Direct Trifluoromethylation of Heteroarenes Using a Commercial CdSe Semiconductor Photocatalyst

A thesis submitted to the faculty of

Indian Institute of Science Education and Research, Pune

towards the partial fulfillment of the requirements for

BS-MS dual degree program.

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Certificate

This is to certify that this dissertation entitled "**Direct trifluoromethylation of heteroarenes using a commercial CdSe semiconductor photocatalyst**" towards the partial fulfillment of the BS-MS dual degree programme at **the Indian Institute of Science Education and Research**, **Pune** represents work carried out by **Mr. Mayur Rahul Taksande** at **King Abdullah University of Science and Technology, Saudi Arabia** under the supervision of **Dr. Magnus A. Rueping**, **Professor, Chemical Science, Physical Science and Engineering Division, King Abdullah University of Science and Technology (KAUST), Saudi Arabia** during the academic year 2019 – 2020

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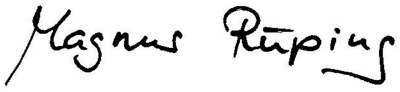
Declaration

I hereby declare that the matter embodied in the report entitled "**Direct trifluoromethylation of heteroarenes using a commercial CdSe semiconductor photocatalyst**" are the results of the work carried out by me at the **KAUST Catalysis Centre, Physical Science and Engineering Division, King Abdullah University of Science and Technology (KAUST), Saudi Arabia**, under the supervision of **Dr. Magnus A. Rueping** and the same has not been submitted elsewhere for any other degree.



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Dedicated to my loving parents and sister...

|| आई-बाबा तुमचा आशीर्वाद ||

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Abbreviations

ACN	acetonitrile
CdS	cadmium sulfide
CdSe	cadmium selenide
CF_3	trifluoromethyl
CF_3I	trifluoroiodomethane
CF_3SO_2Cl	triflyl chloride
CuI	copper iodide
DMF	dimethylformamide
DMSO	dimethylsulfoxide
HAT	Hydrogen Atom Transfer
ISC	Intersystem Crossing
K_2CO_3	potassium carbonate
K_2HPO_4	dipotassium phosphate
KF	potassium fluoride
MLCT	Metal to Ligand Charge Transfer
mmol	millimole
mpg-CN	mesoporous graphitic carbon nitride
NHC	N-Heterocyclic Carbenes
phen	phenanthroline
ppy	2-phenylpyridine
rt	room temperature
SCE	Saturated Calomel Electrode
SET	Single Electron Transfer
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
$TESCF_3$	triethyl(trifluoromethyl)silane
THF	tetrahydrofuram
TMEDA	tetramethylethylenediamine

Abstract

Incorporation of the trifluoromethyl group in biologically active compounds have always been regarded of high importance in medicinal and pharmaceuticals chemistry. The selective installation of the trifluoromethyl group onto small molecules can enhance many of its physicochemical and pharmacokinetic properties. The electron-withdrawing CF_3 moiety on pharmaceuticals provide metabolic and thermal stability, increases electrostatic interaction with a target molecule in the body, improves cellular membrane permeability and lipophilicity and have many other usage and advantages in biology and agrochemicals. As the field of photoredox catalysis develops, the need to find new methodologies to help in modern drug discovery becomes crucial as well. Herewith we have reported a detailed novel study for the incorporation of trifluoromethyl group in heteroarenes using cadmium selenide (CdSe), a commercially available semiconductor photocatalyst. The new catalyst is air and moisture stable, can tolerate high reactive radical intermediates and can be readily recovered by simple centrifugation after use and can be reused several times. Along with a wide variety of substrate scope, we have shown the applicability of our developed methodology to medicinal chemistry and drug development through examples of trifluoromethylation of some biologically active compounds such as RNA-base Uracil, plant hormone Heteroauxin and flavorant Vanillin.

Chapter 1. Introduction

In the 19th century, it was with Friedrich Wöhler's synthesis of urea that synthetic organic chemistry became the tool that could disprove the suppositious notion of Vitalism Theory- the ideology that the creation of all organic molecules was from life itself. [1] He also proposed a doctrine of compound radicals which left a profound impact on the development of chemistry. And along with the synthesis of ammonia at the beginning of the 20th century by Haber and industrial scale-up by Bosch using an iron-based heterogeneous catalyst the course of history was changed forever. The field of organic chemistry was further expedited with the use of catalytic chemistry to lower the activation energy needed for a reaction to move forward and much faster. Since then many new catalytic concepts were developed and one such branch of catalysis, photoredox catalysis, came into light (literally), about a decade ago, with the pioneering work of the MacMillan group, the Yoon group, and the Stephenson group and it continues to develop ever since. [2-4]

1.1 Photoredox Catalysis

Photoredox catalysis is a branch of catalysis which utilizes light energy to promote radical-based organic transformations by generating radical intermediates which then participates in a chemical reaction via single electron transfer (SET) events. This electron transfer produces a long-lives excited triplet state which can either undergo oxidative or reductive quenching by organic substrates. [5]

To be more precise, let's take $Ru(bpy)_3Cl_2$ as a model photoredox catalyst (**Fig.1**). Upon irradiation of visible light on this photocatalyst, an electron gets excited via spin allowed metal to ligand charge transfer (MLCT) event. This MLCT from t_{2g} to π^* orbital produces a singlet excited state which further undergoes rapid intersystem crossing (ISC) to produce a long-lived (τ = 1100 ns) lowest energy triplet excited state. The relaxation to singlet ground requires the emission of photon and inversion of the spin of the excited electron. Hence this photo-excited triplet state is substantially long-

lived as the decay is spin forbidden and can participate in single electron transfer events.

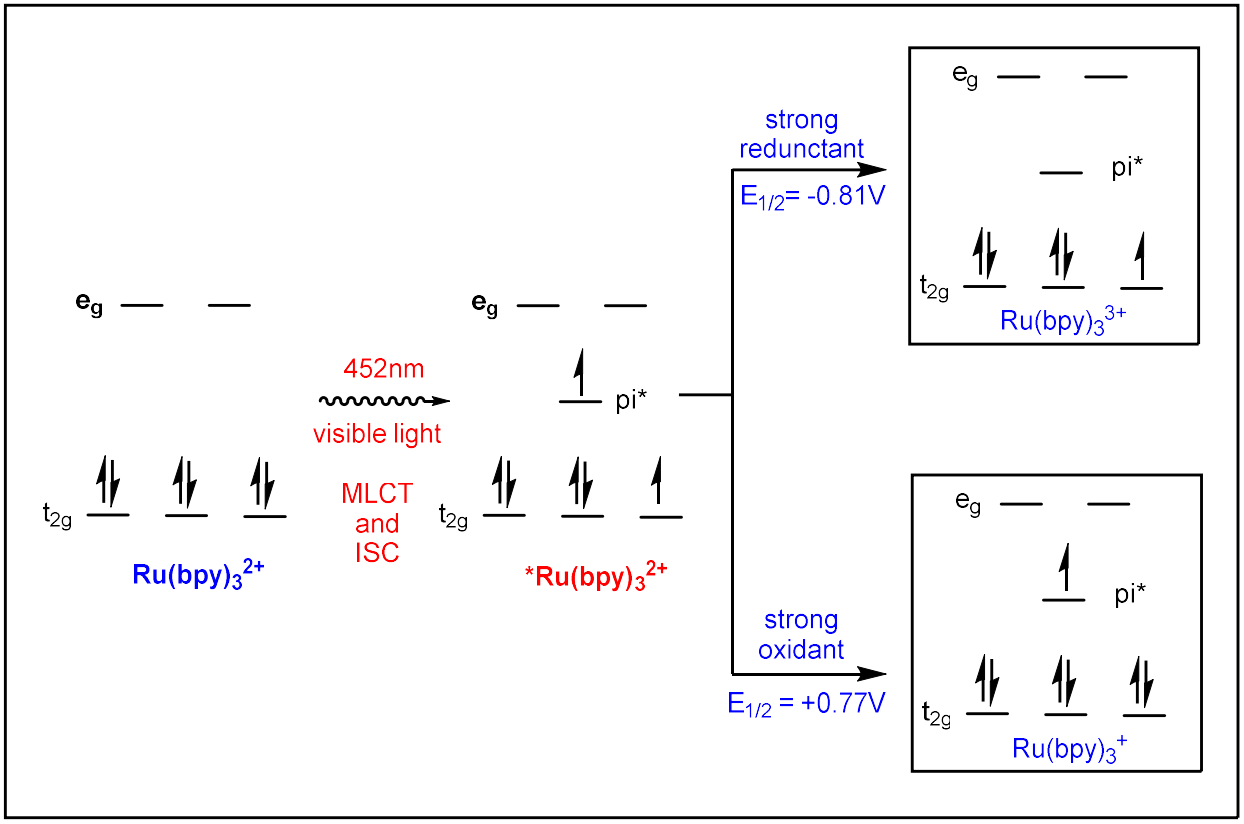


Fig. 1 – Insights into excitation and reactivity of the photocatalyst $Ru(bpy)_3Cl_2$

The photoexcited state of a photocatalyst (in this case $*Ru(bpy)_3^{2+}$) is highly reactive and can undergo redox transformations either by oxidative or by reductive quenching (Fig.2). In the oxidative quenching cycle, the photoexcited catalyst act as a reductant, giving an electron to an acceptor (A) to give an oxidized species. This intermediate is a good oxidant and may accept an electron from electron donor (D) to afford the ground-state species. Alternatively, in the reductive quenching cycle, the photoexcited species is first reduced by an electron donor and then oxidized by an electron acceptor to give the ground state.

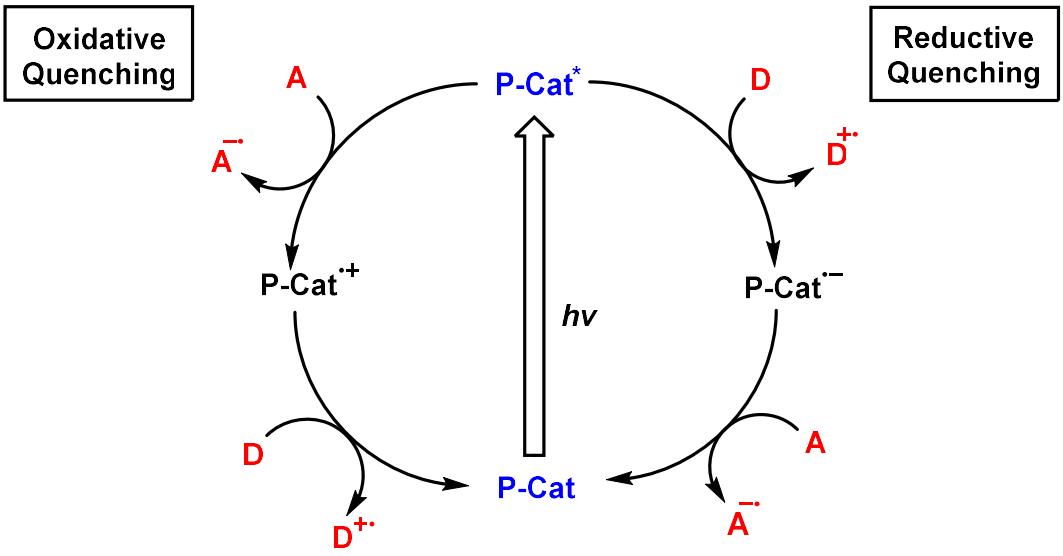


Fig. 2 – A simple mechanistic pathway for photoredox catalysis

The continuous development of the field of photoredox catalysis has opened up many new reaction pathways for the construction of complex molecules using cheap alternatives and mild conditions which would have otherwise been difficult. Some of these transformations include intramolecular [2+2] cycloaddition, reductive cleavage of aliphatic halides, ring-opening of epoxides, decarboxylative functionalization, reductive dehalogenation, etc. [5] Although ruthenium (Ru) and iridium(Ir) were majorly used in photoredox catalysis, many other new concepts such as Nickle Catalysis, Palladium Catalysis, Hydrogen Atom Transfer (HAT) catalysis, NHC catalysis were also developed. [6, 7]

Photoredox catalysts are majorly drawn from three categories of materials:

- Transition metal complexes
- Organic dyes
- Semiconductors

Throughout the past decade, transition metal catalysts and organic dyes have been studied in a wide range of photocatalytic transformation. [6, 7] Despite demonstrating strong forefront and versatility in many organic transformations, they have their own limitations. For e.g. in the case of iridium based photocatalyst fac-$Ir(ppy)_3$, the catalyst gets deactivated when reacted with C(sp3) radicals. [8] Also, some

organic dyes such as acridinium and quinolinium are often not compatible in the presence of strong nucleophiles leading to catalyst deactivation. [6, 9] Hence there is always a greater need to develop new catalysts and study their role in a chemical reaction to overcome such incompatibilities.

1.2 Heterogeneous Photocatalyst

Recently, the field of heterogeneous photoredox catalysis has received much widespread attention in organic synthesis mainly because of its mild, efficient and economical reaction conditions and its potential in industrial scale-ups. Heterogeneous photocatalysts are generally drawn from semiconductors. Upon irradiation of light onto a semiconductor photocatalyst, with photon energy larger than that of the bandgap, an electron-hole pair is generated as electrons get excited from its valence band to its conduction band. [10] This electron-hole pair further diffuses to the surface of the semiconductor to participate in surface redox reaction as illustrated in Fig. 3.

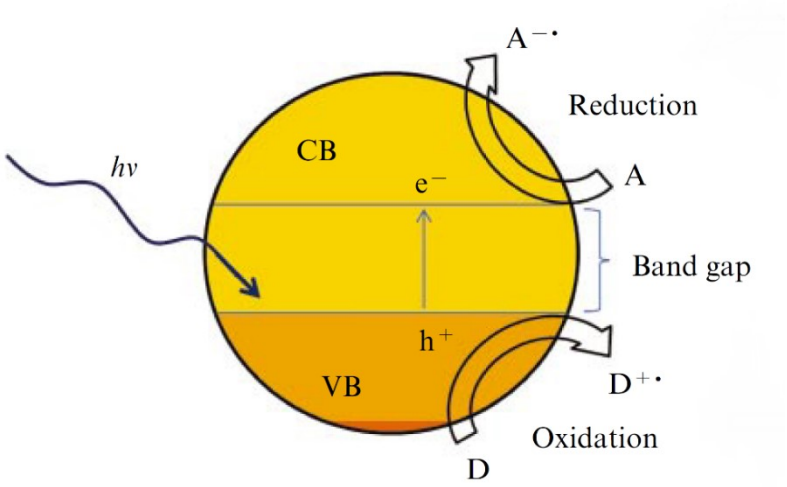


Fig. 3- A general reaction pathway for heterogeneous photocatalyst

However, this photo-generated electron-hole pair can either participates in one of the two aligned redox transformations depending on the reaction type as earlier described by Kisch. [10] A semiconductor photocatalyst reaction can be classified into type: Type A semiconductor photocatalysis and Type B semiconductor photocatalysis. In type A reactions, the intermediates generated by oxidation or reduction reacts

separately generating two different products. Whereas in type B reactions, the final product is obtained by using both the oxidative and reductive transformations simultaneously.

Heterogeneous catalysts are vastly used for industrial scale-up reactions due to their ease of separation from reaction mixtures, their photo and chemical stability against the reactive radical intermediates and strong nucleophiles. The heterogeneous semiconductor photocatalyst has significant potential in organic synthesis mainly because of their characteristic large band gap which facilitates single electron oxidation and reduction of many organic substrates under visible light.

Here in this study we combined the principles of classical photochemistry with heterogeneous catalysis and solid-state chemistry to explore the application of semiconductor photocatalyst CdSe in organic transformations specifically in single-step installation of CF_3 functional group in heteroarenes and showing its immense importance by applying the same to biologically important molecules.

1.3 Fluorine in Chemistry

In the realm of medicinal chemistry, fluorine definitely has a special place because of its strong electronegativity of 3.97 (Pauling's Scale) and a relative small size of 1.47 Å. Selective installation of fluorine on a given molecule can drastically affect its structure, reactivity and functions. Hence it has a wide range of applications in biology, materials, pharmaceuticals and most importantly in drug design. [12, 13] In the case of drug candidates, the presence of fluorine molecule can affect many of its properties such as adsorption, metabolism, distribution, bioavailability, lipophilicity and excretion. [14, 15] Fluorine has made its place in almost 30% of all agrochemicals and 20% of all drugs such as anti-depressant **Prozac®**, anti-biotic **Levaquin®** and **Ciprofloxacin®**, cholesterol-lowering drug **Lipitor®**, etc. Hence extensive studies are carried out to develop new synthetic methodologies to have the desired access to a wide range of fluorinated compounds. [15]

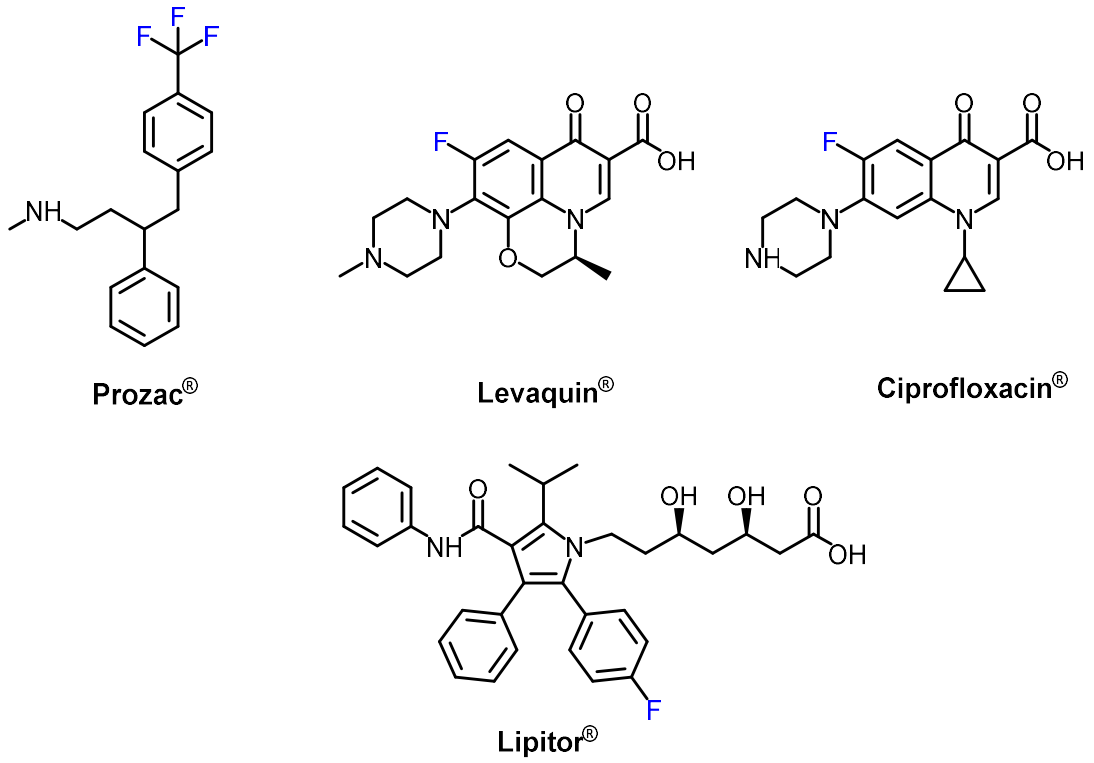


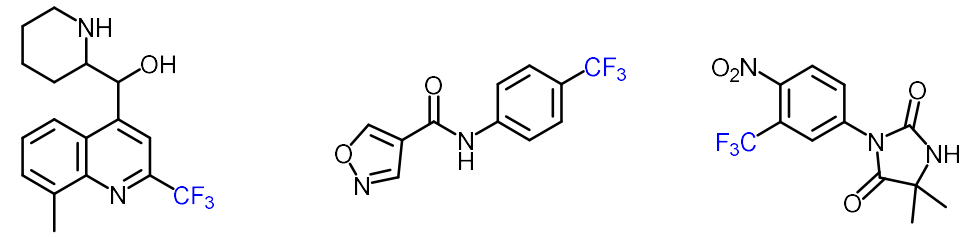
Fig. 4- Some fluorine containing important drugs

1.3.1 The Trifluoromethyl Group

Recent advances in catalytic chemistry have made the incorporation of the fluorine atom in complex biologically active molecules relatively easy. [16, 17] One way to induce fluorine in pharmaceuticals is through trifluoromethylation of the drug candidates. [18] Trifluoromethyl group has electronegativity of 3.2 (Pauling's Scale) similar to that of chlorine and have a van der Waals radius of 2.2 Å. Similar to fluorine, trifluoromethyl incorporation also have many given advantages: [15]

- Used as bioisostere in biology
- Used to adjust steric and electronic properties of the lead compound
- Protect drugs from metabolic oxidation
- Promotes electrostatic interactions with targets
- Improves cellular permeability
- Increases bioavailability and lipophilicity

In addition to many advantages of CF_3 incorporation, many commercially available drugs such as anti-malarial **Lariam®**, antirheumatic **Arava®**, nonsteroidal antiandrogen **Nilandron®**, etc. readily have CF_3 induced in them. Hence the development of methodologies for its incorporation is crucial.

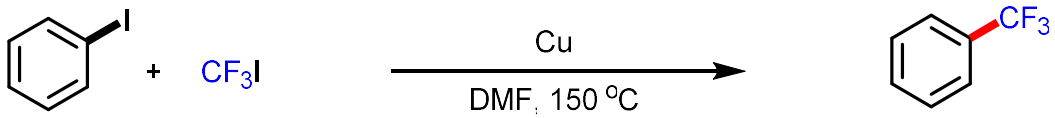


Lariam® (Mefloquine) **Arava®** (Leflunoamide) **Nilandron®** Nilutamide

Fig. 5- Some trifluoromethyl group containing drugs

1.3.2 Incorporation of CF_3 Moiety in Arenes and Heteroarenes

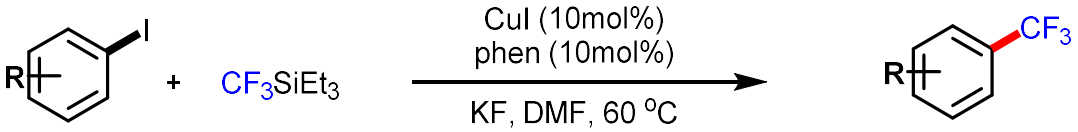
Being one of the most important groups in medicinal chemistry and pharmaceuticals, various methodologies for CF_3 group incorporation have been studied over time. In 1969, the first arene trifluoromethylation reaction via a cross-coupling mechanism was reported. Iodobenzenes was successfully converted to benzotrifluoride with a 45% yield at 150°C using activated cooper-bronze and trifluoroiodomethane (CF_3I) as the trifluoromethyl source (Scheme 1). [18] Since then many new modifications to these initial reaction conditions have been reported. [19, 20] But one major drawback is their limited generality. The same reaction conditions did not apply to a wide range of substrate scope.



Scheme 1. Cu-catalyzed cross-coupling reaction for trifluoromethylation

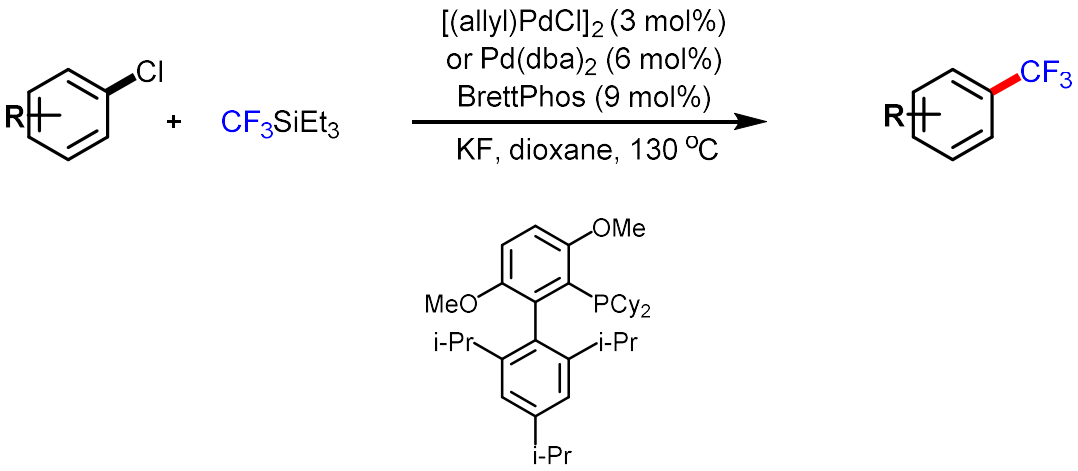
Transition Metal Catalysis

However, in 2009 the first catalytic trifluoromethylation was reported using a copper catalyst CuI. [21] Iodoarenes were cross-coupled with trifluoromethylsilanes in the presence of CuI and 1,10-phenanthroline (phen) to obtain trifluormethylated product in good yields (Scheme 2). Although the details of the reaction mechanism remained unclear, the generation of arylcooper (III) intermediate was thought to be a key step.



Scheme 1. Cu-catalyzed trifluoromethylation of iodoarenes

Later in 2010, a palladium-catalyzed reaction was described by Cho and group using aryl chlorides and $TESCF_3$. [22] This reaction was deployed to a broad range of substrates and resulted in good yield.



BrettPhos

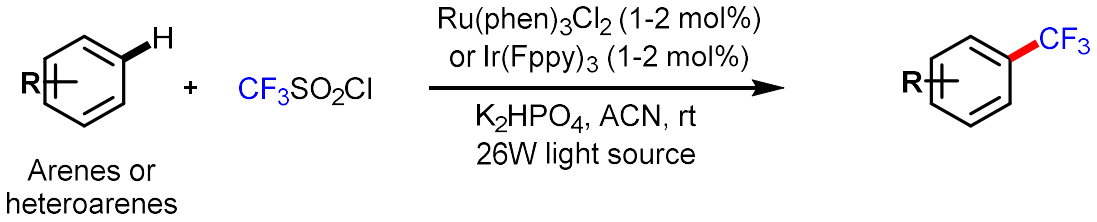
Scheme 3. Pd-catalyzed trifluoromethylation of aryl chlorides

Since then many new cross-coupling trifluoromethylation reactions catalyzed by transition metals using different trifluoromethyl sources have been reported. [23] Although these developed methodologies are quite reliable and applicable to a wide range of substrate scope, the need for pre-functionalization of arenes with halides or boronic

acids limits their application in late-stage drug development. Also, many of these reactions require high temperature and harsh conditions to proceed making it environmentally unfriendly.

Homogeneous Photocatalysis

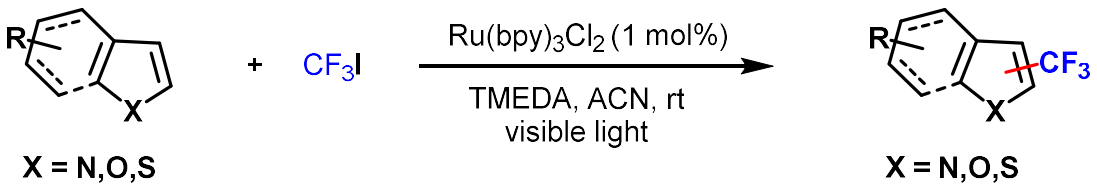
In 2011, MacMillan and group showed an exemplary direct trifluoromethylation reaction for arenes and heteroarenes in a photocatalytic fashion using a household lightbulb and triflyl chloride (CF_3SO_2Cl) as the CF_3 radical source (Scheme 4). [24]



Scheme 4. Ar-CF_3 bond formation by photoredox catalysis

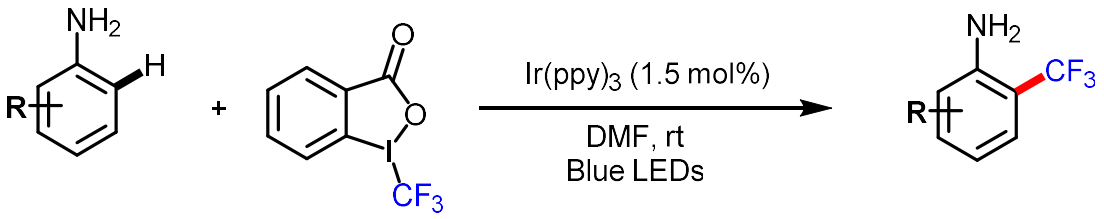
In this reaction, the photocatalyst $Ru(phen)_3^{2+}$ is activated by absorbing light energy and then gets oxidized to $Ru(phen)^{3+}$ concurrent to the reduction of CF_3SO_2Cl to release CF_3 radical via a SET process. This electron-deficient radical then reacts with a hetero(arene) selectively at the most electron-deficient position forming a cyclohexyl radical. This cyclohexyl species further participates in a second SET event to regenerate the photocatalyst followed by deprotonation of the formed cyclohexyl cation species finally obtaining the trifluoromethyl product.

Later in 2012, Cho's group reported a similar transformation using a different photocatalyst $Ru(bpy)_3Cl_2$ and trifluoromethyl source CF_3I. [25]



Scheme 5. Trifluoromethylation of heteroarenes using photocatalyst $Ru(bpy)_3Cl_2$

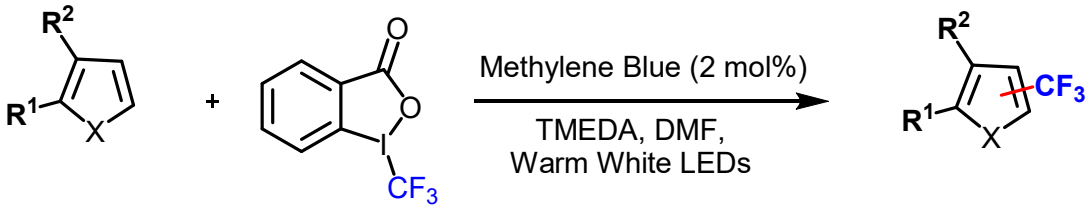
The Togni's reagent was also commonly deployed as a suitable trifluoromethyl reagent. It was found that photocatalysts such as $Ir(ppy)_3$ would facilitate the C-I bond cleavage in the presence of light to give the trifluoromethyl radical (Scheme 6). [26] This reaction was applied to a broad range of substrates to obtain 2-(trifluoromethyl)anilines with good yield.



Togni's reagent

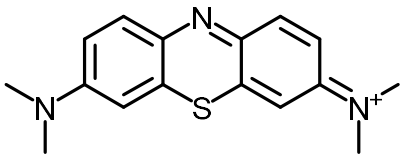
Scheme 6. Trifluoromethylation of anilines

Similarly, methylene blue was also reported to facilitate trifluromethylation of heteroarenes using Togni's reagent with very good efficiency. [27]



X = NH, S

Togni's reagent



Methylene Blue

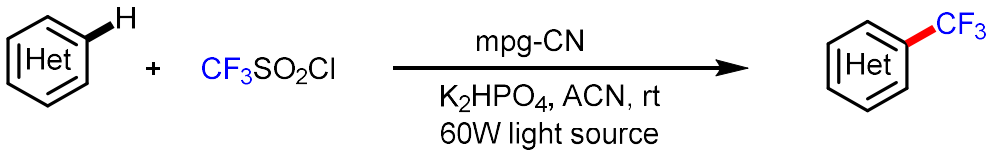
Scheme 7. Using methylene blue as a photocatalyst

Further, as the field developed, many new photo-induced trifluoromethylation reactions were reported. [28] By using the concept of photoredox catalysis, the need for pre-functionilized precursors was no longer required and reactions proceed in much milder conditions. However, a major limitation was the use of expensive Ru and Ir-

based photocatalysts which were relatively toxic thus limiting the application of these methods in pharmaceutical industries. Also, separating these catalysts from reaction mixture requires quite a lot of time and efforts.

Heterogeneous Photocatalysis

In 2015, Blechert et. al first reported the use of a heterogeneous photocatalyst, mesoporous graphitic carbon nitride (mpg-CN), to achieve trifluoromethylation of arenes by reduction of triflyl chloride under visible light. [29] This reaction condition was found compatible with a wide range of heterocycles.



Scheme 8. Trifluoromethylation using a heterogeneous photocatalyst mpg-CN

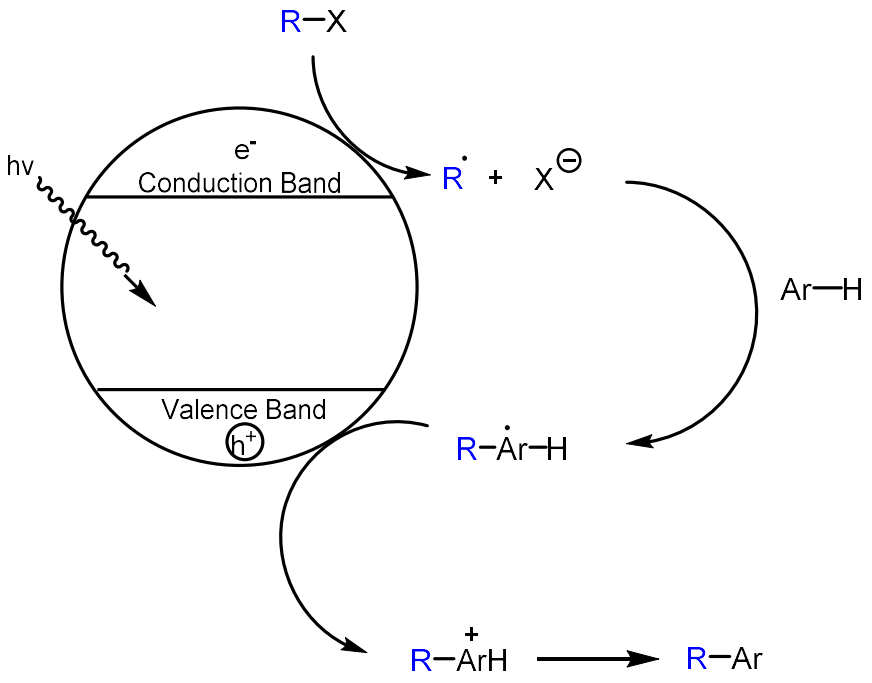
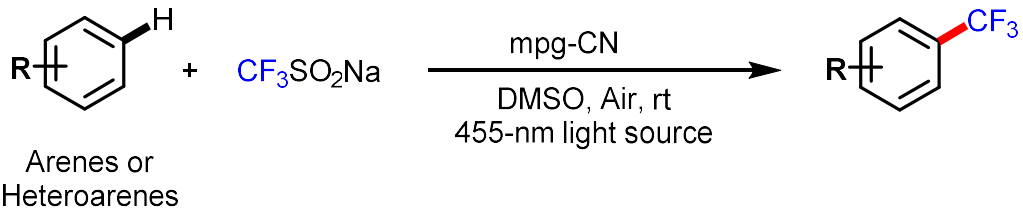


Fig. 6- Arene functionalization pathway in heterogeneous photocatalysts.

As explained earlier, irradiation of light on a heterogeneous photocatalyst results in an electron-hole pair formation on catalyst surface. This pair further participates in

surface redox reactions to achieve the desired product. In Scheme 8, CF_3SO_2Cl gets reduced to CF_3 radical which then reacts with heteroarenes to form an arene-radical complex which further gets oxidized by a hole at the catalyst surface forming a cationic complex. After deprotonation by K_2HPO_4 base, the desired trifluoromethyl product is achieved.

Recently, this protocol was further expedited by König and group to achieve many organic transformations including Ar-CF_3 bond formation reactions by the use of organic semiconductor photocatalyst, mpg-CN. [30] Sodium triflinate (CF_3SO_2Na) was used as the trifluoromethyl source.

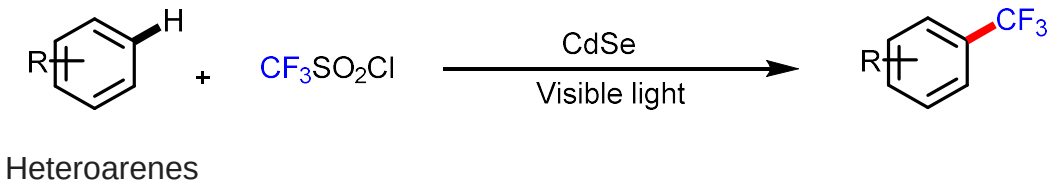


Scheme 9. Trifluoromethylation of arenes and heteroarenes using an organic semiconductor photocatalyst

Heterogeneous catalysts are favorable in industries due their ease of separation from reaction mixture and the relatively low-cost of catalysts as compared to other photocatalysts. This catalysts can be separated from reaction mixtures by a simple centrifugation. Although this protocol provides a huge advantage over the use of transition metal catalysts and homogeneous photocatalysts in achieving trifluomethylation, the problem remains with their availability. This catalyst is not commercially available and need to be synthesized manually by thermal polymerization of dicyandiamide and cyanamide.

This work:

We proposed a methodology for direct trifluoromethylation of heteroarenes by using a commercially available heterogeneous semiconductor photocatalyst CdSe.



Heteroarenes

Scheme 10. The trifluoromethyl approach used in this study

The design plan for this approach is discussed in detail in the following chapter along with a proposed reaction mechanism. Our approach precludes the need for pre-functionalization of arenes, the use of expensive Ru and Ir-based photocatalyst and the need to synthesize a heterogeneous photocatalyst such as mpg-CN to obtain trifluoromethylation products under mild conditions.

Chapter 2. Design Plan

To address the challenges faced by previous methodologies, mainly the need to synthesize the catalyst in heterogeneous system, we thought of using a commercially available heterogeneous photocatalyst to facilitate the trifluoromethylation of heteroarenes. The first part of our design plan was to choose an ideal and commercially available heterogeneous photocatalyst. Recently, cadmium selenide (CdSe) had shown photocatalytic activities for overall water splitting experiments. [31] CdSe photocatalyst has an ideal bandgap of 1.65 eV and is photo and chemically stable in the presence of visible-light-induced highly reactive radical intermediates. It is also stable in most organic solvents and is also cheaper than most of the transition metal catalysts used for homogeneous photocatalysis (e.g. $Ru(phen)_3Cl_2$,$Ir(Fppy)_3$, etc.) which were previously utilized in trifluoromethylation reactions. It is also commercially available thus saving the efforts to synthesize the photocatalyst. Hence, after some optimization studies (Table. 1), we chose CdSe as the catalyst for our proposed photoredox reaction.

For the next part of our design plan, we had to choose a suitable trifluoromethyl reagent which would be compatible with our chosen photocatalyst CdSe. We assumed that our reaction would proceed by the single electron reduction of the trifluoromethyl reagent. Trifluoromethanesulphonyl chloride (CF_3SO_2Cl), also known as triflyl chloride, has a reduction potential of approximately –0.18 V (versus SCE) and had previously been employed as an ideal trifluoromethyl radical source in trifluoromethylation of arenes and heteroarenes. [24, 29] Also, this reagent is much cheaper and much easier to handle as compared to other trifluoromethyl reagents which makes it highly desirable for general use.

For the proposed photoredox cycle (Fig. 7), we hypothesized that the catalyst would generate electron-hole pair upon irradiation of light. The photo-generated electron, which resides in the conduction band of the semiconductor, would then lead to the reduction of trifyl chloride via a SET process. The CF_3SO_2Cl radical anion would then rapidly collapse to generate CF_3 radical along with the evolution of SO_2 gas and

chlorine anion. The highly reactive $^{\bullet}CF_3$ species would then react with the heteroarene at the most electron-rich position in a selective manner. Further, this heteroaryl species would undergo a second single electron transfer (SET) with the strongly oxidizing hole, which was generated previously at the photocatalyst surface, completing the photo redox cycle and thus regenerating the catalyst. Finally, this hetero-aryl species would undergo deprotonation with a suitable base to provide the final trifluoromethyl product.

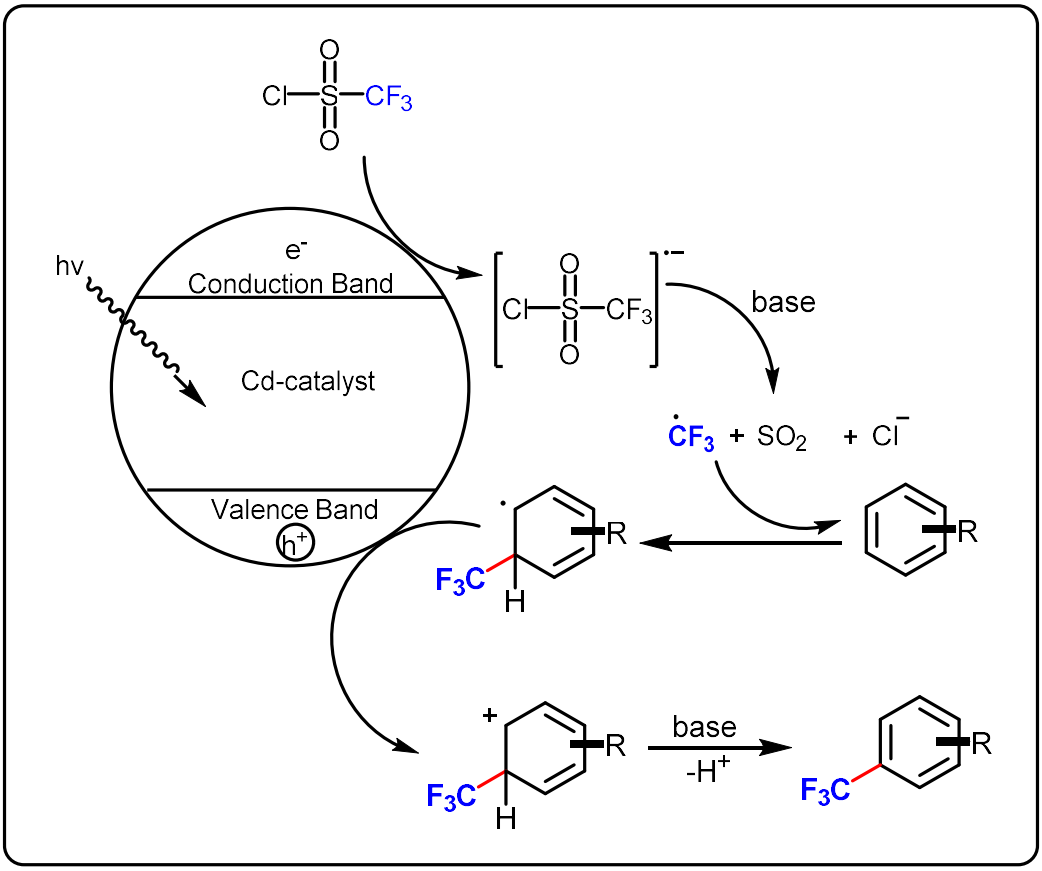
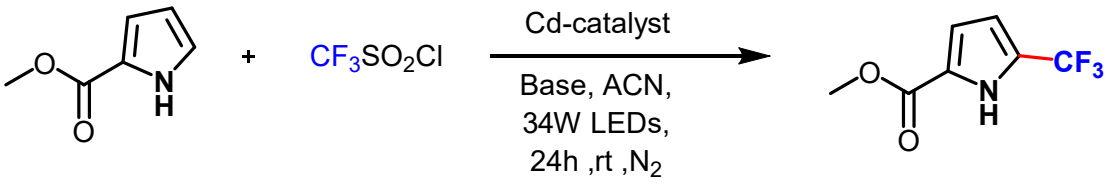


Fig. 7 – Proposed mechanistic pathway for our designed approach

Chapter 3. Results and Discussion

3.1 Optimization Studies



Scheme 11. Model reaction

Based on our design plan to study trifluoromethylation of heteroarenes using commercially available photocatalyst, we optimized our reaction conditions taking 2-pyrolecarboxylate as the model substrate. We used various Cd-based catalysts such as CdSe, CdS and CdTe and some other readily available heterogeneous photocatalysts. As evident from Table 1, using 10 w/w % of CdSe with 0.6 mmol of trifluoromethyl reagent CF_3SO_2Cl and 0.75 mmol of K_2HPO_4 base in acetonitrile solvent, 77% yield was observed upon 20 hours of irradiation with 34W blue LEDs. Additionally, we found that cadmium sulfide (CdS), with a yield of 78% (Table. 1, Entry 2), can also be employed as an alternative photocatalyst for desired trifluoromethylation reaction. CdTe gave a relatively low yield of 59% (Table. 1, Entry 3) as compared to its counterparts CdSe and CdS. Replacing Cd-catalysts with other heterogeneous catalysts (Entry 4-6) resulted in very poor yields.

Further to test that our reaction was not limited kinetically, we increased the reaction time from 20 hours to 48 hours keeping all other reaction conditions the same (Table 1**,** Entry 7-8). It did not increase the yield of the reaction indicating that the reaction was complete and was not limited kinetically.

Entry	Base (2.5 eq.)	Catalyst (10 w/w %)	CF_3SO_2Cl (2 eq.)	Time (hour)	Yield (^{19}F NMR)
1	K_2HPO_4	CdSe	0.6 mmol	20	77%
2	K_2HPO_4	CdS	0.6 mmol	20	78%
3	K_2HPO_4	CdTe	0.6 mmol	20	59%
4	K_2HPO_4	$SrTaO_2N$	0.6 mmol	20	11%
5	K_2HPO_4	$LaTiO_2N$	0.6 mmol	20	22%
6	K_2HPO_4	$CaTaO_2N$	0.6 mmol	20	19%
7	K_2HPO_4	CdS	0.6 mmol	48	74%
8	K_2HPO_4	CdSe	0.6 mmol	48	71%

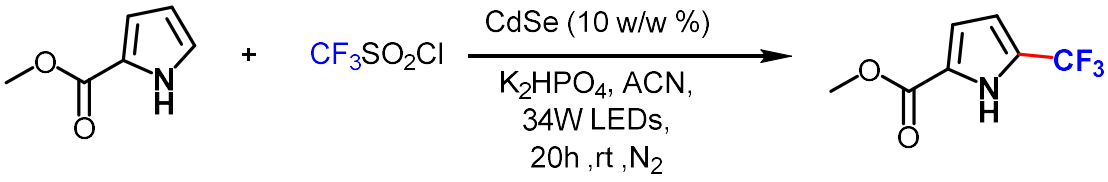
Table 1- Catalyst study for our designed trifluoromethyl reaction

Next, we screened various bases that would be compatible with our catalyst. As evident from Table 2, K_2HPO_4 and K_2CO_3 showed very good results. However, as we moved forward with our project, we observed that reactions proceed much faster in K_2HPO_4 as compared to K_2CO_3. Hence, we chose K_2HPO_4 as an ideal base for our designed reaction. However, as some substrates (e.g, N-phenyl pyrroles and 3-methylindole) were highly reactive in the presence of K_2HPO_4 we used K_2CO_3 as the base. We reasoned that this might because of the higher solubility of K_2HPO_4 in acetonitrile as compared to K_2CO_3.

Entry	Base (2.5 eq.)	Catalyst (10 w/w %)	CF_3SO_2Cl (2 eq.)	Time (hour)	Yield (^{19}F NMR)
1	K_2HPO_4	CdSe	0.6 mmol	20	78%
2	K_2CO_3	CdSe	0.6 mmol	20	70%
3	K_3PO_4	CdSe	0.6 mmol	20	19%
4	Na_2CO_3	CdSe	0.6 mmol	20	39%
5	Cs_2CO_3	CdSe	0.6 mmol	20	31%

Table 2- Base Optimization for the proposed reaction

As shown in **Table 3**. we performed a series of control experiments for our optimized reaction conditions (Scheme 8). To prove that our reaction is indeed photocatalytic, we ran a reaction without the use of catalyst CdSe (Table 3, Entry 2) and another one in the absence of light (Table 3, Entry 3). Both resulted in no reaction thus confirming that our reaction is indeed photocatalytic. We also observed no reaction in the absence of base (Table 3, Entry 4) exhibiting the fact that base was equally important for our proposed reaction. Replacing the solvent acetonitrile (ACN) with tetrahydrofuran (THF) or dimethylformamide (DMF) gave very poor results. To support our proposed radical mechanistic pathway (Fig. 7), we added a free radical scavenger TEMPO under standard reaction conditions. No trifluoromethylation on the heteroarene was observed which supports our hypothesis.

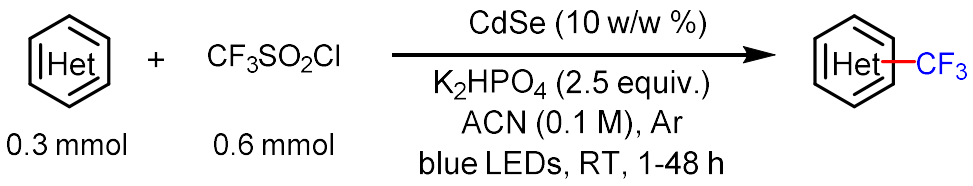


Scheme 12. Optimized conditions

Entry	Change in standard condition	Yield(^{19}F NMR)
1	No change	78%
2	No catalyst	No reaction
3	Absence of light	No reaction
4	Without base	No reaction
5	DCM instead of ACN	70%
6	THF instead of ACN	48%
7	DMF instead of ACN	16%
8	2.5 eq. TEMPO	No Reaction

Table 3 – Results for control experiments with standard reaction conditions

3.2 Substrate Scope



Scheme 13. Optimized reaction conditions for substrate scope

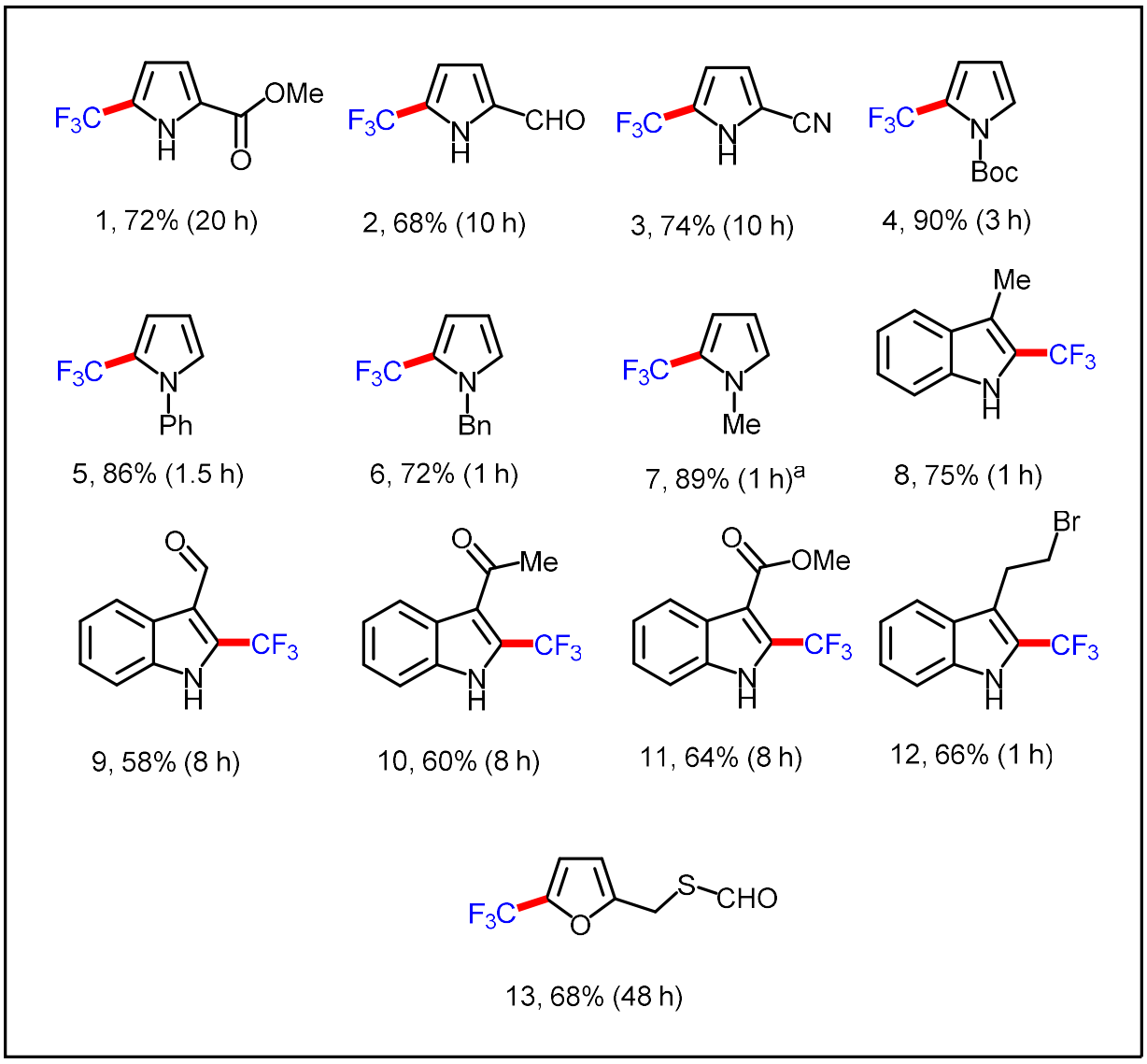


Fig. 8a- Trifluoromethylation of pyrroles, indoles and furan with standard reaction conditions.

With optimized conditions in hand, we found that our new photoredox reaction allows direct trifluoromethylation of a broad range of heteroarenes in the presence of CdSe semiconductor photocatalyst under mild conditions giving moderate to good yields. For example, a variety of protected and unprotected pyrroles with 2-substituted different functional groups such as ester, aldehyde and nitrile can be successfully trifluoromethylated at C_5 carbon and affords the corresponding products in very good yields (Fig. 8a, 1-8).We reasoned that this might be happening due to the formation of conjugated radical and cationic intermediates at the C_5 position which reacts with the photo-generated trifluoromethyl radical. We further expanded our substrate scope to some ring-substituted indoles (Fig. 8a, 8-12) with methyl, carbonyls and alkyl halide substitutions at C_3 carbon. We observed that the reaction took a longer time to complete in the presence of carbonyl groups as compared to alkyl and alkyl halides. We also tried the reaction with an electron-deficient furan substrate (13) which resulted in 68% yield for 48h.

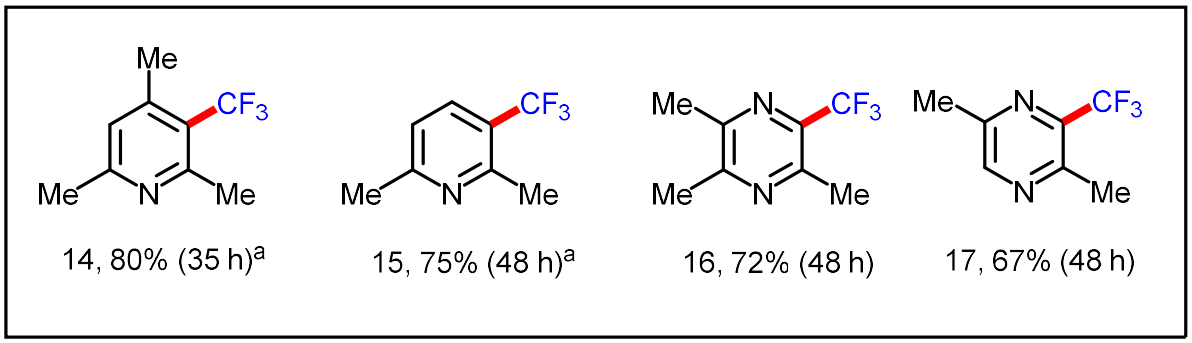


Fig. 8b- Trifluoromethylation of pyridines, pyrazines with standard conditions.

We further wanted to test the extent of our developed protocol on six-atom heterocycles knowing that they are widely found in many valuable pharmaceuticals and there is always a greater need to develop new methodologies for CF_3 cross-coupling reactions in this regard. As shown in Fig. 8b, we found that our developed photoredox protocol was well compatible with a range of methyl-substituted pyridines and pyrazines (14-18, 65% - 75% yield).

3.3 Applications in natural products

Finally, after installing CF_3 moiety on wide range of heteroarenes as illustrated in Fig. 8a and Fig. 8b, we next moved to show the potential and applicability of our developed protocol in pharmaceuticals and medicinal chemistry. As discussed earlier in Section 3.1, incorporation of the trifluoromethyl group on biologically active compounds significantly alters their chemical and physical properties thus providing immense control over the functionalities of a drug candidate.

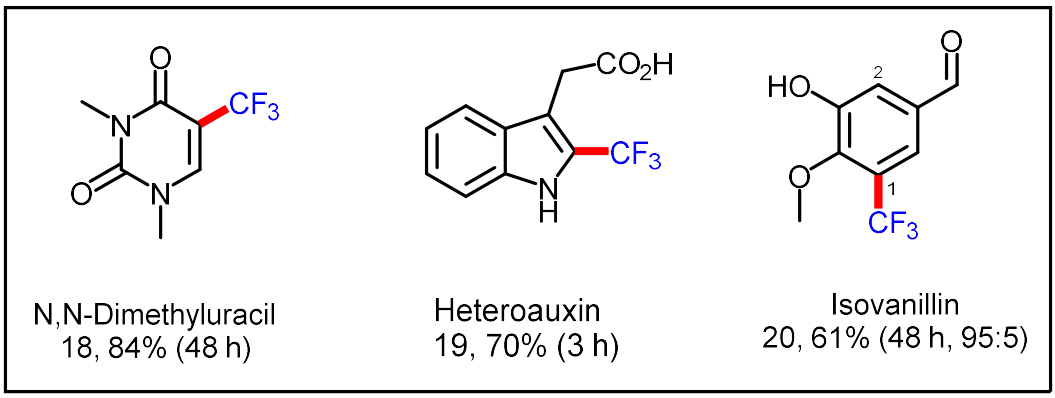


Fig. 9-Application of trifluoromethylation in natural products

We subjected our developed photoredox methodology to some biologically active molecules such as N,N-dimethyl uracil (RNA-base analogue), heteroauxin (growth-promoting hormone in plants) and isovanillin (a flavorant) to obtain their trifluoromethylation products with great efficiency (61-84% isolated yield). High regioselectivity at the highly electron-dense carbon center was observed in the case of uracil and vanillin. The blocking of such metabolically susceptible positions with a CF_3 moiety can prove quite useful in medicinal studies. For example, the CF_3-uracil is an important and widely studied derivative in medicinal chemistry for its potential in cancer treatment. Presence of functional groups such as carboxylic acid in case of heteroauxin, unprotected alcohol and aldehyde in case of vanillin and cyclic ketones in uracil was very well tolerated.

Chapter 4. Experimental Section

4.1 Reagent Information

Unless otherwise noted, all reactions were performed under Argon atmosphere in oven-dried reaction tubes with screw caps. All the commercially available chemicals and reagents were used as provided without further purification. The cadmium selenide (CdSe) catalyst was obtained from Sigma Aldrich. For column chromatography, we used 100-200 mesh sized silica gel available from Aldrich. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator while maintaining the bath-tub temperature at 35^0C.

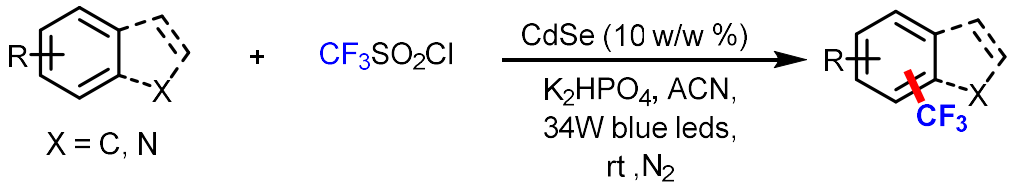
4.2 Analytical Information.

All isolated compounds are characterized by ^{1}H NMR, ^{13}C NMR spectroscopy, GC-MS analysis (Gas Chromatography-Mass Spectroscopy), and FT-IR (Fourier Transform-Infrared Spectroscopy). Copies of the ^{1}H NMR, 13C NMR can be found in Analytical Data section. Unless otherwise stated, NMR spectra were recorded on a Bruker Avance-II 600 (600 and 151 MHz), 500 (500 and 126 MHz) or 400 (400 and 101 MHz) instrument and are internally-referenced to residual protic solvent signals (Note: CDCl3 referenced at δ 7.26 and 77.16 ppm respectively). All ^{1}H NMR experiments are reported as follows unlessotherwise stated: chemical shift (δ ppm), integration, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and coupling constants (Hz). All ^{13}C NMR spectra were reported in ppm in terms of chemical shift and were obtained with ^{1}H-decoupling. All GC analysis was performed on an Agilent 7890A GC system with an FID detector using a J&W HP–5ms column (10 m, 0.1 mm I.D.) with trifluorotoluene as an internal standard. All GC-MS analysis was done by Agilent 7890A GC system with a J&W DB–5ms column (30 m, 0.1 mm I.D.) connected with 5975C inert XL EI/CI MSD (with triple axis detector). The mass scan range was set to 100–2000 m/z, with a resolving power of 100,000. FT-IR was carried out by Thermo-Scientific instrument.

4.3 General Procedures

General Procedure A – Trifluoromethylation of pyrroles and indoles

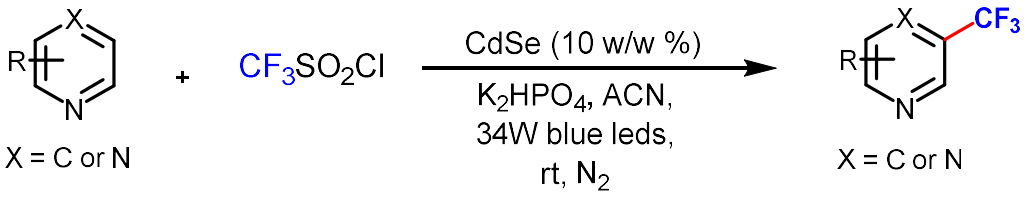
Oven-dried reaction vials were equipped with magnetic stir bars, CdSe (10 w/w %) and heteroarenes (0.3 mmol, 1eq. (if it was solid)). The vials were then taken to the glove box where we added K_2HPO_4 (0.75 mmol, 2.5 eq) and solvent CH_3CN (0.1M, 3mL). The vials were then fitted with silicone septa screw caps and were then taken out of the glove box. We then added triflyl chloride (CF_3SO_2Cl) (0.6 mmol, 2 eq.) and heteroarenes (0.3 mmol, 1 eq., (if it was liquid)) to our reaction vials by a syringe. The resulting solutions were then degassed by alternating vacuum evacuation and then N_2 backfilling (x3).The vials were then sealed with parafilm and were then subjected to irradiation by 34W Blue LEDs for 3-48h under fan cooling. The crude materials were purified by column chromatography on silica gel using the appropriate solvent mixture to obtain the desired trifluoromethyl product.



Scheme 14. The general methodology for direct trifluoromethylation of a heteroaryl C-H bond using Cd-based photocatalyst.

General Procedure B – Trifluoromethylation of pyridines and pyrazines

This procedure is the same as General Procedure A except for the use of 3 eq. of triflyl chloride (CF_3SO_2Cl) and 2.5equivalent of base K_2HPO_4. Pyridines and pyrazines exhibit competitive protonation which inhibits product formation quantitatively. The yield was improved with the addition of excess CF_3SO_2Cl reagent (3 eq.)



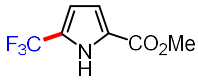
Scheme 15. Trifluoromethylation of six-membered electron deficient heteroarenes

Conclusions

In this work, we have thus introduced a novel photoredox-based method, using a commercially available CdSe semiconductor photocatalyst, which allows the site-selective C-H trifluoromethylation of heteroarenes under mild and economically cheaper conditions. We have shown the immense potential of our developed protocol in medicinal chemistry and late-stage drug synthesis by incorporating the trifluoromethyl group in some biologically active compounds. We successfully overcame the limitations faced by previously developed methods mainly that of higher temperature requirement, pre-activation of substrates, use of expensive photocatalyst and manual synthesis of a heterogeneous photocatalyst. We anticipate that our developed methodology also has a great industrial potential due to its economic generality and wide scope of application in pharmaceuticals and agrochemicals.

Analytical Data

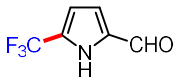
Methyl 5-(trifluoromethyl)-1*H*-pyrrole-2-carboxylate



The title compound was synthesized according to the general procedure employing CdSe (3.7 mg, 10 w/w %), K_2HPO_4 (130.5 mg, 0.75mmol), methyl 1*H*-pyrrole-2-carboxylate (37.5 mg, 0.30 mmol), CF_3SO_2Cl (64 µL, 0.60 mmol), and CH_3CN (0.1 M, 3 mL) for 20 h. The product was purified by column chromatography (silica gel, gradient 1 to 10% diethyl ether/petroleum ether). Yield = 70%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.50 (s, 1H), 6.90 – 6.86 (m, 1H), 6.60 – 6.58 (m, 1H), 3.92 (s, 3H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ 161.65, 125.24, 125.04(q, J_{C-F} = 40.4 Hz),120.56(q, J_{C-F} = 268.6 Hz), 115.12, 111.0 (d, J_{C-F} = 3.0 Hz), 52.29.**^{19}F NMR (377 MHz, $CDCl_3$)** δ– 60.43.**GCMS (EI)** *m/z* calcd. for$C_7H_6F_3NO_2$ [M^+] 193.0, found 193.1.

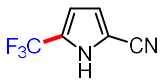
5-(Trifluoromethyl)-1*H*-pyrrole-2-carbaldehyde



The title compound was synthesized according to the general procedure employing CdSe (2.8 mg, 10 w/w %), K_2HPO_4 (130.5 mg, 0.75mmol), 1*H*-pyrrole-2-carbaldehyde (28.5 mg, 0.30 mmol), CF_3SO_2Cl (64 µL, 0.60 mmol), and CH_3CN (0.1 M, 3 mL) for 10 h. The product was purified by column chromatography (silica gel, gradient 1 to 10% diethyl ether/petroleum ether). Yield = 68%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.26 (s, 1H), 9.65 (s, 1H), 7.02 – 6.95 (m, 1H), 6.76 – 6.63 (m, 1H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ 180.65, 133.97, 127.42 (q, J_{C-F} = 40.2 Hz),120.39 (q, J_{C-F} = 268.2 Hz), 120.12,111.44 (q, J_{C-F} = 2.9 Hz).**^{19}F NMR (377 MHz, $CDCl_3$)** δ– 60.92.

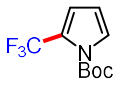
5-(Trifluoromethyl)-1*H*-pyrrole-2-carbonitrile



The title compound was synthesized according to the general procedure employing CdSe (2.7 mg, 10 w/w %), K_2HPO_4 (130.5 mg, 0.75mmol), 1*H*-pyrrole-2-carbonitrile (27.6 mg, 0.30 mmol), CF_3SO_2Cl (64 µL, 0.60 mmol), and CH_3CN (0.1 M, 3 mL) for 10 h. The product was purified by column chromatography (silica gel, gradient 1 to 10% diethyl ether/petroleum ether). Yield = 74%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 6.93 – 6.82 (m, 1H), 6.72 – 6.53 (m, 1H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ 125.71 (q, $J_{C\text{-}F}$ = 40.9 Hz), 120.29, 119.85 (q, $J_{C\text{-}F}$ = 268.0 Hz), 112.84, 110.88 (q, $J_{C\text{-}F}$ = 3.0 Hz), 103.90.**^{19}F NMR (377 MHz, $CDCl_3$)** δ– 60.56.

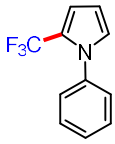
tert-Butyl 2-(trifluoromethyl)-1*H*-pyrrole-1-carboxylate



The title compound was synthesized according to the general procedure employing CdSe (5.0 mg, 10 w/w %), K_2HPO_4 (130.5 mg, 0.75mmol), *tert*-butyl 1*H*-pyrrole-1-carboxylate (50.1 mg, 0.30 mmol), CF_3SO_2Cl (64 µL, 0.60 mmol), and CH_3CN (0.1 M, 3 mL) for 3 h. The product was purified by column chromatography (silica gel, gradient 1 to 10% diethyl ether/petroleum ether). Yield = 90%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, J = 3.3, 1.9 Hz, 1H), 6.73 (dd, J = 3.6, 1.9 Hz, 1H), 6.19 (t, J = 3.5 Hz, 1H), 1.61 (s, 9H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ 147.57, 125.93 (d, $J_{C\text{-}F}$ = 2.3 Hz),121.89 (q, $J_{C\text{-}F}$ = 40.2 Hz), 120.68 (q, $J_{C\text{-}F}$ = 266.3 Hz),117.93 (q, $J_{C\text{-}F}$ = 4.5 Hz), 109.76, 85.78, 27.85.**^{19}F NMR (377 MHz, $CDCl_3$)** δ– 58.31.

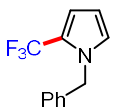
1-Phenyl-2-(trifluoromethyl)-1*H*-pyrrole



The title compound was synthesized according to the general procedure employing CdSe (4.2mg, 10 w/w %), K_2HPO_4 (130.5 mg, 0.75mmol), 1-phenyl-1*H*-pyrrole (42.9 mg, 0.30 mmol), CF_3SO_2Cl (64 µL, 0.60 mmol), and CH_3CN (0.1 M, 3 mL) for 1.5 h. The product was purified by column chromatography (silica gel, gradient 1 to 10% diethyl ether/petroleum ether). Yield = 86%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.43 (m, 3H), 7.39-7.37 (m, 2H), 6.89 (t, J = 2.4 Hz, 1H), 6.74– 6.73 (m, 1H), 6.28 (t, J = 3.3 Hz, 1H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ 139.24, 129.12, 128.62, 127.38 (q, $J_{C\text{-}F}$ = 3.0 Hz), 126.64, 122.35 (q, $J_{C\text{-}F}$ = 38.4 Hz), 121.33 (q, $J_{C\text{-}F}$ = 267.6 Hz), 112.86 (q, $J_{C\text{-}F}$ = 3.0 Hz), 108.36.**^{19}F NMR (377 MHz, $CDCl_3$)** δ– 55.87.**GCMS (EI)** *m/z* calcd. for $C_{11}H_8F_3N$ [M^+] 211.0, found 211.1.

1-Benzyl-2-(trifluoromethyl)-1*H*-pyrrole

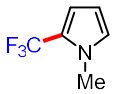


The title compound was synthesized according to the general procedure employing CdSe (4.7mg, 10 w/w %), K_2HPO_4 (130.5 mg, 0.75mmol), 1-benzyl-1*H*-pyrrole (47.1 mg, 0.30 mmol), CF_3SO_2Cl (64 µL, 0.60 mmol), and CH_3CN (0.1 M, 3 mL) for 1 h.

The product was purified by column chromatography (silica gel, gradient 1 to 10% diethyl ether/petroleum ether). Yield = 72%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.34 (m, 3H), 7.18 (d, *J* = 7.1 Hz, 2H), 6.78 (t, *J* = 2.3 Hz, 1H), 6.70 (d, *J* = 3.7 Hz, 1H), 6.24 (t, *J* = 3.3 Hz, 1H), 5.24 (s, 2H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ 137.07, 128.88, 128.02, 127.15, 126.09 (q, $J_{C\text{-}F}$ = 2.3 Hz),121.71 (q, $J_{C\text{-}F}$ = 266.6 Hz), 121.38 (q, $J_{C\text{-}F}$ = 38.1 Hz), 111.90 (q, $J_{C\text{-}F}$ = 3.7 Hz),108.13, 51.51.**^{19}F NMR (377 MHz, $CDCl_3$)** δ– 57.51.

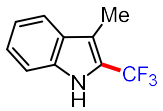
1-Methyl-2-(trifluoromethyl)-1*H*-pyrrole



The title compound was synthesized according to the general procedure employing CdSe (2.4mg, 10 w/w %), K_2CO_3 (103.5 mg, 0.75mmol), 1-methyl-1*H*-pyrrole (24.3 mg, 0.30 mmol), CF_3SO_2Cl (64 µL, 0.60 mmol), and CH_3CN (0.1 M, 3 mL) for 1 h. Then, the reaction mixture was purified by prep TLC using 15% DCM in petroleum ether to provide thetitle compound.Yield = 89% (yield determined by ^{19}F NMR analysis due to the high volatility of the desired product).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71 (d, *J* = 2.3 Hz, 1H), 6.56 (d, *J* = 3.5 Hz, 1H), 6.09 (dd, *J* = 4.2, 2.2 Hz, 1H), 3.72 (s, 3H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ 126.73, 121.64 (q, $J_{C\text{-}F}$ = 267.1 Hz), 121.13 (q, $J_{C\text{-}F}$ = 38.1 Hz), 111.67 (q, $J_{C\text{-}F}$ = 3.5 Hz), 107.31, 34.90.**^{19}F NMR (377 MHz, $CDCl_3$)** δ– 58.83.

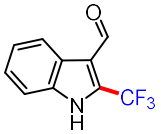
3-Methyl-2-(trifluoromethyl)-1*H*-indole



The title compound was synthesized according to the general procedure employing CdSe (3.9mg, 10 w/w %), K_2CO_3 (103.5 mg, 0.75mmol), 3-methyl-1*H*-indole (39.3 mg, 0.30 mmol), CF_3SO_2Cl (64 µL, 0.60 mmol), and CH_3CN (0.1 M, 3 mL) for 1 h. The product was purified by column chromatography (silica gel, gradient 10 to 15% diethyl ether/petroleum ether). Yield = 75%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.36 (dt, *J* = 15.0, 8.1 Hz, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 2.46 (q, *J* = 1.9 Hz, 3H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ 135.31, 128.19, 124.89, 122.25 (q, $J_{C\text{-}F}$ = 269.6 Hz), 121.66 (q, $J_{C\text{-}F}$ = 36.8 Hz), 120.51, 120.22, 114.20 (d, $J_{C\text{-}F}$ = 3.0 Hz), 111.69, 8.46.**^{19}F NMR (377 MHz, $CDCl_3$)** δ– 58.61.**GCMS (EI)** *m/z* calcd. for$C_{10}H_8F_3N$ [M^+] 199.1, found 199.1.

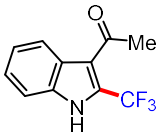
2-(Trifluoromethyl)-1*H*-indole-3-carbaldehyde



The title compound was synthesized according to the general procedure employing CdSe (4.3mg, 10 w/w %), K_2HPO_4 (130.5 mg, 0.75mmol), 1*H*-indole-3-carbaldehyde (43.5 mg, 0.30 mmol), CF_3SO_2Cl (64 µL, 0.60 mmol), and CH_3CN (0.1 M, 3 mL) for 8 h. The product was purified by column chromatography (silica gel, gradient 10 to 15% diethyl ether/petroleum ether). Yield = 58%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 13.43 (s, 1H), 10.24 (s, 1H), 8.25 (d, J = 8.0 Hz, 1H), 7.61 (d, J = 8.2 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H).**^{13}C NMR (101 MHz, DMSO-d_6)** δ 184.22, 135.35, 130.87 (q, $J_{C\text{-}F}$ = 39.0 Hz), 125.80, 124.32, 123.83, 121.98, 120.78 (q, $J_{C\text{-}F}$ = 270.4 Hz), 115.43, 113.18.**^{19}F NMR (377 MHz, DMSO-d_6)** δ– 55.46.

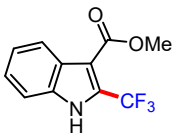
1-(2-(Trifluoromethyl)-1*H*-indol-3-yl)ethan-1-one



The title compound was synthesized according to the general procedure employing CdSe (4.7mg, 10 w/w %), K_2HPO_4 (130.5 mg, 0.75mmol), 1-(1*H*-indol-3-yl)ethan-1-one(47.7 mg, 0.30 mmol), CF_3SO_2Cl (64 µL, 0.60 mmol), and CH_3CN (0.1 M, 3 mL) for 8 h. The product was purified by column chromatography (silica gel, gradient 10 to 15% diethyl ether/petroleum ether). Yield = 60%.

^{1}H NMR (400 MHz, DMSO-d_6) δ 13.07 (s, 1H), 8.09 (d, J = 8.1 Hz, 1H), 7.60 (d, J = 8.2 Hz, 1H), 7.39 (t, J = 7.5 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 2.65 (s, 3H).**^{13}C NMR (101 MHz, DMSO-d_6)** δ 192.60, 134.67, 126.77 (q, $J_{C\text{-}F}$ = 38.3 Hz), 125.26, 124.81, 122.96, 121.86,120.91 (q, $J_{C\text{-}F}$ = 269.9 Hz),116.18, 113.24, 30.90.**^{19}F NMR (377 MHz, DMSO-d_6)** δ– 57.47.

Methyl 2-(trifluoromethyl)-1*H*-indole-3-carboxylate

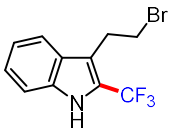


The title compound was synthesized according to the general procedure employing CdSe (5.2mg, 10 w/w %), K_2HPO_4 (130.5 mg, 0.75mmol), methyl 1*H*-indole-3-carboxylate (52.5 mg, 0.30 mmol), CF_3SO_2Cl (64 µL, 0.60 mmol), and CH_3CN (0.1 M, 3 mL) for 8 h. The product was purified by column chromatography (silica gel, gradient 10 to 15% diethyl ether/petroleum ether). Yield = 64%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.09 (s, 1H), 8.26 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.41 – 7.32 (m, 2H), 3.98 (s, 3H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ 163.69, 133.91, 129.04 (q, $J_{C\text{-}F}$

= 38.8 Hz),126.61, 125.67, 123.38, 123.00, 120.52 (q, J_{C-F} = 270.0 Hz), 112.07, 108.41, 51.84.**^{19}F NMR (377 MHz, $CDCl_3$)** δ– 59.86.

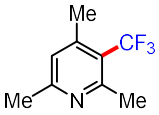
3-(2-Bromoethyl)-2-(trifluoromethyl)-1*H*-indole



The title compound was synthesized according to the general procedure employing CdSe (6.6mg, 10 w/w %), K_2HPO_4 (130.5 mg, 0.75mmol), 3-(2-bromoethyl)-1*H*-indole(66.9 mg, 0.30 mmol), CF_3SO_2Cl (64 µL, 0.60 mmol), and CH_3CN (0.1 M, 3 mL) for 1 h. The product was purified by column chromatography (silica gel, gradient 10 to 15% diethyl ether/petroleum ether). Yield = 66%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.48 (d, *J* = 8.2 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.37 – 7.25 (m, 1H), 3.73 – 3.59 (m, 2H), 3.56 – 3.45 (m, 2H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ 135.22, 127.11, 125.27, 122.38 (q, J_{C-F} = 37.0 Hz), 121.88 (q, J_{C-F} = 268.9 Hz), 121.13, 120.07, 112.01,115.45 (d, J_{C-F} = 3.0 Hz), 31.40, 27.91.**^{19}F NMR (377 MHz, $CDCl_3$)** δ– 58.34.

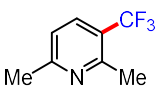
2,4,6-Trimethyl-3-(trifluoromethyl)pyridine



The title compound was synthesized according to the general procedure employing CdSe (3.6mg, 10 w/w %), K_2HPO_4 (130.5 mg, 0.75mmol), 2,4,6-trimethylpyridine (36.3 mg, 0.30 mmol), CF_3SO_2Cl (96 µL, 0.90 mmol), and CH_3CN (0.1 M, 3 mL) for 35 h. Then, the reaction mixture was purified by prep TLC using 20% DCM in petroleum ether to provide thetitle compound.Yield = 80% (yield determined by ^{19}F NMR analysis due to the high volatility of the desired product).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (s, 1H), 2.63 (q, *J* = 3.1 Hz, 3H), 2.47 (s, 3H), 2.40 (q, *J* = 3.1 Hz, 3H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ 159.98, 156.57, 147.21, 125.64 (q, J_{C-F} = 274.9 Hz), 124.46, 121.42 (q, J_{C-F} = 29.9 Hz),24.24 (q, J_{C-F} = 3.8 Hz),23.93, 20.98 (q, J_{C-F} = 3.8 Hz).**^{19}F NMR (377 MHz, $CDCl_3$)** δ– 54.35.

2,6-Dimethyl-3-(trifluoromethyl)pyridine

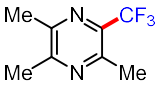


The title compound was synthesized according to the general procedure employing CdSe (3.2mg, 10 w/w %), K_2HPO_4 (130.5 mg, 0.75mmol), 2,6-dimethylpyridine (32.1 mg, 0.30 mmol), CF_3SO_2Cl (96 µL, 0.90 mmol), and CH_3CN (0.1 M, 3 mL) for 48 h.

Then, the reaction mixture was purified by prep TLC using 25% DCM in petroleum ether to provide thetitle compound.Yield = 75% (yield determined by ^{19}F NMR analysis due to the high volatility of the desired product).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.1 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 2.67 (s, 3H), 2.58 (s, 3H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ 161.29, 156.45, 134.25 (d, $J_{C\text{-}F}$ = 5.2 Hz), 124.42 (q, $J_{C\text{-}F}$ = 272.2 Hz), 122.24 (q, $J_{C\text{-}F}$ = 31.6 Hz), 120.27, 24.57, 22.72.**^{19}F NMR (377 MHz, $CDCl_3$)** δ– 61.90.

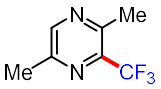
2,3,5-Trimethyl-6-(trifluoromethyl)pyrazine



The title compound was synthesized according to the general procedure employing CdSe (3.6mg, 10 w/w %), K_2HPO_4 (130.5 mg, 0.75mmol), 2,3,5-trimethylpyrazine (36.6 mg, 0.30 mmol), CF_3SO_2Cl (96 µL, 0.90 mmol), and CH_3CN (0.1 M, 3 mL) for 48 h. The product was purified by column chromatography (silica gel, gradient 10 to 15% diethyl ether/petroleum ether). Yield = 72%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.63 (q, *J* = 2.0 Hz, 3H), 2.56 (s, 3H), 2.54 (s, 3H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ 154.95, 148.85, 148.63, 138.49 (q, $J_{C\text{-}F}$= 34.1 Hz), 122.40 (q, $J_{C\text{-}F}$ = 274.3 Hz), 22.09, 21.41, 20.91 (q, $J_{C\text{-}F}$ = 2.5 Hz).**^{19}F NMR (377 MHz, $CDCl_3$)** δ– 65.18.

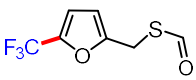
2,5-Dimethyl-3-(trifluoromethyl)pyrazine



The title compound was synthesized according to the general procedure employing CdSe (3.2mg, 10 w/w %), K_2HPO_4 (130.5 mg, 0.75mmol), 2,5-dimethylpyrazine (32.4 mg, 0.30 mmol), CF_3SO_2Cl (96 µL, 0.90 mmol), and CH_3CN (0.1 M, 3 mL) for 48 h. The product was purified by column chromatography (silica gel, gradient 10 to 15% diethyl ether/petroleum ether). Yield = 65%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (s, 1H), 2.67 (d, *J* = 2.3 Hz, 3H), 2.57 (s, 3H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ 150.31, 149.37, 146.32, 140.92 (q, $J_{C\text{-}F}$ = 34.1 Hz), 122.05 (q, $J_{C\text{-}F}$ = 274.8 Hz), 21.00 (d, $J_{C\text{-}F}$ = 2.5 Hz), 20.95.**^{19}F NMR (377 MHz, $CDCl_3$)** δ– 65.90.**GCMS (EI)** *m/z* calcd. for$C_7H_7F_3N_2$ [M^+] 176.1, found 176.0.

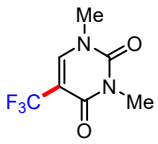
***S*-((5-(Trifluoromethyl)furan-2-yl)methyl)methanethioate**



The title compound was synthesized according to the general procedure employing CdSe (4.2mg, 10 w/w %), K_2HPO_4 (130.5 mg, 0.75mmol), *S*-(furan-2-ylmethyl)methanethioate(42.6 mg, 0.30 mmol), CF_3SO_2Cl (64 µL, 0.60 mmol) and CH_3CN (0.1 M, 3 mL) for 48 h. The product was purified by column chromatography (silica gel, gradient 10 to 15% diethyl ether/petroleum ether). Yield = 68%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.16 (s, 1H), 6.70 (dt, *J* = 2.6, 1.3 Hz, 1H), 6.40 – 6.21 (m, 1H), 4.24 (s, 2H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ 185.81, 153.00, 141.62 (q, J_{C-F} = 42.8 Hz), 118.98 (q, J_{C-F} = 267.0 Hz), 112.77 (q, J_{C-F} = 2.9 Hz), 109.37, 22.83.**^{19}F NMR (377 MHz, $CDCl_3$)** δ– 64.12.

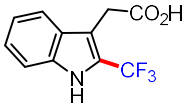
1,3-Dimethyl-5-(trifluoromethyl)pyrimidine-2,4(1*H*,3*H*)-dione



The title compound was synthesized according to the general procedure employing CdSe (4.2mg, 10 w/w %), K_2HPO_4 (130.5 mg, 0.75mmol), 1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione(42.0 mg, 0.30 mmol), CF_3SO_2Cl (64 µL, 0.60 mmol), and CH_3CN (0.1 M, 3 mL) for 48 h. The product was purified by column chromatography (silica gel, gradient 10 to 15% diethyl ether/petroleum ether). Yield = 84%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 1.3 Hz, 1H), 3.47 (s, 3H), 3.32 (s, 3H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ 158.84, 150.99, 143.87 (q, J_{C-F} = 5.9 Hz),122.13 (q, J_{C-F} = 269.7 Hz), 103.95 (q, J_{C-F} = 32.9 Hz), 37.79, 28.05.**^{19}F NMR (377 MHz, $CDCl_3$)** δ– 63.81.**GCMS (EI)** *m/z* calcd. for$C_7H_7F_3N_2O_2$ [M^+] 208.0, found 208.1.

2-(2-(Trifluoromethyl)-1*H*-indol-3-yl)acetic acid

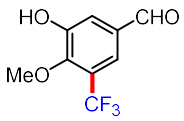


The title compound was synthesized according to the general procedure employing CdSe (5.2mg, 10 w/w %), K_2HPO_4 (130.5 mg, 0.75mmol), 2-(1*H*-indol-3-yl)acetic acid (52.5 mg, 0.30 mmol), CF_3SO_2Cl (64 µL, 0.60 mmol), and CH_3CN (0.1 M, 3 mL) for 3 h. The product was purified by column chromatography (silica gel, gradient 15 to 20% diethyl ether/petroleum ether). Yield = 70%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.42 (b, 1H), 12.08 (s, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 8.3 Hz, 1H), 7.29 (t, *J* = 7.6 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 3.83 (s, 2H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ 171.95, 135.63, 126.89, 124.39, 122.17 (q, J_{C-F} = 268.9 Hz), 121.67 (q, J_{C-F} =

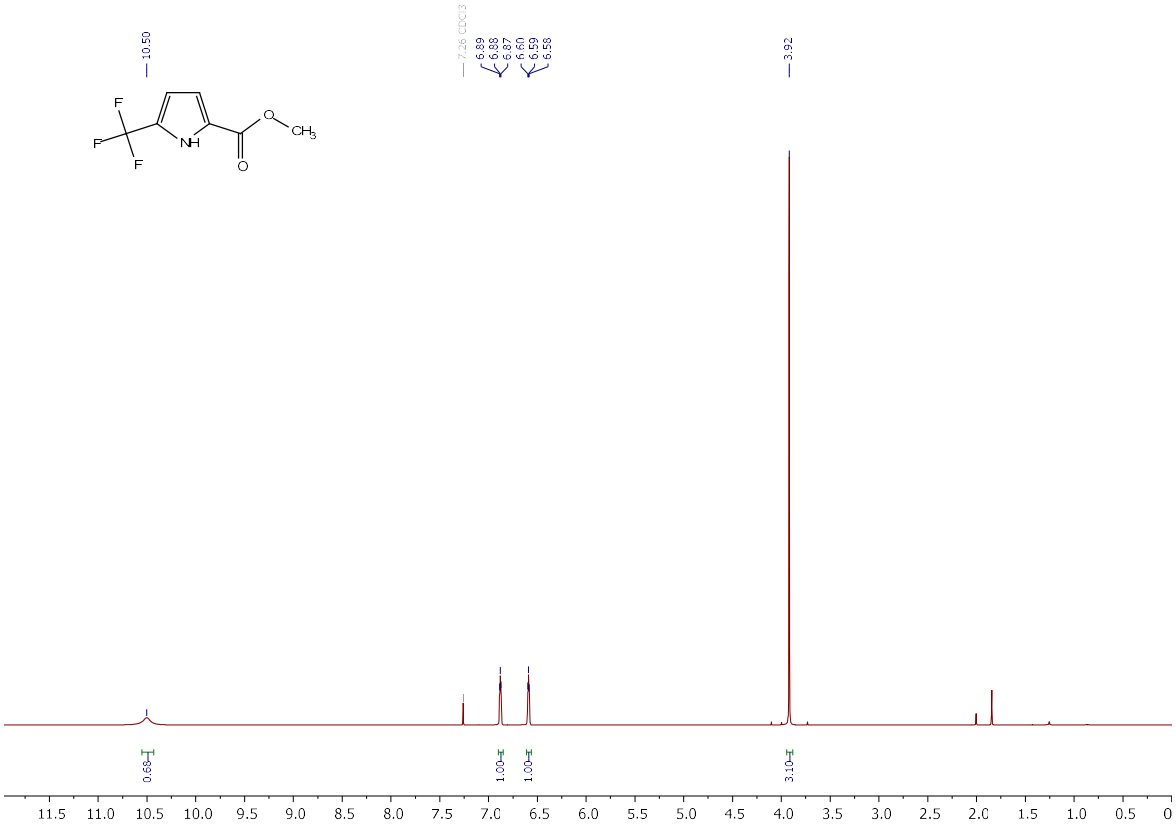
36.0 Hz), 120.18, 120.08, 112.24, 110.37 (d, J_{C-F} = 3.0 Hz), 29.31.**^{19}F NMR (377 MHz, $CDCl_3$)** δ– 56.84.

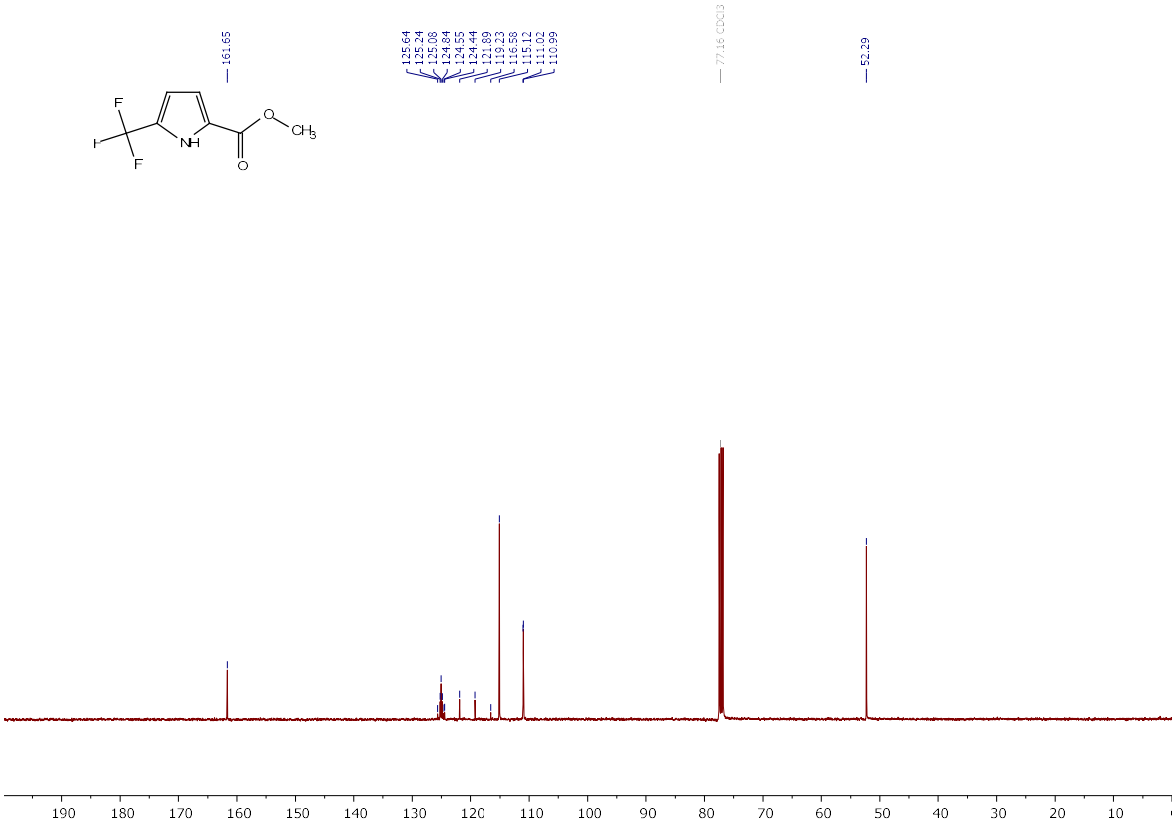
3-Hydroxy-4-methoxy-5-(trifluoromethyl)benzaldehyde



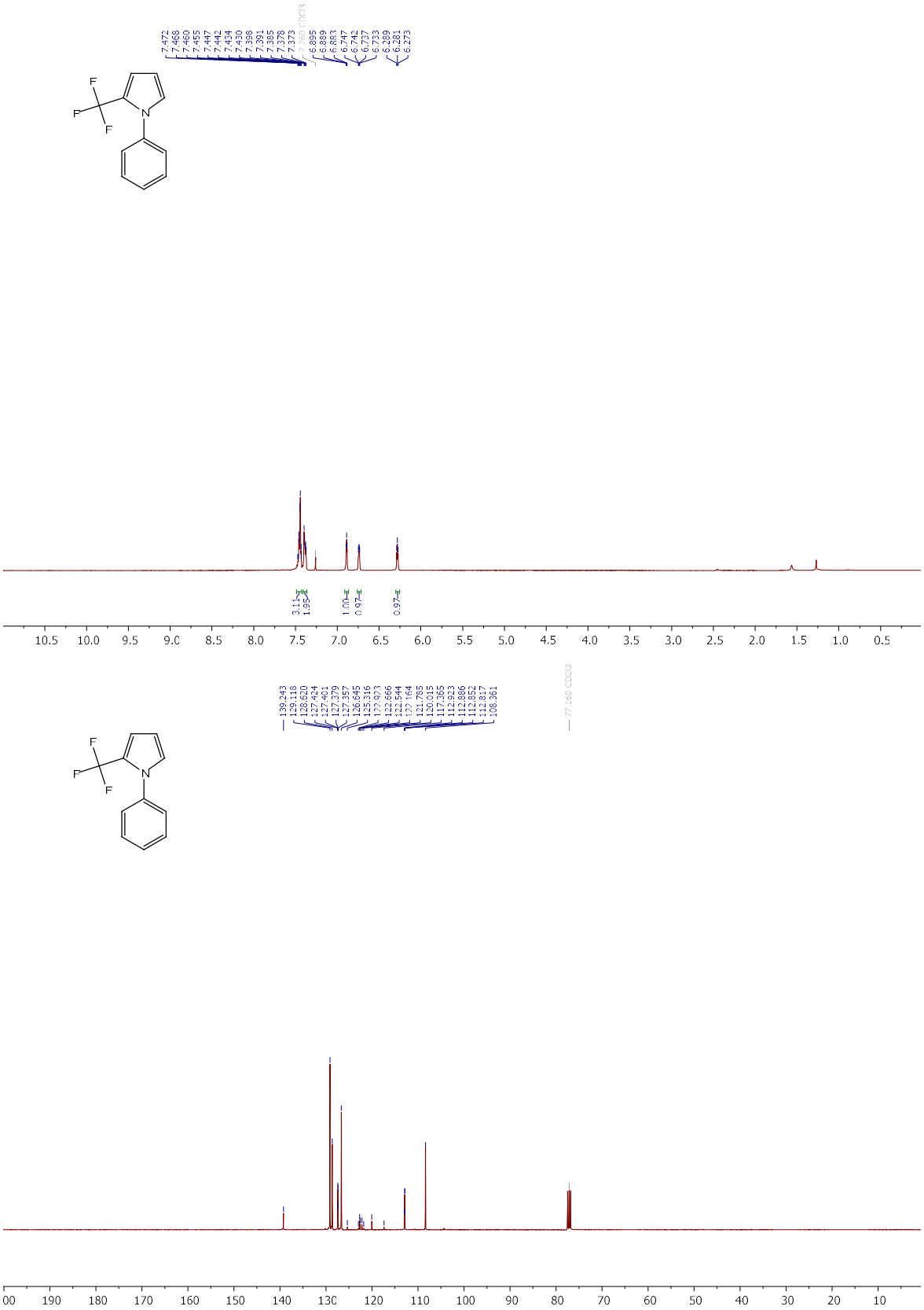
The title compound was synthesized according to the general procedure employing CdSe (4.5mg, 10 w/w %), K_2HPO_4 (130.5 mg, 0.75mmol), 3-hydroxy-4-methoxybenzaldehyde (45.6 mg, 0.30 mmol), CF_3SO_2Cl (64 µL, 0.60 mmol), and CH_3CN (0.1 M, 3 mL) for 48 h. The product was purified by column chromatography (silica gel, gradient 15 to 20% diethyl ether/petroleum ether). Yield = 61%.
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.24 (q, J = 2.1 Hz, 1H), 7.64 (s, 1H), 7.29 (s, 1H), 6.31 (s, 1H), 4.01 (s, 3H).**^{13}C NMR (101 MHz, $CDCl_3$)** δ 187.99 (q, J_{C-F} = 2.9 Hz), 150.34, 148.86, 127.26, 126.54 (q, J_{C-F} = 33.0 Hz), 123.73 (q, J_{C-F}= 274.0 Hz), 112.84 (q, J_{C-F} = 5.9 Hz), 110.30, 56.60.**^{19}F NMR (377 MHz, $CDCl_3$)** δ– 56.84.

^{1}H NMR and ^{13}C NMR spectra of methyl 5-(trifluoromethyl)-1*H*-pyrrole-2-carboxylate

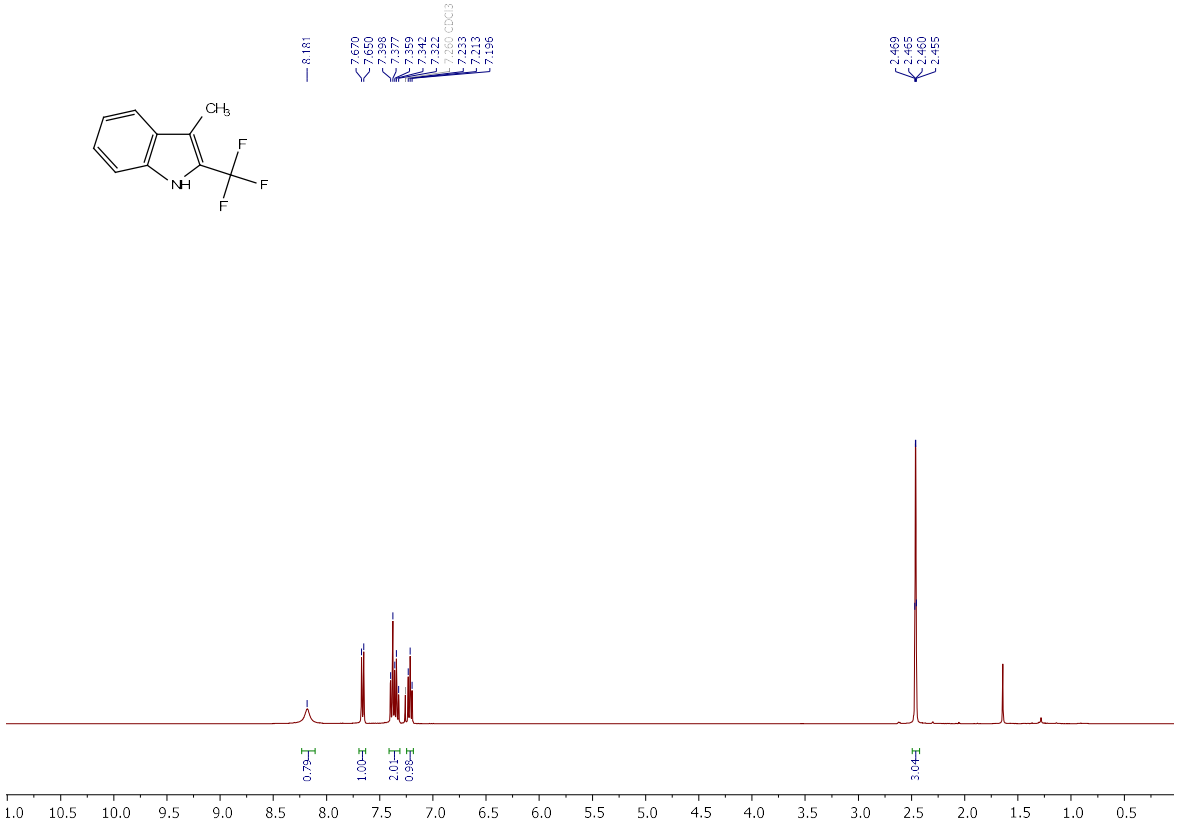


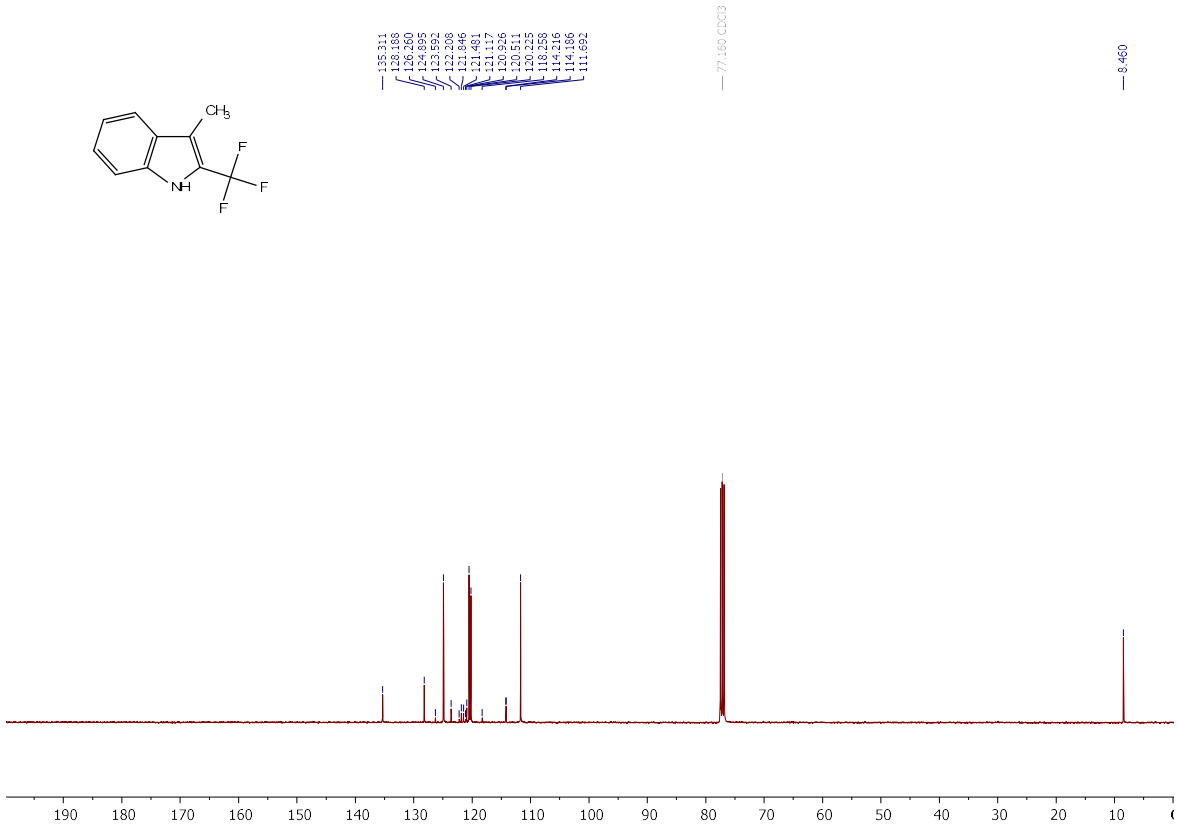


^{1}H NMR and ^{13}C NMR spectra of1-phenyl-2-(trifluoromethyl)-1*H*-pyrrole

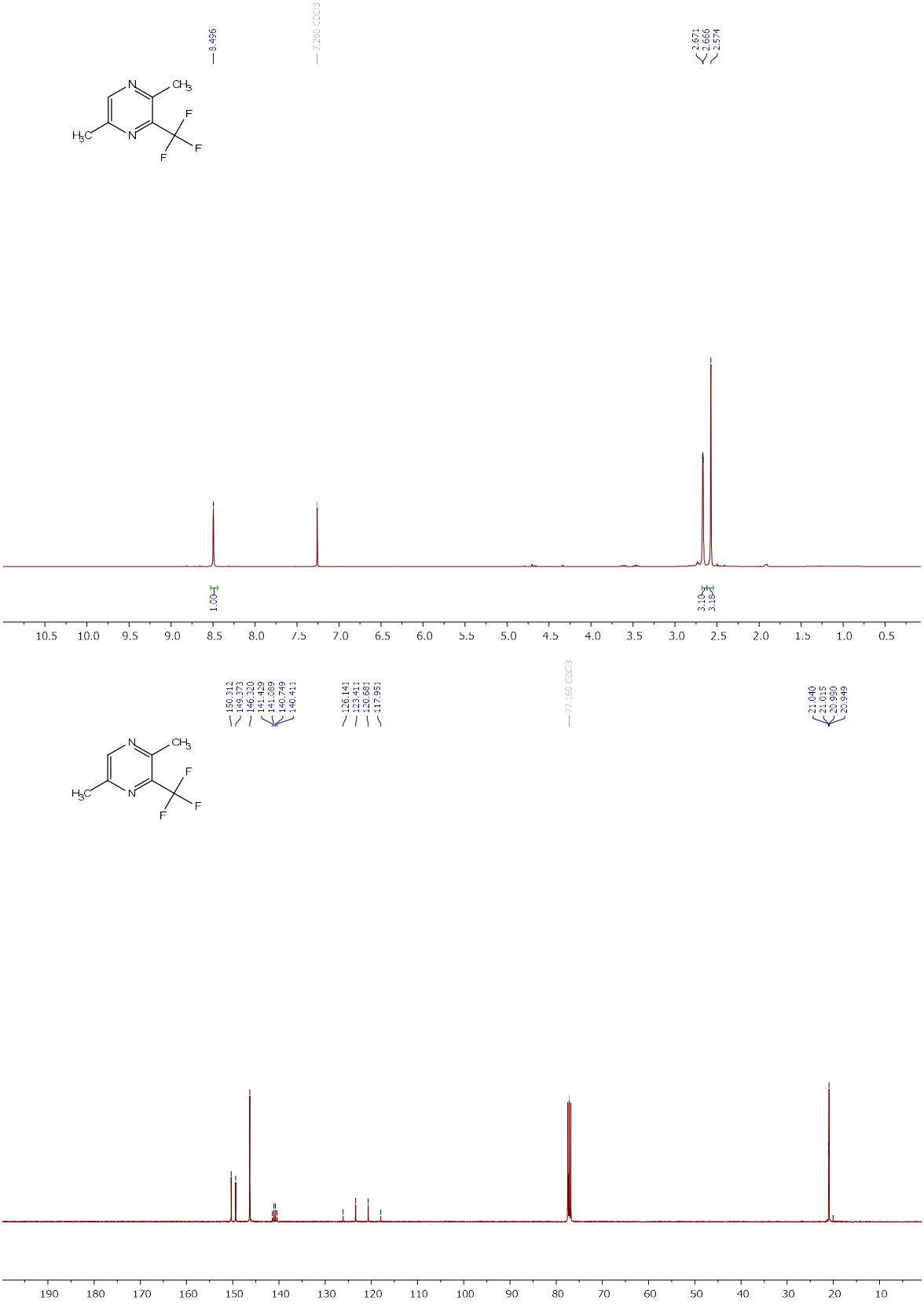


^{1}H NMR and ^{13}C NMR spectra of 3-methyl-2-(trifluoromethyl)-1*H*-indole

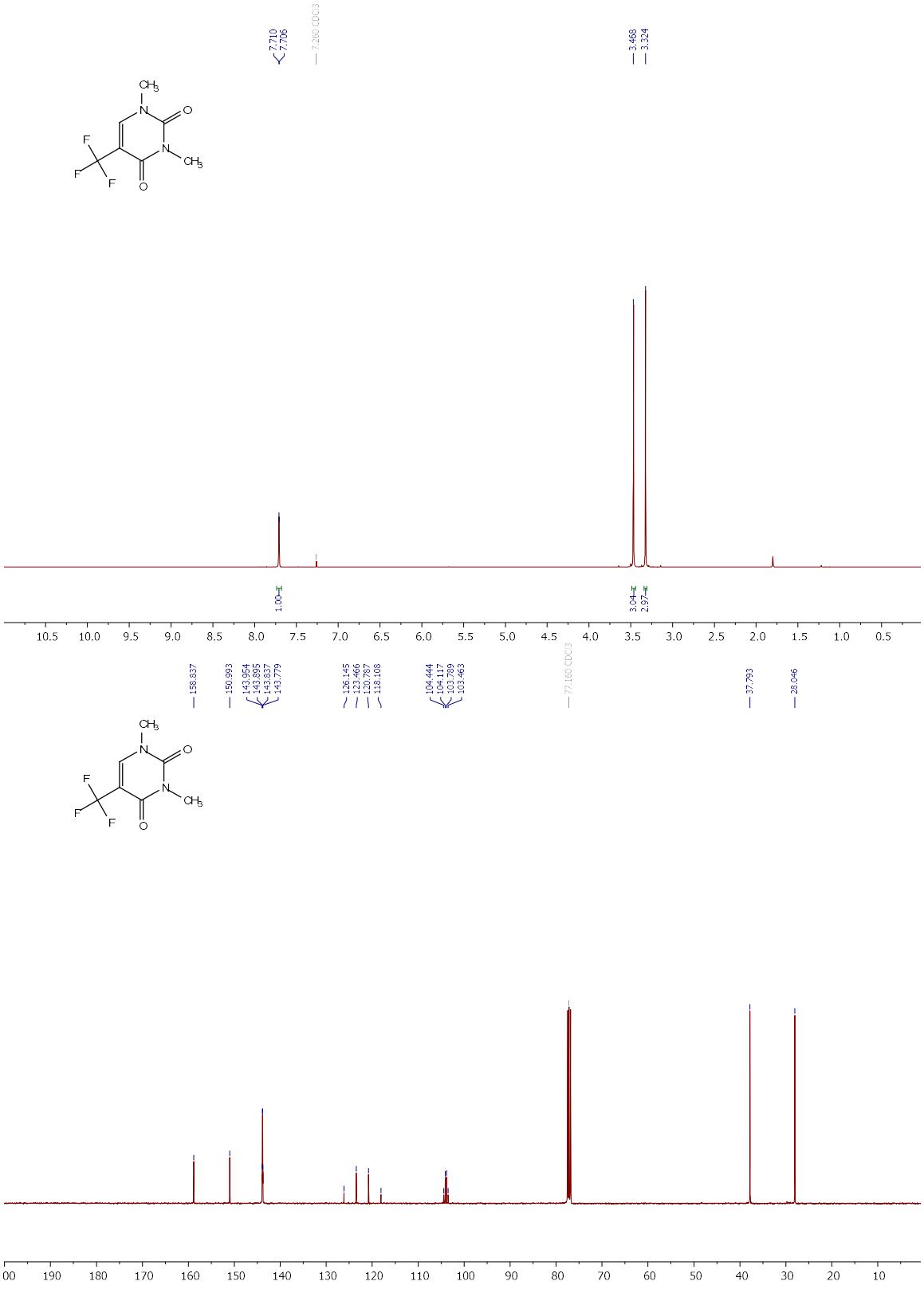




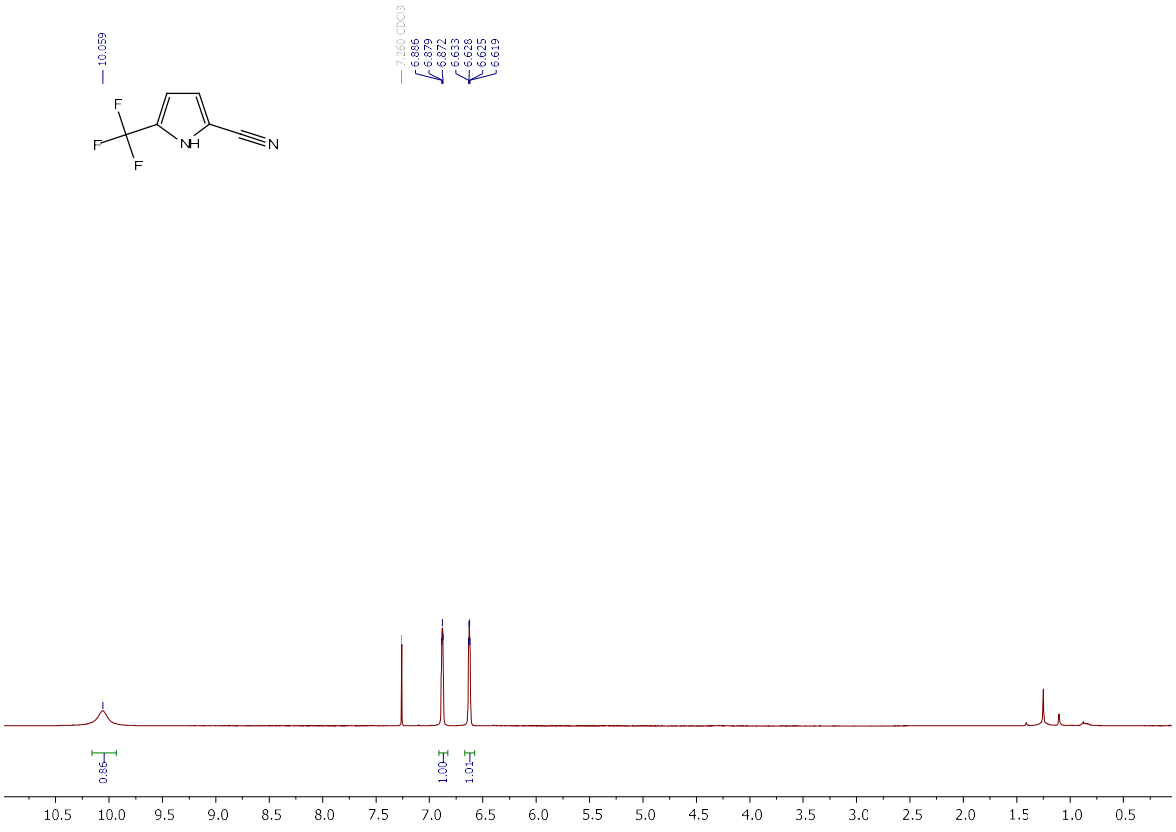
^{1}H NMR and ^{13}C NMR spectra of 2,5-dimethyl-3-(trifluoromethyl)pyrazine

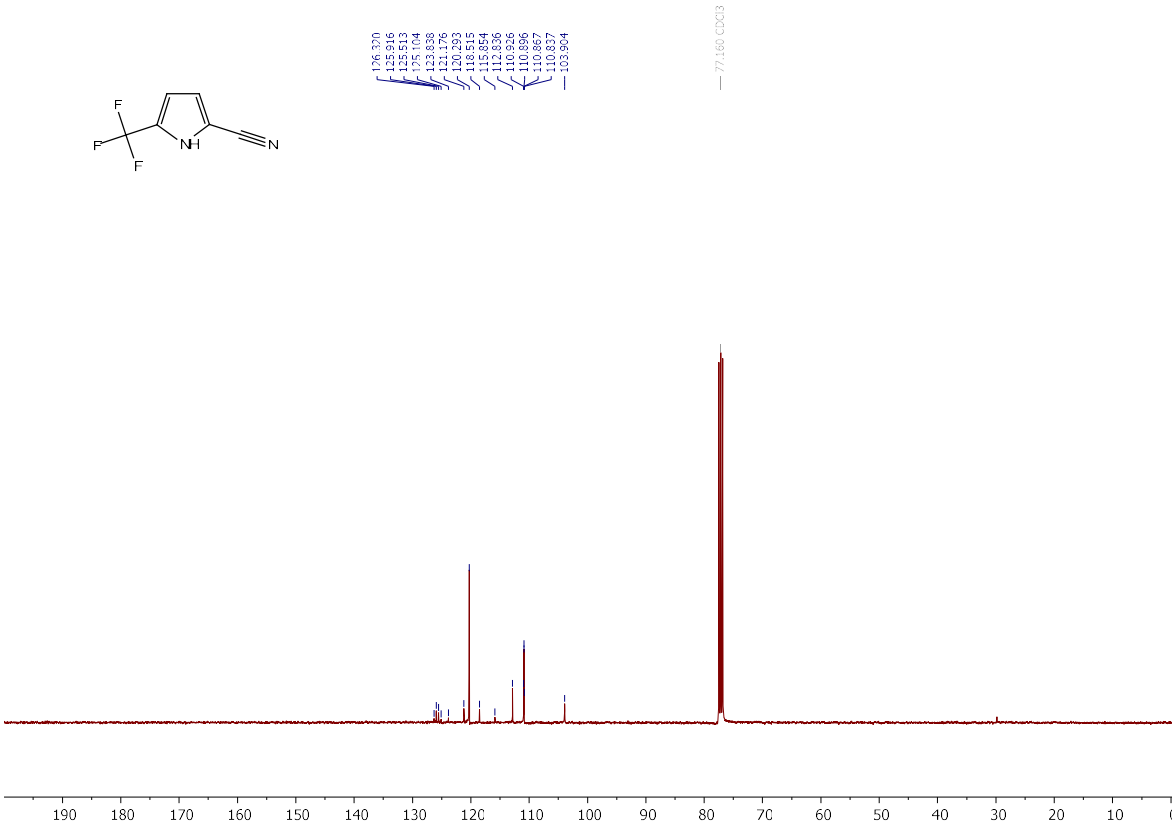


^{1}H NMR and ^{13}C NMR spectra of 1,3-dimethyl-5-(trifluoromethyl)pyrimidine-2,4(1*H*,3*H*)-dione

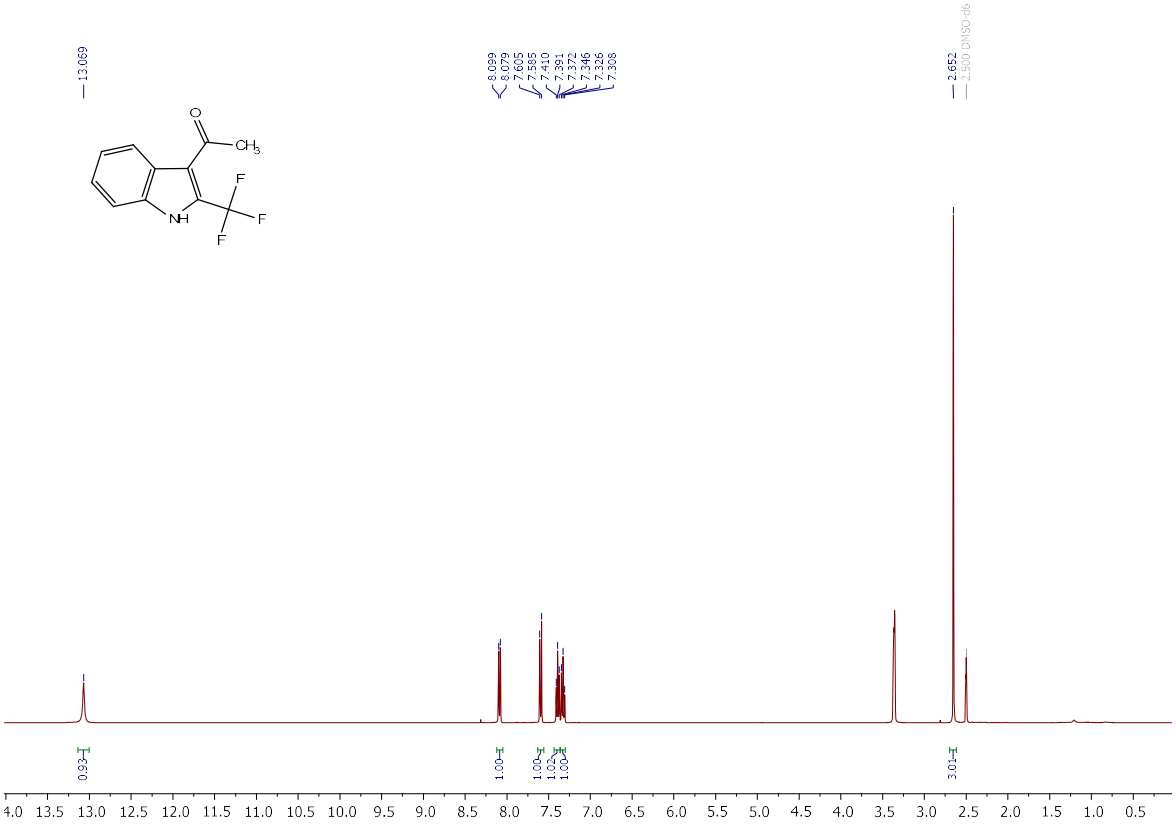


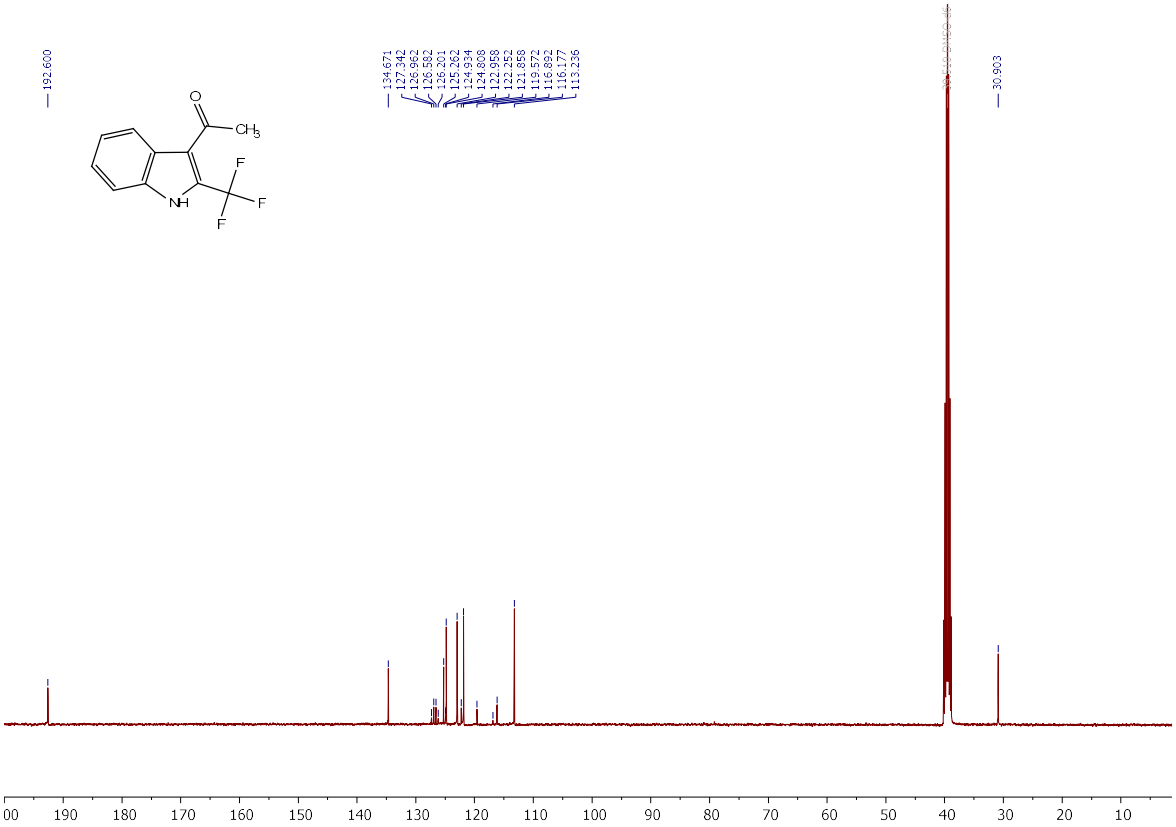
^{1}H NMR and ^{13}C NMR spectra of 5-(trifluoromethyl)-1*H*-pyrrole-2-carbonitrile



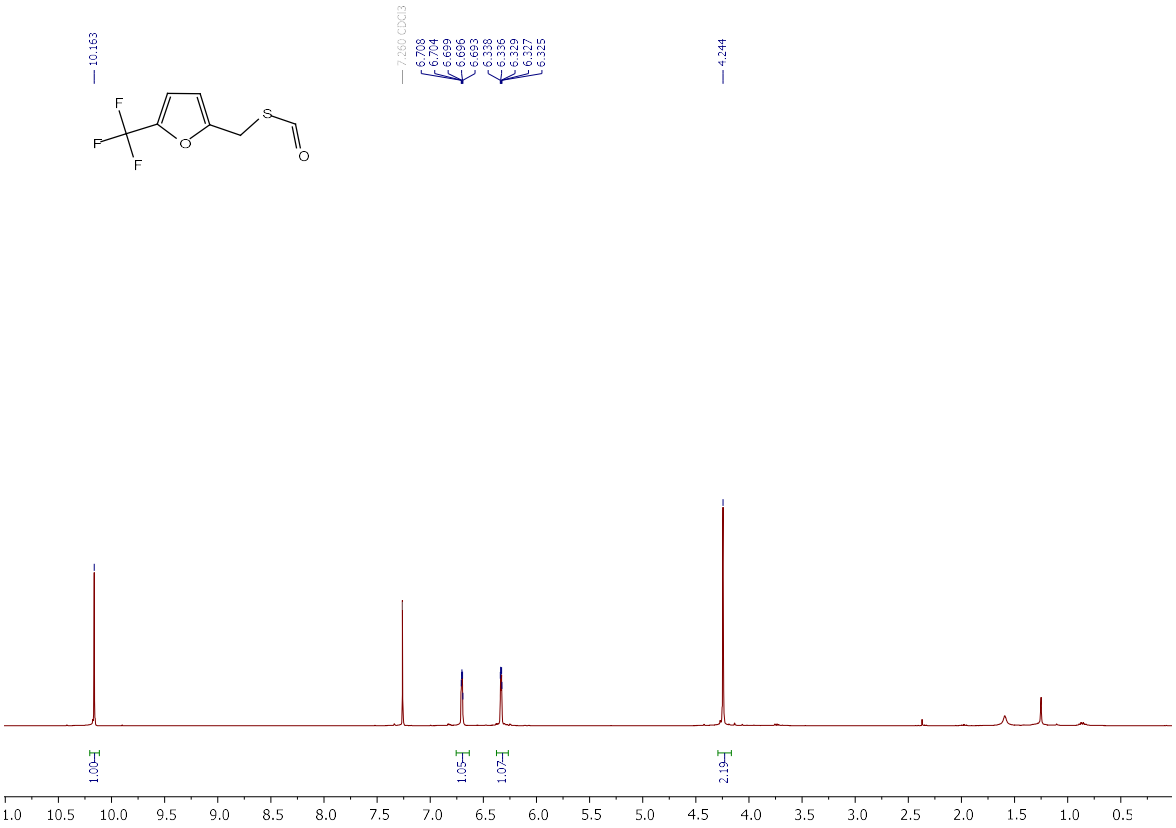


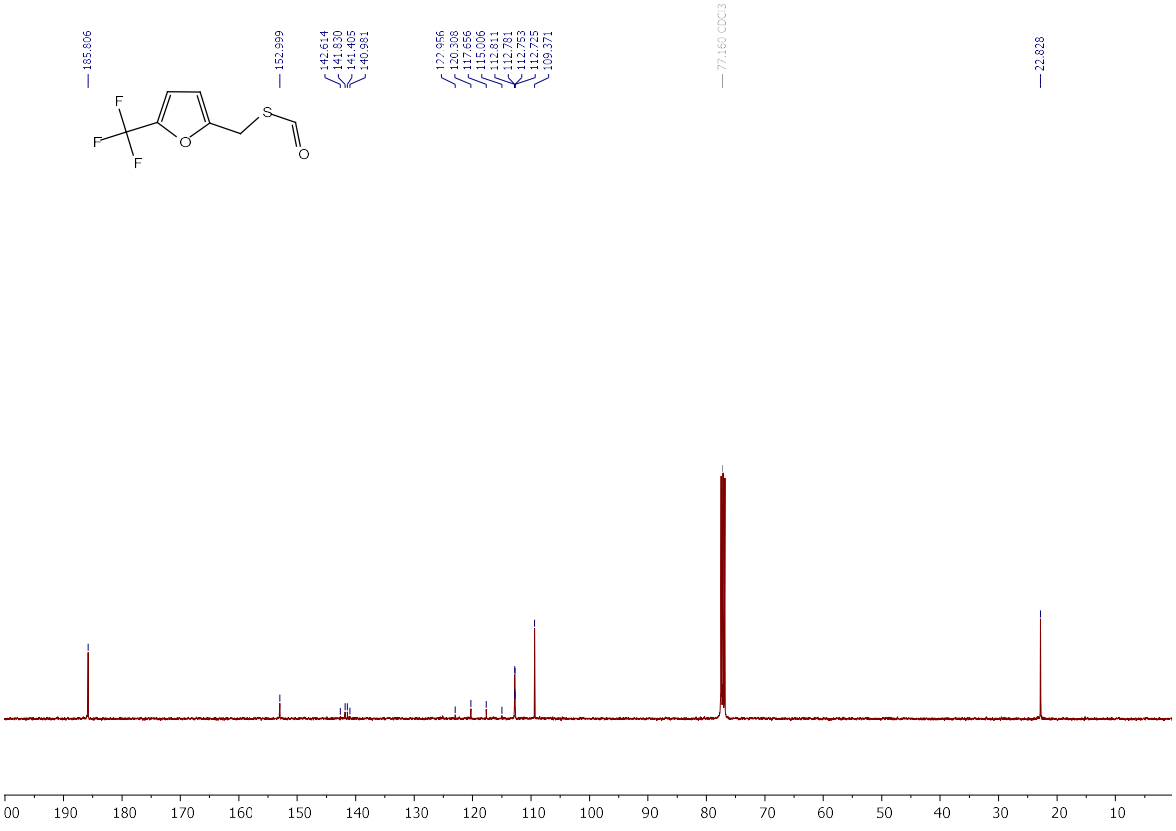
^{1}H NMR and ^{13}C NMR spectra of 1-(2-(trifluoromethyl)-1*H*-indol-3-yl)ethan-1-one



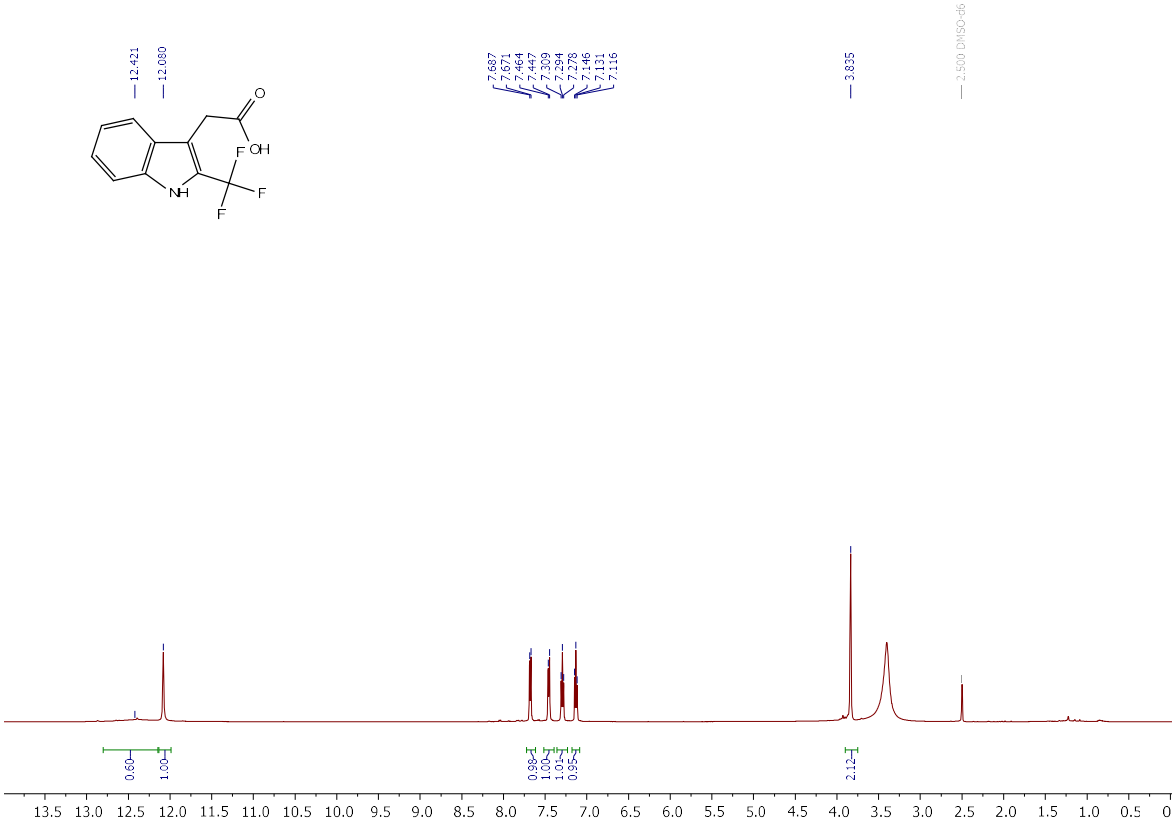


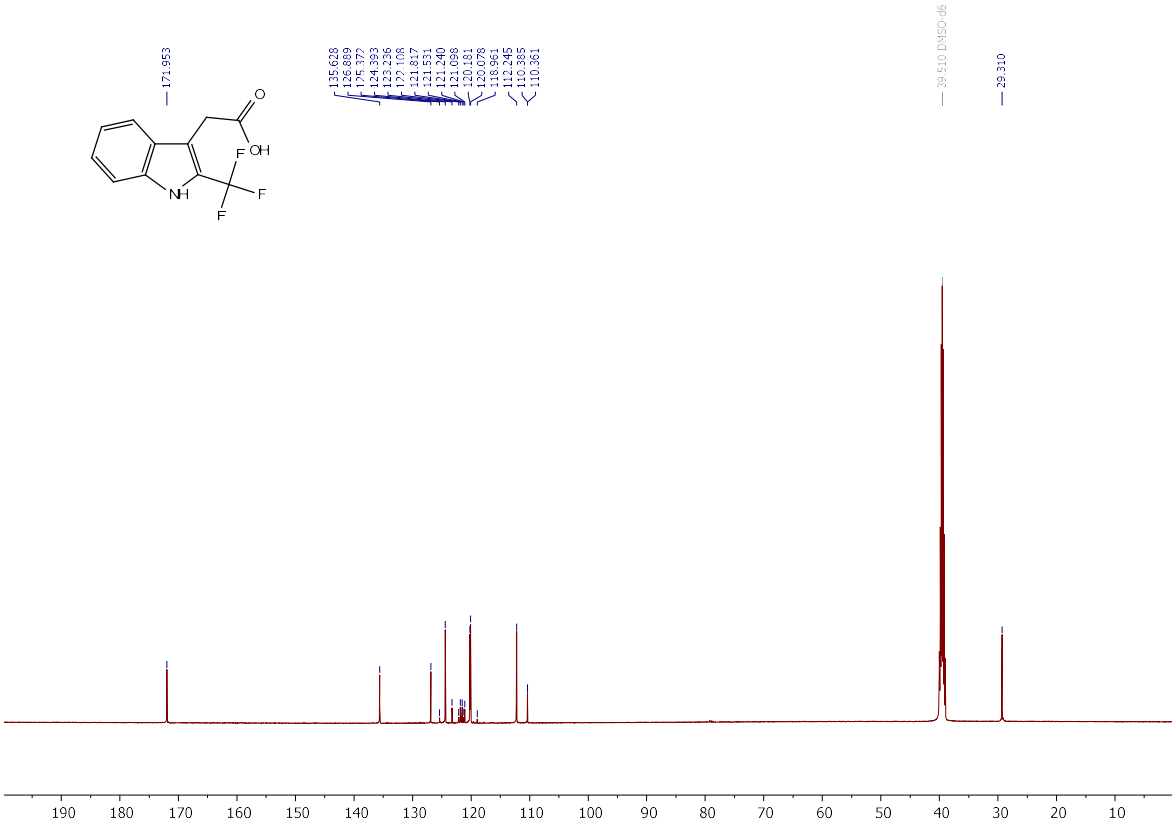
^{1}H NMR and ^{13}C NMR spectra of *S*-((5-(trifluoromethyl)furan-2-yl)methyl)methanethioate



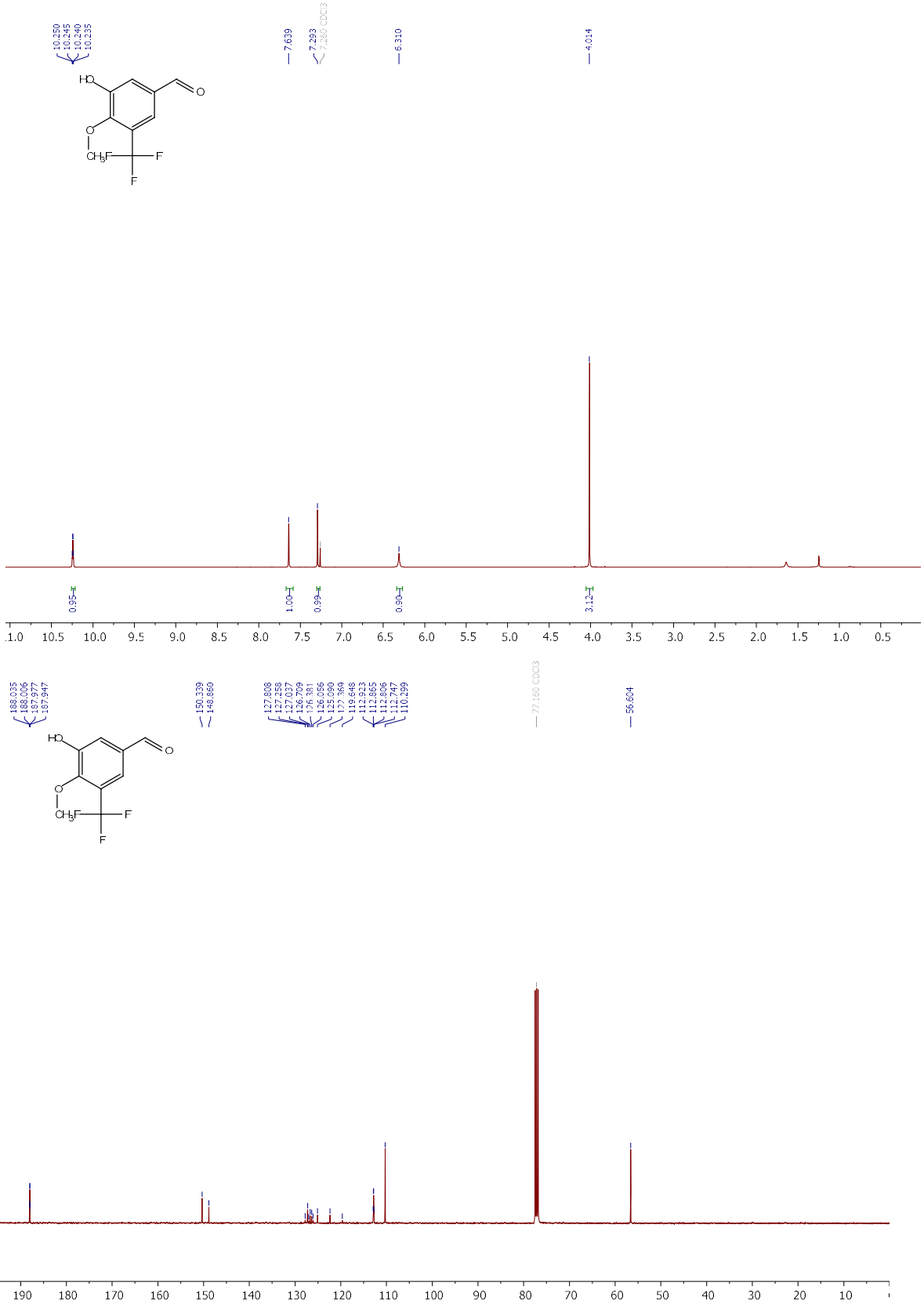


^{1}H NMR and ^{13}C NMR spectra of 2-(2-(trifluoromethyl)-1*H*-indol-3-yl)acetic acid





^{1}H NMR and ^{13}C NMR spectra of 3-hydroxy-4-methoxy-5-(trifluoromethyl)benzaldehyde



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