131.5, 128.7, 128.2, 121.3, 108.7, 108.3, 101.3, 77.5, 75.2, 52.7, 45.9, 43.0; HRMS (ESI TOF): Calculated for $C_{20}H_{17}O_5$ $(M + H)^+$: 337.1076, Found: 337.1075.

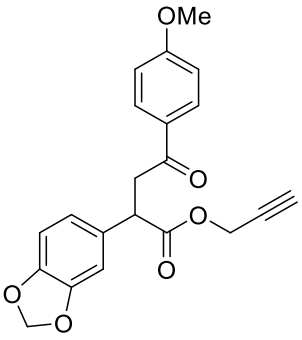
Prop-2-yn-1-yl 2-(benzo[*d*][1,3]dioxol-5-yl)-4-oxo-4-(*p*-tolyl)butanoate (3lb):



Compound **3lb** was synthesized following the general procedure (D). The product was obtained as colourless liquid (0.116 g, 66% yield): R_f = 0.4 petroleum ether/EtOAc (70:30); IR (neat) cm^{-1}: 3291, 2907, 2781, 2125, 1737, 1678, 1607, 1491, 1441, 1363, 1330, 1235,

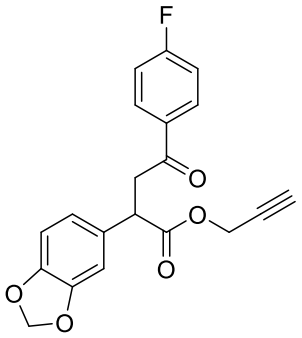
1153, 1034, 989, 930, 861, 808, 751, 672, 632, 565; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 – 7.81 (m, 2H), 7.91 – 7.81 (m, 2H), 6.85 – 6.75 (m, 3H), 5.93 (s, 2H), 4.68 (qd, *J* = 15.6, 2.5 Hz, 2H), 4.22 (dd, *J* = 10.1, 4.3 Hz, 1H), 3.83 (dd, *J* = 18.0, 10.1 Hz, 1H), 3.26 (dd, *J* = 18.0, 4.3 Hz, 1H), 2.44 (t, *J* = 2.5 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.0, 172.7, 148.1, 147.1, 144.3, 133.9, 131.6, 129.4, 128.3, 121.3, 108.6, 108.3, 101.2, 77.5, 75.1, 52.7, 45.9, 42.8, 21.7; HRMS (ESI TOF): Calculated for $C_{21}H_{19}O_5$ $(M + H)^+$: 351.1232, Found: 351.1241.

Prop-2-yn-1-yl 2-(benzo[*d*][1,3]dioxol-5-yl)-4-(4-methoxyphenyl)-4-oxobutanoate (3lc):



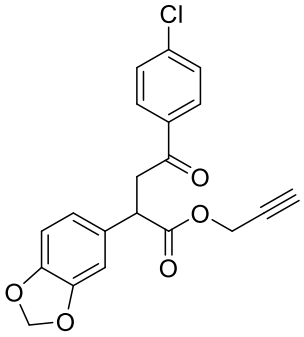
Compound **3lc** was synthesized following the general procedure (D). The product was obtained as colourless liquid (0.143 g, 78% yield): R_f = 0.2 petroleum ether/EtOAc (80:20); IR (neat) cm^{-1}: 3289, 2920, 2310, 2122, 1738, 1674, 1600, 1496, 1442, 1362, 1321, 1245, 1161, 1033, 989, 932, 821, 756, 681, 625; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 – 7.88 (m, 2H), 6.93 – 6.89 (m, 2H), 6.85 (d, *J* = 1.7 Hz, 1H), 6.83 – 6.74 (m, 2H), 5.93 (s, 2H), 4.69 (qd, *J* = 15.6, 2.5 Hz, 2H), 4.22 (dd, *J* = 10.1, 4.3 Hz, 1H), 3.85 (s, 3H), 3.84 – 3.77 (m, 1H), 3.24 (dd, *J* = 17.8, 4.3 Hz, 1H), 2.45 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.9, 172.8, 163.7, 148.0, 147.1, 131.6, 130.4, 129.4, 121.3, 113.8, 108.6, 108.3, 101.2, 77.5, 75.1, 55.5, 52.7, 46.0, 42.6; HRMS (ESI TOF): Calculated for $C_{21}H_{19}O_6$ $(M + H)^+$: 367.1182, Found: 367.1189.

Prop-2-yn-1-yl 2-(benzo[*d*][1,3]dioxol-5-yl)-4-(4-fluorophenyl)-4-oxobutanoate (3ld):



Compound **3ld** was synthesized following the general procedure (D). The product was obtained as colourless liquid (0.097 g, 55% yield): R_f = 0.3 petroleum ether/EtOAc (85:15); IR (neat) cm^{-1}: 3291, 2909, 2124, 1737, 1683, 1597, 1495, 1442, 1406, 1363, 1330, 1233, 1155, 1098, 1036, 992, 931, 822, 755, 676, 635; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 – 7.92 (m, 2H), 7.20 – 7.06 (m, 2H), 7.20 – 7.06 (m, 3H), 5.95 (s, 2H), 4.69 (qd, *J* = 15.6, 2.5 Hz, 2H), 4.23 (dd, *J* = 10.1, 4.3 Hz, 1H), 3.84 (dd, *J* = 18.0, 10.1 Hz, 1H), 3.24 (dd, *J* = 18.0, 4.3 Hz, 1H), 2.44 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.9, 172.7, 166.0 (d, *J* = 255.2 Hz), 148.2, 147.3, 132.9 (d, *J* = 3.0 Hz), 131.3, 130.9 (d, *J* = 9.4 Hz), 121.3, 115.9 (d, *J* = 21.9 Hz), 108.7, 108.3, 101.3, 77.4, 75.2, 52.8, 46.0, 42.9; HRMS (ESI TOF): Calculated for $C_{20}H_{16}FO_5$ $(M + H)^+$: 355.0982, Found: 355.0994.

Prop-2-yn-1-yl 2-(benzo[*d*][1,3]dioxol-5-yl)-4-(4-chlorophenyl)-4-oxobutanoate (3le):



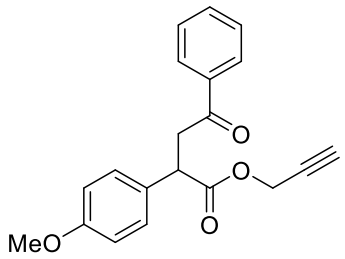
Compound **3le** was synthesized following the general procedure (D). The product was obtained as colourless liquid (0.104 g, 56% yield): R_f = 0.4 petroleum ether/EtOAc (75:25); IR (neat) cm^{-1}: 3290, 2918, 2310, 2123, 1738, 1685, 1589, 1493, 1442, 1397, 1364, 1330, 1239, 1159, 1092, 1037, 993, 932, 818, 679, 636; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 – 7.86 (m, 2H), 7.46 – 7.39 (m, 2H), 6.84 – 6.76 (m, 3H), 5.95 (s, 2H), 4.69 (qd, *J* = 15.6, 2.5 Hz, 2H), 4.22 (dd, *J* = 10.1, 4.2 Hz, 1H), 3.83 (dd, *J* = 18.1, 10.1 Hz, 1H), 3.24 (dd, *J* = 18.1, 4.2

Hz, 1H), 2.45 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.3, 172.6, 148.2, 147.3, 140.0, 134.7, 131.3, 129.6, 129.1, 121.3, 108.7, 108.3, 101.3, 77.4, 75.2, 52.8, 45.9, 42.9; HRMS (ESI TOF): Calculated for $C_{20}H_{16}ClO_5$ $(M + H)^+$: 371.0686, Found: 371.0683.

5.4.6 Gram-scale synthesis of *α*-substituted *γ*-keto ester

A mixture of $Sc(OTf)_3$ (0.123 g, 5 mol%) and *ß*-keto acid **2a** (2.050 g, 12.5 mmol) was stirred in 20 mL THF at -20 °C in 100 mL two necked RB flask under inert atmosphere. Then *α*-aryl-*α*-diazoacetate **1i** (1.020 g, 5 mmol) in 10 mL of THF was added to above reaction mixture drop wise via syringe over 45 minutes and then the reaction mixture was allowed to warm at room temperature & stirred over 24 h. The progress of the reaction was monitored by TLC. Reaction mixture was diluted with 25 mL ethyl acetate and solid Na_2CO_3 (1.590 g, 15 mmol) was added in the reaction mixture. The reaction mixture again stirred at room temperature over 6 h. Whole reaction mixture filtered through sintered funnel and solvent was removed under reduced pressure. The crude product obtained was purified by column chromatography over silica gel to furnish the desired product *α*-substituted *γ*-keto ester **3ia** as a viscous liquid in 71% yield (1.14 gram).

Prop-2-yn-1-yl 2-(4-methoxyphenyl)-4-oxo-4-phenylbutanoate (3ia):

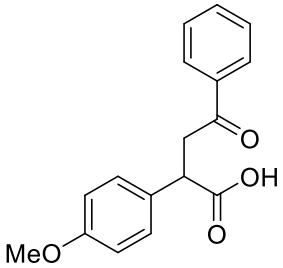


Compound **3ia** was synthesized following the general procedure (D). The product was obtained as colourless liquid (1.140 g, 71% yield): R_f = 0.25 petroleum ether/EtOAc (85:15); IR (neat) cm^{-1}: 3284, 2945, 2839, 2124, 1738, 1683, 1603, 1511, 1449, 1250, 1155, 1027, 990, 835, 758, 685; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 – 7.93 (m, 2H), 7.58 – 7.52 (m, 1H), 7.48 – 7.41 (m, 2H), 7.31 – 7.25 (m, 2H), 6.91 – 6.85 (m, 2H), 4.75 – 4.61 (m, 2H), 4.27 (dd, *J* = 10.1, 4.3 Hz, 1H), 3.90 (dd, *J* = 18.0, 10.1 Hz, 1H), 3.79 (s, 3H), 3.29 (dd, *J* = 18.0, 4.3 Hz, 1H), 2.42 (t, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.6, 172.9, 159.2, 136.5, 133.4, 129.9, 129.0, 128.7, 128.2, 114.4, 77.6, 75.1, 55.4, 52.7, 45.5, 43.0; HRMS (ESI TOF): Calculated for $C_{20}H_{18}NaO_4$ $(M + Na)^+$: 345.1103, Found: 345.1101.

5.4.7 Hydrolysis of the propargyl ester

A mixture of *α*-substituted *γ*-keto ester **3ia** (0.322 g, 1 equiv.) and $LiOH.H_2O$ (0.105 g, 2.5 equiv.) was taken in 25 mL RB flask & 5 mL solvent (THF: MeOH: H2O = 1:1:1) was added in above mixture under open atmosphere. The reaction mixture was stirred at room temperature over 1 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was acidified by using 3 N HCl and adjusted to pH 2-3. The crude product was extracted by using ethyl acetate. Solvent was removed under reduced pressure & crude product was purified by column chromatography over silica gel (100-200 mesh size) to furnish the product **4ia** as a white solid (0.262 g, 92% yield).

2-(4-methoxyphenyl)-4-oxo-4-phenylbutanoic acid (4ia):



The product was obtained as white solid (0.262 g, 92% yield): R_f = 0.4 petroleum ether/EtOAc (50:50); m.p.: 152-154 ^oC; ^1H NMR (400 MHz, DMSO-d_6): δ 12.32 (s, 1H), 8.06 – 7.92 (m, 2H), 7.67 – 7.61 (m, 1H), 7.56 – 7.48 (m, 2H), 7.34 – 7.27 (m, 2H), 6.94 – 6.86 (m, 2H), 4.06 (dd, *J* = 10.6, 3.8 Hz, 1H), 3.86 (dd, *J* = 18.1, 10.6 Hz, 1H), 3.73 (s, 3H), 3.25 (dd, *J* = 18.1, 3.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 198.1, 174.6, 158.4, 136.3, 133.4, 130.9, 129.0, 128.8, 128.0, 114.0, 55.1, 45.3, 42.1; HRMS (ESI TOF): Calculated for $C_{17}H_{15}O_4$ $(M-H)^-$: 283.0971, Found: 283.0974.

5.5 Appendix V: ^{1}H, ^{13}C NMR spectral data of representative compounds

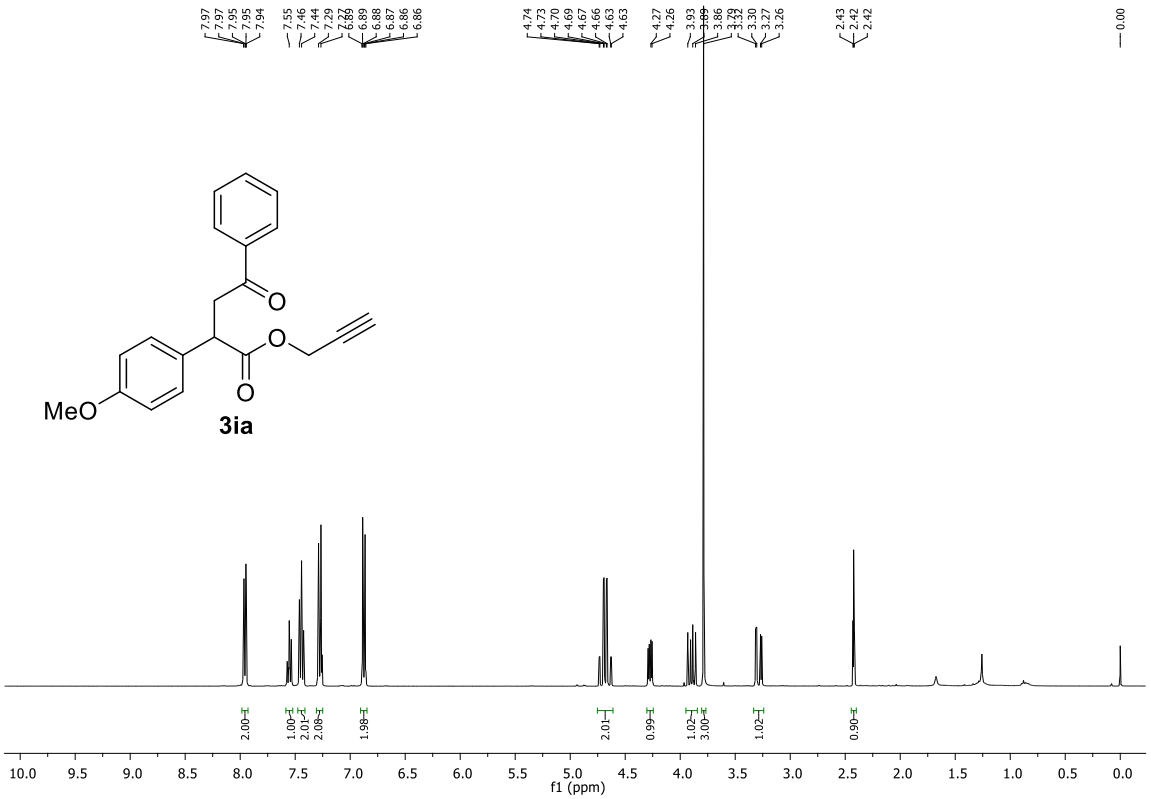


Figure V.1: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3ia**

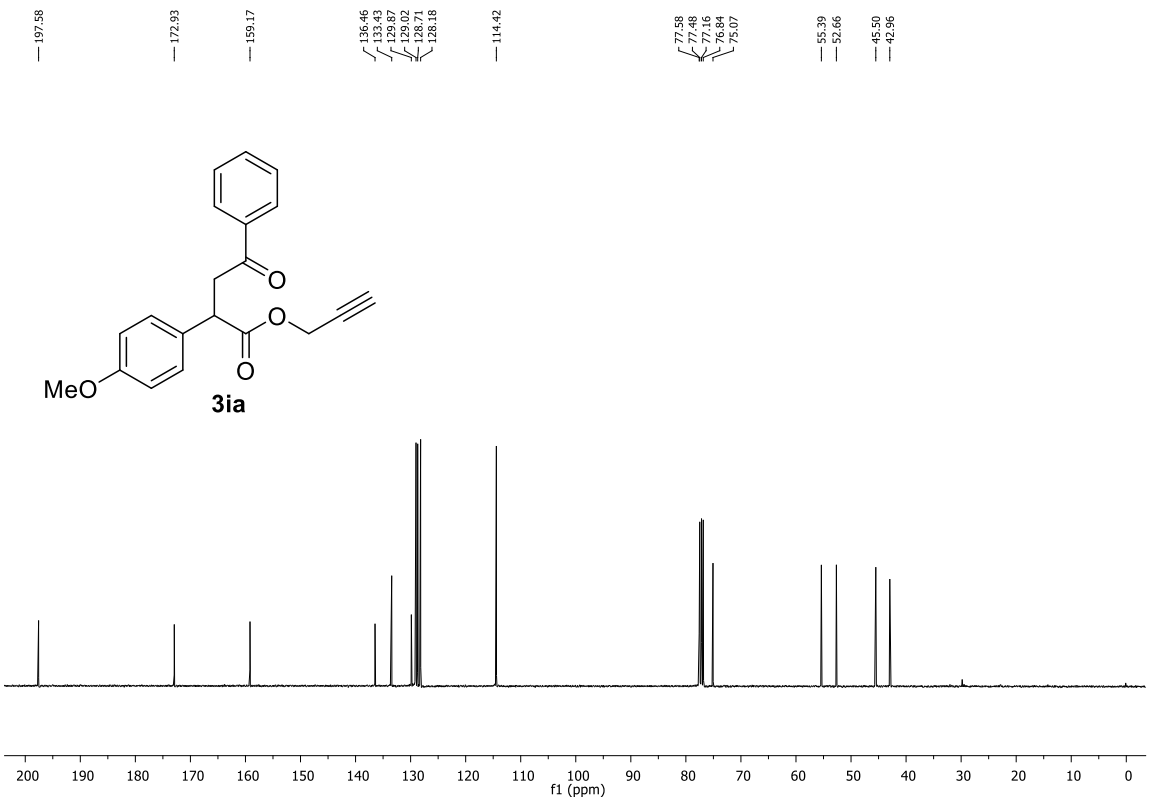


Figure V.2: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3ia**

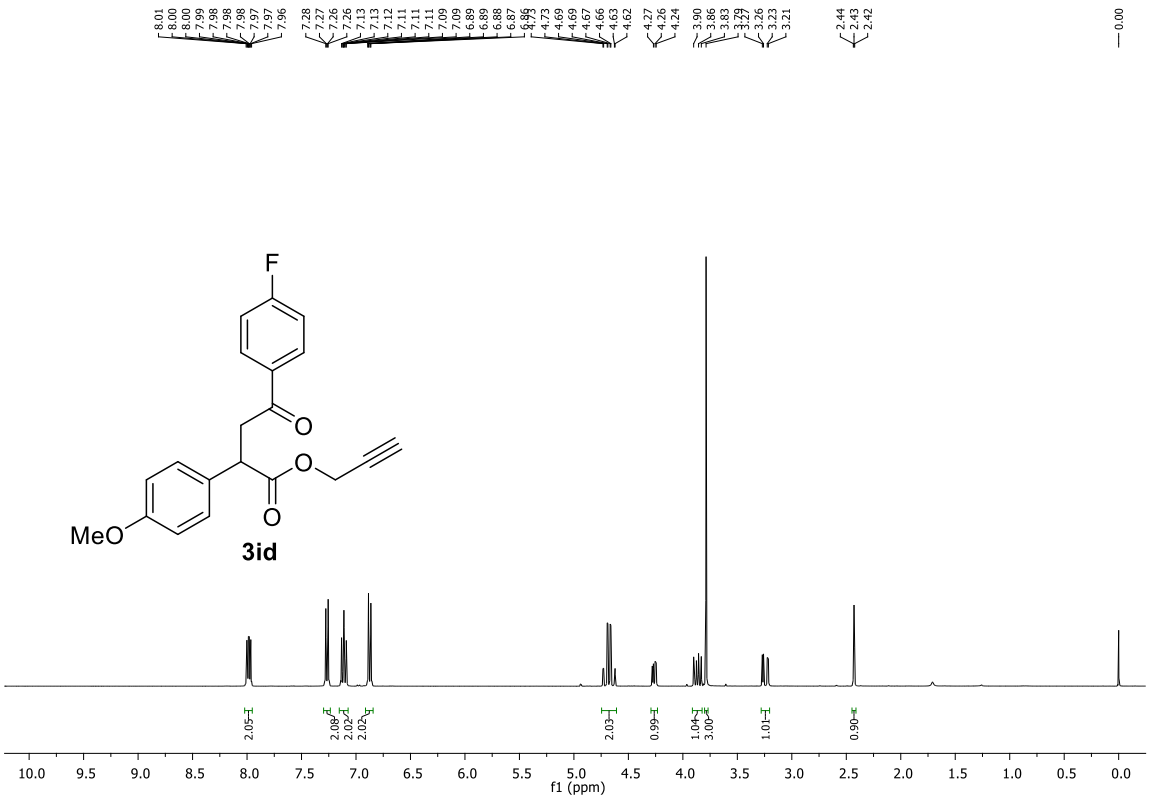


Figure V.3: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3id**

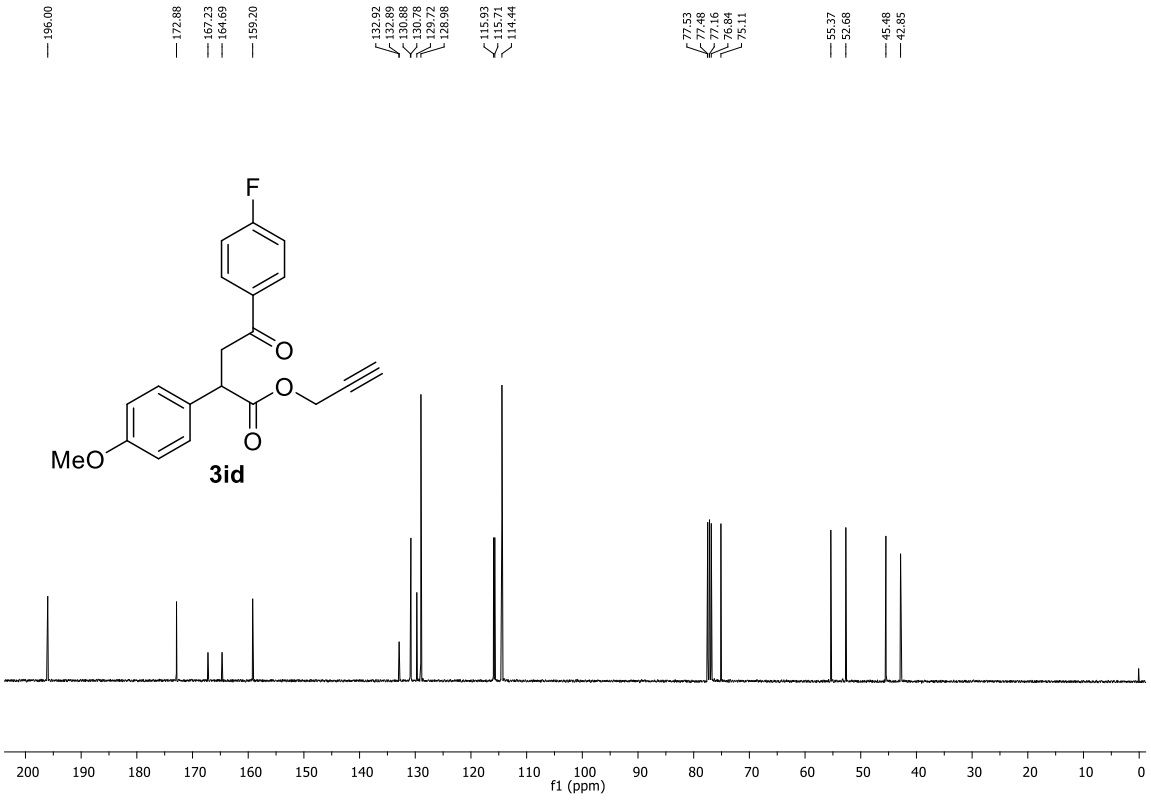


Figure V.4: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3id**

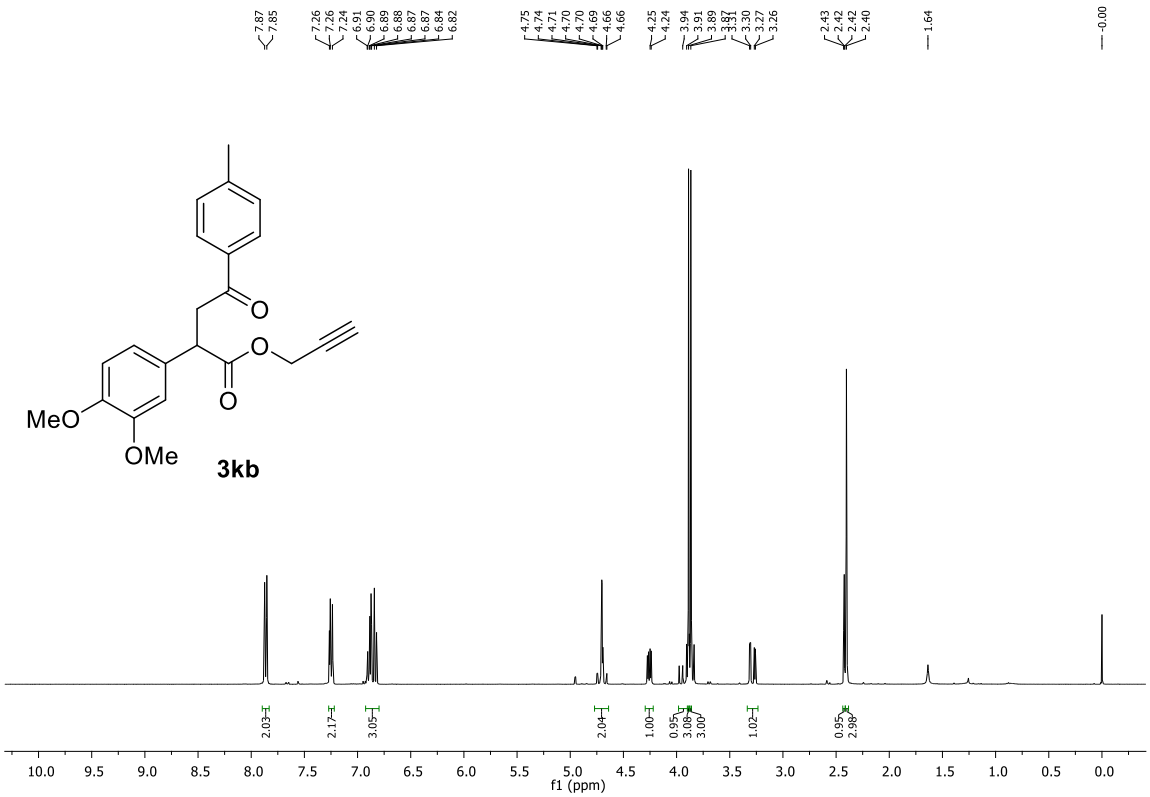


Figure V.5: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3kb**

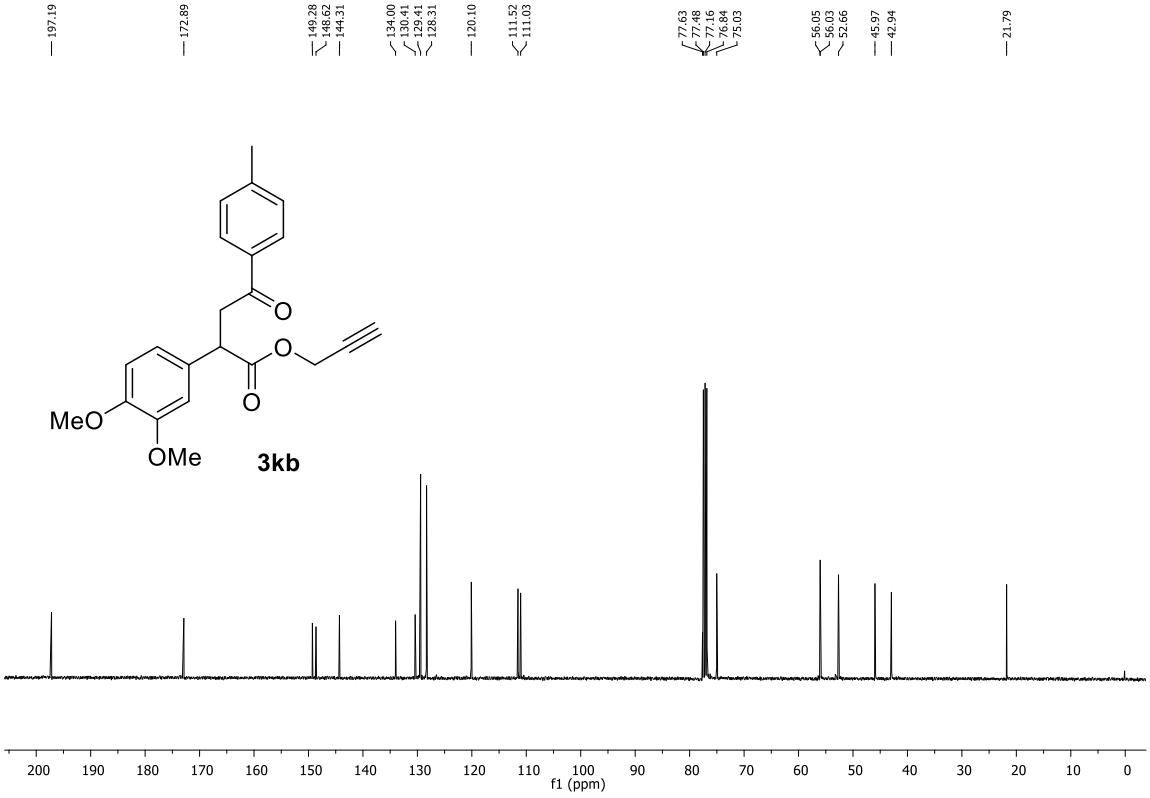


Figure V.6: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3kb**

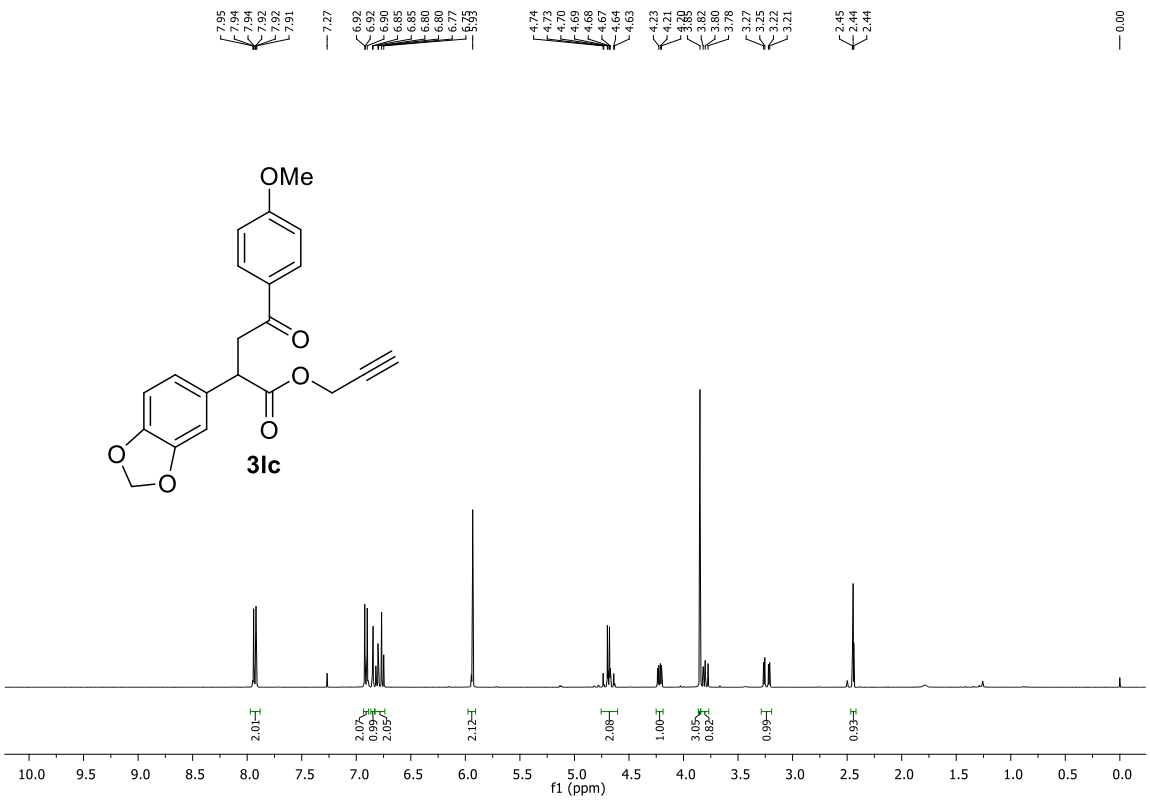


Figure V.7: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **3lc**

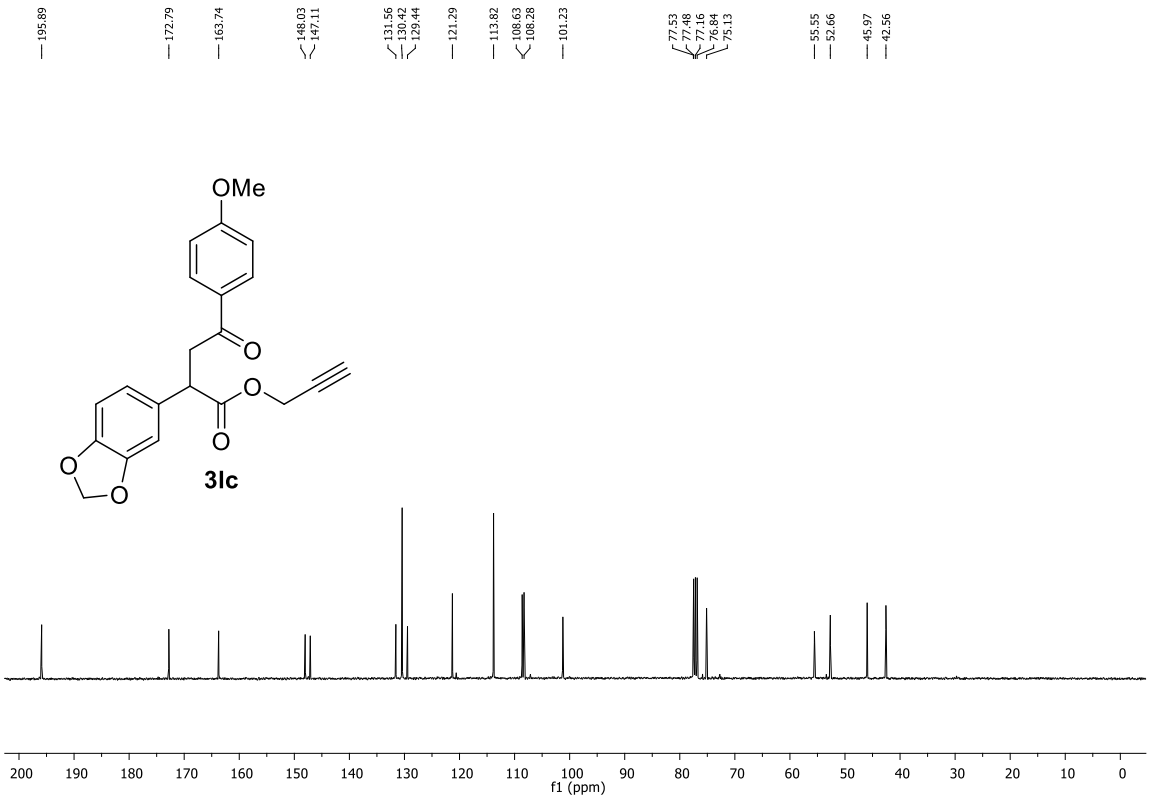


Figure V.8: ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of compound **3lc**

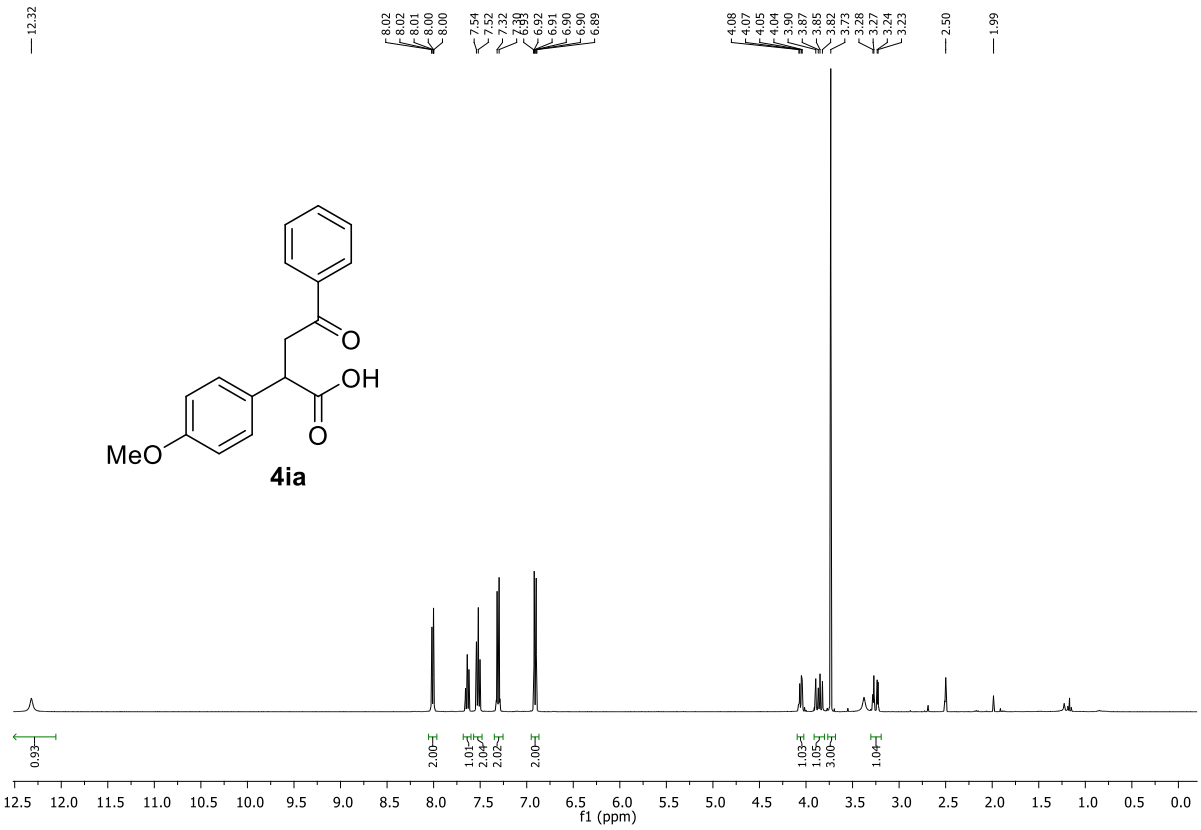


Figure V.9: ^{1}H NMR (400 MHz, DMSO-d_6) spectrum of compound **4ia**

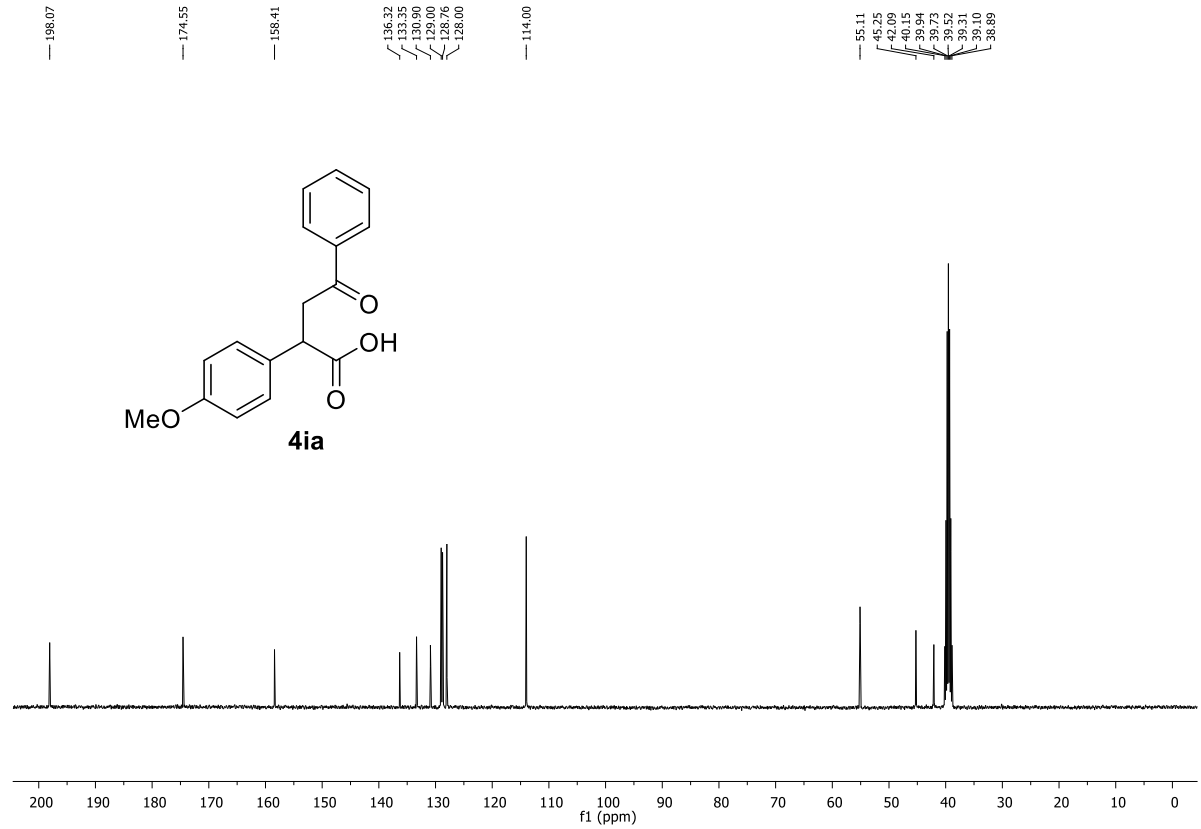


Figure V.10: ^{13}C NMR (100 MHz, DMSO-d_6) spectrum of compound **4ia**

5.6 References and notes

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14. It is speculated that in addition to being weakly electron-withdrawing, the propargyl moiety may also play a previously undescribed role that accelerates aminolysis. From the transition-state calculations it is revealed that the hydrogen on the propargyl moiety appears to be better positioned and oriented to hydrogen bond with the ester oxygen, potentially stabilizing the transition state. (See King, K.; Vong, H.; Maeda, S.; Tanaka, K. *Chem. Eur. J.* **2016**, *22*, 18865.)
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SUMMARY

C-H bond functionalization is a very important field of study in organic synthesis, and it is greatly explored in the synthesis of natural products and pharmaceutical agents. C-H bond functionalization of organic compounds is a powerful method for constructing new carbon-carbon (C-C) and carbon-heteroatom (C-X) bonds. C-H bond functionalization is a process in which the conversion of carbon-hydrogen bond into carbon-carbon bond or carbon-heteroatom bond is carried out irrespective of method and mechanism. Development of novel catalyst system for the functionalization of the unreactive C-H bonds is a major challenge and of great interest to synthetic organic chemists. C-H bond functionalization involves different types of intermediates based on the mechanisms of the reactions. Some of the typical intermediates are organometallic intermediates, carbenoid or ionic intermediates. The direct C-H bond functionalization reduces the number of synthetic steps and also the preactivation of starting materials is avoided thereby increasing the overall atom-efficiency.

Site-selective C-H bond functionalization is a very challenging task due to the inert nature of most C-H bonds and requirement to control chemo- and regioselectivity in molecules that contain multiple C-H bonds. In this regard development of novel C-H bond functionalization protocols to access very important and useful precursors will be essential. As a part of our ongoing research programme, we developed a practical and efficient catalyst system comprising of CuI-DMAP for the homocoupling and heterocoupling of terminal alkynes under aerobic conditions by using oxidative coupling reactions. We have also developed a novel and an expedient catalyst system comprising of early transition state element-scandium for the effective C-H bond functionalization. Early transition state element (scandium) has been explored for the chemo- and regioselective C-H bond functionalization of arenes with propargyl α-aryl-α-diazoacetates. Likewise, scandium catalyst system has also been explored for the effective C-H bond functionalization of 1,3-diketones & β- keto acids with propargyl α-aryl-α-diazoacetates. All of the above methods are highly practical, economical and environmentally friendly.

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Copper(I) iodide–DMAP catalyzed homo- and heterocoupling of terminal alkynes†

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A practical and efficient catalytic system comprising CuI and DMAP has been developed for the oxidative homo- and heterocoupling of terminal alkynes under aerobic conditions at room temperature. The catalytic utility of DMAP for efficient oxidative coupling of terminal alkynes has been explored. The CuI–DMAP catalytic system avoids the need for excess base and specialized ligands in oxidative coupling. Short reaction times make this approach economical and environmentally friendly.

Introduction

Many molecules containing a 1,3-diyne core are widespread in nature and some of these molecules display potent bioactivity against some of the major diseases.[1] 1,3-Diyne scaffolds are also very important for constructing molecular boxes as high efficiency hosts in supramolecular chemistry.[2] These conjugated diyne motifs are essential building blocks for the synthesis of advanced materials such as liquid crystals, conjugated polymers, and molecular wires.[3]

The carbon–carbon triple bond is one of the most versatile functionalities in organic chemistry.[4] The design and synthesis of 1,3-diyene has been of interest for a very long time since the discovery of oxidative dimerization of copper acetylides by Glaser.[5] In the mid-20th century this method was further modified and improved by Eglinton and Galbraith,[6] and Hay.[7] This coupling has been revived by various research groups by varying the metal catalyst.[8] In order to increase the efficiency, Glaser coupling has further been modified by Pd/Cu-catalyzed coupling reactions,[9] and the combination of Cu and Ag[10a] or Ni[10b,c] salts.

The use of copper-catalyzed homocoupling of terminal alkynes remains attractive because copper is economical, and relatively environmentally friendly.[11] Oxidative coupling of terminal alkynes has been optimized by exploring the use of different copper salts, bases and ligands. However the use of stoichiometric amounts of copper salts,[12] excess oxidants,[13] high temperature,[12b,14] excess bases,[13c,15] co-catalysts[9f,10a,b] and low to moderate yields for aliphatic alkynes[15a] are major shortcomings. Careful choice of ligand–base combination is often essential for efficient coupling. Some of these reasons demand the development of an efficient protocol for the homo-coupling of terminal alkynes.

Herein, we describe the catalytic utility of easily accessible DMAP for the efficient and practical oxidative coupling of terminal alkynes along with copper(I) iodide under an atmosphere of air and at room temperature in very short times.

Results and discussion

To explore the feasibility of the reaction we chose phenyl acetylene (**1a**) as a model for the homocoupling reaction using different copper salts and various ligands at room temperature under an atmosphere of air for the initial study. As shown in Table 1, a variety of catalytic systems were screened in different solvents. In our preliminary studies we observed that 2 mol% of CuI and 4 mol% of DMAP in acetonitrile as a solvent at room temperature afforded 1,3-diyne (1,4-diphenylbuta-1,3-diyne) **2a** in 97% in 10 h (entry 18). An increase in the amount of both CuI (5 mol%) and DMAP (10 mol%) in the reaction furnished compound **2a** in 97% yield with a significant reduction in the reaction time from 10 h to 1 h (entry 9). It was gratifying that with the lower catalyst loading of CuI (1 mol%) and DMAP (2 mol%), the reaction did proceed slowly, yielding **2a** (69%, entry 19) in 12 h. The reaction of **1a** catalyzed by CuCl and CuBr proceeded slowly (entries 10 and 11). The homocoupling reaction was also screened in various solvents. We observed that the rate of the reaction was greatly enhanced by more polar solvents such as acetonitrile and acetone.

When TMEDA was used in 10 mol%, the homo-coupling reaction was very sluggish (15%, 1 h, entry 8). However, the CuCl(5 mol%)–TMEDA(10 mol%) catalyst system afforded **2a** in 69% in 1 h (entry 25). Similarly, many other ligands were not very effective in influencing the rate of the reaction (entries 1–8, 20–24). The Cu(II) salt–DMAP catalyst system afforded the homo-coupled product, **2a**, in poor yield (5–18%, entries 26–

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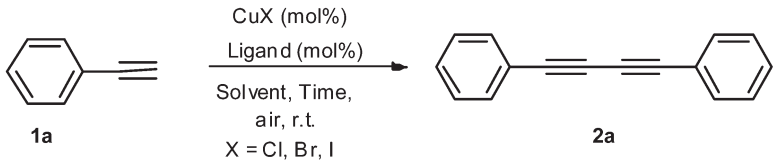
† Electronic supplementary information (ESI) available: Copies of ^{1}H-NMR, ^{13}C-NMR spectra for compounds **2a-2m**; **4a-4e**. See DOI: 10.1039/c3ra23478a

Table 1 Optimization of the reaction conditions for the coupling of terminal alkyne



Entry	CuX (mol%)	Ligand (mol%)	Solvent	Time (h)	Temp	Yield of **2a**[a]
1	CuI (5)	Pyridine (10)	MeCN	3.5	r.t.	21%
2	CuI (5)	Pyridine (10)	CH_2Cl_2	24	r.t.	10%
3	CuI (5)	Pyridine (10)	Acetone	24	r.t.	16%
4	CuI (5)	Imidazole (10)	MeCN	18	r.t.	Trace
5	CuI (5)	Imidazole (10)	Acetone	24	r.t.	Trace
6	CuI (5)	Imidazole (10)	CH_2Cl_2	24	r.t.	Trace
7	CuI (5)	Et_3N (10)	MeCN	24	r.t.	Trace
8	CuI (5)	TMEDA (10)	MeCN	1	r.t.	15%
9	**CuI (5)**	**DMAP (10)**	**MeCN**	**1**	**r.t.**	**97%**
10	CuCl (5)	DMAP (10)	MeCN	1	r.t.	33%
11	CuBr (5)	DMAP (10)	MeCN	2.5	r.t.	48%
12	CuI (5)	DMAP (10)	Acetone	1	r.t.	66%
13	CuI (5)	DMAP (10)	CH_2Cl_2	1	r.t.	22%
14	CuI (5)	DMAP (10)	CH_2Cl_2	10	r.t.	96%
15	CuI (5)	DMAP (10)	Acetone	4	r.t.	97%
16	CuI (10)	DMAP (20)	MeCN	45 min	r.t.	98%
17	CuI (5)	DMAP (5)	MeCN	1	r.t.	69%
18	CuI (2)	DMAP (4)	MeCN	10	r.t.	97%
19	CuI (1)	DMAP (2)	MeCN	12	r.t.	69%
20	CuI (5)	Piperidine (10)	MeCN	1	r.t.	20%
21	CuI (5)	Bipyridine (10)	MeCN	1	r.t.	6%
22	CuI (5)	2,6-Lutidine (10)	MeCN	1	r.t.	Trace
23	CuI (5)	3-Chloropyridine (10)	MeCN	1	r.t.	11%
24	CuI (5)	Quinoline (10)	MeCN	1	r.t.	9%
25	CuCl (5)	TMEDA (10)	MeCN	1	r.t.	69%
26	$CuCl_2$ (5)	DMAP (10)	MeCN	1	r.t.	5%
27	$Cu(OTf)_2$ (5)	DMAP (10)	MeCN	1	r.t.	6%
28	$Cu(OAc)_2$ (5)	DMAP (10)	MeCN	1	r.t.	18%
29	CuI (5)	No Ligand	MeCN	18	r.t.	—

[a] Isolated yield of **2a** after column chromatography; MeCN: acetonitrile; CH_2Cl_2: dichloromethane.

28). The reaction did not proceed in the absence of any ligand (entry 29). It is noteworthy that we observed a remarkable enhancement in the rate of homocoupling reaction of **1a** using the CuI(5 mol%)–DMAP(10 mol%) catalyst system. The screening reactions indicated that CuI–DMAP together facilitated the coupling reaction more in a synergistic way. It is essential to have both CuI and DMAP for the efficient oxidative coupling.

Preliminary results showed that the optimum conditions for the homocoupling reaction involved the use of CuI (5 mol%), DMAP (10 mol%) and air (oxygen) as an oxidant at ambient temperature. We then focused our attention on generalizing the method by exploring the substrate scope using the optimized conditions. Various terminal alkynes (**1a–1k**; Table 2) were used in the homocoupling reaction. The corresponding 1,3-diynes (**2a–2k**) were afforded in excellent yields (up to 98%) in a short time.

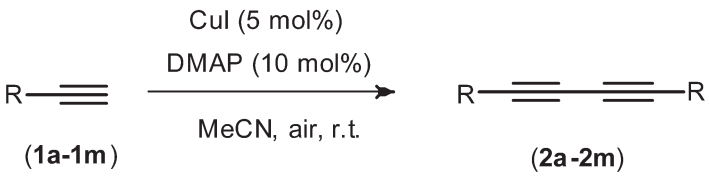
Bivalent sugars with a rigid linker have been explored in lectin cross-binding studies.[16] In this regard peracetylated propargyl glycosides (**1l**, **1m**) were prepared using reported glycosylation procedures with propargyl alcohol.[17] These glycoside (**1l**, **1m**) containing terminal alkynes, when subjected to the homocoupling conditions, gave the corresponding dimeric diyne glycosides (**2l**, **2m**) in good yields (up to 87%) in a short time. More practical and general reaction conditions have been achieved for coupling of these glycosides than those reported earlier.[16,18]

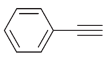
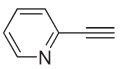
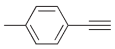
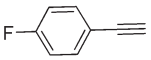
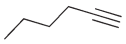
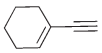
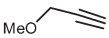
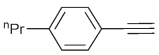
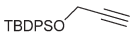
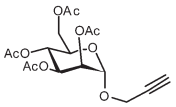
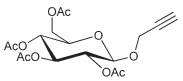
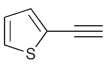
Encouraged by this success we planned to explore this methodology by applying our catalytic system to cross-coupling of two different terminal alkynes. Initially two different terminal alkynes in equimolar ratio (1 : 1) were treated with CuI (5 mol%) and DMAP (10 mol%) in acetonitrile at room temperature under aerobic conditions for 2.5–3.5 h to furnish the coupled products (**3**, **4** and **5**) in very good overall yields (up to 96%) and up to 47% cross-coupled product diynes (**4**) were obtained (Table 3).

However, when two different terminal alkynes in the ratio 1 : 5 were subjected to the coupling reaction with increased catalytic amounts of CuI (10 mol%) and DMAP (20 mol%) in acetonitrile under aerobic conditions, cross-coupled products (**4a–4e**) were formed in very good yields (up to 85%; Table 4).

A variety of functional groups was tolerated under the reaction conditions of both homo- and heterocoupling and

Table 2 CuI-DMAP catalyzed homocoupling of terminal alkynes



Entry	1	2	Time (h)	Yield[a] (%)	Entry	1	2	Time (h)	Yield[a] (%)
1		**2a**	1	97	8		**2h**	1.5	87
2		**2b**	1	98	9		**2i**	1	92
3		**2c**	1.5	85	10		**2j**	1.5	82
4		**2d**	1	87	11		**2k**	1.5	94
5		**2e**	1	96	12		**2l**	1.5	87
6		**2f**	1	90	13		**2m**	3.5	71[b]
7		**2g**	1	94					

[a] Isolated yield after column chromatography. [b] 10 mol% CuI and 20 mol% DMAP was used.

more importantly coupling proceeded very smoothly without the aid of any of metal co-catalysts unlike the previous procedures.[9f,10a,b]

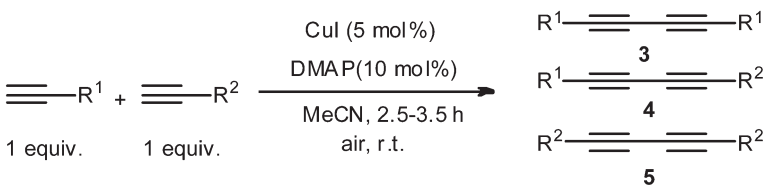
In conclusion, we have developed a practical and efficient catalyst system comprising CuI–DMAP for the homocoupling of terminal alkynes under aerobic conditions at room temperature. Homocoupling led to the formation of 1,3-diynes in good to excellent yields in a very short time. Also heterocoupling was successfully achieved using this catalyst system. We demonstrated for the first time the use of commercially available and non-hazardous DMAP for the smooth coupling of terminal alkynes. It is noteworthy that unlike many previous procedures we have successfully avoided the use of excess base and metal co-catalysts. This approach is highly practical, economical and environmentally friendly.

Experimental section

General

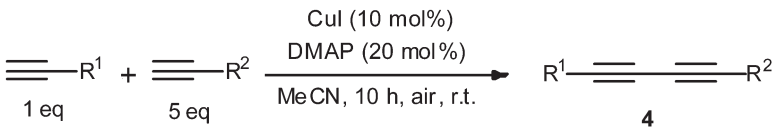
Unless otherwise noted, all reactions were carried out with distilled and dried solvents using oven-dried glassware. All

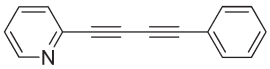
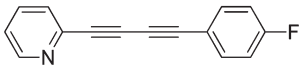
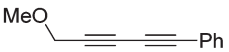
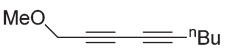
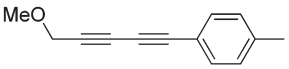
Table 3 Heterocoupling of terminal alkynes in equimolar ratio



Entry	R1	R2	Time (h)	Overall yield (%)	Yield (%) 3	Yield(%) 4	Yield (%) 5
1	**1d**	**1a**	2.5	93	22	44	27
2	**1d**	**1b**	3	96	23	47	26
3	**1d**	**1c**	3.5	83	32	33	18

Table 4 Synthesis of unsymmetrical conjugated diynes



Entry	R^1	R^2	R^1—R^2	4	Yield[a] (%)
1	**1h**	**1a**		**4a**	82
2	**1h**	**1i**		**4b**	85
3	**1d**	**1a**		**4c**	72
4	**1d**	**1c**		**4d**	70
5	**1d**	**1b**		**4e**	74

[a] Isolated yield of **4** after column chromatography.

reagents were purchased from commercial sources and used as received, unless otherwise indicated. Thin-layer chromatography (TLC) was performed using silica gel 60 GF_{254} precoated aluminum backed plates (2.5 mm) with detection by UV light. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6. Chemical shifts in ^{1}H NMR spectra are reported as δ in units of parts per million (ppm) downfield from tetramethylsilane with the solvent resonance as the internal standard or from residual solvent peak as internal standard and J values are given in Hz. ^{13}C NMR spectra are reported as δ in ppm downfield from tetramethylsilane and relative to the signal of chloroform-d and DMSO-d_6. ^{13}C NMR spectra were recorded with complete proton decoupling. Mass samples were analyzed by high resolution mass spectrometry using HRMS-TOF MS AP^+ and HRMS-TOF MS ES^+. FT-IR spectra were obtained using a FT-IR spectrophotometer as neat and reported in cm^{-1}. Optical rotations were measured on a polarimeter. Melting points were measured in an open glass capillary and values are uncorrected.

(A) General procedure for homocoupling of terminal alkynes. A mixture of phenylacetylene **1a** (1.0 mmol), CuI (5 mol%) and DMAP (10 mol%) in acetonitrile (4 mL) was stirred at room temperature in open atmosphere. The reaction mixture was stirred at room temperature for 1–1.5 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The crude product obtained was purified by column chromatography over silica gel to furnish 1,4-diphenylbuta-1,3-diyne **2a** as a white crystalline solid.

(B) General procedure for cross-coupling of two different alkynes. 2-Ethynylpyridine (**1h**) (1.0 mmol), phenylacetylene (**1a**) (5.0 mmol), CuI (10 mol%) and DMAP (20 mol%) were added to acetonitrile (6 mL) at ambient temperature in the open atmosphere. The reaction mixture was stirred at room temperature for 10 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure. The crude product obtained was purified by column chromatography over silica gel to afford 2-(phenylbuta-1,3-diynyl)pyridine (**4a**) as a white solid.

1,4-Diphenylbuta-1,3-diyne (2a). Compound **2a** was synthesized following the general procedure (A). The product was obtained as white crystals (0.0981 g, 97% yield).

R_f 0.7 petroleum ether/EtOAc (95 : 5); m.p.: 87–88 °C (lit.[15b] 88–89 °C); IR(neat) cm^{-1}: 3017, 2925, 2144, 1480, 1436, 909, 747; ^{1}H NMR (400 MHz, $CDCl_3$):δ 7.54 (dd, J = 7.8, 1.8 Hz, 4H), 7.39–7.32 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 132.6, 129.3, 128.6, 121.9, 81.7, 74.0. HRMS (AP^+): Calcd for $C_{16}H_{10}$ (M^+): 202.0783, Found: 202.0784.

1,4-Ditolylbuta-1,3-diyne (2b). Compound **2b** was synthesized following the general procedure (A). The product was obtained as white crystals (0.113 g, 98% yield): m.p.: 182–183 °C (lit.[15b] 182–183 °C); R_f 0.8 petroleum ether/EtOAc (95 : 5), IR(neat) cm^{-1}: 3024, 2918, 2131, 1644, 1499, 1452, 1038, 807. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, J = 8.2 Hz, 4H), 7.14 (d, J = 8.2 Hz, 4H), 2.37 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 139.6, 132.5, 129.4, 118.9, 81.7, 73.6, 21.8. HRMS (AP^+): Calculated for $C_{18}H_{15}$ ($M + H$)$^+$: 231.1174, Found: 231.1182

Dodeca-5,7-diyne (2c). Compound **2c** was synthesized following the general procedure (A). The product was obtained as a pale yellow oil (0.069 g, 85% yield): R_f 0.7 petroleum ether/EtOAc (85 : 15), IR(neat) cm^{-1}: 2931, 2868, 1709, 1460, 1248, 961, 739. ^1H NMR (400 MHz, $CDCl_3$) δ 2.25 (t, J = 6.9 Hz, 4H), 1.57–1.42 (m, 4H), 1.47–1.33 (m, 4H), 0.90 (t, J = 7.3 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): 77.6, 65.4, 30.5, 22.1, 19.0, 13.7. HRMS (ES^+): Calculated for $C_{12}H_{19}$ $(M + H)^+$: 163.1487, Found: 163.1486

1,6-Dimethoxyhexa-2,4-diyne (2d). Compound **2d** was synthesized following the general procedure (A). The product was obtained as a colourless oil (0.06 g, 87% yield): R_f 0.6 petroleum ether/EtOAc (70 : 30), IR (neat) cm^{-1} 2935, 2827, 2243, 1715, 1443, 1285, 1089, 933, 745. ^1H NMR (400 MHz, $CDCl_3$): δ 4.17 (s, 4H), 3.39 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): 75.3, 70.6, 60.3, 58.0. HRMS (ES^+): Calculated for $C_8H_{10}O_2Na$ $(M + Na)^+$: 161.0578, Found: 161.0585.

2,2,13,13-Tetramethyl-3,3,12,12-tetraphenyl-4,11-dioxa-3,12-disilatetradeca-6,8-diyne (2e). Compound **2e** was synthesized following the general procedure (A). The product was obtained as a pale yellow oil (0.282 g, 96% yield): R_f 0.5 petroleum ether/EtOAc (95 : 5); IR(neat) cm^{-1}: 2933, 2893, 2858, 2362, 1590, 1427, 1364, 1074, 818, 695; ^1H NMR (400 MHz, $CDCl_3$): δ 7.7 (dd, J = 7.6, 1.7 Hz, 8H), 7.48–7.33 (m, 12H), 4.37 (s, 4H), 1.07 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$): 135.7, 132.9, 130.1, 127.9, 77.4, 69.5, 53.2, 26.8, 19.3. HRMS (AP^+): Calculated for $C_{38}H_{42}O_2Si_2K$ $(M + K)^+$: 625.2360, Found: 625.2363

1,4-Bis(trimethylsilyl)buta-1,3-diyne (2f). Compound **2f** was synthesized following the general procedure (A). The product was obtained as a white solid (0.0875 g, 90% yield): R_f 0.8 (petroleum ether); m.p.: 108–109 °C (lit.[19] 108–109 °C); IR (neat) cm^{-1}: 2962, 2362, 2065, 1462, 1410, 1248, 835, 745. ^1H NMR (400 MHz, $CDCl_3$): δ 0.19 (s, 18H).^{13}C NMR (100 MHz, $CDCl_3$): 88.1, 86.1, −0.4 (Me_3Si). HRMS (ES^+): Calculated for $C_{10}H_{19}Si_2$ $(M + H)^+$: 195.1025, Found: 195.1024

1,4-Di(thiophen-2-yl)buta-1,3-diyne (2g). Compound **2g** was synthesized following the general procedure (A). The product was obtained as a yellow solid (0.101 g, 94% yield): R_f 0.5 petroleum ether/EtOAc (95 : 5); m.p.: 90–91 °C (lit.[15b] 92–93 °C); IR(neat) cm^{-1}: 3098, 2200, 2136, 1808, 1547, 1217, 893, 705. ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.29 (m, 4H), 7.01 (dd, J = 5.1, 3.7 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): 134.5, 129.1, 127.4, 122.0, 77.9, 76.8. HRMS (ES^+): Calculated for $C_{12}H_7S_2$ $(M + H)^+$: 214.9989, Found: 214.9992.

1,4-Di(pyridin-2-yl)buta-1,3-diyne (2h). Compound **2h** was synthesized following the general procedure (A). The product was obtained as a white solid (0.089 g, 87% yield): R_f 0.4 petroleum ether/EtOAc (85 : 15); m.p.: 116–117 °C (lit.[15b] 120–122 °C); IR(neat) cm^{-1}: 3053, 2997, 2216, 1570, 1455, 988, 751, 683. ^1H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, J = 5.1 Hz, 2H), 7.69 (td, J = 7.8, 1.8 Hz, 2H), 7.55 (d, J = 7.8 Hz, 2H), 7.33–7.22 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.5, 142.0, 136.3, 128.5, 123.9, 81.0, 73.3. HRMS (ES^+): Calculated for $C_{14}H_9N_2$ $(M + H)^+$: 205.0766 Found: 205.0770

1,4-Bis(4-fluorophenyl)buta-1,3-diyne (2i). Compound **2i** was synthesized following the general procedure (A). The product was obtained as a white solid (0.110 g, 92% yield): R_f 0.7 petroleum ether/EtOAc (95 : 5); m.p. 192–193 °C (lit.[15b] 194–195 °C); IR (neat) cm^{-1}: 2925, 2854, 2363, 2141, 1589, 1498, 1222, 1155, 825, 693. ^1H NMR (400 MHz, $CDCl_3$): δ 7.54–7.45 (m, 4H), 7.04 (t, J = 8.7 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) (F-coupled spectrum): δ 163.2 (d, J = 252.0 Hz), 134.7 (d, J = 8.6 Hz), 117.9, 116.1 (d, J = 22.2 Hz), 80.6, 73.7. HRMS (AP^+): Calculated for $C_{16}H_8F_2$ $(M)^+$: 238.0594, Found: 238.0599.

1,4-Dicyclohexenylbuta-1,3-diyne (2j). Compound **2j** was synthesized following the general procedure (A). The product was obtained as a colourless oil (0.086 g, 82% yield): R_f 0.7 petroleum ether, IR (neat) cm^{-1}: 2931, 2860, 2320, 2190, 1709, 1449, 1069, 753. ^1H NMR (400 MHz, $CDCl_3$): δ 6.32–6.12 (m, 2H), 2.28–1.95 (m, 8H), 1.60 (ddd, J = 18.0, 6.9, 3.0 Hz, 9H).^{13}C NMR (100 MHz, $CDCl_3$): 138.3, 120.1, 82.8, 71.7, 28.8, 26.0, 22.3, 21.5. HRMS (AP^+): Calculated for $C_{16}H_{18}$ $(M)^+$: 210.1409, Found: 210.1414.

1,4-Bis(4-propylphenyl)buta-1,3-diyne (2k). Compound **2k** was synthesized following the general procedure (A). The product was obtained as a white solid (0.135 g, 94% yield): R_f 0.8 petroleum ether/EtOAc (95 : 5); m.p.: 105–107 °C (lit.[14b] 107–108 °C): IR(neat) cm^{-1}: 2959, 2866, 1499, 1458, 1213, 747, 667. ^1H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, J = 8.1 Hz, 4H), 7.15 (d, J = 8.1 Hz, 4H), 2.67–2.44 (m, 4H), 1.64 (sex, J = 7.4 Hz, 4H), 0.94 (t, J = 7.3 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 132.5, 128.8, 119.1, 81.7, 73.6, 38.2, 24.4, 13.9. HRMS (AP^+): Calculated for $C_{22}H_{22}$ $(M)^+$: 286.1722, Found: 286.1726.

1,6-Bis(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyloxy)hexa-2,4-diyne (2l). Compound **2l** was synthesized following the general procedure (A). The product was obtained as a white solid (0.34 g, 87% yield): R_f 0.6 chloroform/acetone (90 : 10); m.p.: 53–54 °C (lit.[20] 52–53 °C); $[\alpha]^{24}_D$ = +62 (c = 1.0, $CHCl_3$) (lit.[18] $[\alpha]^{24}_D$ = +62, c = 1, $CHCl_3$); IR (neat) cm^{-1}: 2924, 1743, 1369, 1217, 1045, 755. ^1H NMR (400 MHz, $CDCl_3$: δ 5.34–5.19 (m, 6H), 4.97 (s, 2H), 4.35 (s, 4H), 4.28 (dd, J = 12.2, 4.8 Hz, 2H), 4.09 (d, J = 12.3 Hz, 2H), 3.99 (s, 2H), 2.15 (s, 6H), 2.10 (s, 6H), 2.03 (s, 6H), 1.98 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 170.0, 169.97, 169.8, 96.7, 74.2, 71.0, 69.3, 69.2, 69.0, 66.0, 62.4, 55.6, 21.0, 20.9, 20.8, 20.8. HRMS (ES^+): Calculated for $C_{34}H_{42}O_{20}K$ $(M + K)^+$: 809.1907, Found: 809.1911.

1,6-Bis(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)hexa-2,4-diyne (2m). Compound **2m** was synthesized following the general procedure (A). The product was obtained as a white solid (0.274 g, 71% yield): R_f 0.5 petroleum ether/EtOAc (30 : 70); m.p.: 175–176 °C; $[\alpha]^{25}_D$ = −37 (c = 1.0, $CHCl_3$), IR (neat) cm^{-1}: 2955, 1745, 1435, 1369, 1211, 1035, 753. ^1H NMR (400 MHz, $CDCl_3$): δ 5.24 (t, J = 9.5 Hz, 2H), 5.10 (t, J = 9.6 Hz, 2H), 5.01 (dd, J = 9.5, 8.0 Hz, 2H), 4.73 (d, J = 7.9 Hz, 2H), 4.45 (s, 4H), 4.27 (dd, J = 12.4, 4.5 Hz, 2H), 4.15 (dd, J = 12.4, 2.2 Hz, 2H), 3.75 (ddd, J = 10.0, 4.4, 2.3 Hz, 2H), 2.09 (s, 6H), 2.07 (s, 6H), 2.02 (s, 6H), 2.01 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 170.4, 169.6, 169.5, 98.6, 74.3, 72.8, 72.1, 71, 68.3 (2-C merged), 61.8, 56.6, 20.9, 20.8, 20.7 (2-C). HRMS (ES^+): Calculated for $C_{34}H_{42}O_{20}K$ $(M + K)^+$:809.1907, Found: 809.1915.

Synthesis of unsymmetrical 1,3-diynes

2-(Phenylbuta-1,3-diynyl)pyridine (4a). Compound **4a** was synthesized following the general procedure (B). The product was obtained as a white solid (0.167 g, 82% yield): R_f 0.5

petroleum ether/EtOAc (85 : 15); m.p.: 72–73 °C (lit.[15b] 72–73 °C); IR (neat) cm^{-1}: 3053, 2997, 2216, 1570, 1040, 751. ^1H NMR (400 MHz, $CDCl_3$) δ 8.63–8.54 (m, 1H), 7.67 (td, J = 7.7, 1.7 Hz, 1H), 7.57–7.48 (m, 3H), 7.36 (tdd, J = 8.7, 6.7, 3.6 Hz, 3H), 7.27 (ddd, J = 7.7, 4.8, 1.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 142.4, 136.3, 132.8, 129.7, 128.6, 128.2, 123.6, 121.4, 82.6, 80.3, 73.9, 73.6. HRMS (ES^+): Calculated for $C_{15}H_{10}N$ $(M + H)^+$: 204.0813, Found: 204.0820.

2-((4-Fluorophenyl)buta-1,3-diynyl)pyridine (4b). Compound **4b** was synthesized following the general procedure (B). The product was obtained as a white solid (0.19 g, 85% yield): R_f 0.4 petroleum ether/EtOAc(85 : 15); m.p.: 123–124 °C; IR (neat) cm^{-1}:2925, 2854, 2214, 1888, 1500, 1221, 829, 760. ^1H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, J = 4.7 Hz, 1H), 7.67 (td, J = 7.8, 1.8 Hz, 1H), 7.53 (ddd, J = 7.6, 4.7, 1.9 Hz, 3H), 7.30–7.24 (m, 1H), 7.09–6.96 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) (F-coupled spectrum): δ 163.3 (d, J = 252.2 Hz), 150.5, 142.3 136.3, 134.9 (d, J = 8.6 Hz), 128.2, 123.7, 117.5, 116.1 (d, J = 22.2 Hz), 81.5, 80.3, 73.7, 73.5. HRMS (ES^+): Calculated for $C_{15}H_9FN$ $(M + H)^+$: 222.0719, Found: 222.0721.

(5-Methoxypenta-1,3-diynyl)benzene (4c). Compound **4c** was synthesized following the general procedure (B). The product was obtained as pale yellow oil (0.123 g, 72% yield): R_f 0.6 petroleum ether/EtOAc (85 : 15); IR(neat) cm^{-1}: 2928, 2828, 2225, 1714, 1443, 1352, 1094, 902, 752. ^1H NMR (400 MHz, $CDCl_3$) δ 7.54–7.46 (m, 2H), 7.41–7.28 (m, 3H), 4.25 (s, 2H), 3.43 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 132.7, 129.5, 128.6, 121.5, 78.7, 78.2, 73.4, 71.2, 60.5, 58.0. HRMS (AP^+): Calculated for $C_{12}H_{11}O$ $(M + H)^+$: 171.0810, Found: 171.0814.

1-Methoxynona-2,4-diyne (4d). Compound **4d** was synthesized following the general procedure (B). The product was obtained as a colourless oil (0.106 g, 70% yield): R_f 0.6 petroleum ether/EtOAc (85 : 15), IR (neat) cm^{-1}: 2958, 2871, 2238, 1715, 1457, 1102, 973. ^1H NMR (400 MHz, $CDCl_3$): δ 4.15 (s, 2H), 3.38 (s, 3H), 2.28 (t, J = 6.9 Hz, 2H), 1.57–1.47 (m, 2H), 1.47–1.35 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 81.4, 77.4, 64.6, 60.4, 57.9, 30.3, 22.0, 19.1, 13.6. HRMS (AP^+): Calculated for $C_{10}H_{15}O$ $(M + H)^+$: 151.1123, Found: 151.1119.

1-(5-Methoxypenta-1,3-diynyl)-4-methylbenzene (4e). Compound **4e** was synthesized following the general procedure (B). The product was obtained as a pale yellow oil (0.136 g, 74% yield): R_f 0.6 petroleum ether/EtOAc (85 : 15); IR (neat) cm^{-1}: 2928, 2827, 2234, 1714, 1445, 1353, 1094, 812. ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 8.1 Hz, 2H), 7.13 (d, J = 7.9 Hz, 2H), 4.25 (s, 2H), 3.43 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9, 132.7, 129.3, 118.4, 78.5, 78.4, 72.8, 71.4, 60.5, 58.0, 21.8. HRMS (AP^+): Calculated for $C_{13}H_{12}O$ $(M)^+$: 184.0888, Found: 184.0885.

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