Copper(I) Catalyzed Synthesis of Phenols and Benzo[*d*]isothiazol-3-ones and their Application for the Synthesis of Alkyl Aryl Ethers and Benzo[*d*]isothiazol-3-one-1-oxides

A Thesis Submitted

in Partial Fulfillment of the Requirements

for the Degree of

DOCTOR OF PHILOSOPHY

by

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March 2013

Dedicated

To

My Family Members

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati, India under the supervision of Prof. Tharmalingam Punniyamurthy.

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators.

Guwahati — Rajesh Paul

March 2013

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

CERTIFICATE

This is to certify that Mr. Rajesh Paul has been working under my supervision since July 2008. I am forwarding his thesis entitled "*Copper(I) Catalyzed Synthesis of Phenols and Benzo[disothiazol-3-ones and their Application for the Synthesis of Alkyl Aryl Ethers and Benzo[d]isothiazol-3-one-1-oxides*" being submitted for the Ph.D. degree of this Institute. I certify that he has fulfilled all the requirements according to the rules of this Institute, and regarding the investigations embodied in his thesis and this work has not been submitted elsewhere for a degree.

Guwahati — Prof. Tharmalingam Punniyamurthy

March 2013 — Supervisor

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Finally, no words would suffice to express my feelings to my parents, sister and brother for their sustained help and encouragement in all my academic endeavors. I feel deeply indebted to them for whatever I have achieved so far.

Rajesh Paul

Abstract

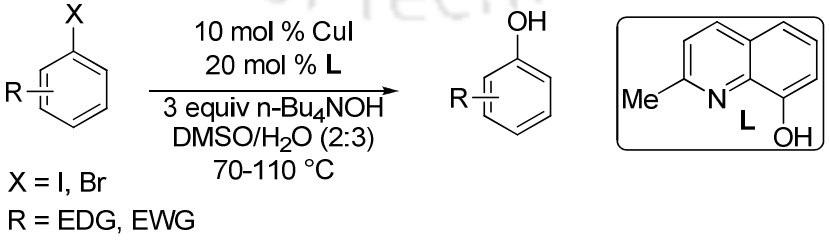
The thesis is divided into five chapters. The first chapter is a general introduction and describes the scope of copper-catalyzed *C-N*, *C-O* and *C-S* bond formation with examples. It also describes the various mechanistic pathways proposed for the reactions.The next two chapters describe copper catalyzed hydroxylation of aryl halides and the one pot conversion the resultant phenoxides to aryl alkyl ethers. The forth and fifth chapters are devoted to the copper catalyzed synthesis of *N*-substituted benzo[*d*]isothizol-3-ones and subsequent titanium catalyzed oxidation to *N*-substituted benzo[*d*]isothiazol-3-one-1-oxide.

Chapter 1. Copper-Catalyzed *C-N*, *C-O* and *C-S* Cross-Coupling Reactions

The copper catalyzed carbon-heteroatom bond formation has evolved as a major synthetic pathway in the last decade. In comparison to palladium based catalysts, they are cheap, less toxic and easily available. In this chapter, a brief review of methods already available in the literature for *C-N*, *C-O* and *C-S* cross-coupling reactions has been provided. Also, a brief review of the various mechanistic pathways proposed for these reactions is discussed.

Chapter 2. Copper(I)-Catalyzed Selective Hydroxylation of Aryl Halides

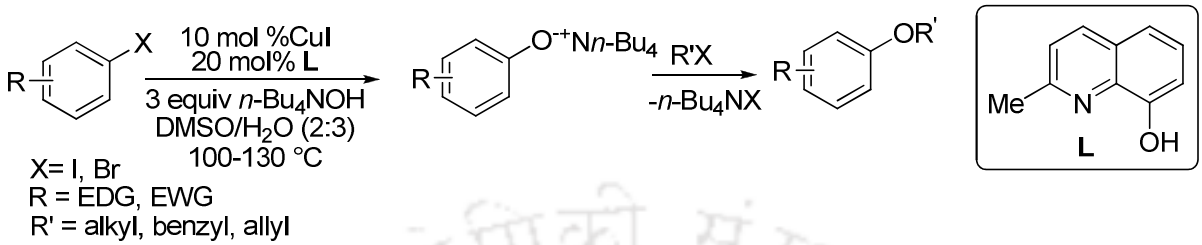
Phenols and their derivatives are structural constituents of numerous natural products, pharmaceuticals and polymers. Transition metal catalyzed *C-O* cross-coupling reactions have been looked upon as a feasible alternative for the synthesis of phenols from aryl halides. In this chapter we have described a selective hydroxylation of aryl iodides and aryl bromides with tetrabutylammonium hydroxide, as a nucleophile catalyzed by a combination of CuI and 8-hydroxyquinalidine in a 2:3 mixture of DMSO-water. The procedure is efficient, general and simple to afford substituted phenols (Scheme 1).



Scheme 1

Chapter 3. One-pot Conversion of Aryl halides to Alkyl-Aryl Ethers

Aryl alkyl ethers are an important constituent of various natural products as well as pharmaceutically important molecules. The traditional method for the synthesis of these ethers is

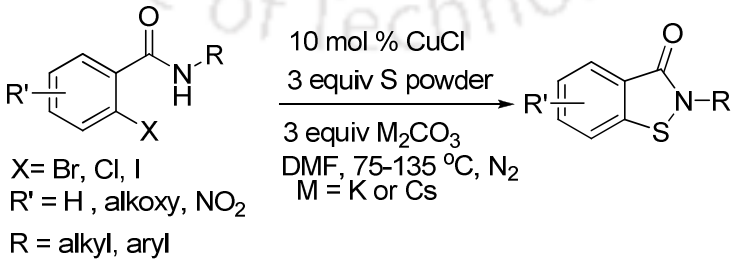


Scheme 2

the famed Williamson ether synthesis. As an application of the technique developed in the first chapter, in this chapter, we describe a one pot conversion of aryl halides to aryl alkyl ethers where the aryl halides are first converted to the corresponding phenoxides and then treated with an alkyl halide (Scheme 2).

Chapter 4. Copper-Catalyzed Synthesis of *N*-Substituted Benzo[*d*]isothiazol-3(2*H*)-ones via *C-S* Cross-Coupling Reaction

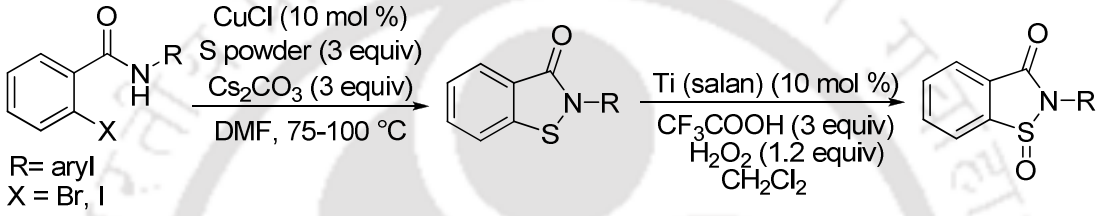
N-Substituted benzo[*d*]isothiazol-3(2*H*)-ones and their analogues have attracted considerable interest in biological and chemical sciences due to their promising antibacterial and antifungal properties. They have also been studied as potential antithrombotic agents, antipsycotic agents as well as models for the development of metallothionein inspired molecular pincers. In this chapter, we describe the synthesis of 2-substituted benzo[*d*]isothiazol-3(2*H*)-ones from 2-halo-*N*-substituted benzamides using CuCl as a catalyst and S powder in the presence of a base. Both *N*-alkyl benzo[*d*]isothiazol-3(2*H*)-ones as well as *N*-aryl benzo[*d*]isothiazol-3(2*H*)-ones could be synthesized by this method (Scheme 3).



Scheme 3

Chapter 5. One-pot Conversion of Benzo[*d*]isothiazol-3(2*H*)-ones to Benzo[*d*]isothiazol-3(2*H*)-one-1-oxides.

N-Substituted benzo[*d*]isothiazol-3(2*H*)-one-1-oxide and their analogues are important structural motifs in the area of biological and pharmaceutical sciences due to their promising antibacterial and antifungal properties. They are alsoknown to be active constituents of several topical ointments as well as other cosmetic products. In this chapter, we describe a tandem one-pot protocol for the conversion of 2-iodobenzamides to the corresponding *N*-substituted benzo[*d*]isothiazol-3(2*H*)-one-1-oxides (Scheme 4).



Scheme 4

Contents

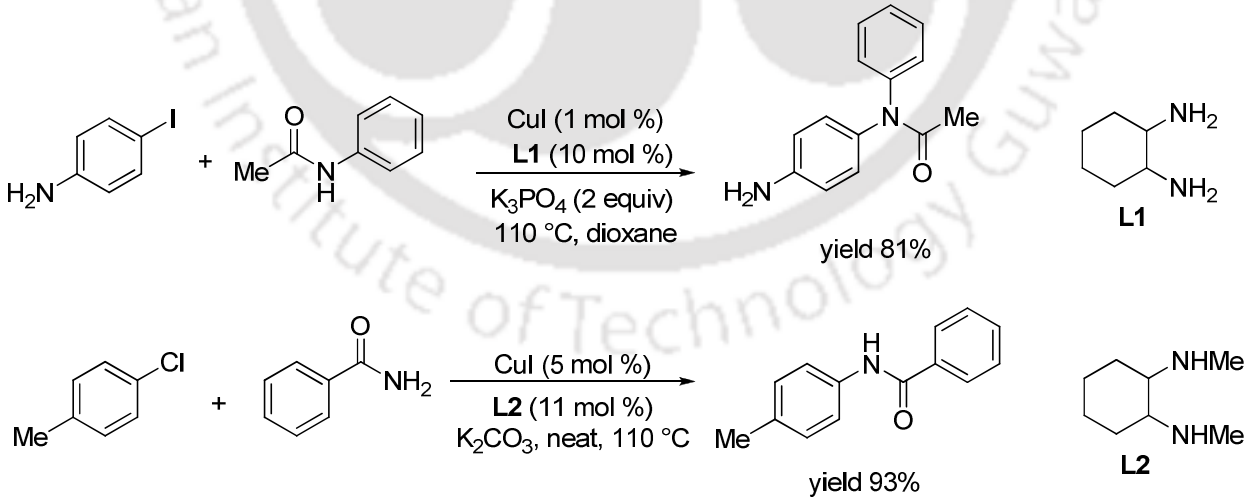
Chapter 1

A General Introduction to Copper-Catalyzed *C-N*, *C-O* and *C-S* Cross-Coupling Reactions

The copper mediated Ullman and Goldberg type cross-coupling reactions are valuable transformations for organic synthesis.[1] They have been extensively applied in both academic and industrial research for the construction of carbon-heteroatom bonds. However, initially these protocols had the drawbacks of requirement of high temperature as well as the need of use of stoichiometric amount of copper.[2] Work carried out in the last few decades have eliminated some of these concerns to a great extent, thereby making copper-catalyzed carbon-heteroatom bond formation a preferred path to the construction of carbon-heteroatom bond.

1.1 Copper-Catalyzed *C-N* Bond Formation

The first major breakthrough in this area came in 2001 when Buchwald and co-workers demonstrated copper based systems in presence of diamine ligands could enable the coupling of aryl halides and amides to be performed under mild reaction conditions using a weak base at moderate temperature (Scheme 1).[3a] They determined that though a range of copper sources were

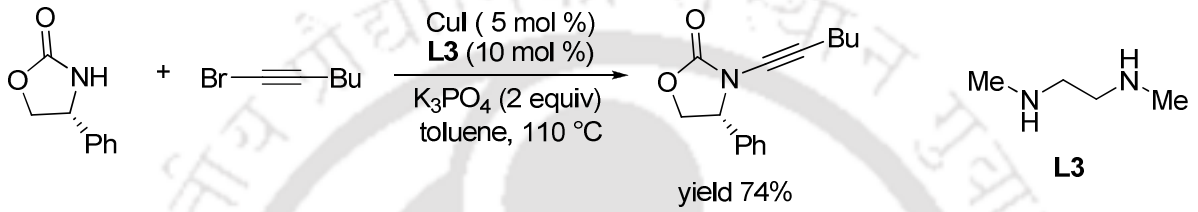


Scheme 1

active, the choice of base was crucial. For aryl iodides, K_2CO_3 was found to be base of choice while in case of aryl bromides, K_3PO_4 afforded the best results. This was explained by the need

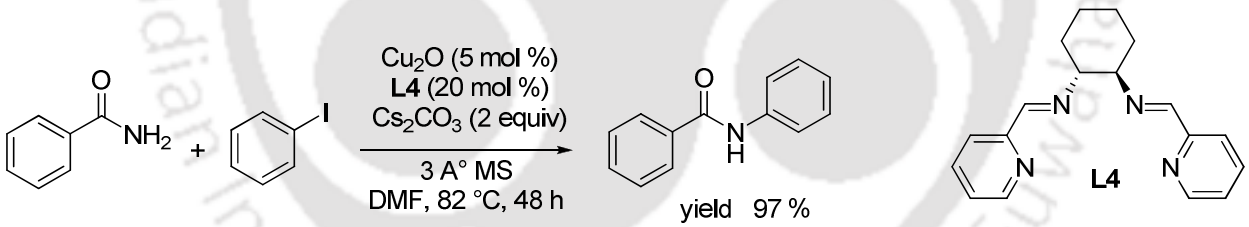
to match the deprotonation with the rate of *C-N* bond formation. If the rate of deprotonation was too high, then the deprotonated amide accumulates and forms an unreactive cuprate complex.[3b] The role of the ligand, as evidenced by kinetic studies, is to prevent the formation of less reactive multiply coordinated cuprate structures.[3c]

Soon after, various copper based systems employing different ligands and bases were explored for the construction of carbon-heteroatom bonds. For example, Husang and co-workers employed CuI in presence of diamine ligand for the successful amidation of alkynyl amides to give ynamides (Scheme 2).[3d]



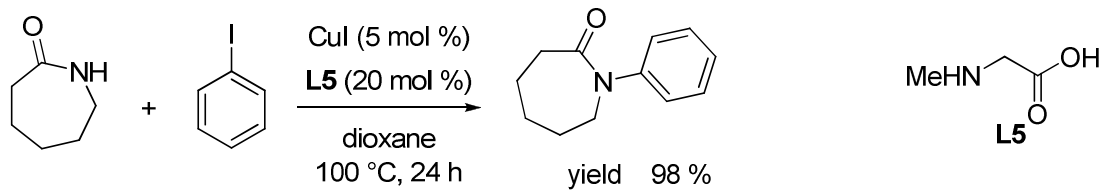
Scheme 2

Taillefer and co-workers have shown the use of Cu_2O in combination with ligand **L4** for the amidation of aryl halides. This reaction functions in DMF in presence of Cs_2CO_3 at 82 °C with up to 97 % yield (Scheme 3).[3e] These conditions are also suitable for *N*-arylation of imidazoles.



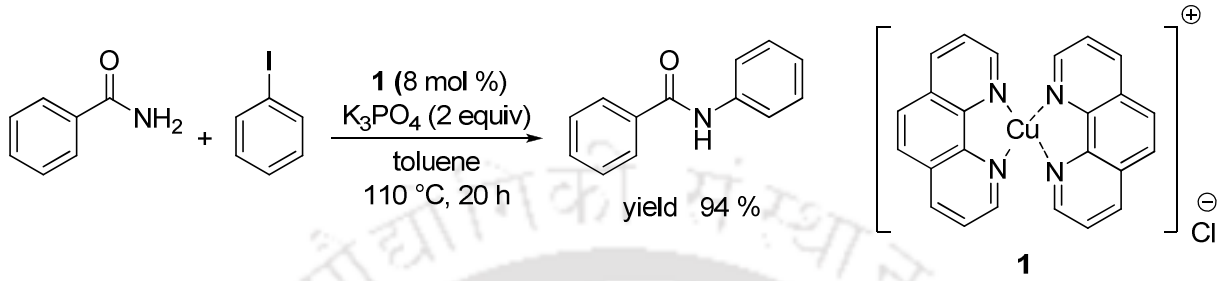
Scheme 3

Liu and co-workers have demonstrated the use of CuI/*N*-methyl glycine system for *N*-arylation of amides. The reaction has occurred efficiently to provide the cross-coupled products at 100 °C in presence of K_3PO_4 in dioxane (Scheme 4).[3f]



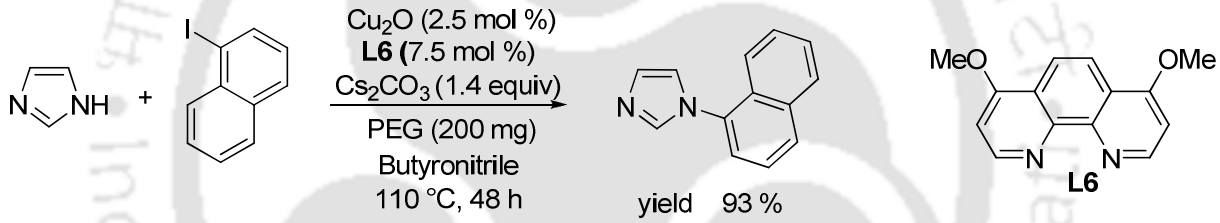
Scheme 4

Moriwaki and co-workers have reported amidation of aryl iodides using copper(I) complex **1** at 110 °C in presence of K_3PO_4 (Scheme 5).[3g] Using this procedure the coupling of benzamide with iodobenzene is accomplished in 94 % yield.



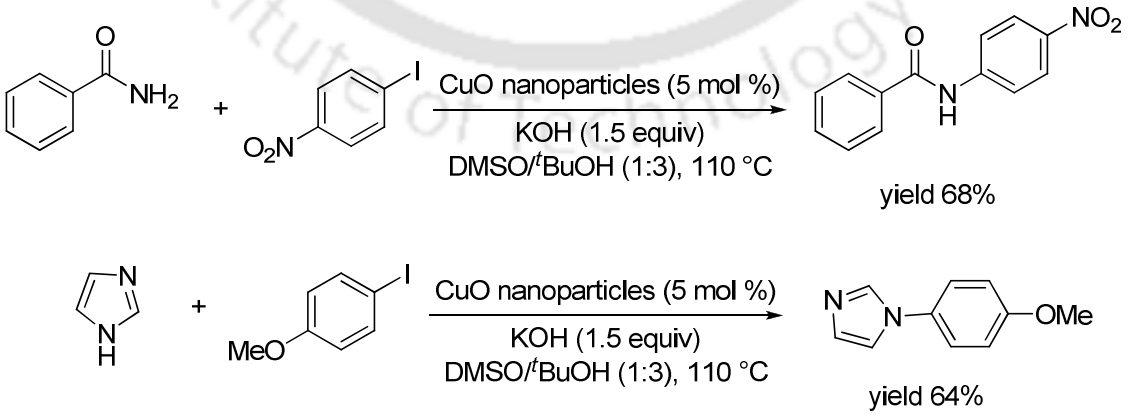
Scheme 5

Buchwald and co-workers have demonstrated the utility of 4,7-dimethoxy-1,10–phenanthroline **L6** for the copper-catalyzed arylation of imidazoles and benzimidazoles with aryl and heteroaryl iodides and bromides in combination with PEG and Cs_2CO_3 (Scheme 6).[3h]



Scheme 6

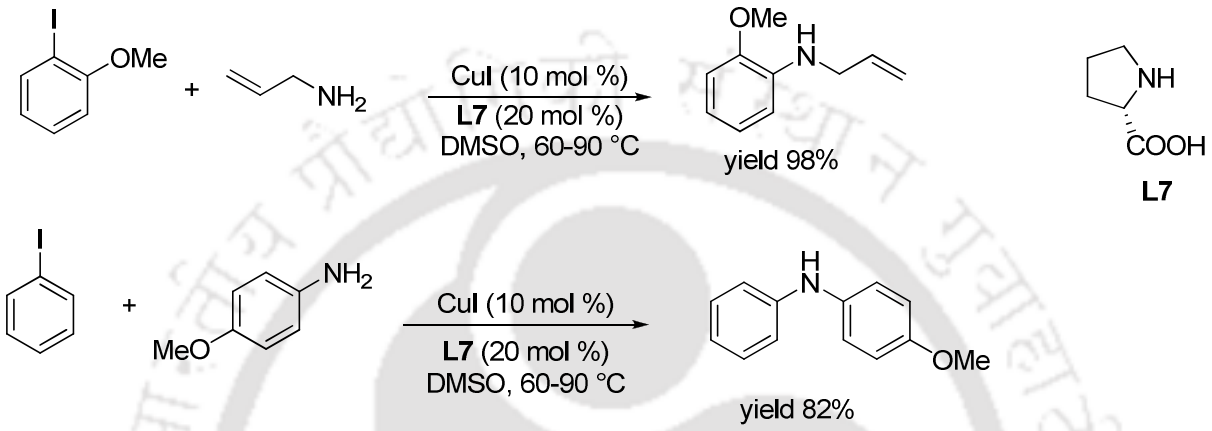
Our group has reported CuO nanoparticles catalyzed *N*-arylation of amides and imdazoles with aryl iodides at 110 °C in presence of KOH (Scheme 7).[3i-j] The procedure is simple, general, ligand-free and efficient to give the cross-coupled products in high yield.



Scheme 7

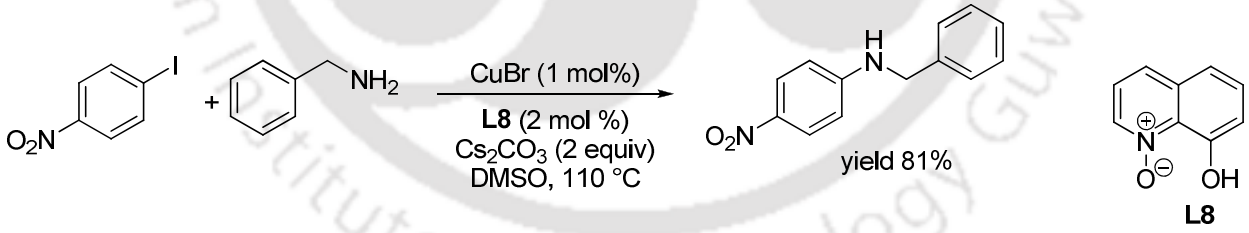
Besides the *N*-arylation of amides and heterocyclic compounds, the cross-coupling reaction of aliphatic and aromatic amines with aryl halides employing copper based systems have also been explored providing the corresponding products in high yield. Some examples follow to explain the scope of such protocols.

Ma and co-workers have demonstrated the use of CuI/amino acid systems for the *N*-arylation of aliphatic and aromatic amines under mild reaction conditions (Scheme 8).[3k]



Scheme 8

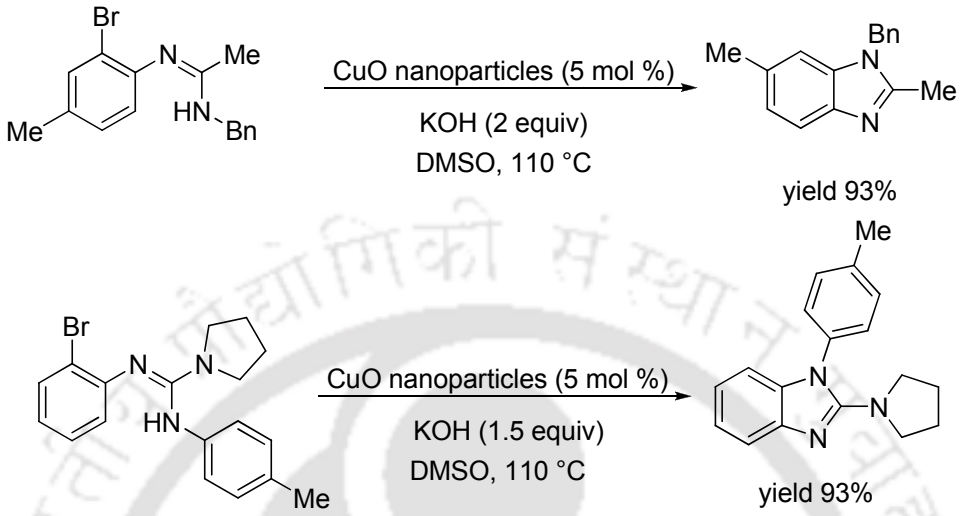
Similarly, Jiang and co-workers demonstrated the *N*-arylation of aryl iodides and aryl bromides using CuBr in combination with an *N*-oxide ligand as a catalyst. The reaction afforded the products in moderate to high yield (Scheme 9).[31]



Scheme 9

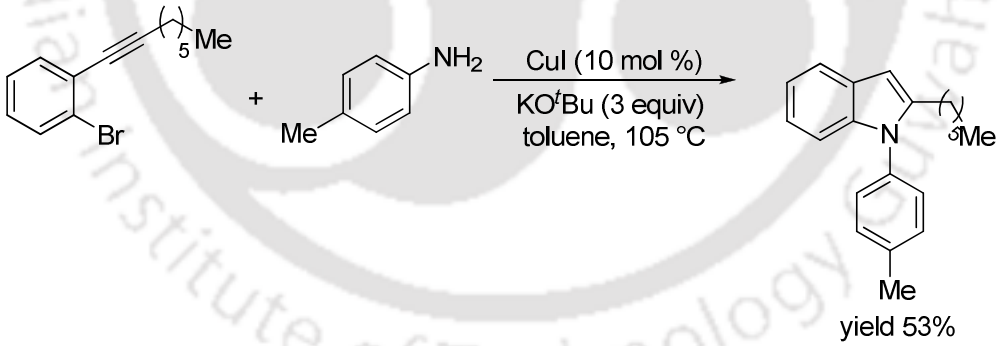
Besides the intermolecular *C-N* cross-coupling reactions, the copper-catalyzed protocols have also been successfully applied for intramolecular cross-coupling reactions. These reactions provide the unique paths for the synthesis of nitrogen containing heterocycles such as indoles and benzimidazoles.

Our group has developed a ligand-free CuO nanoparticles catalyzed intramolecular *C-N* cross-coupling protocol for the synthesis of 2-substituted benzimidazoles and 2-aminobenzimidazoles. The reaction is general and efficient providing the products in high yield (Scheme 10).[3m]



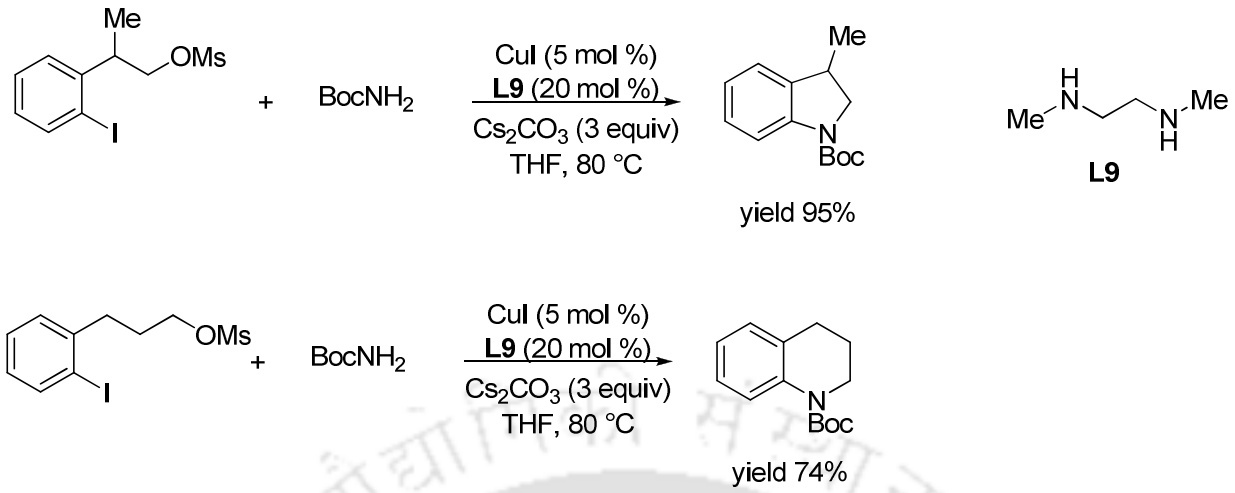
Scheme 10

Heterocyclic compounds may also be generated by the tandem reactions initiated by a *C-N* cross-coupling reaction. Thus, Ackermann and co-workers demonstrated the synthesis of indoles from 2-alkynylaryl bromide and primary amines using CuI as a catalyst (Scheme 11).[3n]



Scheme 11

Buchwald and co-workers have reported copper-catalyzed annulations of functionalized aryl iodides by reaction with primary amines to generate indolines and its homologues (Scheme 12).[3o]

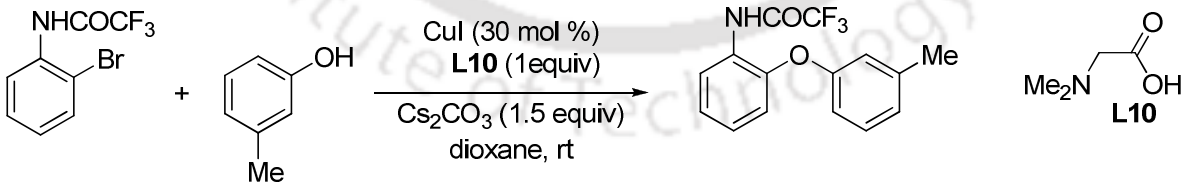


Scheme 12

1.2 Copper-Catalyzed *C-O* Bond Formation

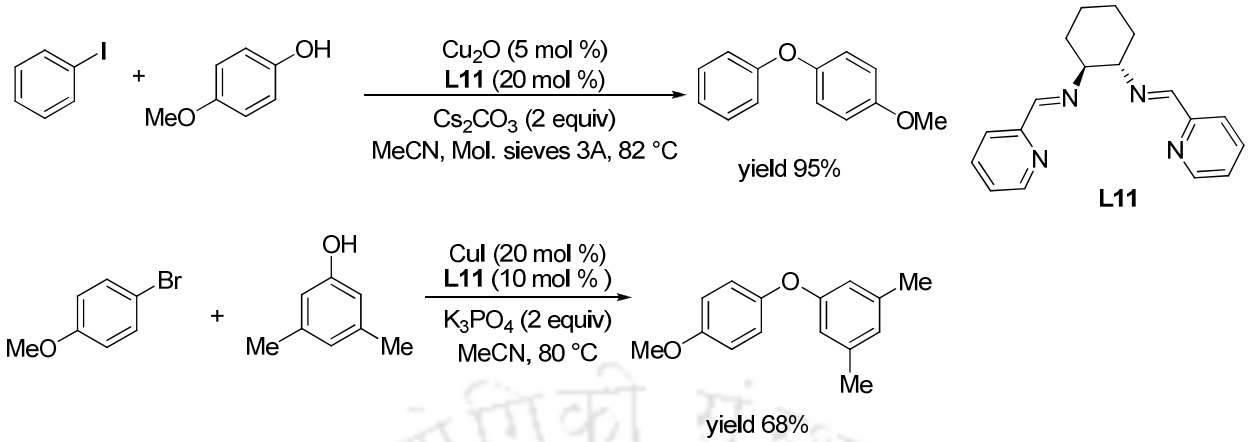
The synthesis of diaryl ethers and its derivatives by classic Ullmann methods has been well explored for a long time. Thus, copper based systems have also been applied for *C-O* cross-coupling reactions. One of the most emphasized reactions is being the formation of alkyl aryl ethers or diaryl ethers by the coupling of aryl halides with an alcohol or phenol, respectively. As with *C-N* cross-coupling reaction, a variety of copper sources assisted by ligands and even ligand-free protocols have been developed for this reaction. Some examples are provided below.

Ma and co-workers have developed a *C-O* cross-coupling protocol employing amino acid **L10** as a ligand with 30% copper loading for coupling of 2-bromotrifluoroacetanilides and tyrosine derivatives at room temperature in high yield (Scheme 13).[4a]



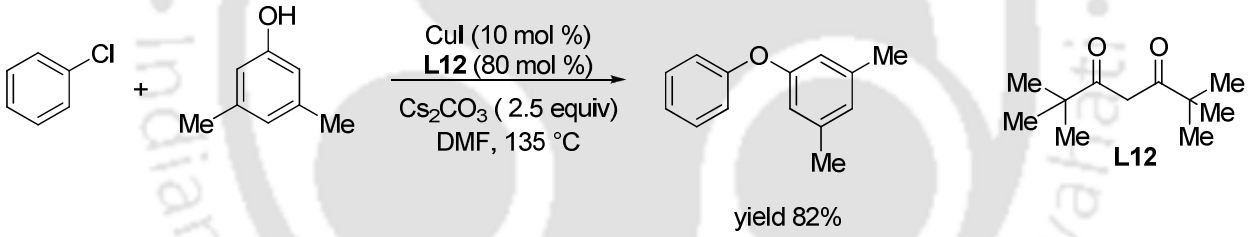
Scheme 13

Taillefer and co-workers have developed a ligand assisted protocol for the synthesis of diaryl ethers using either CuI or Cu_2O as copper source. The reaction has significant functional group tolerance to yield the diaryl ethers in high yield (Scheme 14).[4b]

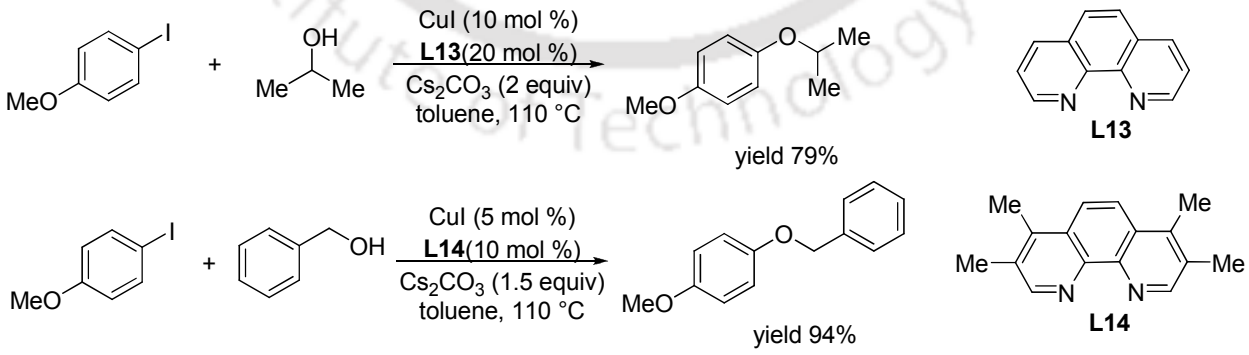


Scheme 14

Later, they achieved an efficient arylation of phenols with aryl chlorides based on the use of the ligand 2,2,6,6-tetramethylheptan-2,5-dione (**L12**) along with CuBr as copper source. With this protocol they were able to condense both activated and unactivated aryl chlorides (Scheme 15).[4c]



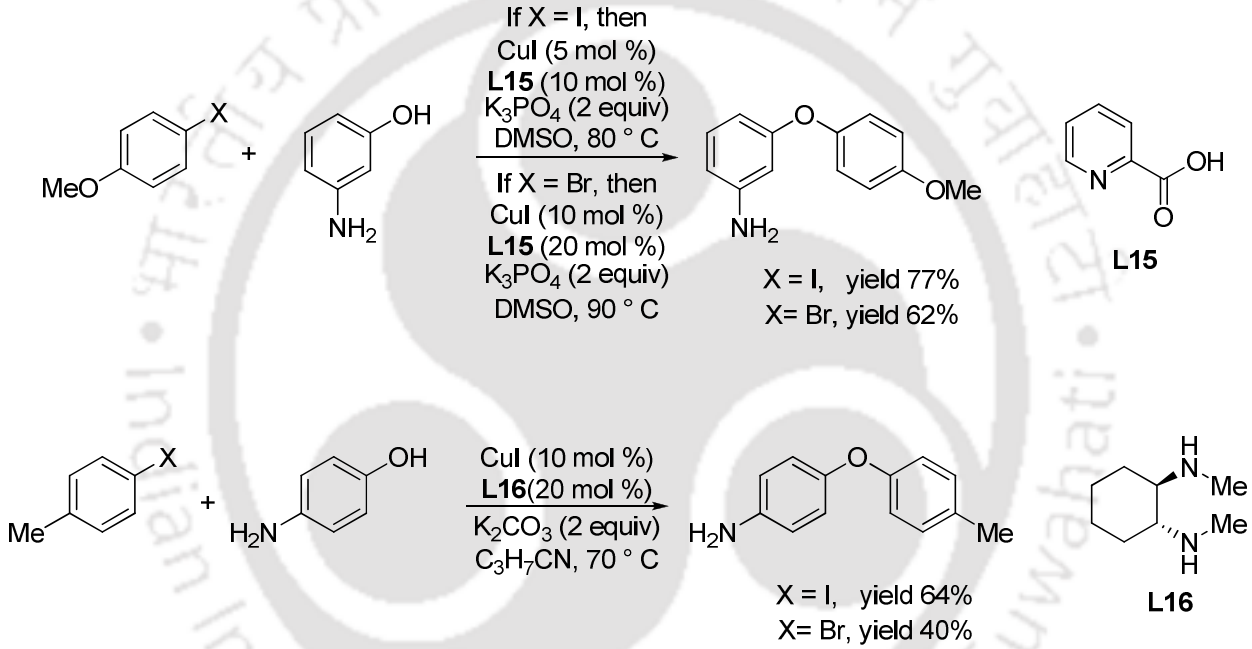
Scheme 15



Scheme 16

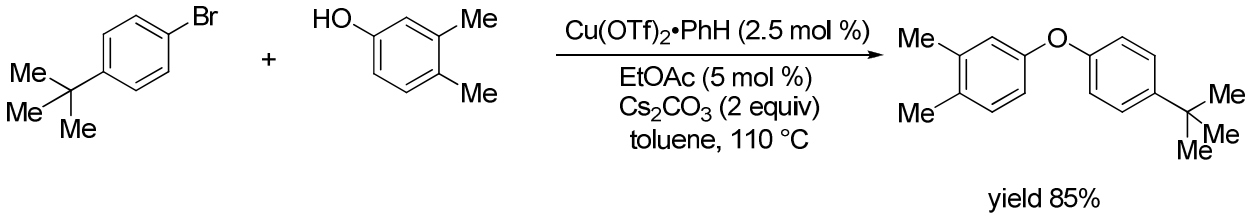
Buchwald and co-workers have demonstrated the synthesis of alkyl aryl ethers via *C-O* cross coupling of aryl iodides and aliphatic alcohols in high yield using CuI as a catalyst along with 1,10-phenanthroline as a ligand.[4d] Later, they were able to improve the protocol by using a substituted phenanthroline derivative to allowing the use of aryl bromides as coupling partners (Scheme 16).[4e]

They have also achieved remarkable chemoselective arylations of 3-and 4-aminophenols using a copper based catalyst. The reaction is general when aryl bromides and aryl iodides are used as coupling partners. However, aryl bromides were usually less efficient providing the products in lower yields as compared to aryl iodides (Scheme 17).[4f]



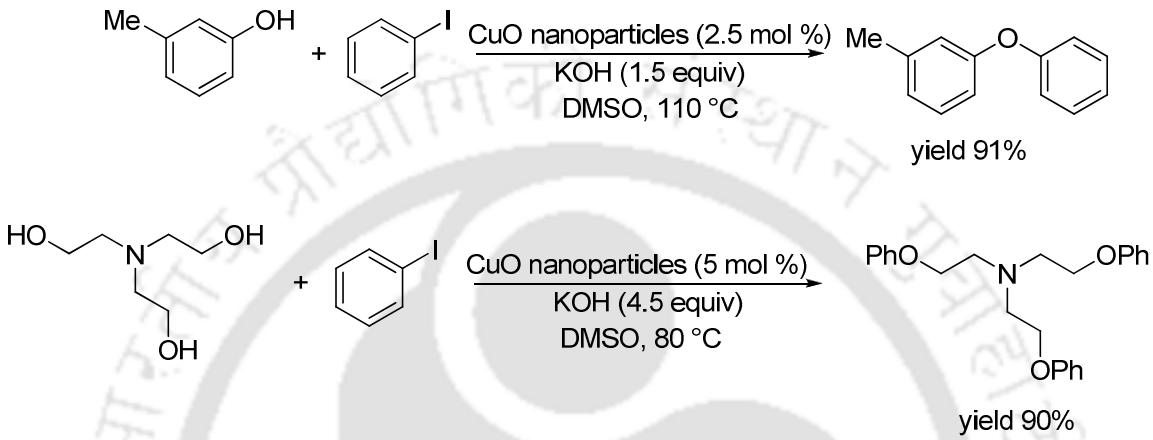
Scheme 17

The *C-O* cross-coupling of aryl halides with phenols has also been performed under "ligand-free" conditions. Thus, Buchwald and co-workers have achieved the synthesis of diaryl ethers using $Cu(OTf)_2 \cdot PhH$ as a catalyst and Cs_2CO_3 as base in toluene (Scheme 18).[4g]



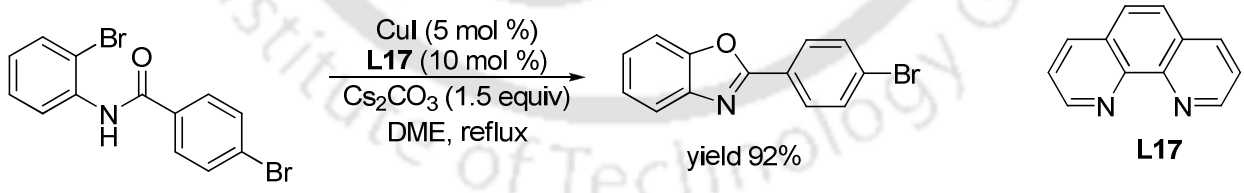
Scheme 18

Our group has developed a ligand-free protocol employing CuO nanoparticles as catalyst. The reaction is efficient in affording the cross-coupling of iodobenzene with a variety of phenols and alcohols. The reaction is heterogeneous in nature and the catalyst is recyclable without any significant loss of reactivity (Scheme 19).[3j]



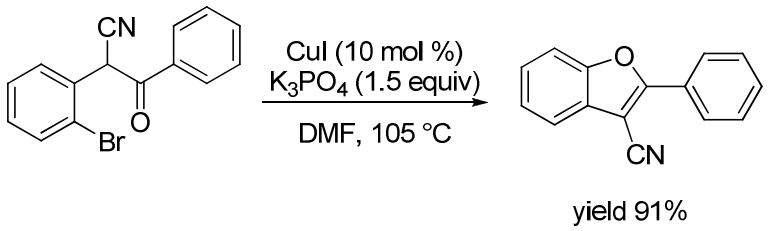
Scheme 19

As with *C-N* cross coupling reaction, intramolecular versions of *C-O* cross-coupling reactions have also been explored. These reactions have been widely applied for the synthesis of oxygen containing heterocycles such as benzoxazoles. Thus, Batey and co-workers have performed the intramolecular cyclization of *N*-2-halophenylanilides to obtain the corresponding benzoxazoles in high yield using CuI/1,10-phenanthroline as catalytic system (Scheme 20).[4h]



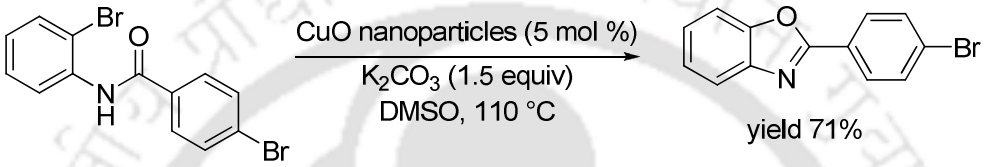
Scheme 20

Similarly, Chen and co-workers have achieved the synthesis of 2,3-disubstituted benzofurans from 2-bromoketones in a ligand-free protocol using CuI as a catalyst (Scheme 21).[4j]



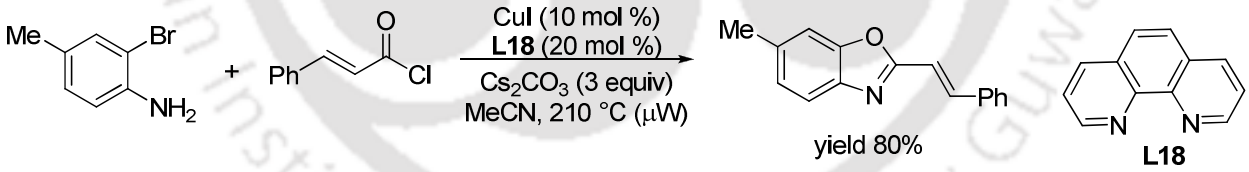
Scheme 21

Our group has developed CuO nanoparticle catalyzed synthesis of 2-arylbenzoxazoles from the corresponding 2-bromoanilides providing the target heterocycles in high yield (Scheme 22).[3m]



Scheme 22

Domino reactions utilizing a *C-O* cross-coupling reaction have also been utilized in the synthesis of heterocyclic compounds. Batey and co-workers have synthesized a library of substituted benzoxazoles by the reaction of substituted 2-bromoanilines with acid chlorides using CuI as a catalyst under microwave irradiation (210 °C) for 15 min (Scheme 23).[4k]

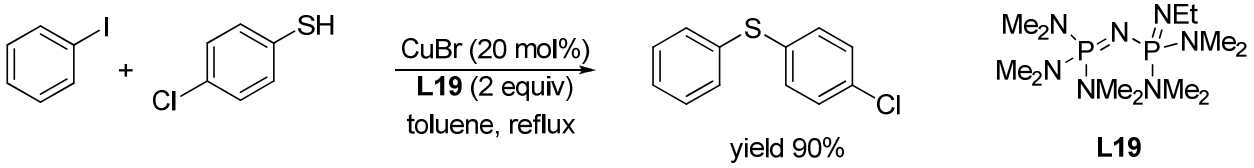


Scheme 23

1.3 Copper-Catalyzed *C-S* Bond Formation

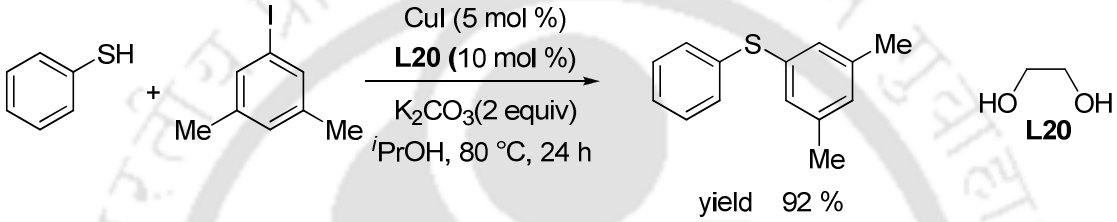
Copper-catalyzed formations of organosulfur compounds have been widely explored. A few of them are detailed below.

Palomo and co-workers demonstrated the ability of CuBr with phosphazene base to catalyze reaction between aryl iodides and thiols to afford biaryl sulfides. Activated aryl bromides were also effective as coupling partners. In spite of high catalyst loading, the reaction is efficient and established the basis for copper-catalyzed *C-S* bond formation (Scheme 24).[5a]



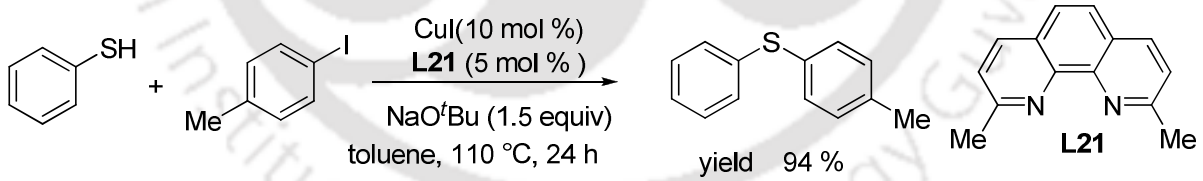
Scheme 24

CuI-1,2-ethylene glycol is used for the coupling of thiols with aryl iodides in the presence of K_2CO_3 in 2-propanol (Scheme 25).[5b] The reaction of aryl iodides having electron withdrawing and –donating groups is demonstrated.



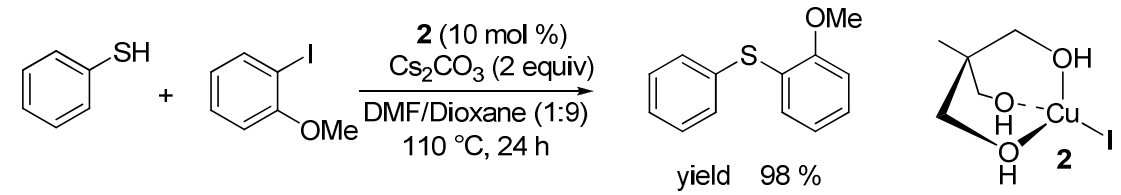
Scheme 25

Venkataraman and co-workers have demonstrated the coupling of aryl thiols with aryl iodides using CuI and neocuproine **L21** in the presence of NaO^{t}Bu in toluene (Scheme 14).[6d] Using this procedure the coupling of thiophenol with 1-iodo-4-methylbenzene is accomplished in 94 % yield (Scheme 26).[5c]



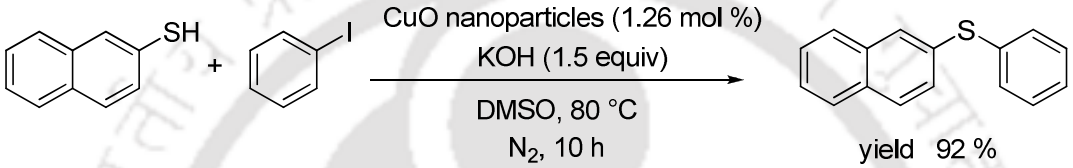
Scheme 26

Copper(I) complex **2** is used for the coupling of aromatic thiols with aryl iodides in the presence of Cs_2CO_3 in 1:9 DMF/dioxane (Scheme 27).[5d] The reaction is efficient and the desired products were obtained in good yield.



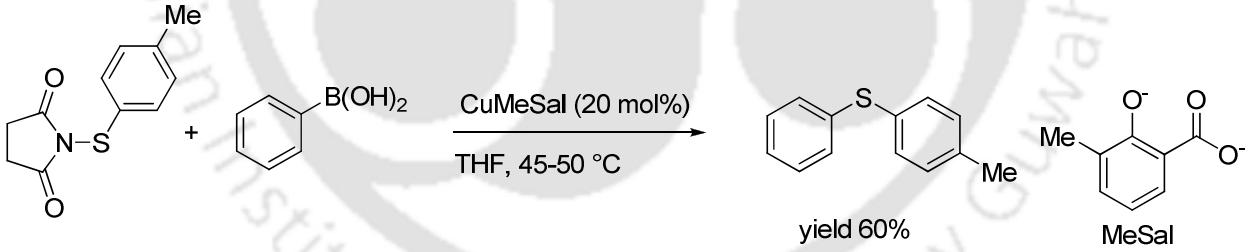
Scheme 27

Our group has reported CuO nanoparticle catalyzed *C-S* cross coupling reactions of thiols with aryl iodides in presence of KOH at moderate temperature (Scheme 28).[5e] The procedure is simple, general, ligand-free and efficient to give the cross-coupled products in high yield.



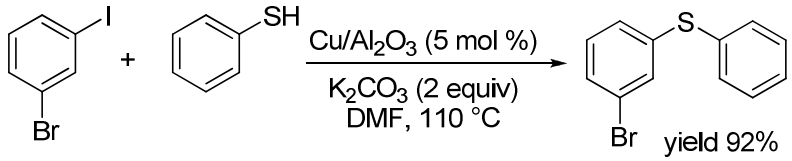
Scheme 28

Liebeskind and co-workers utilized thioimides as a copper-thiolate precursor for the synthesis of aryl sulfides (Scheme 29).[5f] A copper(I)-carboxylate complex catalyzes the cross-coupling of aryl boronic acids with thioimides to generate biaryl sulfides with moderate efficacy.



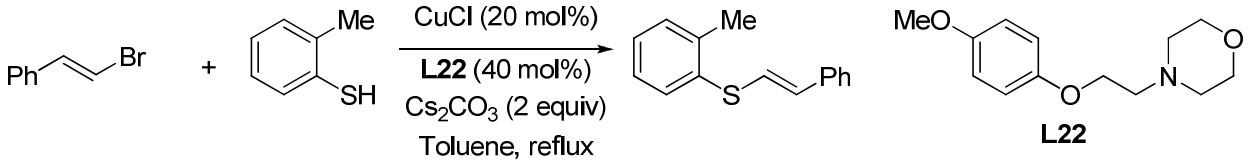
Scheme 29

A highly regioselective process for the thiation of aryl halides was reported by Ranu and co-workers (Scheme 30).[5g] The reaction uses alumina-supported copper catalyst and K_2CO_3 to allow the coupling of iodo group without affecting the bromo group of aryl halides.



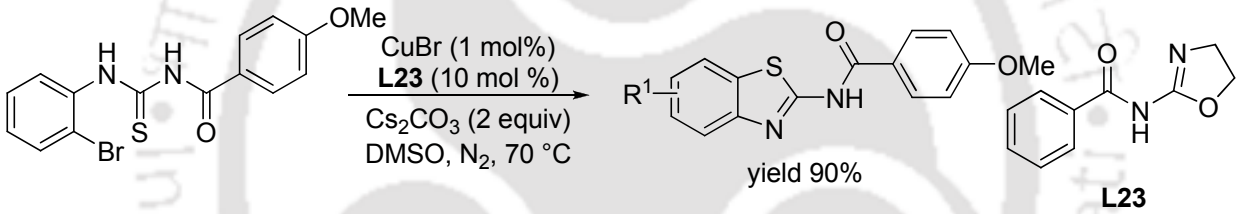
Scheme 30

Moderate yield of alkenylsulfide has been obtained in the reaction of β-bromostyrene with *o*-methylthiophenol in the presence of morpholine derivative as ligand (Scheme 31).[5h]



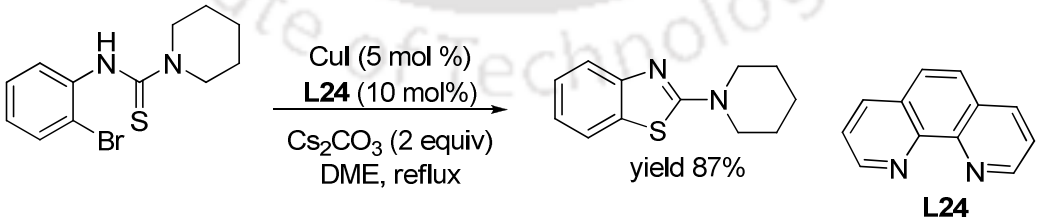
Scheme 31

Intermolecular *C-S* Coupling has also been widely utilized for the synthesis of heterocycles. For example, Pan and co-workers demonstrated an efficient intramolecular *C-S* cross coupling reaction of substituted 1-arylacyl-3-(2-bromophenyl)thiourea using CuI/ *N*-(4,5-dihydroxazol-2-yl)benzamide (Scheme 32). The desired products, *N*-benzothiozol-2-yl-amides are synthesized with high yield.[5i]



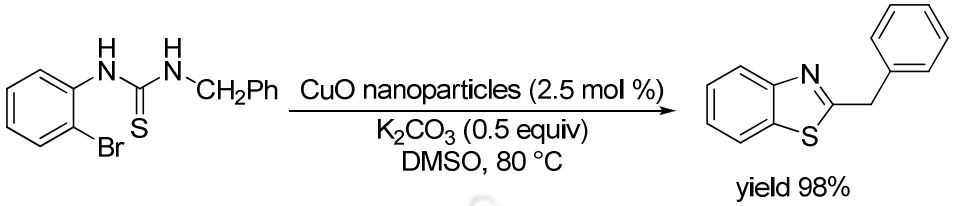
Scheme 32

Similarly, the intramolecular cyclization of 2-haloarylthioureas has been carried out using copper-catalyzed *C-S* coupling strategy (Scheme 33).[5j] The best results were observed using CuI/1,10-phenanthroline in the presence of Cs_2CO_3 in DME under reflux conditions.



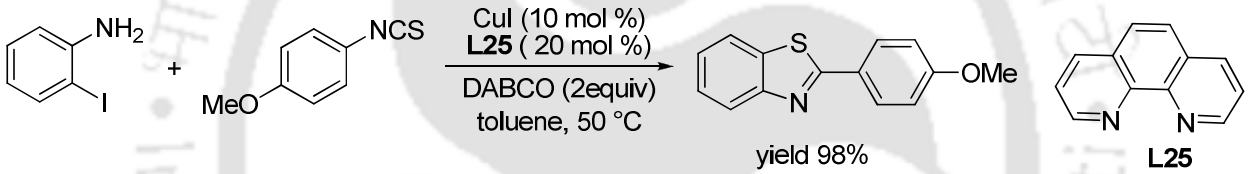
Scheme 33

Our group has reported CuO nanoparticle catalyzed intramolecular *C-S* cross-coupling reactions for the synthesis of 2-aminobenzothiazoles from 2-haloarylthioureas (Scheme 34).[3m] The reaction is efficient and provides the target molecules with high yield.



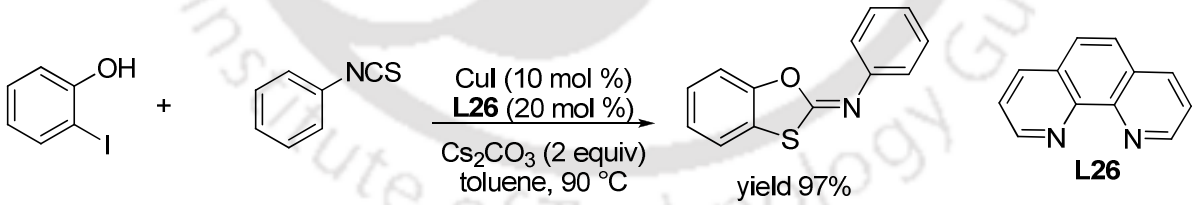
Scheme 34

A copper catalyzed tandem reaction of 2-haloanilines with phenyl isothiocyanate leading to 2-aminobenzothiazoles has been described by Wu and co-workers. They were able to achieve a library of such compounds in high yields (Scheme 35).[5k]



Scheme 35

Bao and co-workers have devised a synthetic protocol for the synthesis of 2-iminobenzo-1,3-oxathiole moieties by using CuI/1,10-phenanthroline as a catalyst (Scheme 36).[5l]

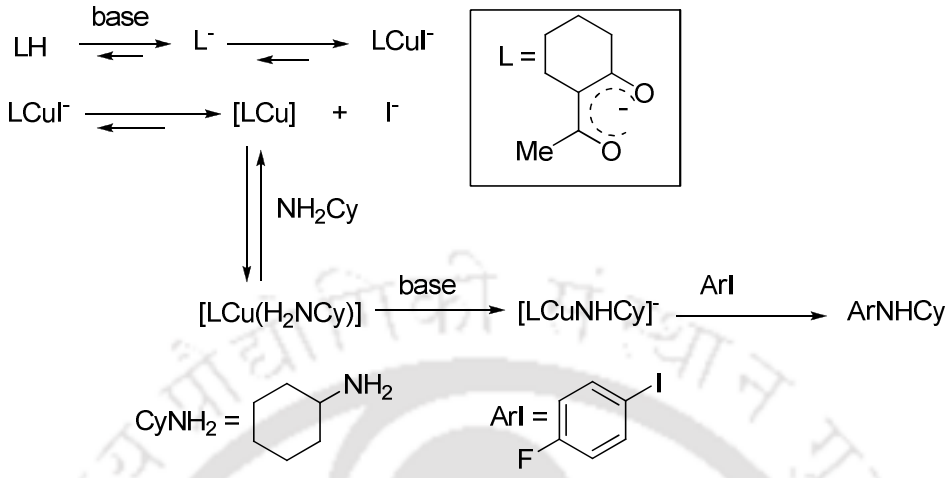


Scheme 36

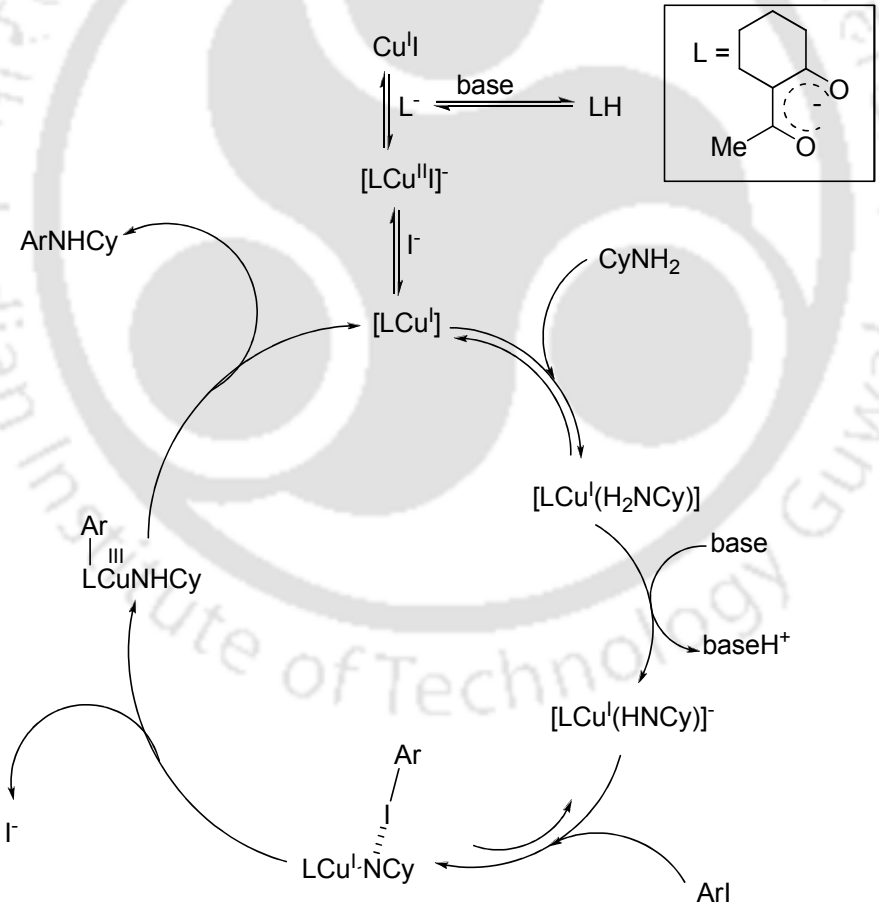
1.4 Mechanistic Studies

The mechanistic details of the copper-catalyzed cross-coupling reactions have been elucidated only recently. Theoritical calculations and experimental studies have now elucidated the precise role of the metal catalyst, the effect of ligand and the role of base. For example, Jutand and co-workers determined that in case of *C-N* cross-coupling reaction catalyzed by 1,3-diketonate

ligands chelated with copper, using CuI as copper source and acetylcyclohexanone as ligand, revealed the following steps (Scheme 37) when studied by cyclic voltametry.[6a]



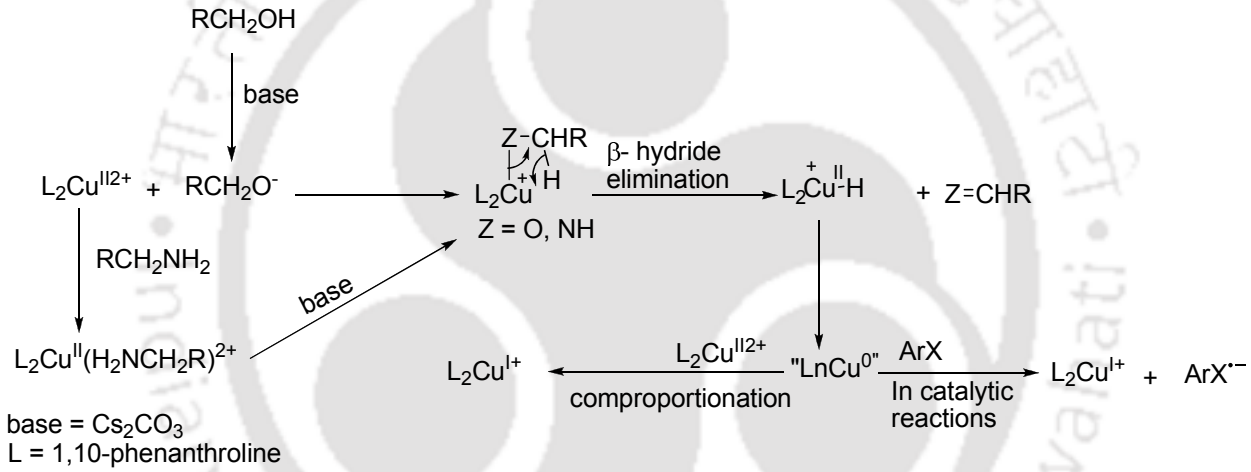
Scheme 37



Scheme 38

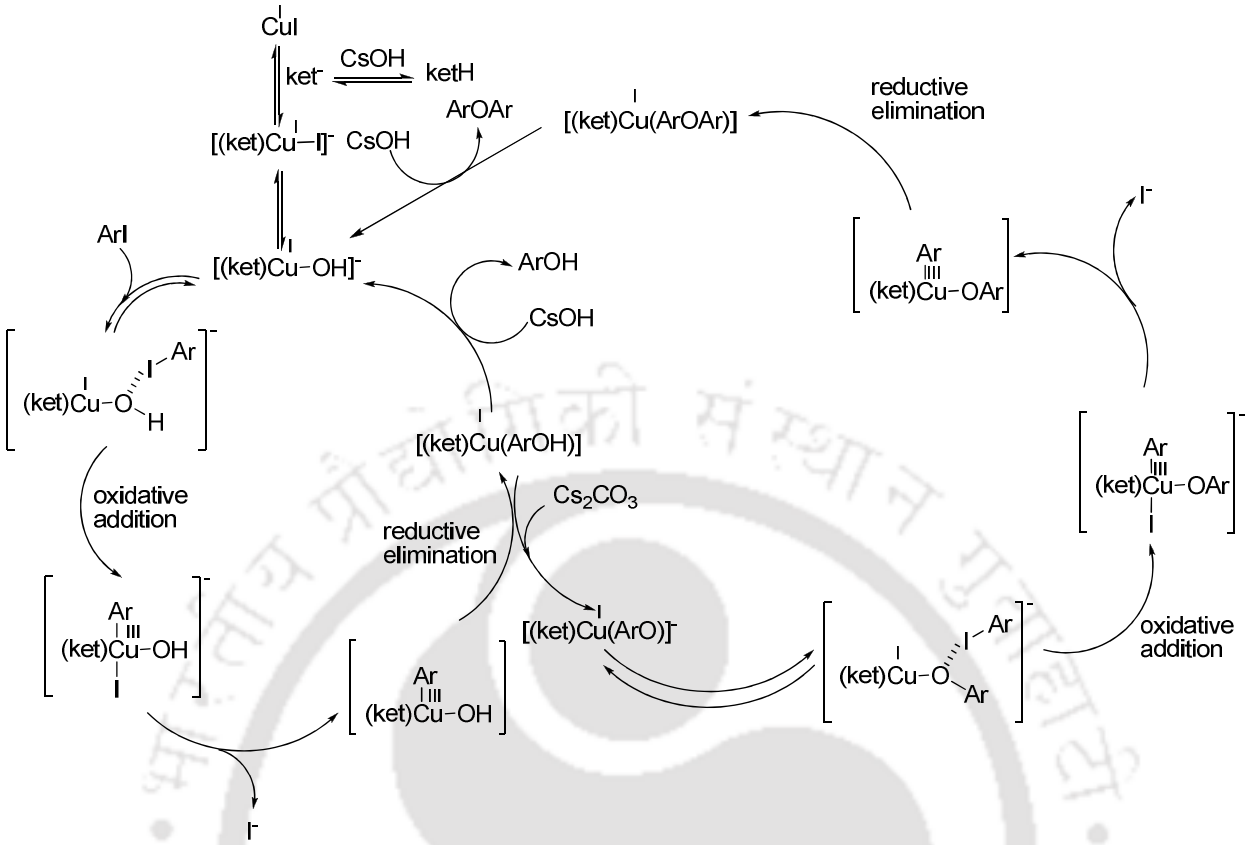
Next, DFT calculations were performed to afford further insights on the nature of the intermediate(s) in the reaction between [(diketonate)CuNHCy]$^-$ and ArI which indicated an activation of the ArI by an interaction with the [(diketonate)CuNHCy]$^-$ followed by an intramolecular oxidative addition followed by a fast reductive elimination. Thus the overall mechanism is proposed in Scheme 38.[6a]

1,10-Phenanthroline has been used as a ligand along with Cu(0) or Cu(II) precursors for *C-N* and *C-O* cross coupling reactions. Jutand and co-workers observed the generation of Cu(I) species, which is the active catalyst, from Cu(II) precursors *in situ* (Scheme 38). Similarly, the cross-coupling reactions of ArX (X = I, Br) and nucleophiles can be performed by using a Cu(0) precursor which will be transformed *in situ* into a Cu(I) species by its reaction with ArX at the very beginning of the catalytic reactions (Scheme 39).[6a]



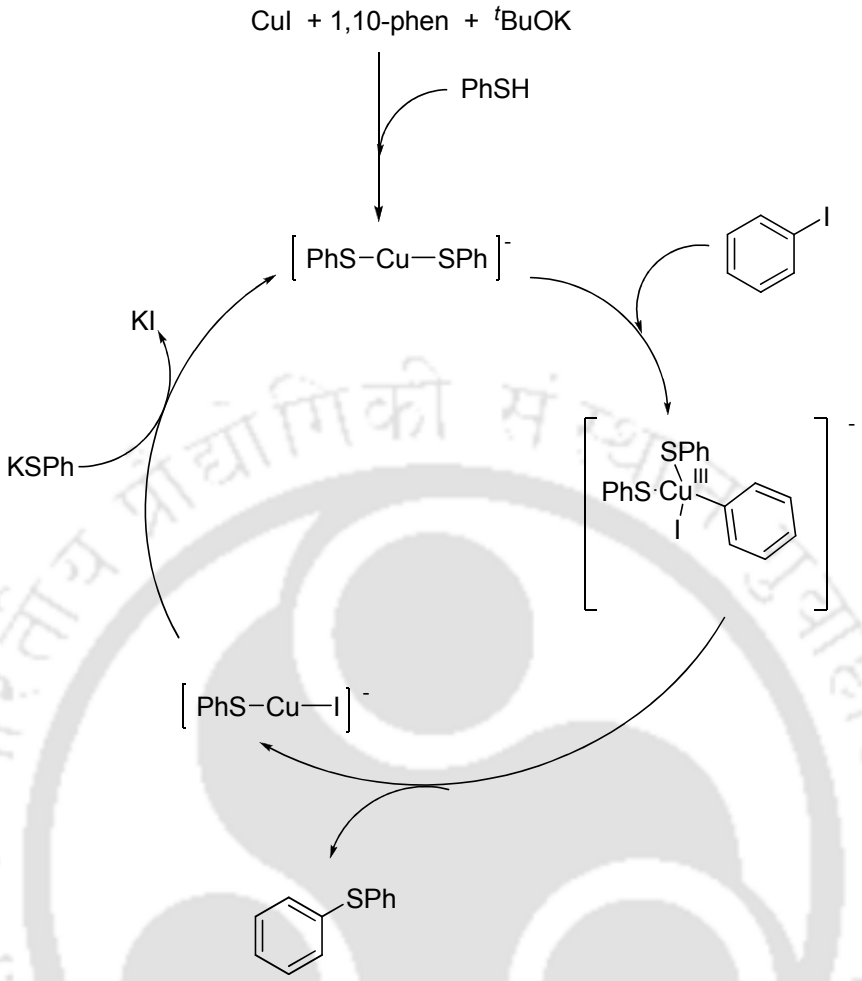
Scheme 39

In case of *C-O* cross-coupling reactions, it has been observed that the use of bases like CsOH yields the corresponding ArOH from ArX (X = Br, I) whereas in the presence of bases like Cs_2CO_3 it affords the corresponding diaryl ether ArOAr. This role of bases has been studied by Jutand and co-workers and proposed a mechanism based on experimental results and theoretical calculations (Scheme 40).[6a]



Scheme 40

Shyu and co-workers have studied *C-S* cross-coupling reaction of iodobenzene and thiophenol using CuI and 1,10-phenanthroline as a catalyst by electrospray ionization mass spectrometry (ESI-MS). They observed the peaks corresponding to the complexes $[Cu(SPh)_2]^-$, $[Cu(SPh)I]^-$ and $K[Cu(SPh)_2(Ph)]^+$. Based on this they proposed a catalytic cycle for this reaction (Scheme 41).[6b]



Scheme 41

In summary, the copper-catalyzed cross-coupling reaction is a well explored synthetic protocol with a wide range of synthetic protocols. In comparison to palladium based catalysts, they are cheap, less toxic and easily available. Also, the palladium-catalyzed protocols often require specifically designed sterically bulky phosphine ligands whereas the requirements of ligands for copper-catalyzed system are less stringent.

1.5 References

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Chapter 2

Copper-Catalyzed Selective Hydroxylation of Aryl Halides

Phenols and their derivatives are structural constituents of numerous natural products, pharmaceuticals and polymers (Figure 1).[1] Industrially, phenol is prepared by the famed hydroperoxide rearrangement of cumene to phenol (Hock process). The process involves several steps involving synthesis of cumene from benzene (step 1) followed by oxidation of cumene to hydroperoxide (step 2) and finally rearrangement to the final products, acetone and phenol (Figure 2).

The classical non-oxidative preparation routes of these classes of compounds include the dienone-phenol rearrangement,[2a-b] benzannulation,[2c-d] cycloaddition,[2e] Fries rearrangement[2f] and nucleophilic substitution of activated aryl halides[2h] (Figure 3). However, these protocols generally have limitations due to non-availability of the suitable starting materials, and in some cases, the requirement of harsh reaction conditions.[3] To alleviate some of these concerns, in recent time, much attention has been devoted to the development of synthetic protocols employing the carbon-heteroatom cross-coupling reactions.[4]

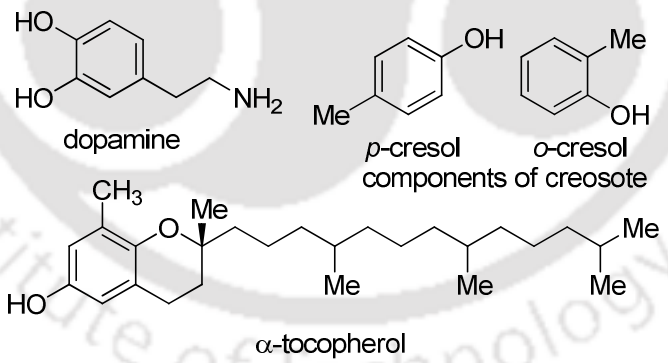


Figure 1. Examples of biologically and industrially important phenols.

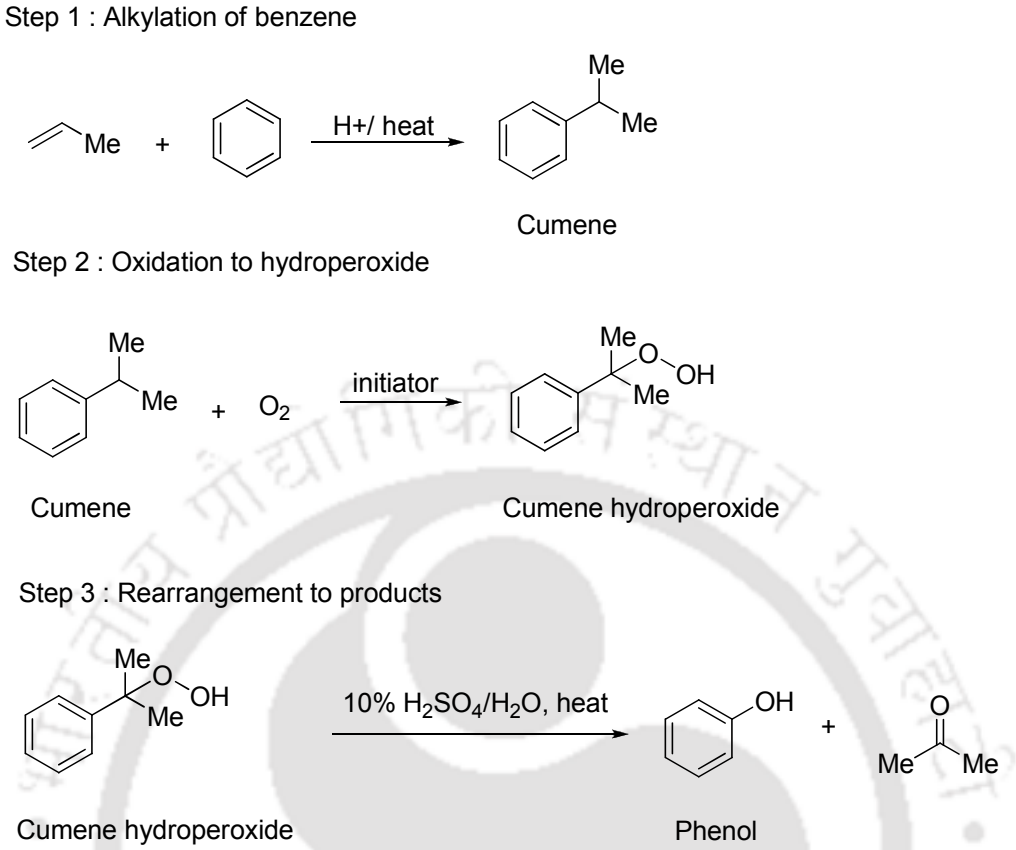


Figure 2. Hock process for industrial preparation of phenol.

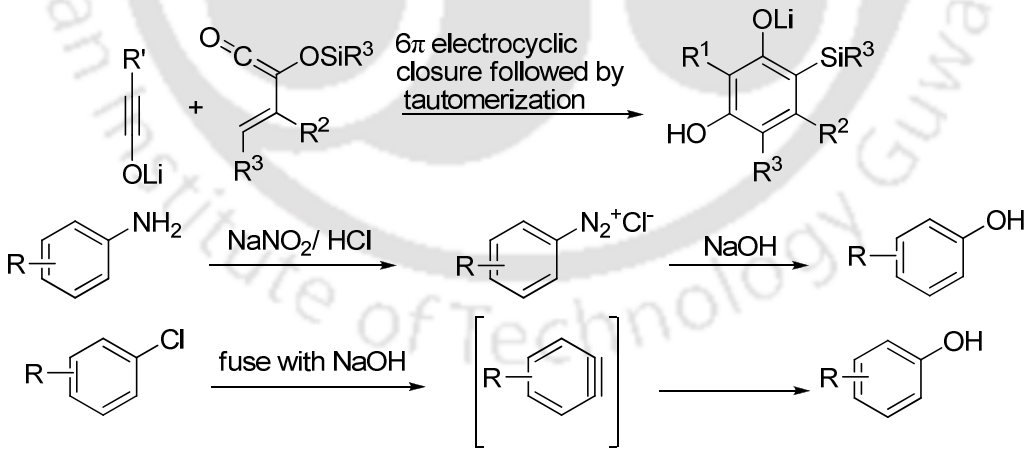
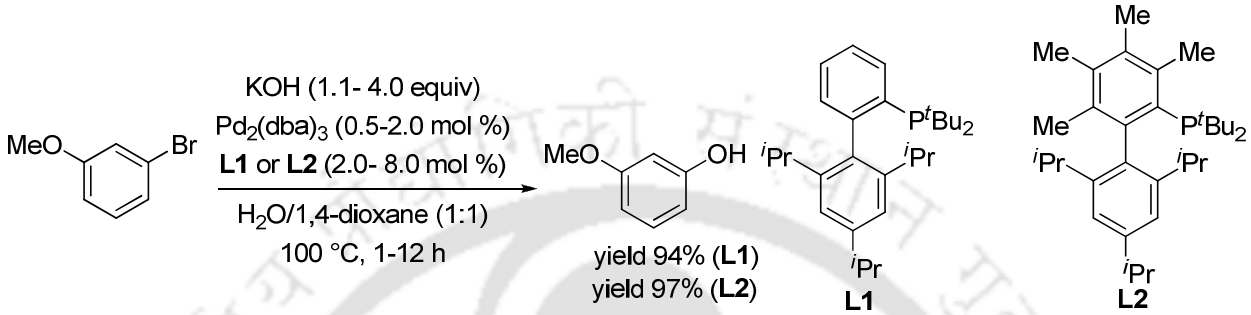


Figure 3. Some traditional routes to phenols.

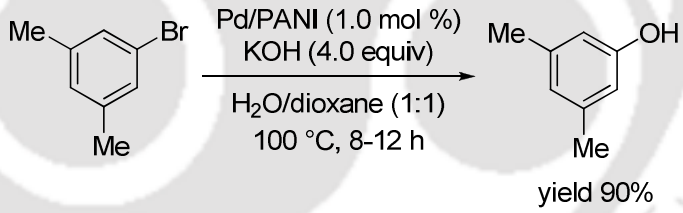
2.1 Palladium Catalysts

The first employment of *C-O* cross-coupling for hydroxylation of aryl halides was first achieved when Buchwald and co-workers demonstrated the hydroxylation of aryl bromides and aryl iodides using $Pd_2(dba)_3$ and a bulky monodentate phosphine ligand **L1** or **L2** in the presence of KOH in DMSO (Scheme 1).[5a]



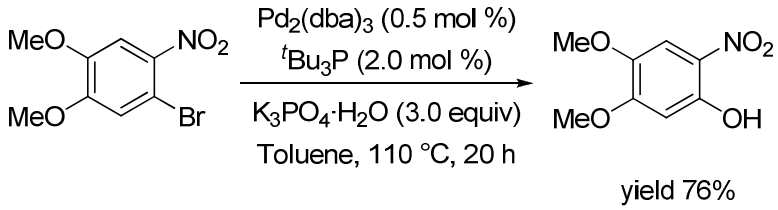
Scheme 1

Palladium nanofibers supported on polyaniline (PANI) were also studied for the hydroxylation of aryl halides (Scheme 2). Under these conditions, aryl bromides and aryl chlorides could be transformed into their corresponding phenols in good to excellent yields.[5b]



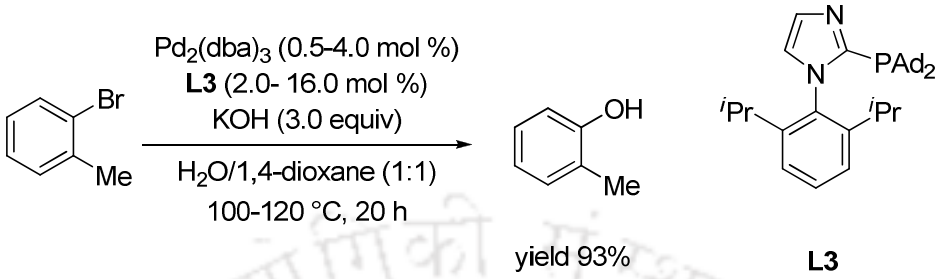
Scheme 2

Kwong and co-workers also demonstrated the conversion of aryl bromides and aryl chlorides to the corresponding phenols using Pd-complex generated *in situ* from $Pd_2(dba)_3$ and $^tBu_3P$ as a catalyst in the presence of potassium phosphate in toluene at 110 °C (Scheme 3).[5c]



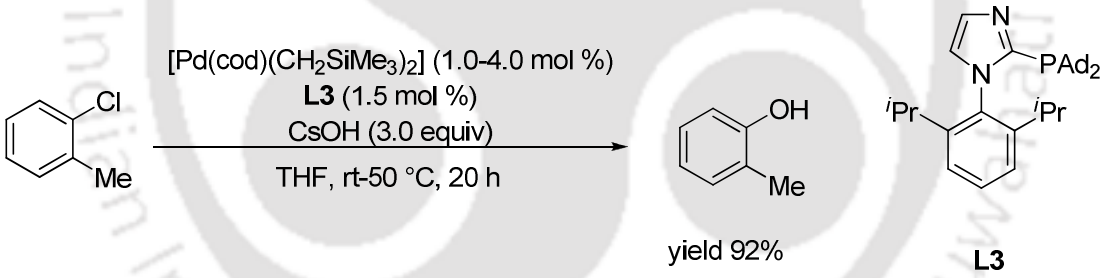
Scheme 3

Subsequently, Beller and co-workers studied the hydroxylation of aryl halides using $Pd_2(dba)_3$ and imidazole based ligand **L3** in the presence of CsOH under heating (Scheme 4). The protocol was compatible with both aryl bromides and aryl chlorides.[5d]



Scheme 4

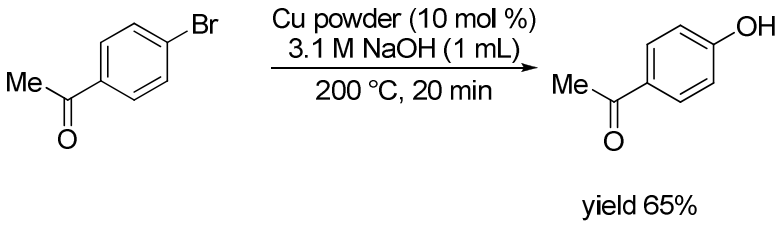
Later, they developed a protocol for palladium-catalyzed hydroxylation under ambient conditions. They used $[Pd(cod)(CH_2SiMe_3)_2]$ as a palladium source along with ligand **L4** in the presence of CsOH at moderate temperature (Scheme 5). The reaction is compatible with aryl bromides and aryl chlorides bearing electron withdrawing groups or bulky groups on the aryl ring.[5e]



Scheme 5

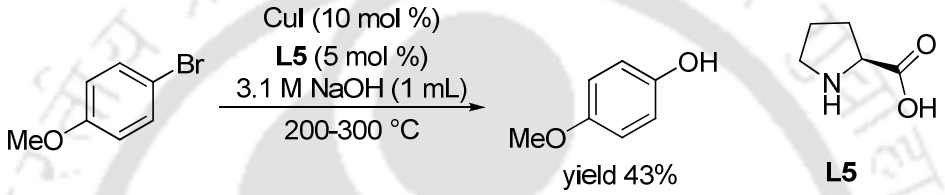
2.2 Copper Catalysts

Subsequently, copper based systems were developed for hydroxylation of aryl halides. Leadbeater and co-workers achieved the first hydroxylation of aryl halides by using copper powder as catalyst in the presence of 3.1 M solution of NaOH under microwave irradiation (Scheme 6). This protocol allows the conversion of aryl halides bearing electron withdrawing groups to their corresponding phenols in moderate yields.[6a]



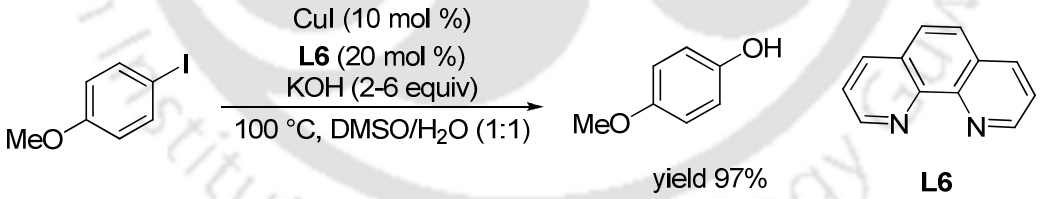
Scheme 6

They also used CuI as a catalyst along with L-proline **L5** as an additive to achieve the same conversion in near critical water under microwave irradiation to obtain good to excellent yields for various aryl halides (Scheme 7).[6a]



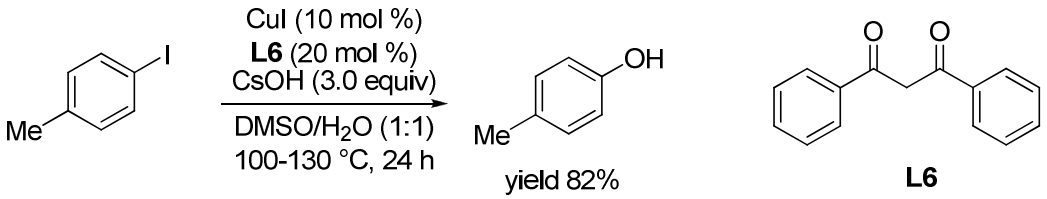
Scheme 7

Subsequently, conversion of aryl halides to phenols was developed under conventional heating conditions. Thus, You and co-workers demonstrated the conversion of aryl bromides and aryl iodides using CuI-1,10-phenanthroline as a catalyst in a 1:1 mixture of DMSO/H_2O as solvent at 100 °C under inert atmosphere (Scheme 8).[6b]



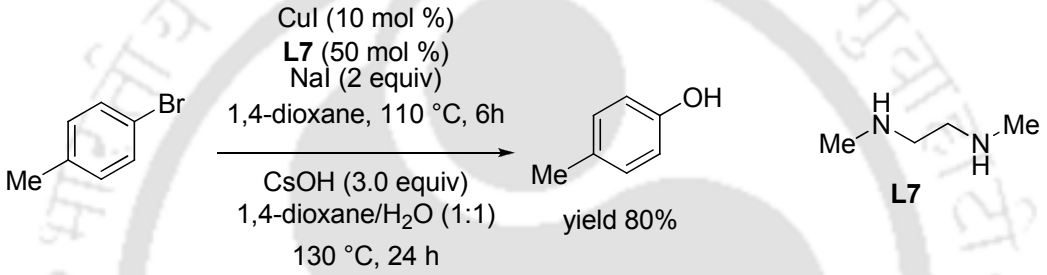
Scheme 8

Similarly, Taillefer and co-workers also achieved the conversion of aryl iodides to their corresponding phenols using CuI-1,3-diphenylpropane-1,3-dione **L6** as a catalyst in a 1:1 mixture of DMSO/H_2O using CsOH as hydroxide source (Scheme 9).[6c]



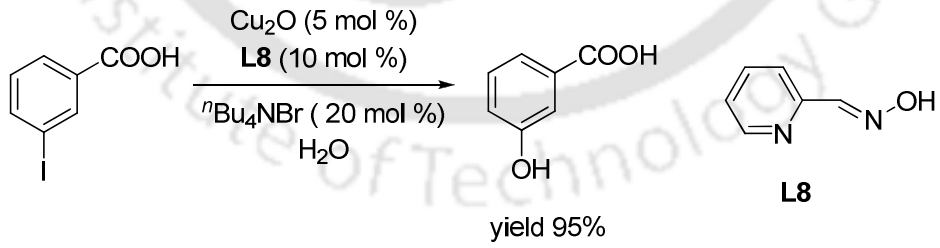
Scheme 9

They also developed a protocol for the conversion of aryl bromides to the corresponding phenols which involved *in situ* conversion of aryl bromides to aryl iodides using CuI and *N*,*N*-dimethylethanamine **L7** followed by the treatment with CsOH in a 1:1 mixture of 1,4-dioxane and water (Scheme 10).[6c]



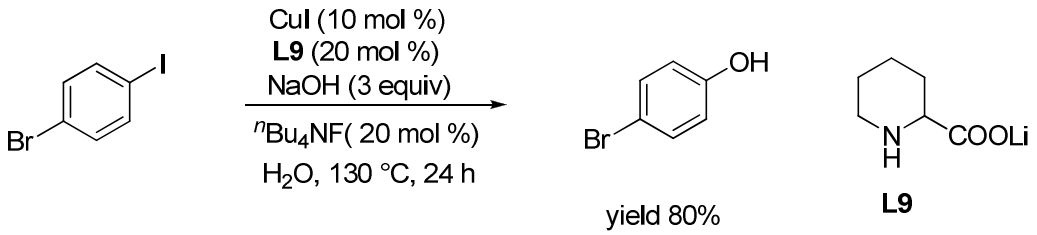
Scheme 10

The hydroxylation of aryl bromides and aryl iodides were also achieved by using Cu_2O and pyridine-2-aldoxime in the presence of CsOH as hydroxide source in water (Scheme 11). The protocol required addition of tetrabutylammonium bromide as a phase transfer catalyst.[6d]



Scheme 11

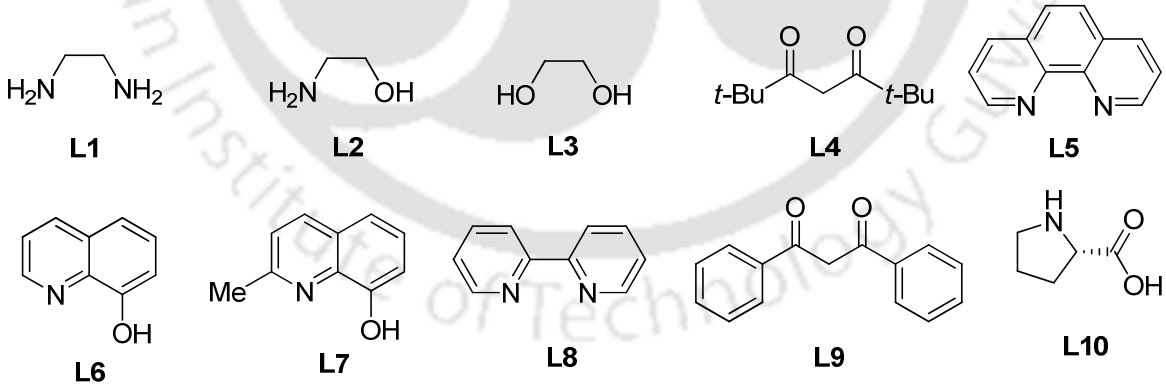
Similarly, Zhou and co-workers carried out the hydroxylation of aryl bromides and aryl iodides using CuI and lithium picolinate as a catalyst in the presence of NaOH as hydroxide source and tetrabutylammonium fluoride as a phase transfer catalyst (Scheme 12).[6e]



Scheme 12

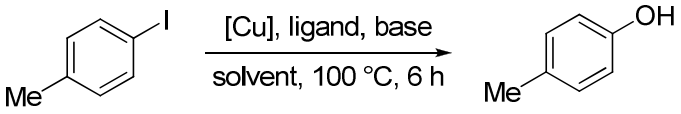
2.3 Present Study

The copper catalyzed hydroxylation has been pursued with great interest and a wide variety of methods have been developed in this regard. However, since these methods mostly require water as a co-solvent or solvent, the reactions require prolonged heating at high temperature. Also the use of an inorganic base coupled with the use of catalytic systems preferentially soluble in organic solvents compared to water led to prolonged reaction time. CuI along with ligands have been successfully used as catalyst for various *C-N*, *C-O* and *C-S* cross-coupling reactions. Tetrabutylammonium hydroxide is a strong base that can dissolve efficiently in both organic and non-organic media. In this chapter, we have described a selective hydroxylation of aryl iodides and aryl bromides with tetrabutylammonium hydroxide, as a nucleophile catalyzed by a combination of CuI and 8-hydroxyquinalidine in a 2:3 mixture of DMSO-water. The procedure is efficient, general and simple to afford substituted phenols.



Initially, the reaction conditions were optimized using 1-iodo-4-methylbenzene as a model substrate using different ligands, copper sources, bases and solvents at varied temperature (Table 1). Of the screened ligands, 8-hydroxyquinoline[7] **L6** and 8-hydroxyquinalidine[8] **L7** were effective and the latter gave the best result of 100% conversion, whereas ethane-1,2-diamine[9] **L1**, 2-aminoethanol[10] **L2**, ethane-1,2-diol[11] **L3**, 2,2,6,6-tetramethylheptane-3,5-dione[12] **L4**, 1,10-

Table 1. Optimization of the Reaction Conditions.



Entry	Ligand	Solvent	Base	[Cu]	Conv.(%)[a,b]
1	-	DMSO	$^{n}Bu_4NOH$	CuI	n.r.
2	-	H_2O	$^{n}Bu_4NOH$	CuI	10
3	-	DMSO/H_2O (1:1)	$^{n}Bu_4NOH$	CuI	20
4	-	DMSO/H_2O (2:3)	$^{n}Bu_4NOH$	CuI	30
5	-	DMSO/H_2O (1:2)	nBu$_4$NOH	CuI	14
6	-	DMF/H_2O (2:3)	$^{n}Bu_4NOH$	CuI	n.r.
7	-	CH_3CN/H_2O (2:3)	$^{n}Bu_4NOH$	CuI	<5
8	-	THF/H_2O (2:3)	$^{n}Bu_4NOH$	CuI	<5
9	-	DMSO/H_2O (2:3)	$^{n}Bu_4NOH$	CuBr	11
10	-	DMSO/H_2O (2:3)	$^{n}Bu_4NOH$	Cu_2O	17
11	-	DMSO/H_2O (2:3)	$^{n}Bu_4NOH$	$Cu(OAc)_2 \cdot H_2O$	n.r.
12	-	DMSO/H_2O (2:3)	KOH	CuI	19
13	-	DMSO/H_2O (2:3)	CsOH	CuI	21
14	-	DMSO/H_2O (2:3)	K_3PO_4	CuI	<5
15	-	DMSO/H_2O (2:3)	K_2CO_3	CuI	n.r.
16	-	DMSO/H_2O (2:3)	Cs_2CO_3	CuI	n.r.
17	**L1**	DMSO/H_2O (2:3)	$^{n}Bu_4NOH$	CuI	23
18	**L2**	DMSO/H_2O (2:3)	$^{n}Bu_4NOH$	CuI	16
19	**L3**	DMSO/H_2O (2:3)	$^{n}Bu_4NOH$	CuI	n.r.
20	**L4**	DMSO/H_2O (2:3)	$^{n}Bu_4NOH$	CuI	n.r.
21	**L5**	DMSO/H_2O (2:3)	$^{n}Bu_4NOH$	CuI	n.r.
22	**L6**	DMSO/H_2O (2:3)	$^{n}Bu_4NOH$	CuI	81
23	**L7**	DMSO/H_2O (2:3)	$^{n}Bu_4NOH$	CuI	100
24	**L7**	DMSO/H_2O (2:3)	$^{n}Bu_4NOH$	CuI	63[c]
25	**L7**	DMSO/H_2O (2:3)	$^{n}Bu_4NOH$	CuI	67[d]
26	**L8**	DMSO/H_2O (2:3)	$^{n}Bu_4NOH$	CuI	n.r.

27	**L9**	DMSO/H_2O (2:3)	$^nBu_4NOH$	CuI	16
28	**L10**	DMSO/H_2O (2:3)	$^nBu_4NOH$	CuI	40

[a] 1-Iodo-4-methylbenzene (1 mmol), Cu source (10 mol %), ligand (20 mol %) and base (3 mmol) were stirred at 100 °C for 6 h in DMSO/H_2O (1 mL) under air.

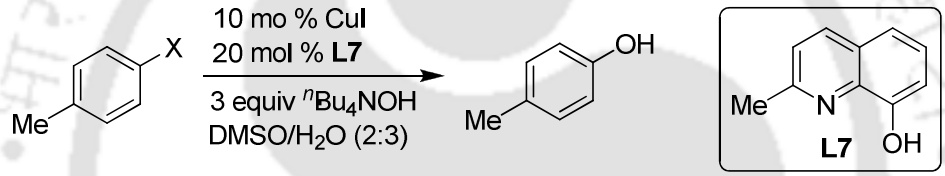
[b] Determined by 400 MHz ^1H NMR.

[c] CuI (5 mol %) and ligand (10 mol %) used.

[d] CuI (10 mol %) and ligand (10 mol %) used.

n.r. = no reaction.

Table 2. Copper(I) Catalyzed Hydroxylation of Different Aryl Halides.



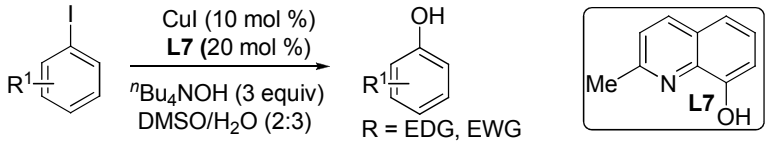
Entry	X	Time (h)	Temp (°C)	Yield (%)[a,b]
1	I	7	100	97
2	Br	14	130	93
3	Cl	14	140	10

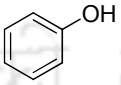
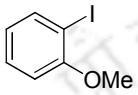
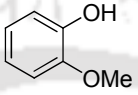
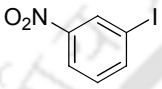
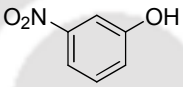
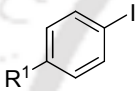
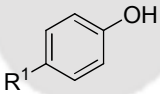
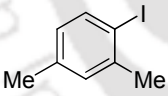
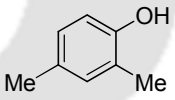
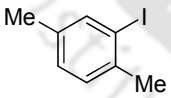
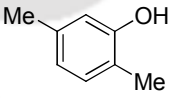
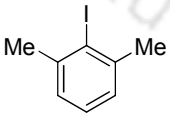
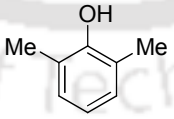
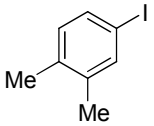
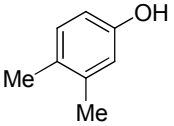
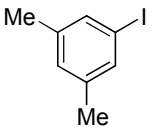
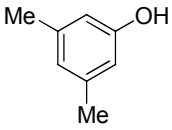
[a] Aryl halide (1 mmol), CuI (10 mol %), 8-hydroxyquinaldine **L7** (20 mol %) and $^nBu_4NOH$ (3 mmol) were stirred in a 2:3 DMSO/H_2O (1 mL).

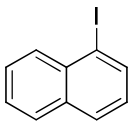
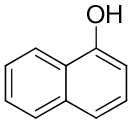
[b] Isolated yield.

phenanthroline[13] **L5**, dibenzoylmethane[14] **L9**, 2-(pyridin-2-yl)pyridine[15] **L8** and L-proline[6a,16] **L10** afforded inferior results. Control experiments confirmed that only 30% yield of the desired product without the aid of the ligand. The catalytic activity of the copper sources, CuBr, CuI, Cu_2O, CuO and $Cu(OAc)_2 \cdot H_2O$ were compared, and CuI was found to be superior to others. Among the studied a set of bases, K_2CO_3, K_3PO_4, KOH, Cs_2CO_3, CsOH and $^nBu_4NOH$, the latter provided the best results. A 2:3 mixture of DMSO and water was found to be the solvent of

Table 3. Copper(I)-Catalyzed Hydroxylation of Aryl Iodides.



Entry	Substrate	Product	Time (h)	Yield (%)[a,b]
1			7	98
2			10	94
3			5	98 [c]
				
4	R^1 = Br	R^1 = Br	7	89
5	R^1 = Cl	R^1 = Cl	7	96
6	R^1 = OMe	R^1 = OMe	7	85
7	R^1 = Me	R^1 = Me	7	97
8	R^1 = NO_2	R^1 = NO_2	5	96 [c]
9			10	91
10			10	93
11			10	88
12			10	96
13			10	95

14			10	85

[a] Aryl iodide (1 mmol), CuI (10 mol %), 8-hydroxyquinaldine **L7** (20 mol %) and $^{n}Bu_4NOH$ (3 mmol) were stirred at 100 °C in 2:3 DMSO/H_2O (1 mL).

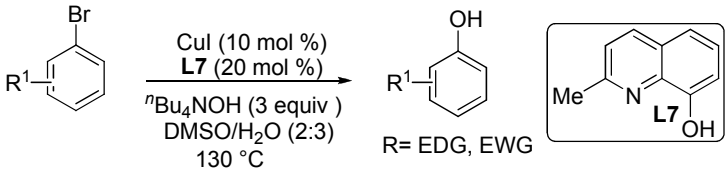
[b] Isolated yield. [c] Reaction temperature = 70 °C.

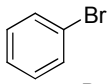
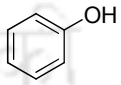
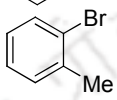
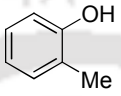
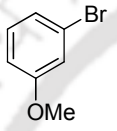
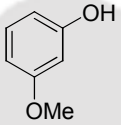
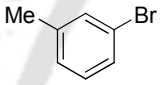
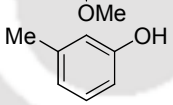
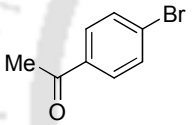
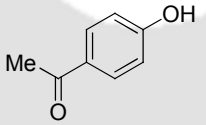
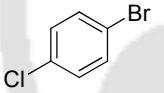
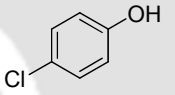
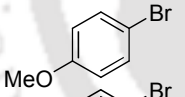
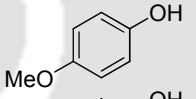
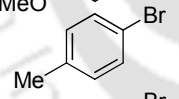
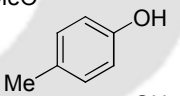
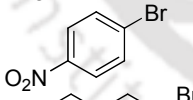
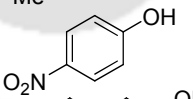
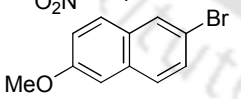
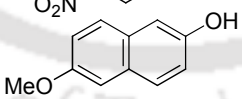
choice for this process. Solvents such as DMSO, water, DMF-water, CH_3CN-water and THF-water were found to be less effective providing the phenol in <10% conversion. The optimum temperature was 100 °C. Either lowering of the catalyst amount (5 mol %) or copper to ligand ratio to 1:1 led the reaction in <63% conversion.

The reaction conditions were further investigated for the hydroxylation of less reactive aryl bromide and aryl chloride (Table 2). 1-Bromo-4-methylbenzene could be converted to give the respective phenol at 130 °C in 93% yield. However, 1-chloro-4-methyl-benzene was less effective affording the product at 140 °C in 10% yield. The scope of the procedure was then explored for the reactions of other aryl iodides (Table 3). Iodobenzene proceeded hydroxylation in 7 h with 98% yield (entry 1). Likewise, aryl iodides having 2-methoxy, 4-bromo, 4-chloro, 4-methoxy and 4-methyl groups could be converted to the corresponding phenols in 85-97% yield (entries 2 and 4-7). Similarly, disubstituted aryl iodides such as 2,4-dimethyliodobenzene, 2,5-dimethyliodobenzene, 2,6-dimethyliodobenzene, 3,4-dimethyliodobenzene and 3,5-dimethyliodobenzene underwent reaction to yield the corresponding phenols in 88-95% yield (entries 10-13). In addition, 1-iodonaphthalene could be converted into 1-naphthol in 85% yield (entry 14). In case of activated aryl iodides, 1-iodo-3-nitrobenzene and 1-iodo-4-nitrobenzene, the reactions proceeded at 70 °C in 5 h with 95-98% yield.

Next, the hydroxylation of aryl bromides were examined (Table 4). Bromobenzene underwent hydroxylation to give the phenol in 14 h with 95% yield (entry 1). Similarly, aryl bromides containing 2-methyl, 3-methoxy and 3-methyl groups, could be transformed to the respective phenols in 74-84% yield (entries 2, 3 and 4). Also 1-bromo-4-chlorobenzene, 1-bromo-4-methoxybenzene and 1-bromo-4-methylbenzene underwent reaction to give the corresponding

Table 4. Copper(I)-Catalyzed Hydroxylation of Aryl Bromides.



Entry	Substrate	Product	Time (h)	Yield (%)[a,b]
1			14	95
2			21	84
3			21	74
4			14	91
5			21	96[c]
6			14	81
7			21	75
8			14	93
9			8	97[c]
10			21	81

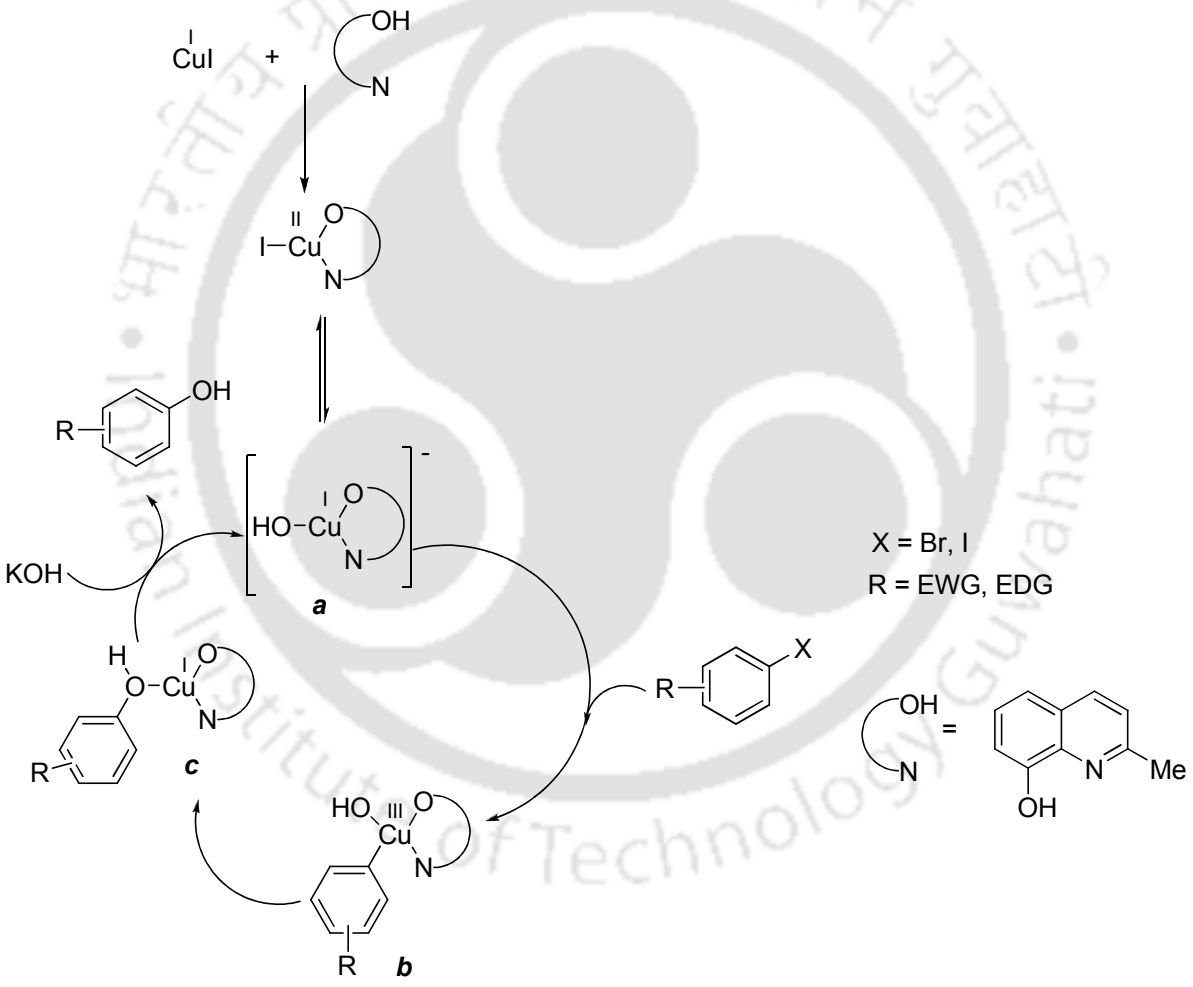
[a] Aryl bromide (1 mmol), CuI (10 mol %), 8-hydroxyquinaldine **L7** (20 mol %) and $^{n}Bu_4NOH$ (3 mmol) were stirred at 130 °C in 2:3 DMSO/H_2O (1 mL).

[b] Isolated yield.

[c] Reaction temperature = 90 °C.

target products in 75-93% yield (entries 6-8). In the case of activated aryl bromides such as 1-(4-bromophenyl)-ethanone and 1-bromo-4-nitrobenzene, the reaction occurred efficiently at 90 °C with 96% and 97% yield, respectively (entries 5 and 9). Similarly, 6-methoxy-2-bromonapthalene could be transformed into 6-methoxynaphthalen-2-ol in 81% yield (entry 10).

Regarding the mechanism,[6e] the reaction may involve a copper-hydroxyquinaldine complex ***a***. This may undergo oxidative addition with aryl halides followed by elimination of halide to form ***b*** which may now reductive elimination to form ***c***. The species ***c*** may now ligand exchange with hydroxide ion to form the products. (Scheme 14).



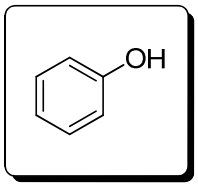
Scheme 14

In summary, the selective hydroxylation of aryl halides with $^{n}Bu_4NOH$ has been described in shorter time by the combined use of CuI and 8-hydroxyquinaldine at moderate temperature. The process is efficient, general and simple to synthesis substituted phenols and avoids the use of inert conditions.

2.4 Experimental Conditions

General Information. CuI (98%), Cu_2O (97%), $^{n}Bu_4NOH{\cdot}30H_2O$ (>97%), K_3PO_4 (98%), Cs_2CO_3 (99%) and $CsOH{\cdot}H_2O$ (99.5%) were purchased from Aldrich and $Cu(OAc)_2{\cdot}H_2O$ (>98%) was purchased from Merck and used without further purification. Aryl iodides were prepared according to the literature.[17] Chromatography was carried out with silica gel (230-400 mesh) using ethyl acetate and hexane as eluent. Analytical TLC was performed with Rankem silica gel G & GF254 plates. NMR spectra (400 MHz for ^{1}H and 100 MHz for ^{13}C) were recorded using DRX-400 Varian spectrometer using $CDCl_3$ and DMSO-d_6 as solvents and Me_4Si as an internal standard. Chemical shifts (δ) are reported in ppm and spin-spin coupling constants (*J*) are given in Hz. Melting points were determined using Buchi B-540 melting point apparatus and are uncorrected. Elemental analysis was carried out using Perkin Elmer-2400 CHNS analyzer.

General Procedure for Hydroxylation of Aryl Halides. To a stirred solution of CuI (19.0 mg, 10 mol %) and 8-hydroxyquinaldine **L7** (31.8 mg, 20 mol %) in DMSO (0.4 mL) for 0.1 h, aryl halide (1 mmol), $^{n}Bu_4NOH$ (2399 mg, 3 mmol) and H_2O (0.6 mL) were added and the reaction mixture was stirred at 70-100 ^{o}C (aryl iodides) or 90-130 °C (aryl bromides) for the appropriate time. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. The reaction mixture was then cooled to room temperature and acidified with 0.5 M HCl (0.5 mL). The resulting mixture was extracted with ethyl acetate (3 x 10 mL) and dried over Na_2SO_4. Evaporation of the solvent gave a residue that was purified on a short pad of silica gel column chromatography using ethyl acetate and hexane as eluent.



Phenol (Table 3, Entry 1).[5d]

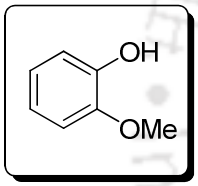
Colorless liquid; yield: 98%.

R_f = 0.46 (EtOAc-hexane, 1:9).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (t, *J* = 8.8 Hz, 2H), 6.92 (t, *J* = 8.8 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 2H), 5.55 (br s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.6, 129.9, 120.9, 115.6.

Anal. Calcd for C_6H_6O: C, 76.57; H, 6.43. Found: C, 76.59; H, 6.41.



2-Methoxyphenol (Table 3, Entry 2).[5a]

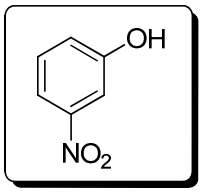
Yellow oil; yield: 94%.

R_f = 0.42 (EtOAc-hexane, 3:17).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.93-6.83 (m, 4H), 5.61 (s, 1H), 3.87 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.7, 145.8, 121.6, 120.3, 114.7, 110.9, 56.0.

Anal. Calcd for $C_7H_8O_2$: C, 67.73; H, 6.50. Found: C, 67.76; H, 6.52.



3-Nitrophenol (Table 3, Entry 3).

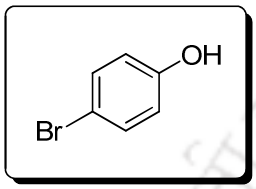
White solid; yield: 98%; mp 95 °C (lit.[18a] 95 °C).

R_f = 0.27 (EtOAc-hexane, 3:17).

^{1}H NMR (400 MHz, $CDCl_3$/DMSO-d_6 (3:1)): δ = 7.77 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 2.0 Hz, 1H), 7.39 (dt, *J* = 8.4, 2.0 Hz, 1H), 7.18 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$/DMSO-d_6 (3:1)): δ = 156.7, 149.3, 130.4, 122.3, 115.9, 110.7.

Anal. Calcd for $C_6H_5NO_3$: C, 51.80; H, 3.62; N, 10.07. Found: C, 51.84; H, 3.63; N, 10.10.



4-Bromophenol (Table 3, Entry 4).[18b]

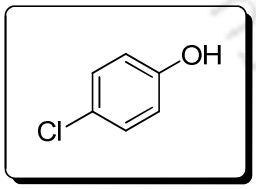
Yellow solid; yield: 85%; mp 64 °C (lit.[18c] 63-64 °C).

R_f = 0.51 (EtOAc-hexane, 1:9).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (d, *J* = 8.4 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 2H), 5.00 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.1, 132.6, 117.4, 112.8.

Anal. Calcd for C_6H_5BrO: C, 41.65; H, 2.91. Found: C, 41.69; H, 2.93.



4-Chlorophenol (Table 3, Entry 5).[18d]

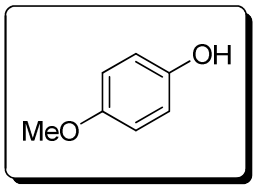
Yellow oil; yield: 89%.

R_f = 0.50 (EtOAc-hexane, 1:9).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18 (d, *J* = 8.8 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.2, 129.6, 125.7, 116.8.

Anal. Calcd for C_6H_5ClO: C, 56.06; H, 3.92. Found: C, 56.10; H, 3.93.



4-Methoxyphenol (Table 3, Entry 6).[5c]

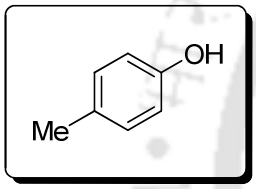
White solid; yield: 96%. mp 53 °C (lit.[5d] 53-55 °C).

R_f = 0.42 (EtOAc-hexane, 3:17).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.79-6.73 (m, 4H), 5.16 (s, 1H), 3.75 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.9, 149.7, 116.3, 115.1, 56.0.

Anal. Calcd for $C_7H_8O_2$: C, 67.73; H, 6.50. Found: C, 67.77; H, 6.51.



4-Methylphenol (Table 3, Entry 7).[5d]

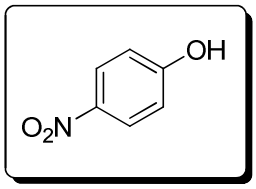
Yellow oil; yield: 97%.

R_f = 0.47 (EtOAc-hexane, 1:9).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.03 (d, J = 8.4 Hz, 2H), 6.74 (d, J = 8.4 Hz, 2H), 5.56 (s, 1H), 2.27 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.4, 130.3, 130.1, 115.3, 20.6.

Anal. Calcd for C_7H_8O: C, 77.75; H, 7.46. Found: C, 77.79; H, 7.49.



4-Nitrophenol (Table 3, Entry 8).[5c]

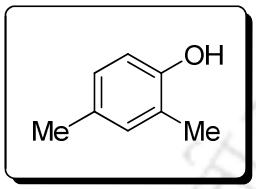
Yellow solid; yield: 95%; mp 114 °C (lit.[18e] 114 °C).

R_f = 0.28 (EtOAc-hexane, 3:17).

^{1}H NMR (400 MHz, $CDCl_3$/DMSO-d_6 (3:1)): δ = 7.98 (dd, *J* = 9.2, 2.0 Hz, 2H), 6.79 (dd, *J* = 9.2, 2.0 Hz, 2H), 2.74 (br s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$/DMSO-d_6 (3:1)): δ = 163.7, 140.4, 126.0, 115.7.

Anal. Calcd for $C_6H_5NO_3$: C, 51.80; H, 3.62; N, 10.07. Found: C, 51.83; H, 3.60; N, 10.12.



2,4-Dimethylphenol (Table 3, Entry 9).[18f]

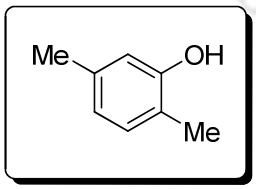
Colorless oil; yield: 91%.

R_f = 0.45 (EtOAc-hexane, 1:9).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.95 (s, 1H), 6.90 (d, *J* = 8.0 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 5.14 (br s, 1H), 2.27 (s, 3H), 2.24 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.6, 131.8, 130.0, 127.5, 123.8, 114.9, 20.6, 15.9.

Anal. Calcd for $C_8H_{10}O$: C, 78.65; H, 8.25. Found: C, 78.68; H, 8.28.



2,5-Dimethylphenol (Table 3, Entry 10).[5a]

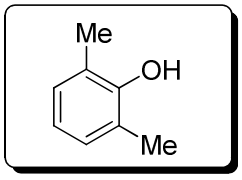
White solid; yield: 93%; mp 75 °C (lit.[5a] 75-76 °C).

R_f = 0.47 (EtOAc-hexane, 1:9).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.01 (d, *J* = 7.6 Hz, 1H), 6.68 (d, *J* = 7.6 Hz, 1H), 6.60 (s, 1H), 4.80 (br s, 1H), 2.28 (s, 3H), 2.21 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.8, 137.3, 131.0, 121.6, 120.7, 115.9, 21.1, 15.5.

Anal. Calcd for $C_8H_{10}O$: C, 78.65; H, 8.25. Found: C, 78.69; H, 8.26.



2,6-Dimethylphenol (Table 3, Entry 11).[5a]

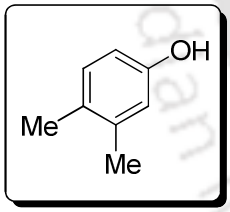
Colourless oil; yield: 88%.

R_f = 0.47 (EtOAc-hexane, 1:9).

^{1}H NMR (400 MHz, $CDCl_3$) : δ = 6.91 (d, *J* = 7.6 Hz, 2H), 6.69 (t, *J* = 7.6 Hz, 1H), 4.6 (s, 1H) 2.17 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.4, 128.8, 123.2, 120.4, 16.0.

Anal. Calcd for $C_8H_{10}O$: C, 78.65; H, 8.25. Found: C, 78.67; H, 8.23.



3,4-Dimethylphenol (Table 3, Entry 12).[18g]

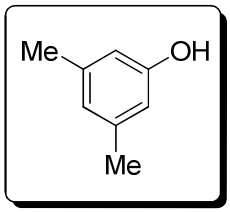
White solid; yield: 96%; mp 63 °C (lit.[18h] 63 °C).

R_f = 0.46 (EtOAc-hexane, 1:9).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.95 (d, *J* = 8.0 Hz, 1H), 6.61 (d, *J* = 8.0 Hz, 1H), 6.57 (s, 1H), 2.16 (s, 3H), 2.14 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.5, 138.2, 130.7, 128.9, 116.8, 112.6, 20.0, 18.9.

Anal. Calcd for $C_8H_{10}O$: C, 78.65; H, 8.25. Found: C, 78.68; H, 8.24.



3,5-Dimethylphenol (Table 3, Entry 13).[5b]

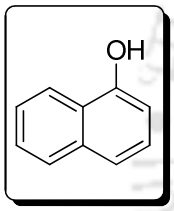
White solid; yield: 95%; mp 64 °C (lit.[7d] 64-65 °C).

R_f = 0.47 (EtOAc-hexane, 1:9).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.58 (s, 1H), 6.47 (s, 2H), 5.43 (s, 1H), 2.25 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.6, 139.7, 122.7, 113.3, 21.4.

Anal. Calcd for $C_8H_{10}O$: C, 78.65; H, 8.25. Found: C, 78.69; H, 8.24.



1-Naphthol (Table 3, Entry 14).

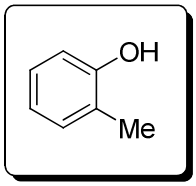
Violet solid; yield: 84%; mp 95 °C (lit.[18i] 94-95 °C).

R_f = 0.40 (EtOAc-hexane, 1:9).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21-8.19 (m, 1H), 7.84-7.82 (m, 1H), 7.52-7.45 (m, 3H), 7.31 (t, J = 8.4 Hz, 1H), 6.81 (dd, J = 7.6, 1.2 Hz, 1H), 5.49 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.5, 134.9, 127.8, 126.6, 126.0, 125.5, 124.5, 124.7, 120.9, 108.8.

Anal. Calcd for $C_{10}H_8O$: C, 83.31; H, 5.59. Found: C, 83.34; H, 5.60.



2-Methylphenol (Table 4, Entry 2).

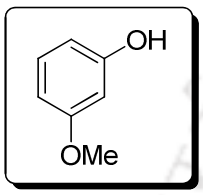
Yellow oil; yield: 84%.

R_f = 0.48 (EtOAc-hexane, 1:9).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14-7.12 (m, 2H), 6.87 (t, *J* = 7.2 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 4.98 (br s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.9, 131.2, 127.3, 124.0, 120.9, 115.1, 15.9.

Anal. Calcd for C_7H_8O: C, 77.75; H, 7.46. Found: C, 77.79; H, 7.49.



3-Methoxyphenol (Table 4, Entry 3).[5a]

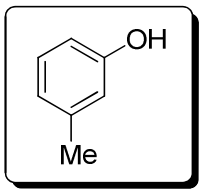
Yellow oil; yield: 74%.

R_f = 0.40 (EtOAc-hexane, 3:17).

^{1}H NMR (400 MHz, $CDCl_3$/DMSO-d_6 (3:1)): δ = 7.13 (t, *J* = 7.6 Hz, 1H), 6.48 (d, *J* = 9.6 Hz, 1H), 6.41 (m, 2H), 5.05 (s, 1H), 3.76 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$/DMSO-d_6 (3:1)): δ = 161.0, 156.9, 130.3, 108.8, 106.5, 55.5.

Anal. Calcd for $C_7H_8O_2$: C, 67.73; H, 6.50. Found: C, 67.77; H, 6.51.



3-Methylphenol (Table 4, Entry 4).

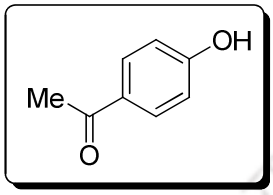
Yellow oil; yield: 91%.

R_f = 0.47 (EtOAc-hexane, 1:9).

^{1}H NMR (400 MHz, $CDCl_3$/DMSO-d_6 (3:1)): δ = 7.13 (t, *J* = 8.0 Hz, 1H), 6.75 (d, *J* = 7.6 Hz, 1H), 6.66-6.63 (m, 2H), 5.61 (m, 1H), 2.29 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$/DMSO-d_6 (3:1)): δ = 155.6, 140.0, 129.6, 121.86, 114.3, 112.5, 21.50.

Anal. Calcd for C_7H_8O: C, 77.75; H, 7.46. Found: C, 77.73; H, 7.48.



4-Hydroxyacetophenone (Table 4, Entry 5).[18c]

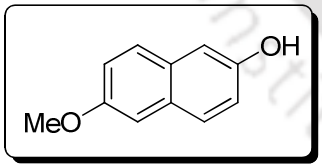
White solid; yield: 96%; mp 106 °C; (lit.[18c] 106-107 °C).

R_f = 0.31 (EtOAc-hexane, 1:3).

^{1}H NMR (400 MHz, $CDCl_3$/DMSO-d_6 (3:1)): δ = 7.85 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 2.51 (s, 3H), 2.0 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$/DMSO-d_6 (3:1)): δ = 196.8, 162.1, 130.6, 128.9, 115.3, 26.1.

Anal. Calcd for $C_8H_8O_2$: C, 70.57; H, 5.92. Found: C, 70.60; H 5.94.



6-Methoxy-2-naphthol (Table 4, Entry 10).[5c]

White solid; yield: 81%; mp 145 °C (lit.[18j] 145-147 °C).

R_f = 0.41 (EtOAc-hexane, 3:17).

^{1}H NMR (400 MHz, $CDCl_3$/DMSO-d_6 (3:1)) δ = 8.61 (s, 1H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.03-6.94 (m, 4H), 3.77 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$/DMSO-d_6 (3:1)): δ = 155.6, 153.4, 130.1, 129.0, 128.0, 127.7, 118.9, 118.8, 109.5, 105.9, 55.2.

Anal. Calcd for $C_{11}H_{10}O_2$: C, 75.84; H, 5.79. Found: C, 75.87; H, 5.77.

2.5 References

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d1	1.000	dp	y
nt	5000	hs	nn
ct	4896	PROCESSING	
TRANSMITTER		lb	2.00
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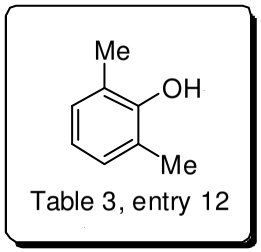
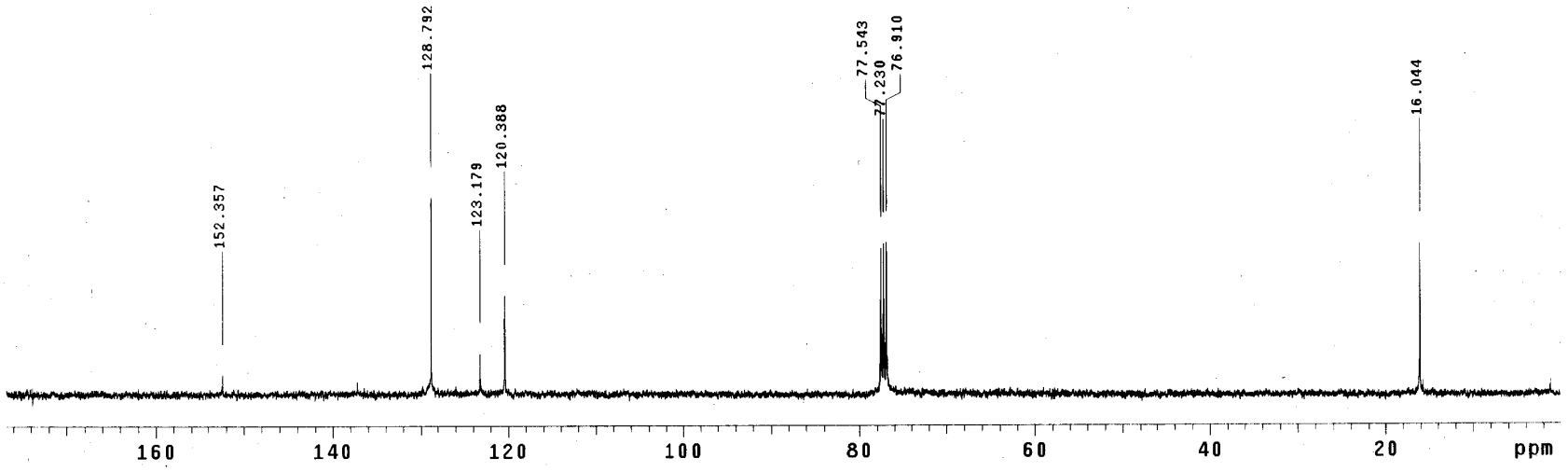
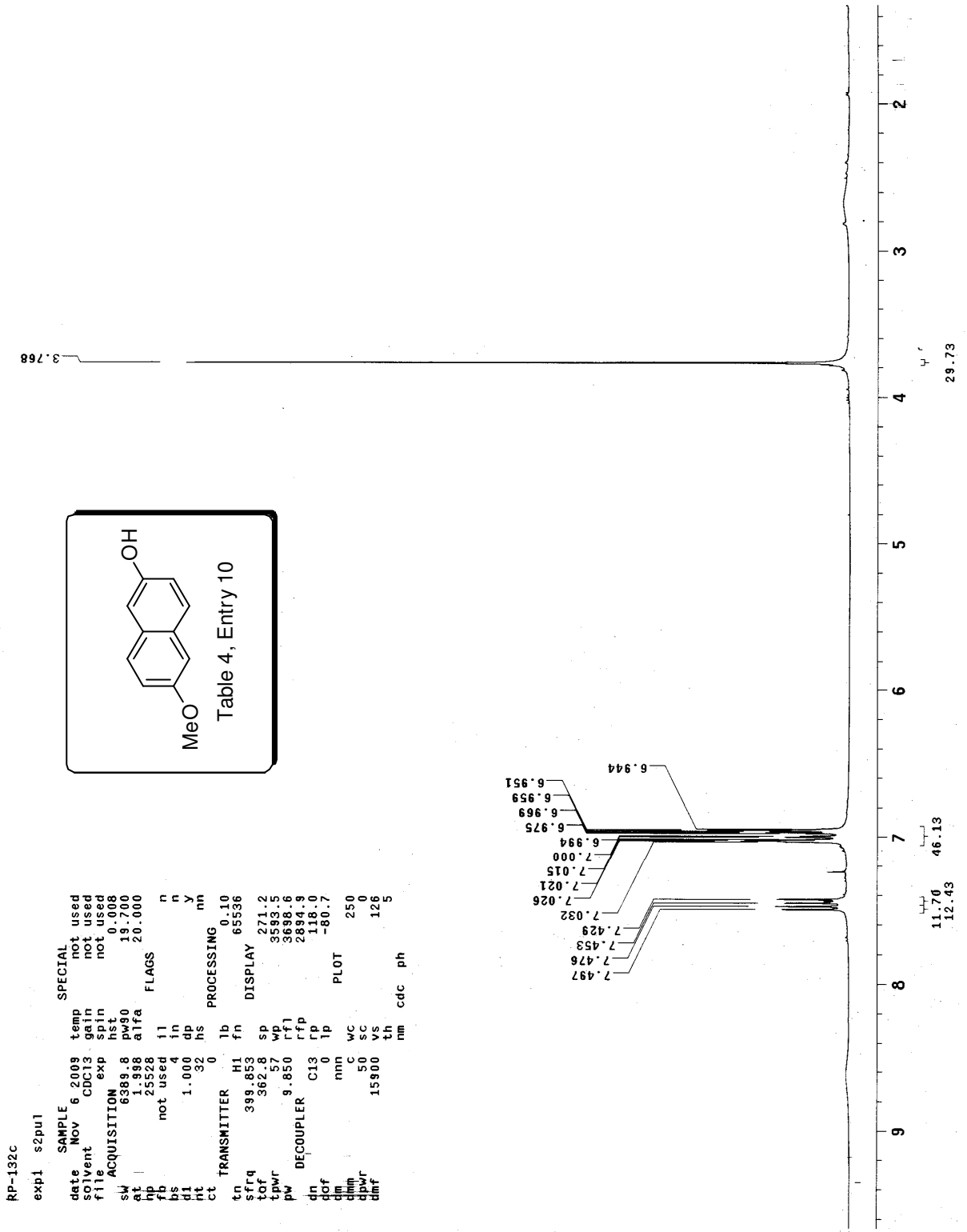
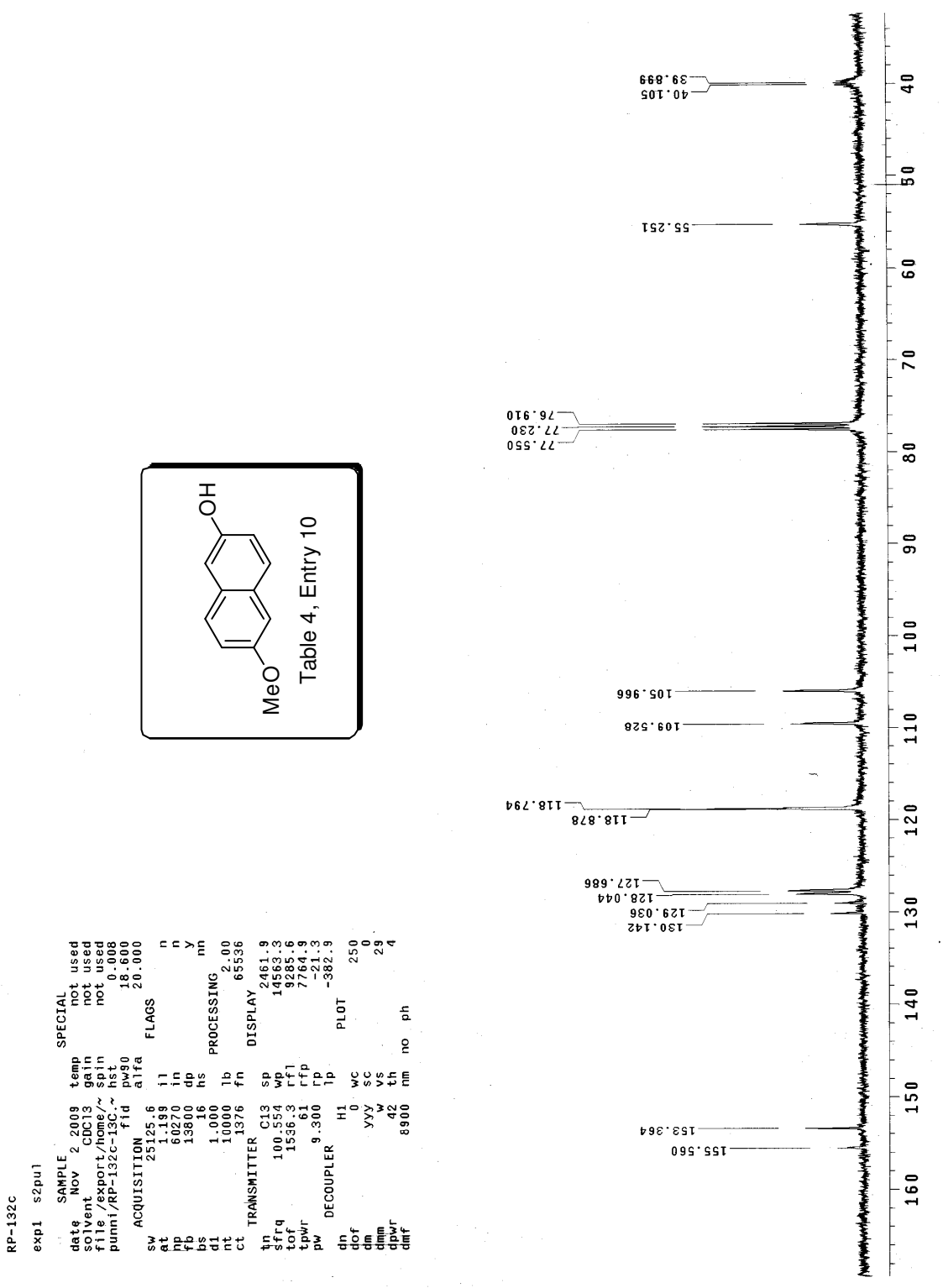


Table 3, entry 12







One-Pot Conversion of Aryl halides to Alkyl Aryl Ethers

3.1 Introduction

Alkyl aryl ethers are important moieties of various natural products and biologically and active molecules[1] such as potent fibrinogen receptor antagonist MK383[2] and PPAR α/γ agonist (Figure 1).[3] They are also important in material sciences as the alkylation of phenols generating hydrophobic molecules.[4] Thus the synthesis of this class of molecules is of importance.

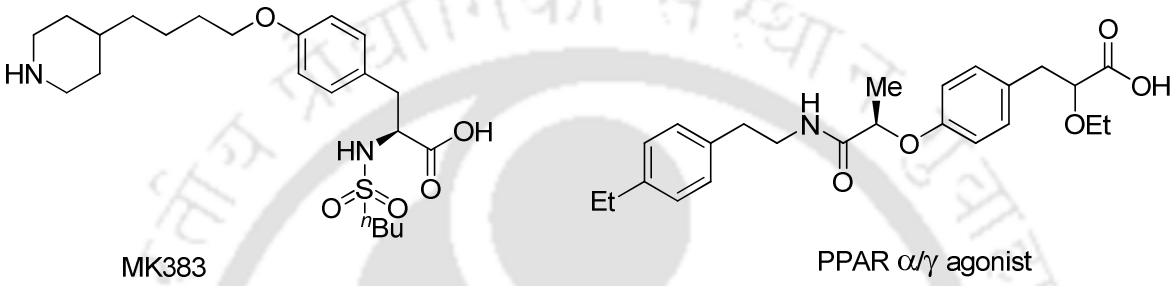
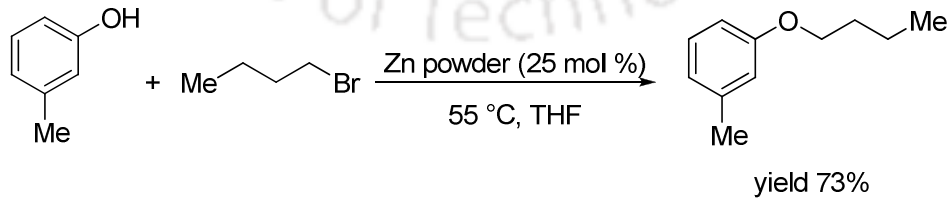


Figure 1. Examples of some biologically important ethers.

There is a wide range of methods, available in literature for the synthesis of alkyl aryl ethers. The following are some examples of the methodologies employed in the synthesis of alkyl aryl ethers.

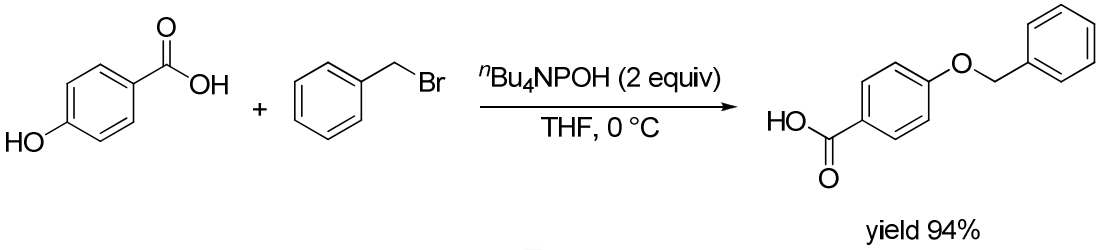
3.2 Williamson Ether Synthesis

Williamson ether synthesis[8] is a well known reaction for the synthesis of alkyl aryl ethers. This method employs the reaction of an alkyl halide with phenol in the presence of a base or acid. Thus, Gupta and co-workers demonstrated the synthesis of the target ethers from phenols and alkyl bromide mediated by zinc powder in THF at 55 °C (Scheme 1).[5g]



Scheme 1

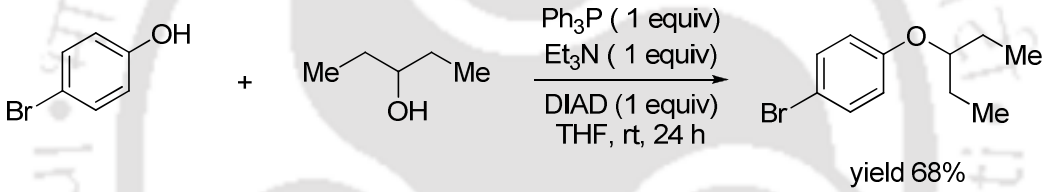
On the other hand, Faul and co-workers have achieved the alkylation of phenols by alkyl halides using tetrabutylphosphonium hydroxide as a base in high yields (Scheme 2).[8h]



Scheme 2

3.3 Mitsunobu Reaction

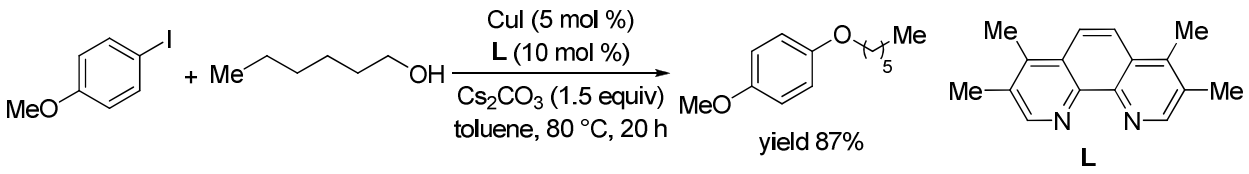
The synthesis of alkyl aryl ethers may also be carried out by employing Mitsunobu reaction.[7] When various phenols were treated with secondary alcohols in the presence of stoichiometric amounts of triphenylphosphine, triethylamine and diisopropyl azadicarboxyalate (DIAD) in THF at 0 °C, alkyl aryl ethers were obtained in good yields (Scheme 3).[7f]



Scheme 3

3.4 Transition Metal-Catalyzed *C-O* Cross-Coupling Reaction

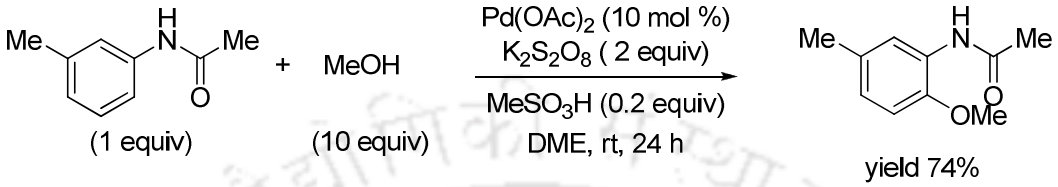
In recent time, transition metal-catalyzed cross-coupling reaction[9] has become a prominent tool for the construction of carbon-heteroatom bond. Both of these methodologies have been widely applied for *C-O* bond formation leading to the synthesis of alkyl aryl ethers. Buchwald and co-workers utilized CuI and 3,4,7,8-tetramethyl-1,10-phenanthroline as a catalyst for cross-coupling of alcohols with aryl halides to generate alkyl aryl ethers (Scheme 4).[9d]



Scheme 4

3.5 *C-H* Functionalization

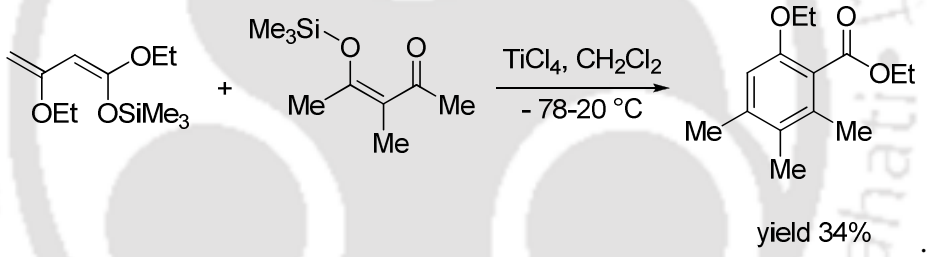
C-H functionalization[10] has also received great attention due to its high E-factor and easy availability of suitably substituted substrates. Wang and co-workers have demonstrated the directed *C-H* functionalization leading to the formation of alkyl aryl ethers using $Pd(OAc)_2$ as catalyst in the presence of potassium persulfate as oxidant (Scheme 5).[10d]



Scheme 5

3.6 Electrocyclization

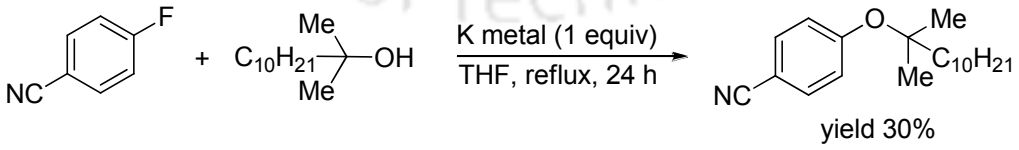
Langer and co-workers described the [3+3] electrocyclization of 3-alkoxy-1-silyloxy-1,3-butadienes and 3-(siloxy)alk-2-en-1-ones for synthesis of alkyl aryl ethers in good to moderate yields (Scheme 6).[6c]



Scheme 6

3.7 Aromatic Nucleophilic Substitution (S_NAr)

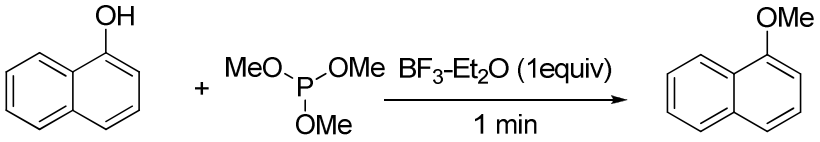
Aromatic nucleophilic substitution (S_NAr)[5] has been applied to the reaction of activated fluorobenzenes with sterically hindered alcohols for the synthesis of alkyl aryl ethers (Scheme 7).[5a]



Scheme 7

3.8 Alkylation of Phenols using Trimethoxyphosphine

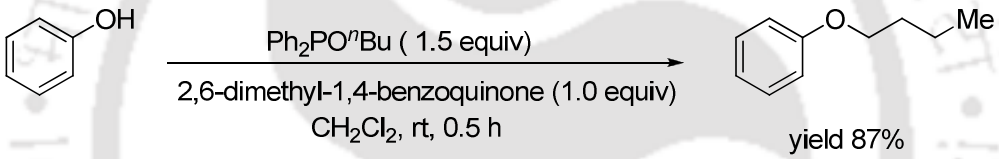
The methylation of phenols was achieved by using trimethoxyphosphine as a methylating agent in the presence of $BF_3{\cdot}Et_2O$ as a Lewis acid under microwave irradiation (Scheme 8).[6a]



Scheme 8

3.9 Oxidation-Reduction Condensation

Mukaiyama and co-workers demonstrated the preparation of alkyl aryl ethers *via* an oxidation-reduction condensation employing alkoxydiphenyl phosphines, 2,6-dimethyl-1,4-benzoquinone and phenols under neutral conditions in good yields (Scheme 9).[6b]

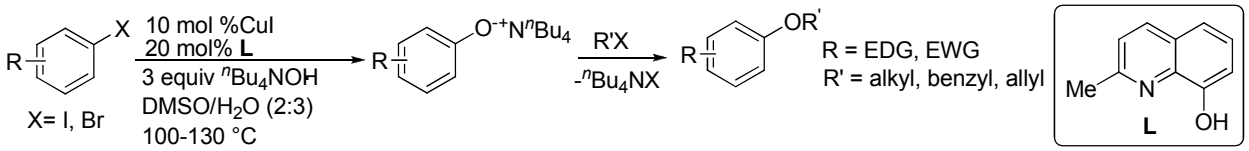


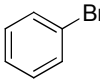
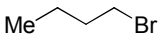
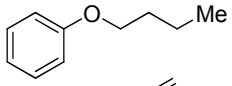
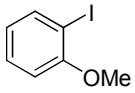
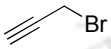
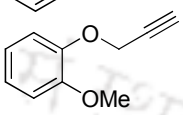
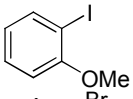
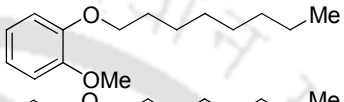
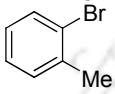
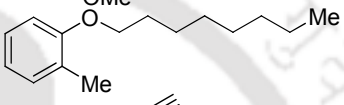
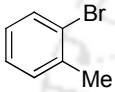
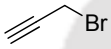
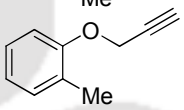
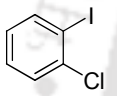
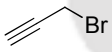
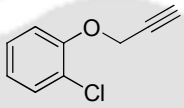
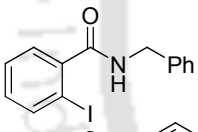
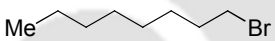
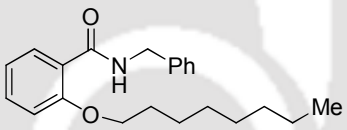
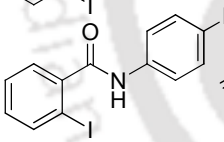
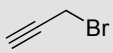
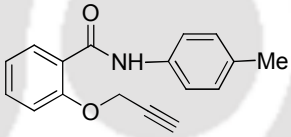
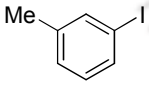
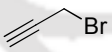
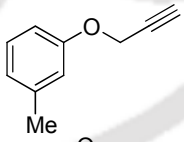
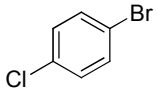
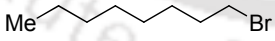
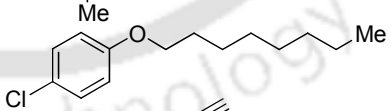
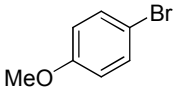
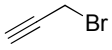
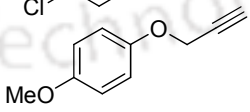
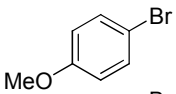
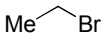
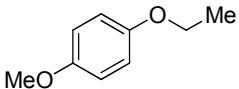
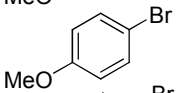
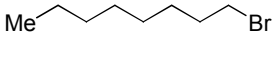
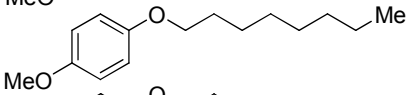
Scheme 9

3.10 Present Study

As an application of the technique developed in the first chapter, in this chapter, we describe a one-pot conversion of aryl halides to aryl alkyl ethers where the aryl halides are first converted to the corresponding phenoxides and then treated with an alkyl halide. In this method, no additional phase transfer catalyst (PTC) is required as the tetrabutylammonium halide generated in the first step performs the role of PTC (Table 1). Thus, a variety of alkyl halides were coupled with the phenoxides to generate the alkyl aryl ethers. For examples, 2-methoxyiodobenzene could be transformed to the corresponding phenoxide which then proceeded reaction with 3-bromoprop-1-ene and 1-bromooctane to provide 1-methoxy-2-(prop-2-ynyloxy)benzene and 1-methoxy-4-octyloxybenzene in 84% and 86% yield, respectively (entries 2 and 3). *N*-Benzyl-2-iodobenzamide and *N*-(4-methylphenyl)-2-iodobenzamide underwent similar transformation with 1-bromooctane and 3-bromoprop-1-ene to give *N*-benzyl-2-octyloxybenzamide and *N*-(4-

Table 1. One-Pot Synthesis of Alkyl Aryl Ethers from Aryl Halides.



Entry	Aryl Halide	R'X	Product	Time (h)	Yield (%)
1				24	87
2				31	84
3				31	86
4				28	81
5				28	79
6				21	81
7				21	84
8				21	90
9				25	75
10				25	70
11				40	68
12				36	67
13				45	70
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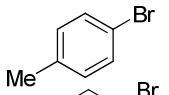
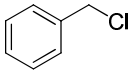
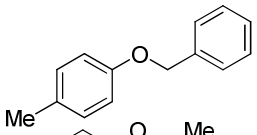
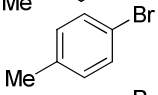
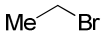
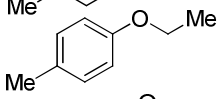
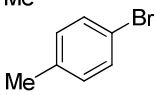
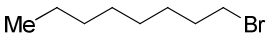
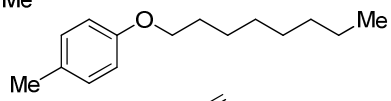
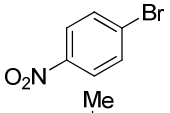
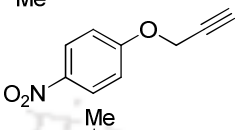
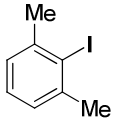
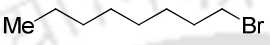
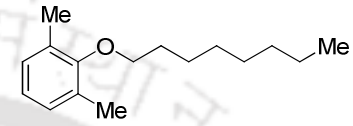
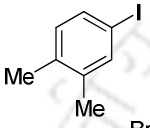
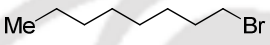
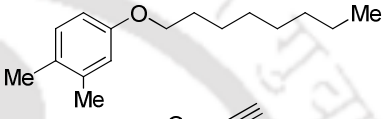
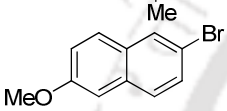
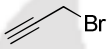
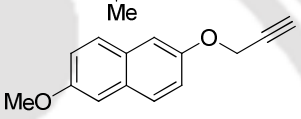
15				28	89
16				18	87
17				32	89
18				27	90
19				28	85
20				29	89
21				40	75

[a] Aryl halide (1 mmol), CuI (10 mol %), 8-hydroxyquinaldine **L** (20 mol %) and $^{n}Bu_4NOH$ (3 mmol) were stirred for 10-21 h at 100 °C (aryl iodide) or 130 °C (aryl bromide) in 2:3 DMSO/H_2O (1 mL). The phenoxide was in situ treated with alkyl/allyl halide (2 mmol) and the stirring was continued at 100 ° C for 4-21 h.

[b] Isolated yield.

methylphenyl)-2-(prop-2-ynyloxy)benzamide and 84% and 90% yield, respectively (entries 7 and 8). Similarly, aryl iodides having 2-chloro, 3-methyl, 2,6-dimethyl and 3,4-dimethyl substituents could be transformed into phenoxides which *in situ* readily proceeded reaction with 1-bromooctane to give the corresponding ethers in 85-89% yield (entries 6,9,19 and 20).

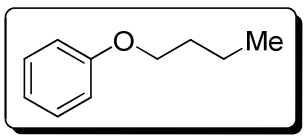
Regarding aryl bromides, the phenoxide generated from bromobenzene underwent reaction with 1-bromobutane to give butoxybenzene in 87% yield (entry 1). Similarly, aryl bromides having 2-methyl, 4-chloro, 4-methyl, 4-methyl and 4-nitro substituents underwent reaction with 3-bromoprop-1-ene, (chloromethyl)benzene or 1-bromooctane to provide the respective ethers in 70-90% yield (entries 4,5,10-18). Also, 6-methoxy-2-bromonaphthalene could be converted to the respective phenoxide, which then on reaction with 3-bromoprop-1-ene provided 2-methoxy-6-(prop-2-ynyloxy)naphthalene in 76% yield (entry 21).

In summary, we have devised the synthesis of alkyl aryl ethers from aryl bromdes and aryl iodides. The reaction involves the generation of phenoxides followed by treatment with an alkyl halide. The reaction is general and efficient and provides the target molecules in high yield.

3.11 Experimental Conditions

General Information. CuI (98%), $^{n}Bu_4NOH{\cdot}30H_2O$ (>97%), aryl bromides and alkyl halides were purchased from Aldrich and used without further purification. Aryl iodides were prepared according to the literature.[11] Chromatography was carried out with silica gel (230-400 mesh) using ethyl acetate and hexane as eluent. Analytical TLC was performed with Rankem silica gel G & GF254 plates. NMR spectra (400 MHz for ^{1}H and 100 MHz for ^{13}C) were recorded using DRX-400 Varian spectrometer using $CDCl_3$ and DMSO-d_6 as solvents and Me_4Si as an internal standard. Chemical shifts (δ) are reported in ppm and spin-spin coupling constants (*J*) are given in Hz. Melting points were determined using Buchi B-540 melting point apparatus and are uncorrected. Elemental analysis was carried out using Perkin Elmer-2400 CHNS analyzer.

General Procedure for the Synthesis of Alkyl Aryl Ethers. To a stirred solution of CuI (19.0 mg, 10 mol %) and 8-hydroxyquinaldine **L** (31.8 mg, 20 mol %) in DMSO (0.4 mL) for 0.1 h, aryl halide (1 mmol), $^{n}Bu_4NOH$ (2399 mg, 3 mmol) and H_2O (0.6 mL) were added and the resultant reaction mixture was stirred at 100 °C (aryl iodide) or 130 °C (aryl bromide) for the appropriate time. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. The reaction mixture was then cooled to room temperature and treated with alkyl or allyl halide (2 mmol). The resultant mixture was further stirred at 100 °C for 4-21 h. The reaction mixture was then cooled to room temperature and extracted with ethyl acetate (3 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on a short pad of silica gel using ethyl acetate and hexane as eluent.



Butoxybenzene (Table 1, Entry 1).

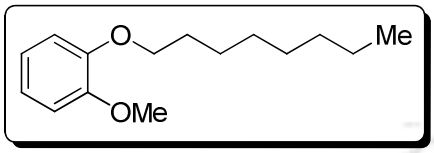
Colourless oil; yield: 87%.

R_f = 0.68 (Hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (d, *J* = 7.6 Hz, 1H), 7.21 (t, *J* = 8.0 Hz, 1H), 6.91-6.48 (m, 3H), 4.04 (t, *J* = 6.4 Hz, 2H), 1.85-1.78 (m, 2H), 1.57-1.48 (m, 2H), 1.00 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$):δ = 155.6, 129.9, 121.0, 115.6, 68.7, 31.3, 19.3, 13.8.

Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 79.90; H, 9.42.



1-Methoxy-2-(octyloxy)benzene (Table 1, Entry 2).

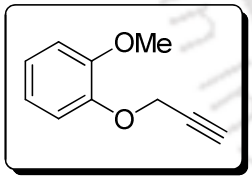
Yellow oil; yield: 84%.

R_f = 0.42 (Hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.91 (m, 4H), 4.03 (t, *J* = 6.8 Hz, 2H), 3.87 (s, 3H), 1.88-1.84 (m, 2H), 1.48-1.46 (m, 2H), 1.36-1.31 (m, 8H), 0.93 (t, *J* = 6.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.7, 145.8, 121.6, 120.3, 114.7, 110.9, 68.9, 55.9, 31.9, 29.5, 29.3, 26.1, 22.7, 14.2.

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.25; H, 10.22.



1-Methoxy-2-(prop-2-ynyloxy)benzene (Table 1, Entry 3)

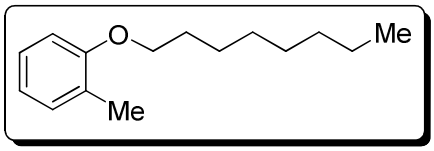
Colourless oil, yield 86%.

R_f = 0.50 (Hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.95-6.84 (m, 4H), 5.63 (s, 2H), 3.76 (s, 3H), 2.52 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.8, 145.8, 121.6, 120.3, 114.7, 110.9, 78.8, 74.7, 56.5, 55.6.

Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21. Found: C, 74.16; H, 6.17.



1-Methyl-2-(octyloxy)benzene (Table 5, Entry 4).

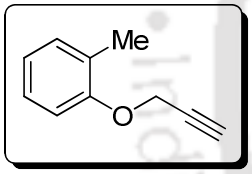
Colourless oil; yield: 81%.

R_f = 0.63 (Hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13 (d, *J* = 7.2 Hz, 1H), 6.83-6.78 (m, 3H), 3.96 (t, *J* = 6.4 Hz, 2H), 2.22 (s, 3H), 1.80-1.75 (m, 2H), 1.56-1.33 (m, 2H), 1.32-1.27 (m, 8H), 0.89 (t, *J* = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ =157.5, 130.7, 127.0, 126.9, 120.2, 111.1, 68.1, 32.0, 29.6, 29.5, 26.4, 22.9, 16.4, 16.4, 14.3.

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.75; H, 10.96.



1-Methyl-2-(prop-2-ynyloxy)benzene (Table 1, Entry 5).[12a]

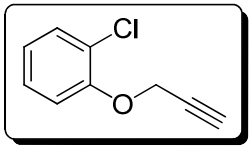
Colourless oil; yield: 79%.

R_f = 0.68 (Hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 7.6 Hz, 1H), 6.99-6.95 (m, 3H), 4.74 (d, *J* = 2.5 Hz, 2H), 2.53 (t, *J* = 2.5 Hz, 1H), 2.26 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.9, 131.1, 127.4, 126.8, 121.5, 111.9, 79.2, 75.3, 56.1, 16.4.

Anal. Calcd for $C_{10}H_{10}O$: C, 82.16; H, 6.89. Found: C, 82.10; H, 6.90.



1-Chloro-2-(prop-2-ynyloxy)benzene (Table 1, Entry 6).[12b]

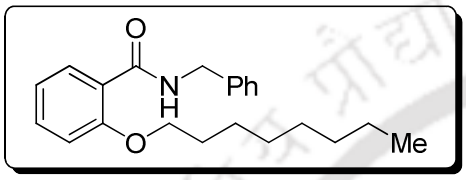
Colourless oil; yield: 81%.

R_f = 0.75 (Hexane)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 8.0 Hz, 1H), 7.26 (t, *J* = 8.8 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 6.97 (t, *J* = 8.0 Hz, 1H), 4.68 (d, *J* = 2.5 Hz, 2H), 2.51 (t, *J* = 2.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.2, 130.5, 127.7, 123.3, 122.5, 114.8, 78.1, 76.3, 56.8.

Anal. Calcd for C_9H_7ClO: C, 64.88; H, 4.23. Found: C, 64.82; H, 4.19.



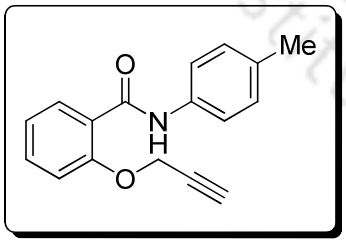
***N*-Benzyl-2-(octyloxy)benzamide (Table 1, Entry 7).**

White solid; yield: 84%.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.34 (br s, 1H), 8.28 (d, *J* = 8.0 Hz, 1H), 7.47-7.26 (m, 5H), 7.05 (t, *J* = 8.0 Hz, 2H), 6.94 (d, *J* = 8.4 Hz, 1H), 4.67 (d, *J* = 5.2 Hz, 2H), 4.06 (t, *J* = 6.4 Hz, 2H), 1.69-1.62 (m, 2H), 1.31-1.17 (m, 10 H), 0.88 (t, *J* = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.1, 157.0, 138.4, 132.6, 132.1, 128.5, 127.7, 127.2, 121.1, 120.8, 112.1, 68.9, 47.6, 31.2, 29.6, 28.9, 25.7, 22.3, 13.8.

Anal. Calcd for $C_{22}H_{29}NO_2$: C, 77.84; H, 8.61; N, 4.13. Found: C, 77.78; H, 8.58; N, 4.17.



2-(Prop-2-ynyloxy)-*N*-*p*-tolylbenzamide (Table 1, Entry 8).

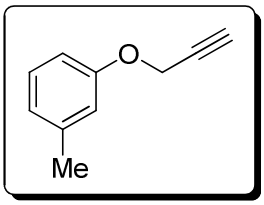
Colourless oil; yield: 90%.

R_f = 0.48 (Ethyl acetate : Hexane 1:10).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.69 (s, 1H), 8.30 (d, *J* = 8.0 Hz, 1H), 7.59 (d, *J* = 5.2 Hz, 2H), 7.19-7.15(m, 3H), 7.07(d, *J* = 5.2 Hz, 2H), 4.88 (d, *J* = 2.5 Hz, 2H), 2.67 (t, *J* = 2.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.8, 155.4, 136.0, 134.9, 133.8, 133.1, 132.6, 129.6, 122.6, 120.4, 112.9, 79.1, 75.8, 56.1, 16.4.

Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.90; H, 5.74; N, 5.23.



1-Methyl-3-(prop-2-ynyloxy)benzene (Table 1, Entry 9).

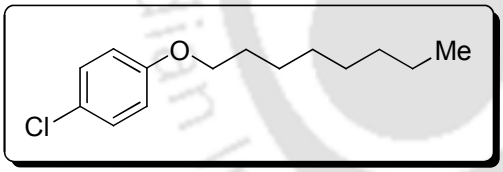
Yellow oil; yield: 75%.

R_f = 0.47 (EtOAc-hexane, 1:9).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.13 (t, *J* = 8.0 Hz, 1H), 6.75 (d, *J* = 7.6 Hz, 1H), 6.66-6.63 (m, 2H), 4.74 (d, *J* = 2.5 Hz, 2H), 2.53 (t, *J* = 2.5 Hz, 1H), 2.29 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.6, 140.0, 129.6, 120.8, 116.3, 112.5, 78.9, 75.5, 55.8, 21.6.

Anal. Calcd for C_7H_8O: C, 82.16; H, 6.89. Found: C, C, 82.22; H, 6.83.



1-Chloro-4-(octyloxy)benzene (Table 1, Entry 10).

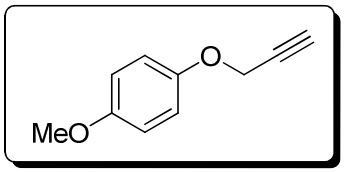
Yellow oil; yield: 70%.

R_f = 0.76 (Hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 9.2 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 3.91 (t, *J* = 6.4 Hz, 2H), 1.77-1.75 (m, 2H), 1.43-1.39 (m, 2H), 1.31-1.26 (m, 8H), 0.87(t, *J* = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ =157.9, 129.4, 125.5, 116.0, 68.5, 32.0, 29.6, 29.4, 29.4, 26.2, 22.9, 14.3.

Anal. Calcd for $C_{14}H_{21}ClO$: C, 69.84; H, 8.79. Found: C, 69.83; H, 8.81.



1-Methoxy-4-(prop-2-ynyloxy)benzene (Table 1, Entry 11).[12a]

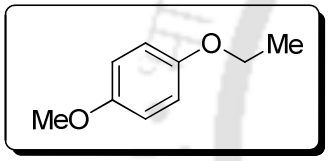
Colourless oil; yield: 68%.

R_f = 0.50 (Hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.94 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 4.66 (d, *J* = 2.5 Hz, 2H), 3.76 (s, 3H), 2.52 (t, *J* = 2.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.8, 150.7, 116.3, 115.1, 78.8, 74.7, 56.5, 56.0.

Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21. Found: C, 74.12; H, 6.16.



1-Ethoxy-4-methoxybenzene (Table 1, Entry 12).

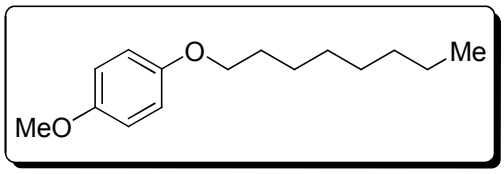
Colourless oil; yield: 67%.

R_f = 0.50 (Hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.94 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 4.01 (q, *J* = 6.8 Hz, 2H), 1.40 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.8, 150.7, 116.3, 115.1, 64.4, 56.0, 15.1.

Anal. Calcd for $C_9H_{12}O_2$: 71.03; H, 7.95. Found: C, 70.92; H, 7.91.



1-Methoxy-4-(octyloxy)benzene (Table 1, Entry 13).[12c]

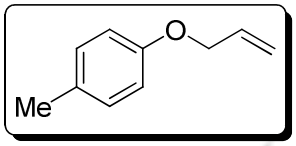
Colourless oil; yield: 70%.

R_f = 0.41 (Hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.90 (m, 4H), 4.03 (t, *J* = 6.8 Hz, 2H), 3.87 (s, 3H), 1.88-1.84, (m, 2H), 1.48-1.46 (m, 2H), 1.36-1.31 (m, 8H), 0.93. (t, *J* = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.9, 149.8, 113.0, 111.8, 68.9, 55.9, 31.9, 29.5, 29.3, 29.3, 26.1, 22.7, 14.2.

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.21; H, 10.21.



1-(Allyloxy)-4-methylbenzene (Table 1, Entry 14).[12d]

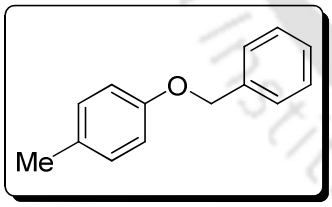
Colourless oil; yield: 70%.

R_f = 0.64 (Hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.07 (d, *J* = 8.4 Hz, 2H), 6.81 (d, *J* = 8.4 Hz, 2H), 6.11-6.03 (m, 1H), 5.41 (d, *J* = 11.2 Hz, 1H), 5.27 (d, *J* =10.4 Hz, 1H), 4.50 (m, 2H), 2.27 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.9 133.7, 130.3, 130.1, 117.7, 114.8, 69.1, 20.7.

Anal. Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 81.01; H, 8.14.



1-(Benzyloxy)-4-methylbenzene (Table 1, Entry 15).[12e]

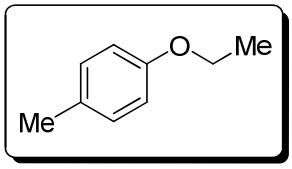
Yellow oil; yield: 89%.

R_f = 0.70 (Hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46-7.34 (m, 5H), 7.12 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 5.06 (s, 2H), 2.31 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.3, 137.4, 130.3, 130.0, 128.7, 128.1, 127.6, 114.9, 70.2, 20.7.

Anal. Calcd for $C_{14}H_{14}O$: C 84.81, H 7.72. Found: C 84.79, H 7.75.



1-(Ethoxy)-4-methylbenzene (Table 1, Entry 16).[12f]

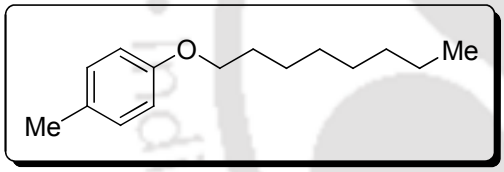
Colourless oil; yield: 87%.

R_f = 0.69 (Hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.07 (d, *J* = 8.4 Hz, 2H), 6.80 (d, *J* = 8.4 Hz, 2H), 4.01 (q, *J* = 6.8 Hz, 2H), 2.27 (s, 3H), 1.40 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.9, 130.1, 129.8, 114.5, 63.6, 20.6, 15.1.

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.34; H, 8.85.



1-Methyl-4-(octyloxy)benzene (Table 1, Entry 17).[12g]

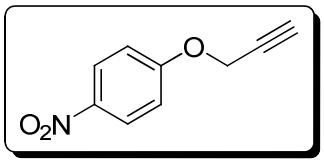
Colourless oil; yield: 89%.

R_f = 0.68 (Hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.09 (d, *J* = 8.4 Hz, 2H), 6.82 (d, *J* = 8.4 Hz, 2H), 3.94 (t, *J* = 6.4 Hz, 2H), 2.29 (s, 3H), 1.78-1.76 (m, 2H), 1.45-1.40 (m, 2H), 1.35-1.30 (m, 8H), 0.91(t, *J* = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.2, 130.3, 130.0, 114.5, 68.2, 32.0, 29.6, 29.5, 29.48, 26.3, 22.9, 20.7, 14.3.

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.73; H, 10.96.



1-Nitro-4-(prop-2-ynyloxy)benzene (Table 1, Entry 18).[12h]

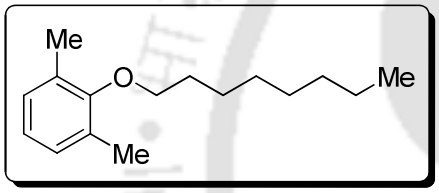
Pale yellow solid; yield 90%.

R_f = 0.54 (Ethyl acetate : Hexane 1:10)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.18 (d, *J* = 9.2 Hz, 2H), 7.03 (d, *J* = 9.2 Hz, 2H), 4.76 (d, *J* = 2.5 Hz, 2H), 2.56 (t, *J* = 2.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.5, 140.4, 125.9, 115.7, 78.1, 76.3, 56.8.

Anal. Calcd for $C_7H_9NO_3$: C, 61.02; H, 3.98; N, 7.91. Found: C, 60.97; H, 3.95; N, 7.87.



1,3-Dimethyl-2-(octyloxy)benzene (Table 1, Entry 19).

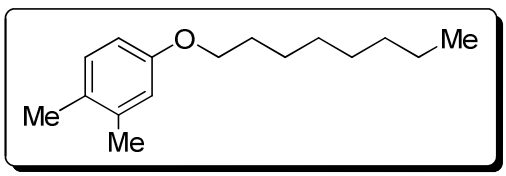
Yellow oil; yield: 85%.

R_f = 0.68 (Hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.01 (d, *J* = 8.0 Hz, 2H), 6.92 (t, *J* = 8.0 Hz, 1H), 3.77 (t, *J* = 6.4 Hz, 2H), 2.28 (s, 6H), 1.82-1.78 (m, 2H), 1.52-1.48 (m, 2H), 1.36-1.33 (m, 8H), 0.91(t, *J* = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.4, 131.6, 129.4, 127.1, 68.4, 32.1, 29.6, 29.5, 26.4, 22.9, 20.7, 16.4, 14.3.

Anal. Calcd (%) for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 81.95; H, 11.20.



1,2-Dimethyl-4-(octyloxy)benzene (Table 1, Entry 20).

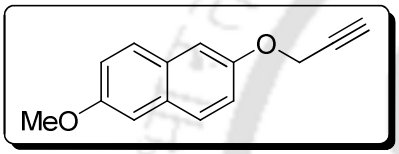
Colourless oil; yield: 89%.

R_f = 0.67 (Hexane).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.01 (d, *J* = 8.4 Hz, 1H), 6.69 (s, 1H), 6.63 (d, *J* = 8.4 Hz, 1H), 3.91 (t, *J* = 6.8 Hz, 2H), 2.21 (s, 3H), 2.17(s, 3H), 1.76-1.72 (m, 2H), 1.44-1.40 (m, 2H), 1.30-1.26 (m, 8H), 0.89 (t, *J* = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.5, 137.8, 130.4, 128.5, 116.4, 111.6, 68.2, 32.0, 29.6, 29.5, 26.3, 22.9, 20.2, 19.0, 14.3.

Anal. Calcd for $C_{16}H_{26}O$: C, 81.99; H, 11.18. Found: C, 81.96; H, 11.15.



2-Methoxy-6-(prop-2-ynyloxy)naphthalene (Table 1, Entry 21).

Yellow oil; yield: 75%.

R_f = 0.71 (EtOAc-hexane, 3:17).

^{1}H NMR (400 MHz, $CDCl_3$/DMSO-d_6 (3:1)): δ = 7.49 (d, *J* = 8.4 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.03-6.94 (m, 4H), 4.66 (d, *J* = 2.5 Hz, 2H), 3.77 (s, 3H), 2.52 (t, *J* = 2.5 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$/DMSO-d_6 (3:1)): δ = 155.6, 152.4, 131.1, 129.0, 128.0, 128.7, 118.9, 117.8, 109.9, 105.9, 79.1, 75.0, 56.5, 55.4.

Anal. Calcd for $C_{11}H_{10}O_2$: C, 79.22; H, 5.70. Found: C, C, 79.18; H, 5.72.

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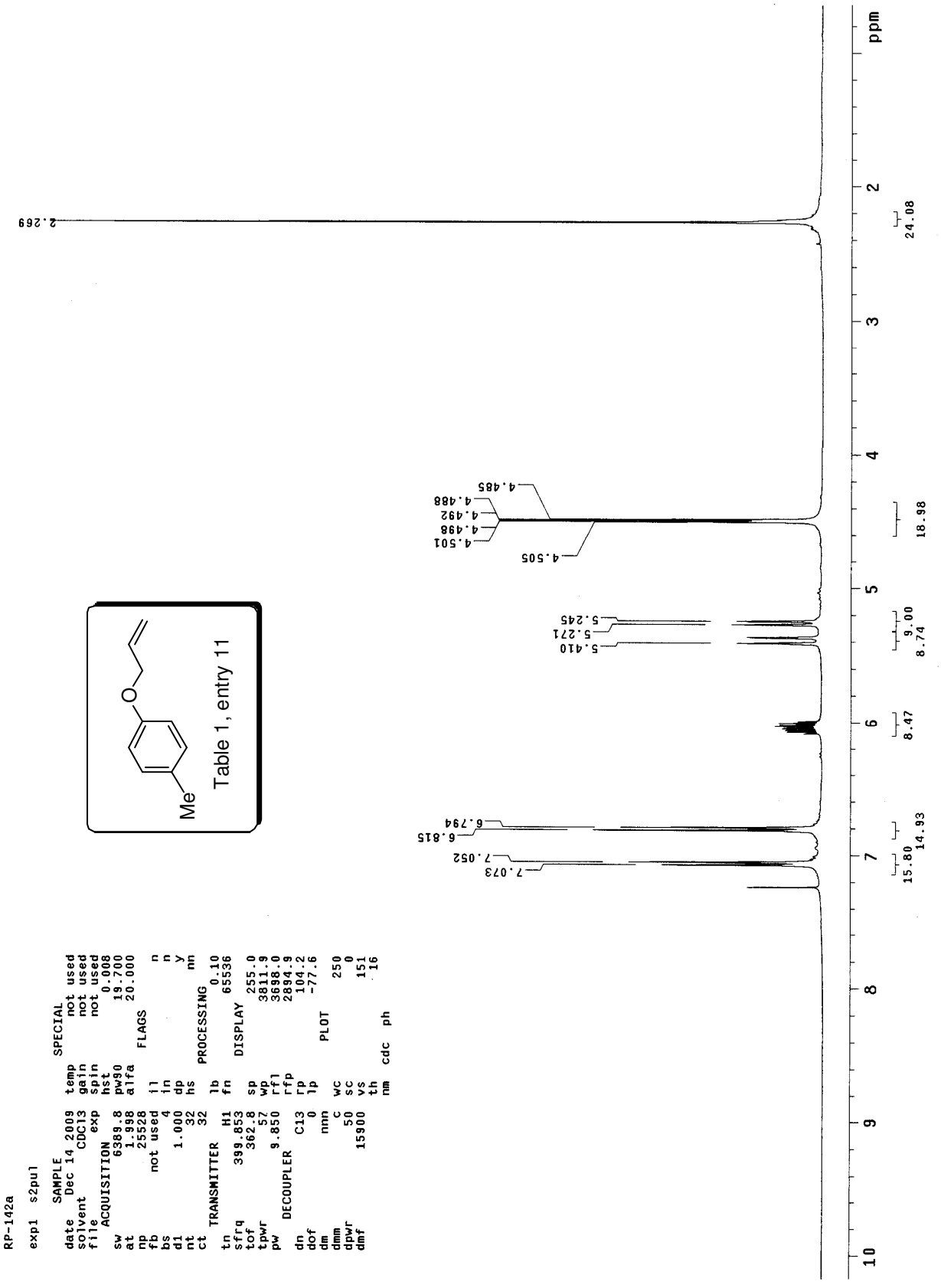

.P-142a

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		pw90	18.600
ACQUISITION		alfa	20.000
sw	25125.6	FLAGS	
at	1.199	il	n
np	60270	in	n
fb	13800	dp	y
bs	16	hs	nn
d1	1.000	PROCESSING	
nt	10000	lb	2.00
ct	10000	fn	65536
TRANSMITTER		DISPLAY	
tn	C13	sp	-1503.9
sfrq	100.554	wp	25124.9
tof	1536.3	rfl	9269.5
tpwr	61	rfp	7764.9
pw	9.300	rp	-20.4
DECOUPLER		lp	-397.8
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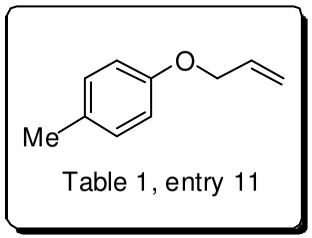
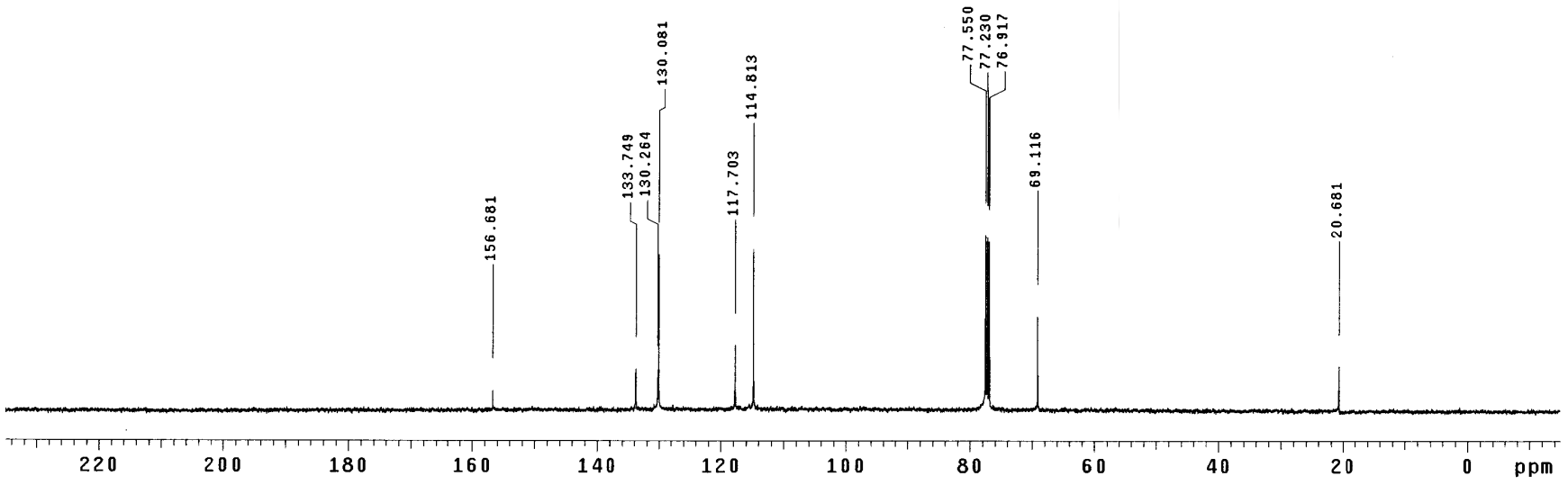
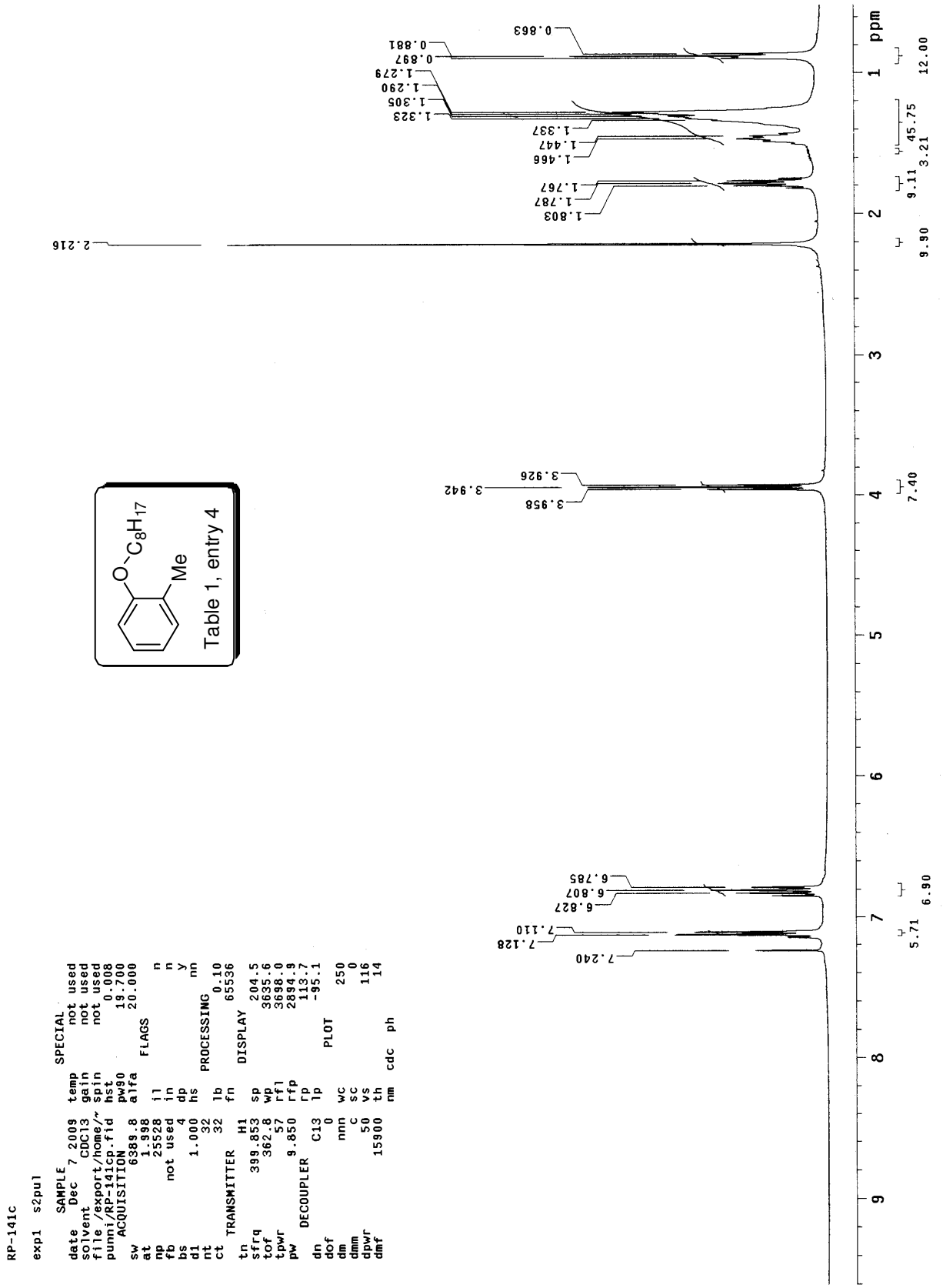


Table 1, entry 11





TH-1181_08612202

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bs	16		
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d1	0	wbs	
tof	0	wnt	
nt	15000		
ct	15000		
alock	n		
gain	not used		
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dp	y		
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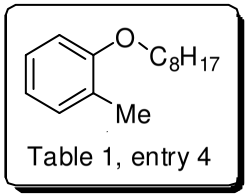
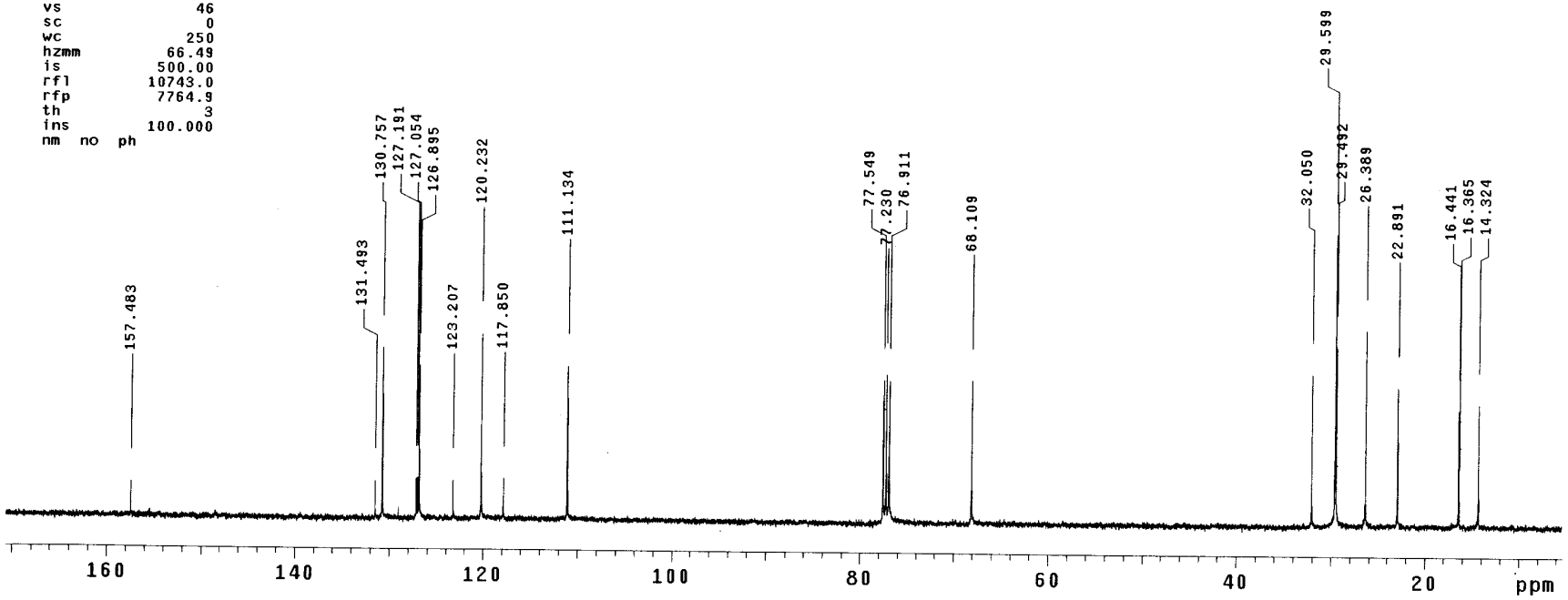


Table 1, entry 4



Copper-Catalyzed Synthesis of *N*-Substituted Benzo[*d*]isothiazol-3(2*H*)-ones

4.1 Introduction

N-Substituted benzo[*d*]isothiazol-3(2*H*)-ones and their analogues have attracted considerable interest in biological and chemical sciences due to their promising antibacterial and antifungal properties (Figure 1).[1,2] They have also been studied as potential antithrombotic agents,[3a] antipsycotic agents[3b] as well as models for the development of metallothionein inspired molecular pincers.[3c] Furthermore, they are being investigated as potential inhibitors of phosphomannose[11] and NADPH-oxidase.[3e] In addition, benzo[*d*]isothiazol-3(2*H*)-ones have been utilized for the development of glutamate receptor subtype-2.[3f]

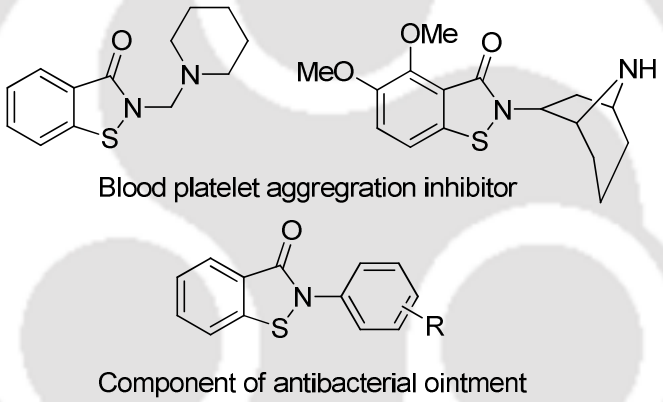
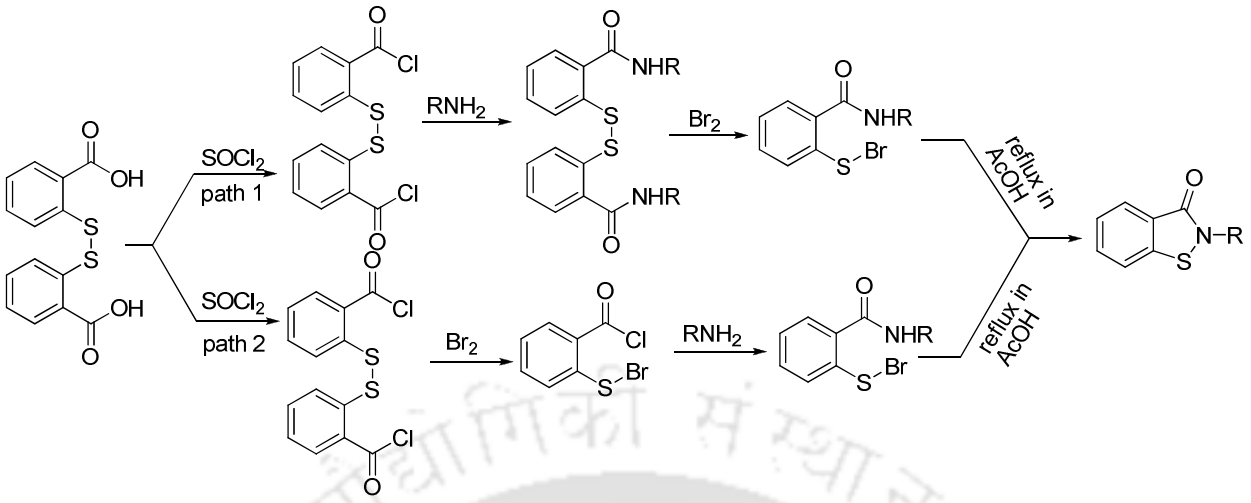


Figure 1. Examples of biologically and industrially important benzo[*d*]isothiazol-3(2*H*)-ones.

4.2 Classical Synthesis of *N*-Substituted Benzo[*d*]isothiazol-3(2*H*)-ones

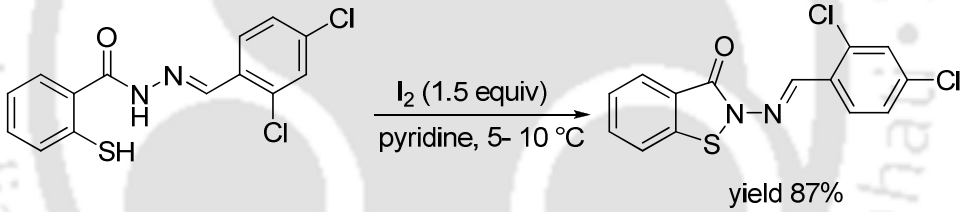
The synthesis of *N*-substituted benzo[*d*]isothiazol-3(2*H*)-ones discovered by Gait and co-workers uses 2,2'-dithiodibenzoyl chloride which was either first oxidized to 2,2'-dithiodibenzoyl chloride, followed by diamidation and cyclization (path1) or first amidation to form *bis*(2-carbamoylphenyl)disulfide, followed by cyclization (path 2) (Scheme 1).[4a]



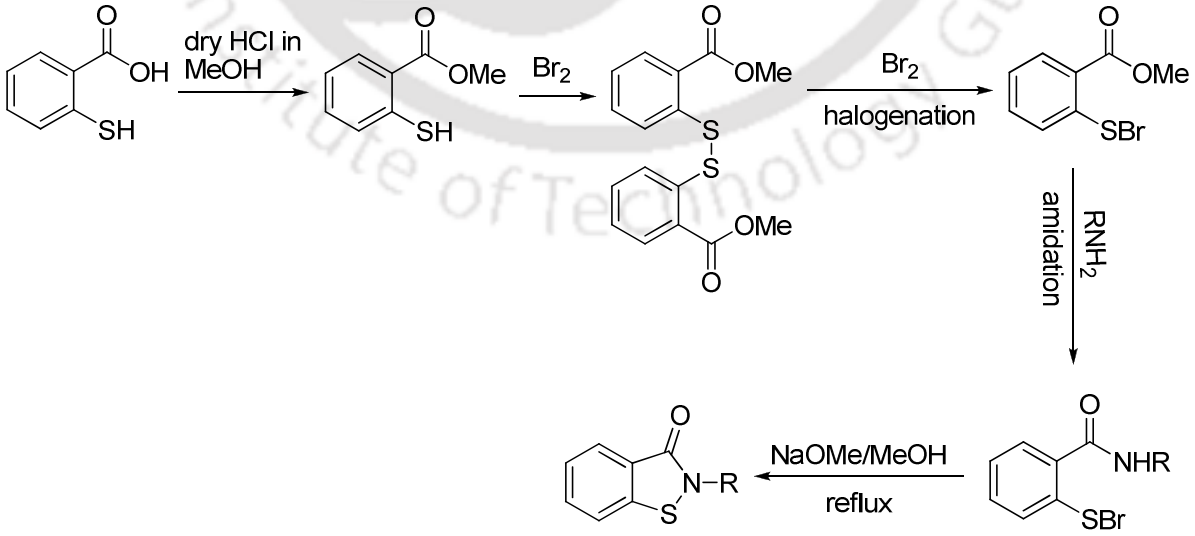
Scheme 1

4.3 Methods for Synthesis of *N*-Substituted Benzo[*d*]isothiazol-3(2*H*)-ones

Schroeder and co-workers observed the formation of *N*-benzalaminobenzo[*d*]isothiazol-3(2*H*)-one from the corresponding benzalthiosalicylhydrazide when it is treated with an excess of iodine in pyridine at 5-10 °C (Scheme 2).[4b]



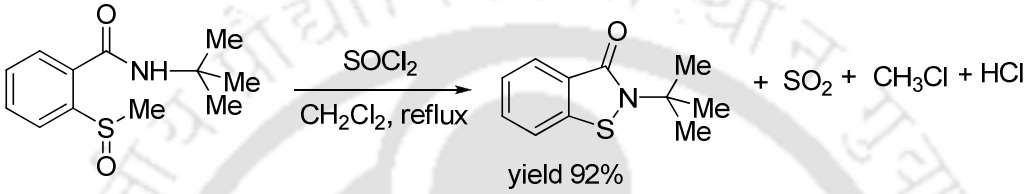
Scheme 2



Scheme 3

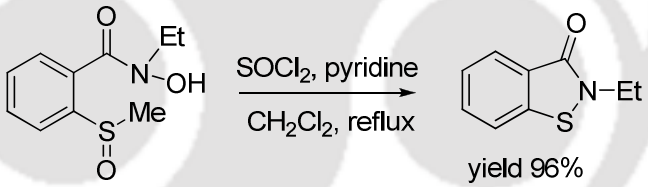
Grivas demonstrated a modified procedure for the synthesis of *N*-substituted benzisothiazol-3-ones from 2-thiobenzoic acid, which is converted into the corresponding methyl-2-thiobenzoate. The resulting methyl-2-thiobenzoate was then oxidized with bromine to form dimethyl 2,2'-disulfanediyldibenzoate followed by halogenation, amidation and finally cyclization by refluxing with sodium methoxide in methanol (Scheme 3).[4c]

Uchida and co-workers studied the conversion of *N*-alkyl and *N*-aryl-(2-methylsulfinyl)-benzamides to the corresponding benzo[*d*]isothiazol-3-ones by refluxing with thionyl chloride in dichloromethane (Scheme 4).[4d]



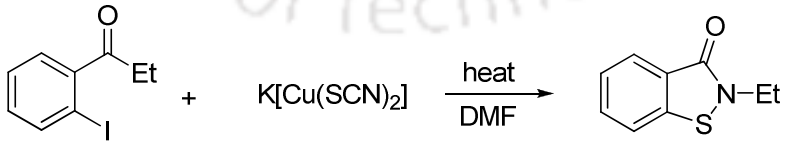
Scheme 4

Similarly, *N*-alkyl- or *N*-aryl-*N*-[(2-methylthio)benzoyl] hydroxylamines could be converted into the corresponding benzo[*d*]isothiazol-3-ones by refluxing them with thionyl chloride in either dichloromethane or carbon tetrachloride (Scheme 5).[4d]



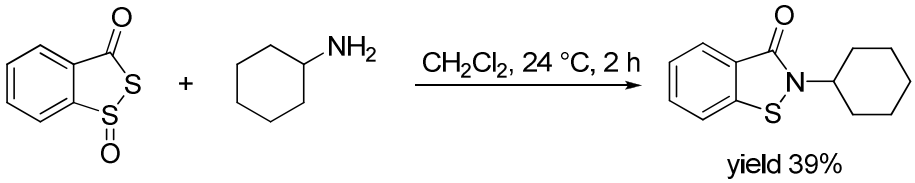
Scheme 5

Abe and co-workers observed the cyclization of *N*-ethyl-2-iodobenzamide into the corresponding benzo[*d*]isothiazol-3-one by treatment with stoichiometric amount of potassium [di(thiocyanato)copper(II)] in hot dimethyl formamide (Scheme 6).[4f]



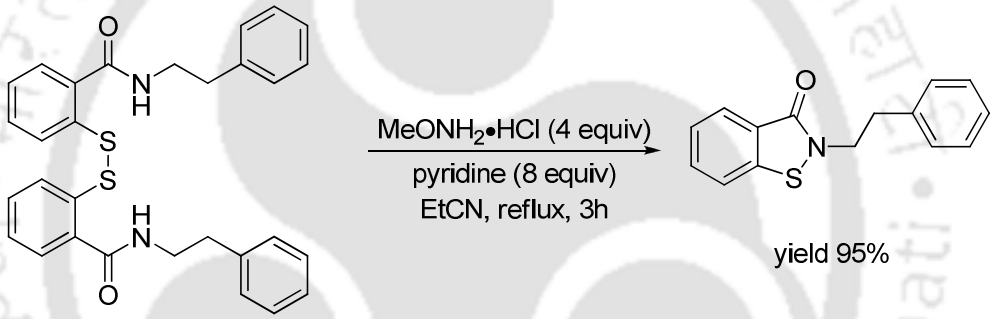
Scheme 6

Gates and co-workers described a general synthesis of *N*-substituted benzo[*d*]isothiazol-3-ones from 1,2-dithiolan-1-oxides by treating them with an alkyl amine or a substituted aniline in the dichloromethane at 24 °C for 2 h (Scheme 7).[4g]



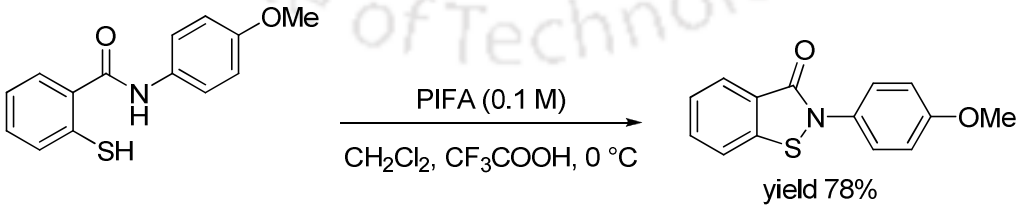
Scheme 7

Shimizu and co-workers synthesized benzo[*d*]isothiazol-3-ones from the corresponding 2,2'-dithiobenzamides by refluxing with an excess of *O*-methylhydoxyamine in propionitrile (Scheme 8).[4k]



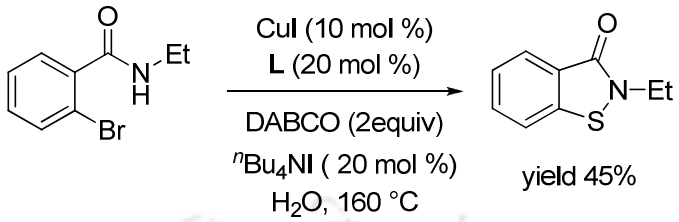
Scheme 8

Recently, Sanmartin and co-workers synthesized *N*-aryl benzo[*d*]isothiazol-3-ones from the corresponding *N*-substituted 2-mercaptobenzamides by treating them with [phenyliodine(III)-bis(trifluoroacetate)] (PIFA) as oxidant in dichloromethane at 0 °C (Scheme 9).[4l]



Scheme 9

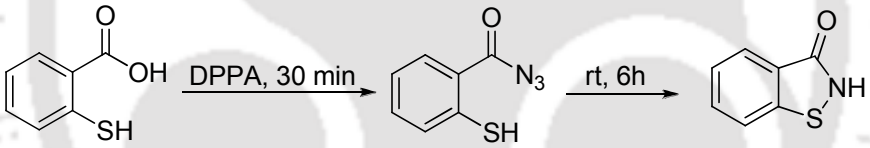
Xi and co-workers described the synthesis of *N*-alkyl benzo[*d*]isothiazol-3-ones from the corresponding *N*-alkyl-2-bromobenzamides using a combination of CuI and 1,10-phenanthroline in water at 160 °C (Scheme 10).[4m]



Scheme 10

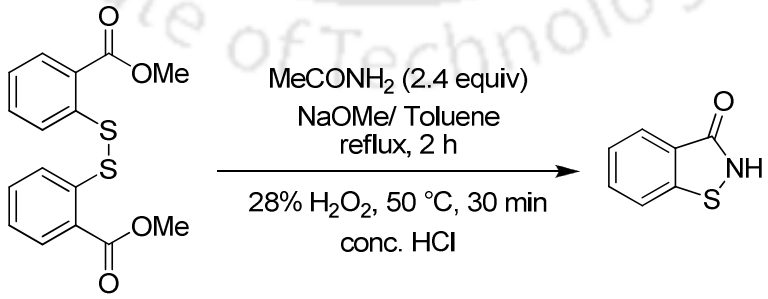
Besides the synthesis of *N*-substituted benzo[*d*]isothiazol-3-ones, there exist in literature, a few reports of the synthesis of unsubstituted benzo[*d*]isothiazol-3-ones. A few of them are detailed below.

Kajiwara and co-workers developed a protocol for the synthesis of benzo[*d*]isothiazol-3(2*H*)-one from 2-mercaptobenzoic acid by treating with diphenyl phosphoryl azide (DPPA) and then stirring at room temperature (Scheme 11). [4i]



Scheme 11

Nam and co-workers were able to synthesize benzo[*d*]isothiazol-3(2*H*)-one from 2,2'-dithiobenzoate by treating with an excess of acetamide and sodium methoxide in toluene with a yield of 90% (Scheme 12).[4j]

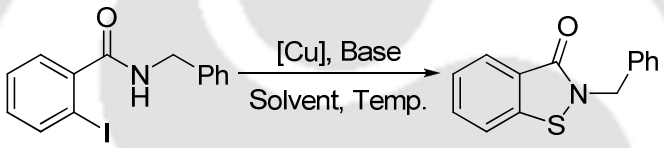


Scheme 12

4.4 Present Study

In recent times, transition metal catalyzed cross-coupling reaction has become an important tool for the synthesis of carbon-heteroatom bond formation.[5] Copper-catalyzed formation of organosulfur compounds have been widely explored.[6] In this contribution, we report the synthesis of 2-substituted benzo[*d*]isothiazol-3(2*H*)-ones from 2-halo-*N*-substituted benzamides using CuCl as a catalyst and S powder in the presence of a base. The reaction conditions for this cyclization were optimized using *N*-benzyl-2-iodobenzamide as a model substrate (Table 1). After screening through a number of metal salts and bases in different solvents at varied temperatures, we found that a 10 mol % of CuCl in presence of 1 equiv of K_2CO_3 in DMF at 75 °C as the ideal condition for this transformation.

Table 1. Optimization of Reaction Conditions.



Entry	Catalyst	Solvent	Sulfur source	Temp. (°C)	Conv. (%)[a,b]
1	CuCl	DMF	S powder	75	78
2	CuCl	DMSO	S powder	75	70
3	CuCl	toluene	S powder	75	n.d.
4	CuBr	DMF	S powder	75	70
5	CuI	DMF	S powder	75	65
6	$Cu(OAc)_2 \cdot H_2O$	DMF	S powder	75	45
7	CuCl	DMF	Thiourea	75	51
8	CuCl	DMF	S powder	70	60
9	-	DMF	S powder	75	n.d..
10	CuCl	DMF	S powder	100	60[c]

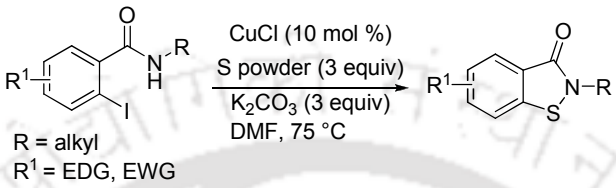
[a] Determined by 400 MHz ^{1}H NMR.

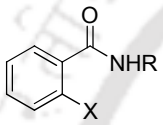
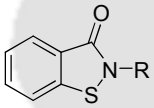
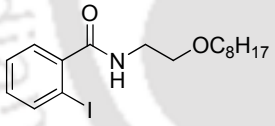
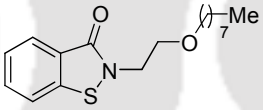
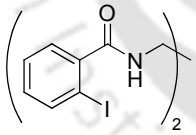
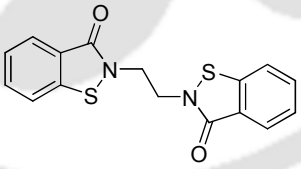
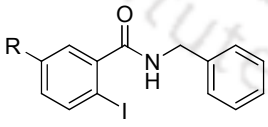
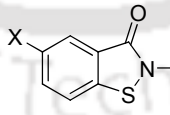
[b] *N*-Benzyl-2-iodobenzamide (0.5 mmol), Cu source (10 mol %), sulfur powder (1.5 mmol) and K_2CO_3 (1.5 mmol) were stirred in 1 mL of DMF at 75 °C for 6 h under N_2.

[c] *N*-Benzyl-2-bromobenzamide (0.5 mmol), CuCl (10 mol %), sulfur powder (1.5 mmol) and K_2CO_3 (1.5 mmol) were stirred in 1 mL of DMF at 100 °C for 6 h under N_2. n.d.= not detected.

The scope of the procedure was investigated for the synthesis of a series of *N*-alkyl benzo[*d*]isothiazol-3(2*H*)-ones (Table 2). 2-Iodobenzamides having *N*-butyl, *N*-cyclohexyl, *N*-isopropyl, *N*-(1-phenylethyl) and *N*-(3,4-dimethoxyphenethyl) substituents proceeded reactions to give the corrosponding *N*-alkyl benzo[*d*]isothiazol-3(2*H*)-ones in 83-93% yield (entries 1-5).

Table 2. Copper-Catalyzed Synthesis of 2- Alkylbenzo[*d*]isothiazol-3(2*H*)-ones.

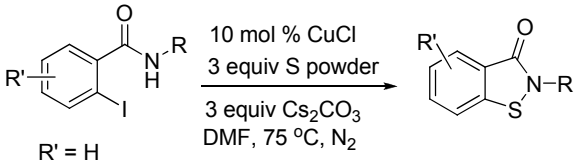


Entry	Substrate	Product	Time (h)	Yield (%)[a,b]
1	 X = Br, I	 R = n-butyl	9	93
2		R = cyclohexyl	8	95
3		R = isopropyl	8	90
4		R = 2-phenylethyl	8	87
5		R = 3,4-dimethoxy-phenethyl	8	83
6			10	90
7			12	81[c]
				
8		R = OMe	16	67
9		R = OC_8H_{17}	16	72

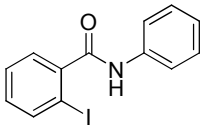
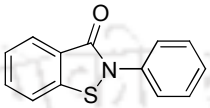
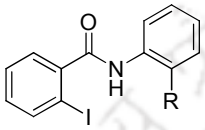
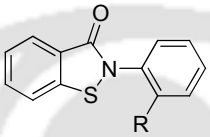
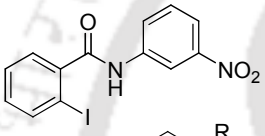
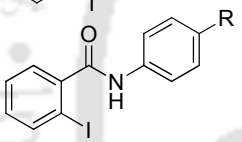
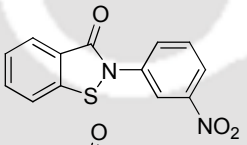
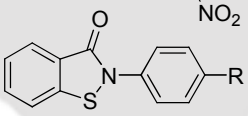
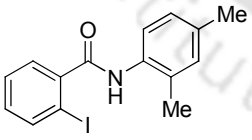
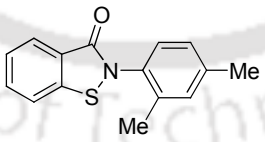
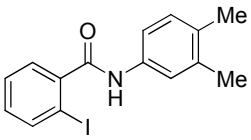
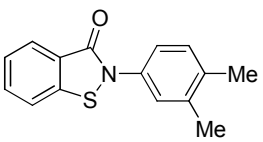
[a] *N*-Substituted-2-iodobenzamide (0.5 mmol), CuI (10 mol %), sulfur powder (1.5 mmol) and K_2CO_3 (1.5 mmol) were stirred in 1 mL of DMF at 75 °C under N_2.

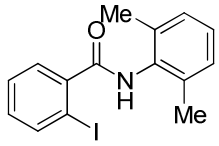
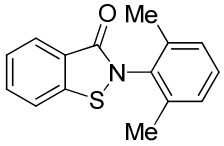
[b] CuCl (20 mol%), sulfur powder (3 mmol) and K_2CO_3 (3 mmol) were used.

Table 3. Copper-Catalyzed Synthesis of *N*- Arylbenzo[*d*]isothiazol-3(2*H*)-ones.



R' = H
R = aryl

Entry	Substrate	Product	Time (h)	Yield (%)[a]
1			14	90
2	 R= OMe		10	84
3	R= Me		12	88
4	 	 	10	n.d.
5	R = Cl		18	85
6	R = OMe		10	89
7	R = Me		12	93
8	R = NO_2		10	n.d.
9	R = N_2Ph		21	63
10			14	92
11			14	91

12			14	86

[a] *N*-Substituted-2-iodobenzamide (0.5 mmol), CuCl (10 mol %), sulfur powder (1.5 mmol) and Cs_2CO_3 (1.5 mmol) were stirred at 75 °C in DMF (1 mL) under N_2. n.d. = not detected.

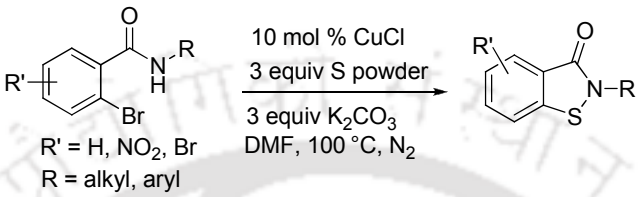
Similarly, 2-iodo-*N*-(2-(octyloxy)ethyl)benzamide and *N,N'*-(ethane-1,2-diyl)-bis(2-iodobenzamide) could be transformed into the respective *N*-alkyl benzo[*d*]isothiazol-3(2*H*)-ones in 90% and 81% yield, respectively (entries 6 and 7). Furthermore, *N*-benzyl-2-iodobenzamides having 5-methoxy and 5-octyloxy substituents underwent reactions to afford the target products in 67% and 72% yield respectively (entries 8 and 9).

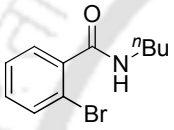
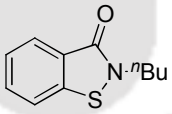
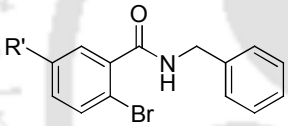
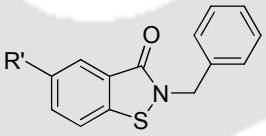
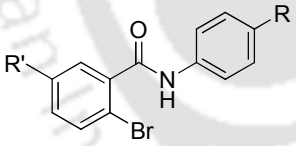
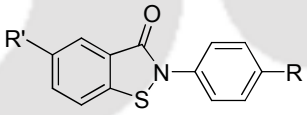
Next, the synthesis of *N*-aryl benzo[*d*]isothiazol-3(2*H*)ones was studied (Table 3). These reactions were found to be more effective using Cs_2CO_3 compared to that of K_2CO_3. Thus, 2-iodobenzamides with *N*-phenyl, *N*-(2-methoxphenyl), *N*-(2-methylphenyl), *N*-(4-chlorophenyl), *N*-(4-methoxyphenyl), *N*-(4-methylphenyl) and 4-((phenyldiazenyl)phenyl) substituents proceeded reactions to afford the desired products in 63-90% yield (entries 1-3, 5-7 and 9). In contrast, the substrates having *N*-(3-nitrophenyl) and *N*-(4-nitrophenyl) substituents were decomposed and the target compounds were not obtained (entries 4 and 8). However, *N*-substituted 2-iodobenzamides having *N*-(2,4-dimethylphenyl), *N*-(2,6-dimethylphenyl) and *N*-(3,4-dimethylphenyl) substituents proceeded reactions with 86-92% yield (entries 10-12).

To reveal the reactivity of the other aryl halides, the substrates with 2-bromo substituent (Table 4) and 2-chloro substituent (Table 5) were employed under the reaction conditions. Thus, *N*-butyl-2-bromobenzamide underwent reaction with 60% yield, whereas *N*-benzyl-2-bromo-5-nitrobenzamide and *N*-benzyl-2-bromo-5-bromobenzamide proceeded reactions with 78% and 90% yield, respectively (Table 4, entries 2 and 3). Similarly, *N*-aryl-2-bromobenzamides underwent reactions to give the corresponding benzo[*d*]isothiazol-3(2*H*)-ones in moderate yields. For examples, 2- chlorobenzamides having *N*-alkyl groups, *N*-benzyl-2-chloro-5-nitrobenzamide and *N*-benzyl-2-chloro-5-bromobenzamide, gave the target molecules in 35% and 21% yield, respectively (Table 5, entries 1 and 2), whereas *N*-(4-methoxyphenyl)-2-chloro-5-nitrobenzamide and *N*-(4- methylphenyl)-2-chloro-5-nitrobenz-amide proceeded reactions at 135 ^{o}C with 45% and 30% yield, respectively (Table 5, entries 3 and 4). Crystallization of *N*-(4-

methoxy)phenylbenzo[*d*]isothiazol-3(2*H*)-one in $CHCl_3$ yielded crystals whose structure was determined using a single crystal X-ray analysis (Figure 2).

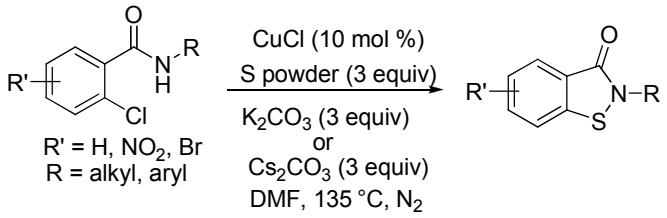
Table 4. Synthesis of *N*-Alkyl benzo[*d*]isothiazol-3(2*H*)-ones from *N*-Substituted-2-bromo-benzamides.

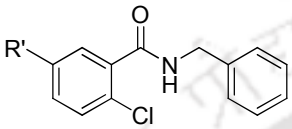
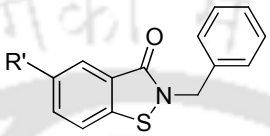
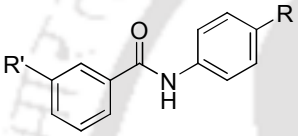
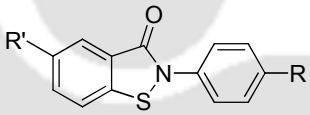


Entry	Substrate	Product	Time (h)	Yield (%)[a]
1			9	60
2	 R' = NO_2		10	78
3	R' = Br		10	90
4	 R' = H, R = Cl		18	50
5	R' = H, R = OMe		10	54
6	R' = NO_2, R= Me		10	71

[a] *N*-Substituted-2-bromobenzamide (0.5 mmol, CuCl (10 mol %), sulfur powder (1.5 mmol) and K_2CO_3/Cs_2CO_3 (1.5 mmol) were stirred at 100 °C in DMF (1 mL) under N_2.

Table 5. Synthesis of *N*-Substituted Benzo[*d*]isothiazol-3(2*H*)-ones from *N*-Substituted-2-chlorobenzamides.



Entry	Substrate	Product	Time (h)	Yield (%)[a]
1		 R' = NO_2	28	35
2		R' = Br	28	21
3		 R' = NO_2, R= Me	28	30
4		R' = NO_2, R=OMe	24	45

[a] N-Substituted-2-chlorobenzamide (0.5 mmol, CuCl (10 mol %), sulfur powder (1.5 mmol) and K_2CO_3/Cs_2CO_3 (1.5 mmol) were stirred at 135 °C in DMF (1 mL) under N_2.

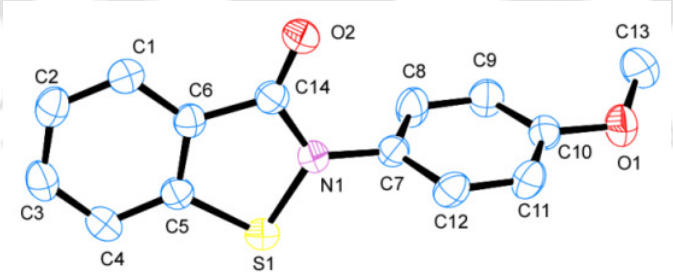
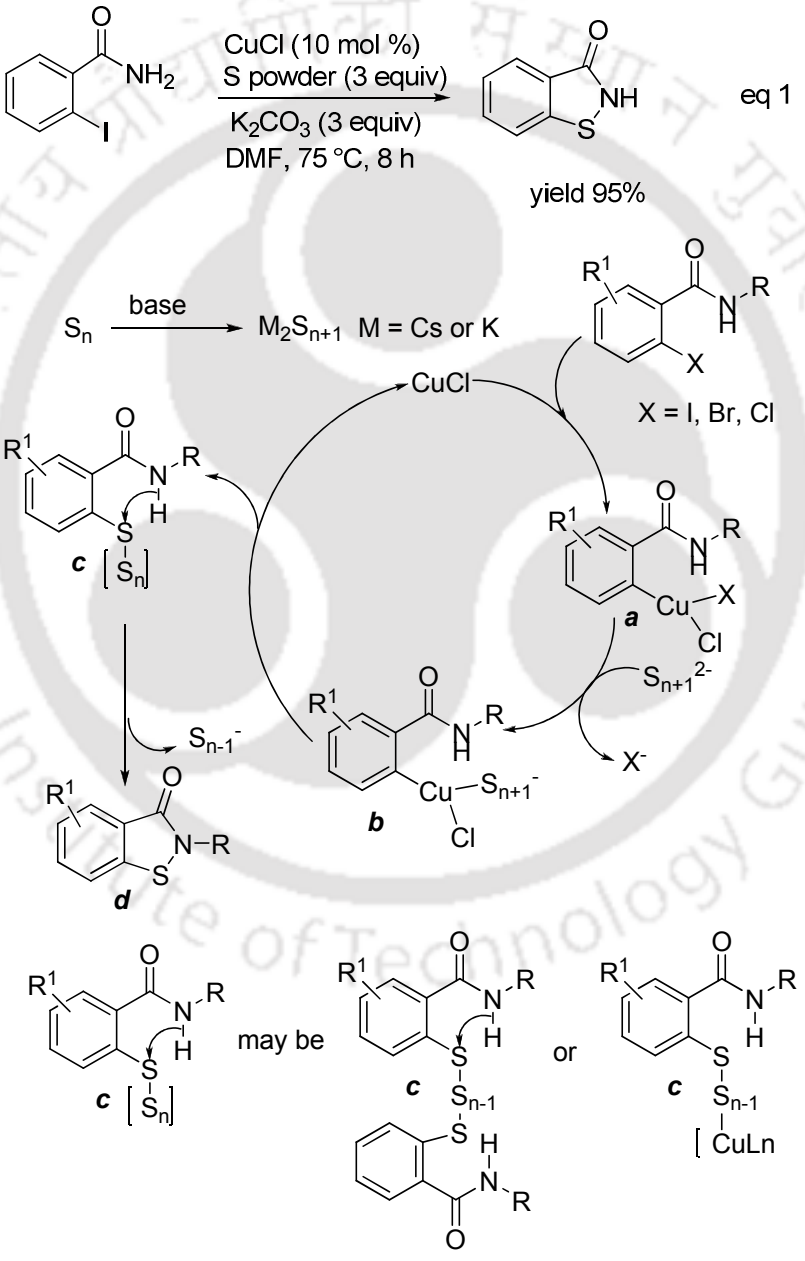


Figure 2. ORTEP diagram of 2-(4-methoxyphenyl)benzo-[*d*]isothiazol-3(2*H*)-one**.** Thermal ellipsoids are drawn at a 40% probability level. Hydrogen atoms have been omitted for clarity

Using this protocol 2-iodobenzamide could be converted into benzo[*d*]isothiazol-3(2*H*)-one in 95% yield (eq 1). Regarding the mechanism, the rate of the reaction was not affected using

TEMPO, which suggests that the process may not involve a radical intermediate. Thus, dispropornation of the sulfur with a trace of moisture can give sulfide anion that could react with CuCl and sulfur to form $MCuS_{n+1}$ (M = K or Cs). Oxidative addition of CuS_{n+1}^- with the 2-halobenzamide may lead to the formation of copper(III)-species ***a*** that may undergo reaction with the polysulfide anion[7] to form the intermediate ***b***. Reductive elimination of ***b*** may give ***c*** that could transform into the target molecule ***d*** in the presence of base *via* nucleophilic substitution (Scheme 11).[4f]



Scheme 11

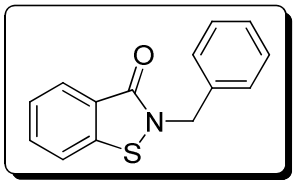
In summary, copper-catalyzed synthesis of *N*-substituted benzoisothiazol-3-ones has been developed from *N*-substituted 2-halobenzamides and sulfur powder *via C-S* cross-coupling reaction followed by *N-S* bond formation. The protocol is general and efficient and yields the target heterocycles in high yields.

4.5 Experimental Conditions

General Information. CuCl (98%) and sulfur powder (97%) were purchased from Rankem and $Cu(OAc)_2 \cdot H_2O$ (98%) was purchased from Merck and used without further purification. 2-Iodobenzoic acid (98%), 2-bromobenzoic acid (97%) and anilines were purchased from Aldrich. Column chromatography was performed with Rankem silica gel (60-120 mesh). The substituted 2-halobenzamides were prepared according to the reported procedures.^{1}NMR (^{1}H and ^{13}C) spectra were recorded with a Varian 400 spectrometer. Melting points were determined with a Büchi B-545 apparatus and are uncorrected. X-Ray data were collected on a Bruker SMART APEX equipped with a CCD area detector using Mo Kα radiation. The structure was solved by direct method using *SHELLX-97* (Göttingen, Germany). Elemental analysis was carried out using Perkin Elmer-2400 CHNS analyzer.

General Procedure for the Preparation of *N*-Substituted Benzo[*d*]isothiazol-3(2*H*)-ones. An oven dried round bottom flask (10 mL) was charged with *N*-substituted 2-halobenzamide (0.5 mmol), CuCl (10 mol %), sulfur powder (1.5 mmol) and K_2CO_3 or Cs_2CO_3 (1.5 mmol) in DMF (1 mL) under nitrogen atmosphere. The resultant mixture was stirred at 75-135 °C under nitrogen balloon for the appropriate time. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. The reaction mixture was then cooled to room temperature and diluted with ethyl acetate (10 mL). The organic layer was separated and washed with brine (1 x 5 mL) and water (3 x 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using hexane and ethyl acetate as eluent.

Characterization Data of 2-Substituted Benzo[*d*]isothiazol-3(2*H*)-ones



***N*-Benzylbenzo[*d*]isothiazol-3(2*H*)-one[4c] (Table 1, Entry 1).**

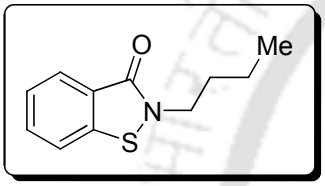
Colorless solid; yield: 88%; mp 88-89 °C (lit.[9a] 89 °C);

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.99 (d, *J* = 7.6 Hz, 1H), 7.49 (t, *J* = 7.2 Hz, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.33-7.23 (m, 6H), 4.96 (s, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 165.5, 140.5, 136.3, 131.9, 128.9, 128.5, 128.4, 126.9, 125.6, 124.5, 120.5, 47.6.

FT-IR (KBr): 3078, 3022, 2962, 2923, 1667, 1592, 1445, 1336, 1261, 1243, 1184, 1064, 1029 cm^{-1}.

Anal Calcd for $C_{14}H_{11}NOS$: C, 69.68; H, 4.59; N, 5.80; S, 13.29. Found: C, 69.64; H, 4.56; N, 5.83; S, 13.31.



***N*-Butylbenzo[*d*]isothiazol-3(2*H*)-one[9b] (Table 2, Entry 1).**

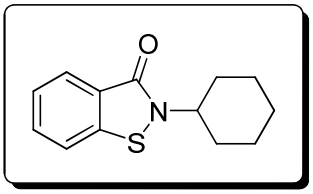
Yellow oil; yield: 93%.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.01 (d, *J* = 8.0 Hz, 1H), 7.58-7.50 (m, 2H), 7.36 (t, *J* = 7.2 Hz, 1H), 3.88 (t, *J* = 7.2 Hz, 2H), 1.75 (t, *J* = 7.2 Hz, 2H), 1.71-1.33 (m, 2H), 0.95 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 165.5, 140.3, 131.7, 126.8, 125.6, 125.2, 120.4, 43.8, 31.7, 19.9, 13.8.

FT-IR (neat): 2962, 2857, 1682, 1490, 1449, 1261, 1091 cm^{-1}.

Anal Calc for $C_{11}H_{13}NOS$: C, 63.74; H, 6.32; N, 6.76; S, 15.47, Found: C, 63.71; H, 6.35; N, 6.73; S, 15.50.



***N*-Cyclohexylbenzo[*d*]isothiazol-3(2*H*)-one[9a] (Table 2, Entry 2).**

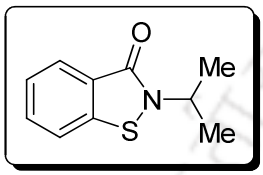
Colorless solid; yield: 95%; mp = 86-87 °C (lit.[9a] 87-88 °C).

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.01 (d, *J* = 8.0 Hz, 1H), 7.54-7.50 (m, 1H), 7.36-7.31 (m, 2H), 4.59-4.53 (m, 1H), 2.01 (d, *J* = 10.4 Hz, 1H), 1.85 (d, *J* = 12.8 Hz, 2H), 1.71-1.67 (m, 1H), 1.55-1.38 (m, 5H), 1.21-1.12 (m, 1H)

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 164.9, 140.4, 131.5, 126.6, 125.6, 125.4, 120.5, 53.3, 33.06, 25.7, 25.4.

FT-IR (KBr): 2929, 2854, 1651, 1448, 1332, 1305, 1262, 1240, 1210, 1191, 1149, 1062 cm^{-1}.

Anal. Calcd for $C_{13}H_{15}NOS$: C, 66.92; H, 6.48; N, 6.02; S, 13.74. Found: C, 66.95; H, 6.46; N, 6.00; S, 13.76.



***N*-Isopropylbenzo[*d*]isothiazol-3(2*H*)-one[9d] (Table 2, Entry 3).**

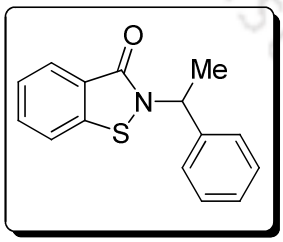
Yellow oil; 93% yield.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.01 (d, *J* = 7.6 Hz, 1H), 7.57-7.54 (m, 1H), 7.36 (t, *J* = 6.4 Hz, 2H), 5.01 (sep, *J* = 6.0 Hz, 1H), 1.40 (d, *J* = 6.4 Hz, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 164.9, 140.1, 131.5, 126.4, 125.5, 125.4, 120.5, 46.1, 22.2.

FT-IR (neat): 2935, 2851, 1641, 1447, 1332, 1239, 1192, 1034 cm^{-1}.

Anal. Calcd for $C_{10}H_{11}NOS$: C, 62.15; H, 5.74; N, 7.25; S, 16.59, Found: C, 62.15; H, 5.74; N, 7.25; S, 16.59.



***N*-(1-Phenylethyl)benzo[*d*]isothiazol-3(2*H*)-one (Table 2, Entry 4).**

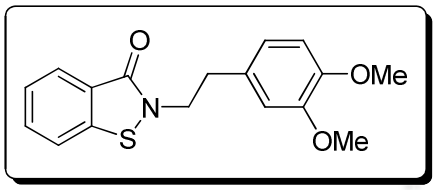
Yellow oil; yield: 87%.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.83-7.81 (m, 1H), 7.40-7.25 (m, 7H), 7.14-7.05 (m, 1H), 5.33 (q, *J* = 6.8 Hz, 1H), 1.63 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 165.1, 140.6, 132.5, 131.7, 128.8, 128.6, 128.3, 127.4, 126.7, 125.5, 120.5, 52.3, 19.3.

FT-IR (neat): 2935, 2851, 1640, 1440, 1331, 1229, 1192, 1092, 1034 cm^{-1}.

Anal. Calcd for $C_{15}H_{13}NOS$: C, 70.56; H, 5.13; N, 5.49; S, 12.56, Found: C, 70.53; H, 5.15; N, 5.53; S, 12.52.



***N*-(3,4-dimethoxyphenethyl)benzo[*d*]isothiazol-3(2*H*)-one (Table 2, Entry 5).**

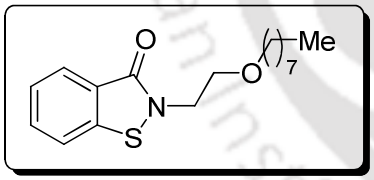
Yellow solid; yield: 83%; mp 105-107 °C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.95 (d, *J* = 7.6 Hz, 1H), 7.51-7.47 (m, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.31 (t, *J* = 7.2 Hz, 1H), 6.71-6.65 (m, 3H), 4.04 (t, *J* = 6.8 Hz, 2H), 3.75 (s, 3H), 3.70 (s, 3H), 2.94 (t, *J* = 6.8 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 165.4, 149.1, 147.9, 140.3, 131.8, 130.3, 126.7, 125.5, 124.6, 120.9, 120.2, 112.1, 111.4, 55.9, 55.8, 45.2, 35.2.

FT-IR (KBr): 2935, 2067, 1639, 1518, 1446, 1337, 1263, 1230, 1185, 1143, 1026 cm^{-1}.

Anal. Calcd for $C_{17}H_{17}NO_3S$: C, 67.74; H, 5.43; N, 4.44; S, 10.17, Found: C, C, 67.71; H, 5.45; N, 4.46; S, 10.15.



***N*-(2-(Octyloxy)ethyl)benzo[*d*]isothiazol-3(2*H*)-one (Table 2, Entry 6).**

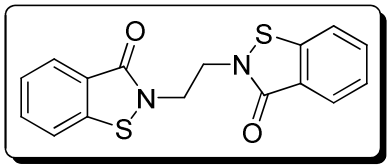
Yellow oil; yield: 90%.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.97 (d, *J* = 8.0 Hz, 1H), 7.52(t, *J* = 8.0 Hz, 1H), 7.34-7.30 (m, 1H), 7.03(t, *J* = 7.6 Hz, 1H), 4.03 (t, *J* = 5.2 Hz, 2H), 3.65 (t, *J* = 4.8 Hz, 2H), 3.43-3.39 (m, 2H), 1.57-1.49 (m, 2H), 1.28-1.19 (m, 10H), 0.83(t, *J* = 6.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 165.7, 140.0, 131.9, 126.7, 125.4, 124.3, 120.3, 71.6, 69.4, 44.2, 31.9, 29.8, 29.6, 26.4, 26.3, 22.8, 14.3.

FT-IR (neat): 2935, 2851, 1641, 1467, 1331, 1192, 1034 cm^{-1}.

Anal. Calcd for $C_{17}H_{25}NO_2S$: C, 66.41; H, 8.20; N, 4.56; S, 10.43, Found: C, 66.38; H, 8.22; N, 4.54; S, 10.46.



***N*,*N*'-(Ethane-1,2-diyl)dibenzo[*d*]isothiazol-3(2*H*)-one (Table 2, Entry 7).**

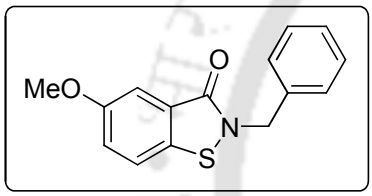
Colorless solid; yield: 81%; mp 165-167 °C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.01 (d, *J* = 8.0 Hz, 2H), 7.58 (t, *J* = 7.2 Hz, 2H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.38 (t, *J* = 7.2 Hz, 2H), 4.21 (s, 4H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 165.8, 140.9, 132.2, 126.9, 126.8, 125.8, 120.6, 43.1.

FT-IR (KBr): 2964, 2924, 2853, 1644, 1505, 1447, 1330, 1304, 1261, 1097, 1065, 1019 cm^{-1}.

Anal. Calcd for $C_{16}H_{12}N_2O_2S$: C, 58.52; H, 3.52; N, 9.78; S, 11.20. Found: C, 58.55; H, 3.54; N, 9.76; S, 11.22.



***N*-Benzyl-5-methoxybenzo[*d*]isothiazol-3(2*H*)-one (Table 2, Entry 8).**

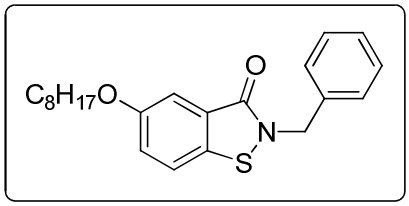
Colorless solid, yield: 67%; mp 134-135 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.38 (s, 1H), 7.83-7.81(m, 1H), 7.33-7.31 (m, 5H), 7.24-7.21 (m, 1H), 5.01 (s, 2H), 3.80 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.9, 155.4, 140.5, 139.9, 136.0, 135.8, 129.1, 128.6, 128.4, 126.6, 122.2, 55.7, 47.9.

FT-IR (KBr): 2917, 2840, 1651, 1591, 1576, 1408, 1266 cm^{-1}.

Anal. Calcd for $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83; N, 5.16; S 11.82. Found: C, 66.44; H, 4.78; N, 5.19, S, 11.83.



***N*-Benzyl-5-(octyloxy)benzo[*d*]isothiazol-3(2*H*)-one (Table 2, Entry 9).**

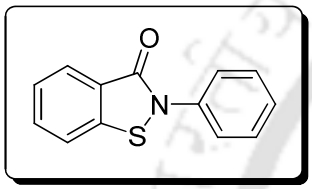
Yellow liquid; yield: 72%.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.38 (s, 1H), 7.83-7.81(m, 1H), 7.33-7.31 (m, 5H), 7.24-7.21 (m, 1H), 5.01 (s, 2H), 4.03 (t, *J* = 5.2 Hz, 2H), 1.57-1.49 (m, 2H), 1.28-1.19 (m, 10H), 0.83(t, *J* = 6.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 163.9, 155.2, 140.5, 139.9, 136.0, 135.8, 129.1, 128.6, 126.6, 124.0, 122.2, 69.4, 55.7, 31.9, 29.8, 29.6, 26.4, 22.8, 14.3.

FT-IR (neat): 2917, 2840, 1651, 1591, 1576, 1408, 1376, 1299, 1266, 1021 cm^{-1}.

Anal. Calcd for $C_{22}H_{27}NO_2S$: C, 71.51; H, 7.36; N, 3.79; S, 8.68. Found: C, 71.54; H, 7.33; N, 3.81; S, 8.71.



***N*-Phenylbenzo[*d*]isothiazol-3(2*H*)-one[9d] (Table 3, Entry 1).**

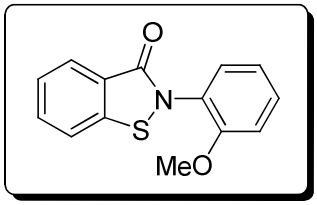
Colorless solid; yield: 90%; mp 140-142 °C (lit.[7] 141.5-142.5 °C).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.12 (d, *J* = 8.0 Hz, 1H), 7.72-7.65 (m, 2H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.49-7.42 (m, 2H), 7.34 (t, *J* = 7.2 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.3, 140.2, 139.8, 136.0, 132.8, 132.7, 129.7, 127.5, 126.2, 125.8, 120.4.

FT-IR (KBr): 2963, 2923, 2840, 1633, 1412, 1261, 1095, 1022 cm^{-1}.

Anal. Calcd for $C_{13}H_9NOS$: C, 68.70; H, 3.99; N, 6.16; S, 14.11. Found: C, 68.72; H, 3.97; N, 6.18; S, 14.14.



***N*-(2-Methoxyphenyl)benzo[*d*]isothiazol-3(2*H*)-one (Table 3, Entry 2).**

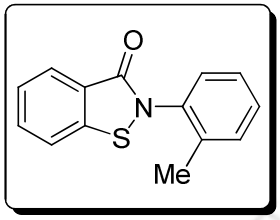
Colorless solid; yield: 84%; mp 105-107 °C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.09 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 6.8 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.42-7.37 (m, 3H), 7.03 (t, *J* = 8.0 Hz, 2H), 3.81 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 165.1, 156.9, 141.6, 139.5, 132.1, 130.7, 130.3, 127.2, 125.4, 124.6, 123.9, 120.9, 112.5, 56.0.

FT-IR (KBr): 2923, 2923, 2851, 1663, 1593, 1497, 1445, 1333, 1261, 1094, 1021 cm^{-1}.

Anal. Calcd for $C_{14}H_{11}NO_2S$: C, 65.35; H, 4.31; N, 5.44; S, 12.46. Found: C, 65.38; H, 4.29; N, 5.47; S, 12.44.



***N*-(2-Methylphenyl)benzo[*d*]isothiazol-3(2*H*)-one (Table 3, Entry 3).**

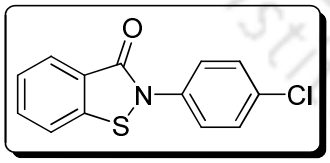
Colorless solid; yield: 88%; mp 122-124 °C (lit.[2] 122-123 °C).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07 (d, *J* = 8.0 Hz, 1H), 7.63 (t, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.49 (s, 1H), 7.46-7.38 (m, 2H), 7.34 (t, *J* = 8.0 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 2.38 (s, 3H).

^{13}C NMR ($CDCl_3$, 100MHz) δ 164.4, 140.2, 139.6, 137.3, 132.5, 129.4, 128.2, 127.4, 125.9, 125.6, 125.1, 121.9, 120.3, 21.6.

FT-IR (KBr): 2963, 2917, 1644, 1504, 1331, 1016 cm^{-1}.

Anal. Calcd for $C_{14}H_{11}NOS$: C, 69.68; H, 4.59; N, 5.80; S, 13.29, Found: C, 69.64; H, 4.61; N, 5.78; S, 13.27.



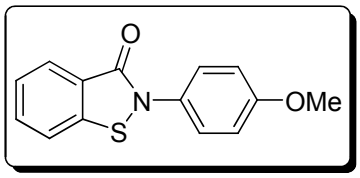
***N*-(4-Chlorophenyl)benzo[*d*]isothiazol-3(2*H*)-one[7] (Table 3, Entry 5).**

Colorless solid; yield: 85%; mp 127-128 °C (lit.[7] 128-129 °C).

^{1}H NMR ($CDCl_3$, 400MHz) δ = 8.08 (d, *J* = 8.0 Hz, 1H), 7.65-7.63 (m, 2H), 7.57 (d, *J* = 8.0 Hz, 2H), 7.43-7.39 (m, 3H)

^{13}C NMR ($CDCl_3$, 400MHz) δ = 163.1, 138.6, 134.8, 131.6, 128.5, 128.1, 126.2, 124.9, 124.6, 123.6, 119.1.

FT-IR (KBr): 2962, 2926, 2851, 1661, 1591, 1490, 1444, 1325, 1303, 1261, 1122, 1028 cm^{-1}. Anal. Calcd for $C_{13}H_8ClNOS$: C, 59.66; H, 3.08; N, 5.35; S, 12.25. Found: C, 59.64; H, 3.10; N, 5.33; S, 12.27.



***N*-(4-Methoxyphenyl)benzo[*d*]isothiazol-3(2*H*)-one[7] (Table 3, Entry 6):**

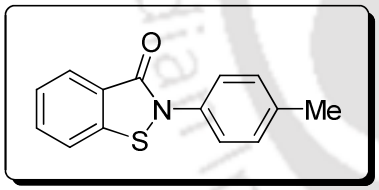
Colorless solid; yield: 89%; mp 146-147 °C (lit.[7] 147-149 °C).

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.08 (d, *J* = 8.0 Hz, 1H), 7.62 (t, *J* =6.8 Hz, 1H), 7.55-7.51 (m, 3H), 7.41 (t, *J* = 7.6 Hz, 1H), 6.96 (d, *J* =6.8 Hz, 2H), 3.8 (s, 3H)

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 164.5, 158.9, 140.2, 132.3, 129.8, 127.3, 127.0, 125.9, 124.8, 120.2, 114.7, 55.7.

FT-IR (KBr): 2923, 2854, 1663, 1591, 1490, 1445, 1331, 1267, 1095 cm^{-1}.

Anal. Calcd for $C_{14}H_{11}NO_2S$: C, 65.35; H, 4.31; N, 5.44; S, 12.40. Found: C, 65.36; H, 4.33; N, 5.46; S, 12.42.



***N*-p-tolylbenzo[*d*]isothiazol-3(2*H*)-one[7] (Table 3, Entry 7).**

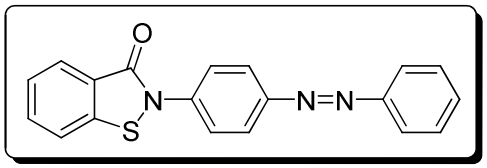
Colorless solid; yield: 93%; mp 135-136 °C (lit.[7] 136-137 °C).

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.02 (d, *J* = 8.0 Hz, 1H), 7.56-7.54 (m, 1H), 7.47 (d, *J* = 6.4 Hz, 4H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.18 (d, *J* = 7.6 Hz, 1H), 2.29 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 164.4, 140.1, 137.4, 134.7, 132.4, 130.1, 128.1, 127.3, 125.9, 124.9, 120.2, 21.3.

FT-IR (KBr): 2923, 2917, 2851, 1644, 1504, 1446, 1331, 1261, 1096, 1019 cm^{-1}.

Anal. Calcd for $C_{14}H_{11}NOS$: C, 69.68; H, 4.59; N, 5.80; S, 13.29. Found: 69.65; H, 4.56; N, 5.77; S, 13.25.



***N*-(4-(phenyldiazenyl)phenyl)benzo[*d*]isothiazol-3(2*H*)-one (Table 3, Entry 9).**

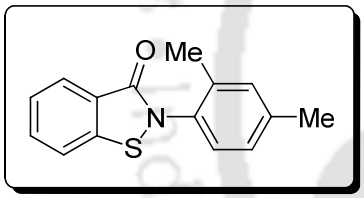
Orange solid; yield: 63%; mp 147-149 °C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.10 (d, *J* = 8.0 Hz, 1H), 7.65-7.61 (m, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.45-7.36 (m, 8H), 7.22 (d, *J* = 8.0 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 164.4, 152.8, 150.6, 139.8, 132.8, 131.4, 129.3, 127.5, 127.3, 126.2, 124.3, 124.2, 124.1, 123.1, 120.4.

FT-IR (KBr): 3066, 2961, 2924, 2854, 2852, 1653, 1594, 1526, 1497, 1446, 1327, 1261, 1101, 1018 cm^{-1}.

Anal. Calcd for $C_{19}H_{13}N_3OS$: C, 68.86; H, 3.95; N, 12.68; S, 9.68. Found: C, 68.84; H, 3.96; N, 12.64 S, 9.71.



***N*-(2,4-dimethylphenyl)benzo[*d*]isothiazol-3(2*H*)-one (Table 3, Entry 10).**

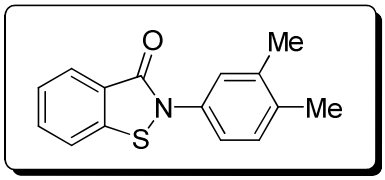
Colorless solid; yield: 92%; mp 114-115 °C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.00 (d, *J* = 8.0 Hz, 1H), 7.55 (t, *J* =7.2 Hz, 1H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.30 (t, *J* = 8.4 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 7.04 (s,1H), 6.98 (d, *J* = 8.0 Hz, 1H), 2.26 (s, 3H), 2.15 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 164.7, 141.3, 139.7, 137.4, 132.2, 132.0, 131.3, 128.8, 127.7, 127.2, 125.7, 124.1, 120.4, 21.3, 17.9.

FT-IR (KBr): 2923, 2854, 1659, 1593, 1500, 1446, 1329, 1309, 1262, 1104, 1017 cm^{-1}.

Anal. Calcd for $C_{15}H_{13}NOS$: C, 73.56; H, 5.13; N, 5.49; S, 12.56. Found: C, 73.54; H, 5.16; N, 5.47; S, 12.54.



***N*-(3,4-Dimethylphenyl)benzo[*d*]isothiazol-3(2*H*)-one (Table 3, Entry 11).**

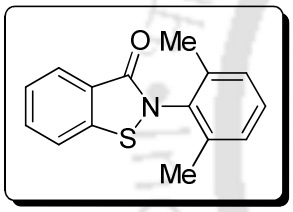
Colorless solid; 91% yield: 91%; mp 114-116 °C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.07 (d, *J* = 8.0 Hz, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.43-7.34 (m, 3H), 7.19 (d, *J* = 8.0 Hz, 1H), 2.28 (s, 3H), 2.26 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.3, 140.2, 137.9, 136.2, 134.8, 132.3, 130.5, 127.2, 126.2, 125.8, 124.9, 122.5, 120.2, 20.0, 19.5.

FT-IR (KBr): 2920, 2849, 2920, 1637, 1467, 1350, 1307, 1261, 1101, 1021 cm^{-1}.

Anal. Calcd for $C_{15}H_{13}NOS$: C, 70.56; H, 5.13; N, 5.49; S, 12.56. Found: C, 70.59; H, 5.11; N, 5.51; S, 12.54.



***N*-(2,6-Dimethylphenyl)benzo[*d*]isothiazol-3(2*H*)-one (Table 3, Entry 12).**

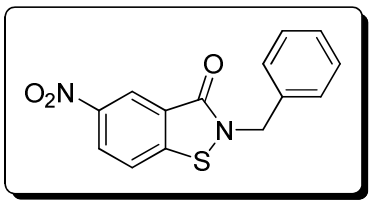
Colorless solid; yield: 86%; mp 116-117 °C

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.04 (d, *J* = 8.4 Hz, 1H), 7.57 (d, *J* = 7.2 Hz, 1H), 7.51(d, *J* = 7.6 Hz, 1H), 7.36-7.34 (m, 1H), 7.12-7.07 (m, 3H), 2.26 (s, 3H), 2.12 (s, 3H);

^{13}C NMR ($CDCl_3$, 100MHz) δ = 164.7, 141.4, 136.9, 134.6, 134.5, 132.3, 131.2, 130.5, 129.6, 127.3, 125.8, 20.9.

FT-IR(KBr): 2920, 2849, 2920, 1637, 1470, 1307, 1265, 1111, 1021 cm^{-1}.

Anal. Calcd for $C_{15}H_{13}NOS$: C, 70.56; H, 5.13; N, 5.49; S, 12.56. Found: C, 70.58; H, 5.15; N, 5.52; S, 12.54.



***N*-Benzyl-5-nitrobenzo[*d*]isothiazol-3(2*H*)-one (Table 4, Entry 2).**

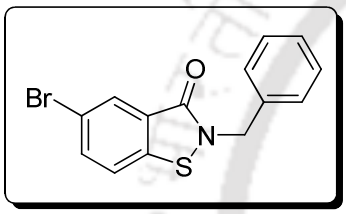
Yellow solid; yield: 35%; mp 178-180 °C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.33-8.31 (m, 1H), 7.36-7.35 (m, 1H), 6.93-6.90 (m, 1H), 6.46-6.34 (m, 5H), 5.02 (s, 2H).

^{13}C NMR (100 MHz, DMSO-d_6) δ = 165.1, 146.7, 139.3, 138.3, 137.8, 132.0, 129.1, 128.0, 127.7, 126.1, 124.3, 55.6.

FT-IR (KBr): 3399, 2962, 2977, 2857, 1651, 1591, 1513, 1408, 1340, 1299, 1261, 1094, 1021 cm^{-1}.

Anal. Calcd for $C_{14}H_{10}N_2O_3S$: C, 58.73; H, 3.52; N, 9.78; S, 11.20. Found: C, 58.76; H, 3.50; N, 9.75; S, 11.23.



***N*-benzyl-5-bromobenzo[*d*]isothiazol-3(2*H*)-one (Table 4, Entry 3).**

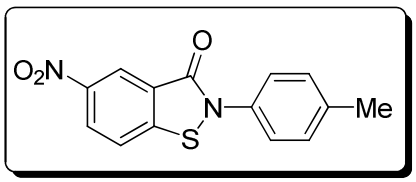
Colorless solid; yield: 90%; mp 139-140 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18-8.17 (m, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.36-7.30 (m, 6H), 5.23 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 138.8, 133.5, 131.7, 131.4, 131.3, 130.6, 129.9, 128.3, 126.9, 125.9, 42.5.

FT-IR (KBr): 2930, 1627, 1331, 1356, 1252, 1075, 1041 cm^{-1}.

Anal. Calcd for $C_{14}H_{10}BrNOS$: C, 52.51; H, 3.15; N, 4.37; S, 10.01. Found: C, 52.48; H, 3.16; N, 4.35; S, 10.08.



5-nitro-*N*-p-tolylbenzo[*d*]isothiazol-3(2*H*)-one (Table 4, Entry 6).

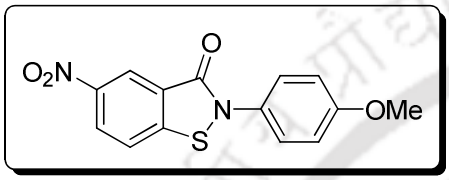
Yellow solid; yield: 35%; mp 111-112 °C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.77-8.71 (m, 1H), 8.43-8.39 (m, 1H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.18 (d, *J* = 8.4 Hz, 2H); 2.28 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 163.7, 148.4, 137.0, 134.7, 133.8, 130.8, 129.9, 129.8, 126.7, 123.0, 121.3, 21.2.

FT-IR (KBr): 2930, 2923, 2256, 1651, 1048, 1025 cm^{-1}.

Anal. Calcd for $C_{14}H_{10}NO_3S$: C, 58.73; H, 3.52; N, 9.78; S, 11.20. Found: C, 58.76; H, 3.55; N, 9.75; S, 11.18.



***N*-(4-Methoxyphenyl)-5-nitrobenzo[*d*]isothiazol-3(2*H*)-one (Table 5, Entry 4).**

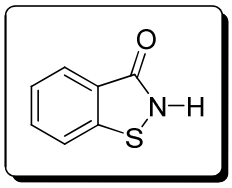
Yellow solid; yield: 45%; 114-115 °C

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.68-8.67 (m, 1H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 3H), 3.73 (s, 3H)

^{13}C NMR ($CDCl_3$, 100MHz) δ = 162.4, 156.0, 146.2, 137.9, 137.2, 131.6, 131.4, 125.6, 123.9, 121.5, 114.0, 55.3.

FT-IR (KBr): 2255, 2128, 1651, 1510, 1246, 1048, 1025, 1002 cm^{-1}.

Anal. Calcd for $C_{14}H_{10}NO_4S$: C, 55.62; H, 3.33; N, 9.27, S, 10.61. Found: C, 55.66; H, 3.31; N, 9.30, S, 10.63.



Benzo[*d*]isothiazol-3(2*H*)-one (eq 1).[8]

Colorless solid; yield: 95%; mp 158-159 °C (lit.[9] 158-160 °C).

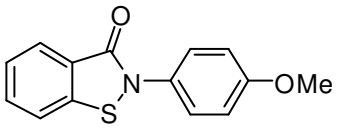
^{1}H NMR ($CDCl_3$, 400 MHz) δ = 11.5 (s, 1H), 7.97 (d, *J* = 8.8 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 7.2 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 1H)

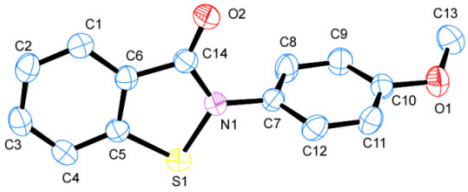
^{13}C NMR ($CDCl_3$, 100 MHz) δ = 164.9, 147.4, 130.1, 124.9, 124.7, 124.2, 121.5.

FT-IR (KBr): 2929, 2854, 1651, 1448, 1305, 1262, 1210, 1191, 1062 cm^{-1}.

Anal Calc for C_7H_5NOS: C, 55.61; H, 3.33; N, 9.26; S, 21.21. Found: C, 55.63; H, 3.31; N, 9.28; S, 21.19.

Crystal Structure of *N*-(4-methoxyphenyl)benzo[*d*]isothiazol-3(2*H*)-one





Crystal number: Summary of Data CCDC 876574 Thermal ellipsoids are drawn at a 40% probability level. Hydrogen atoms have been omitted for clarity.

Formula: $C_{14}\ H_{11}\ N\ O_2\ S$

Identification code	RP-O1	
Molecular formula	$C_{14}\ H_{11}\ N\ O_2\ S$	
Formula weight	257.31	
Temperature	298(2) K	
Wavelength	0.71073A	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit Cell dimensions	a = 10.5093(14)	α = 90
	b = 13.6166(17)	β = 114.028(6)
	c= 9.1287(12)	γ = 90
Volume	1193.1(3)	
Z	4	
Density (calculated)	1.432 Mg/m^3	
Absorption coefficient	0.263	
F(000)	536.0	

Crystal size	0.50 x 0.16 x 0.10 mm^3
Theta range for data collection	2.85-29.94°
Index ranges	-15<=h<=15, 8<=k<=9, 18<=l<=16
Reflections collected	3340
Independent reflections	3340[R(int) = 0.0947]
Completeness to theta	98%
Absorption correction	None
Refinement method	Full matrix least squares on F^2
Data/restraints/parameters	3340/1/ 208
Goodness of fit on F^2	1.023
Final R indices[I>2sigma(I)]	*R1*= 0.0388, *wR2* = 0.0879
R indices (all data)	*R1*= 0.0854, *wR2* = 0.0947\

4.6 References

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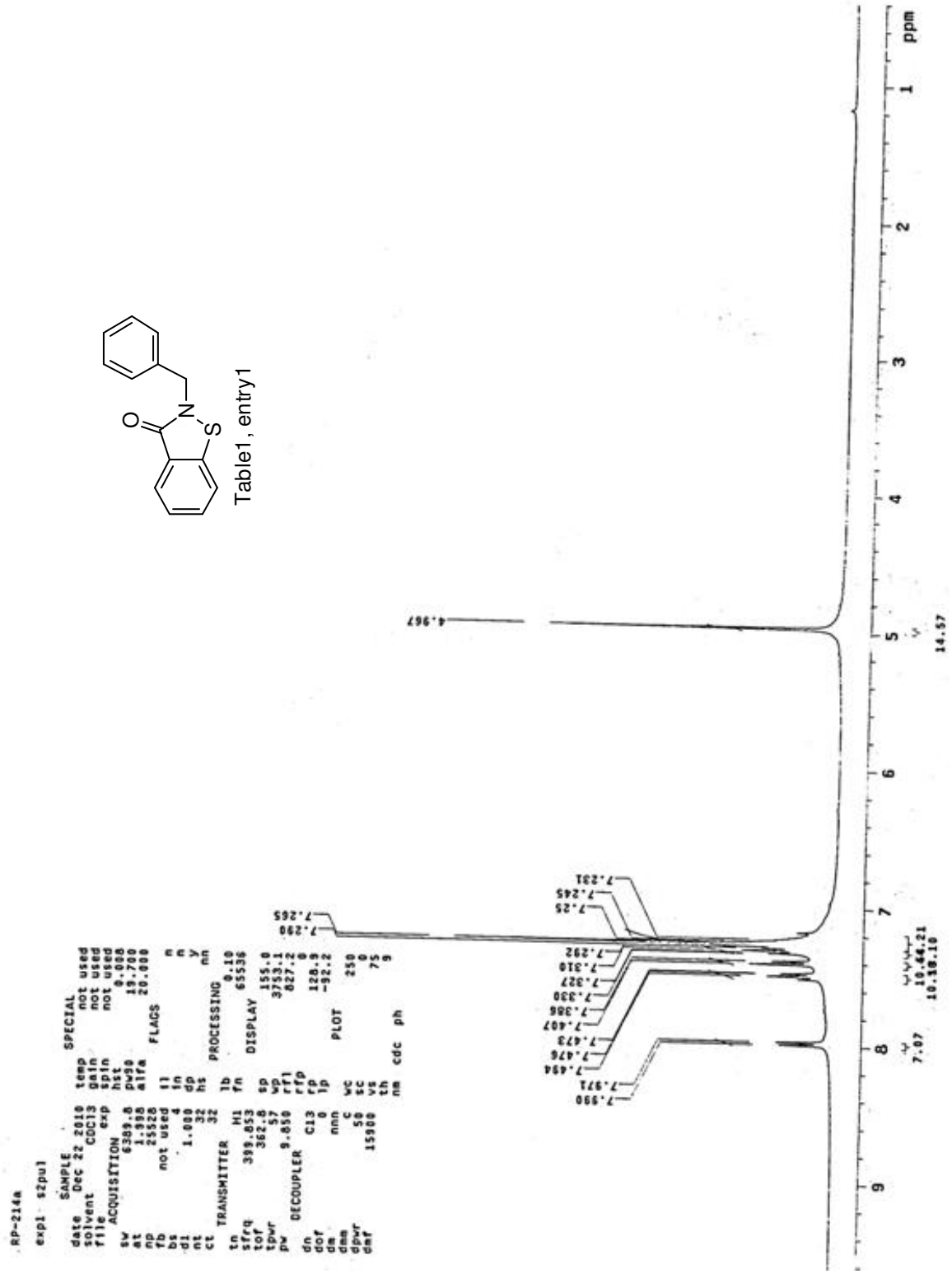
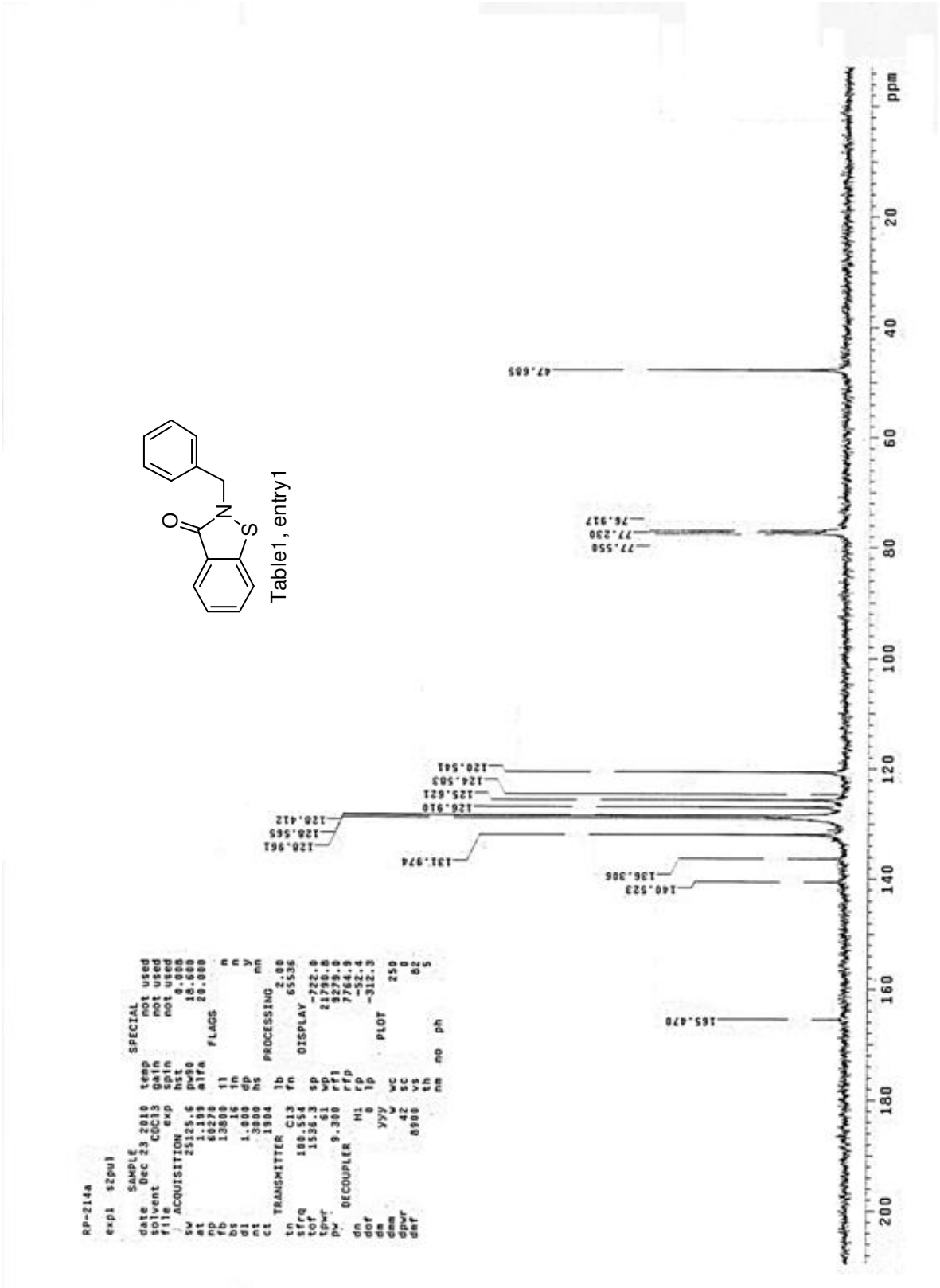
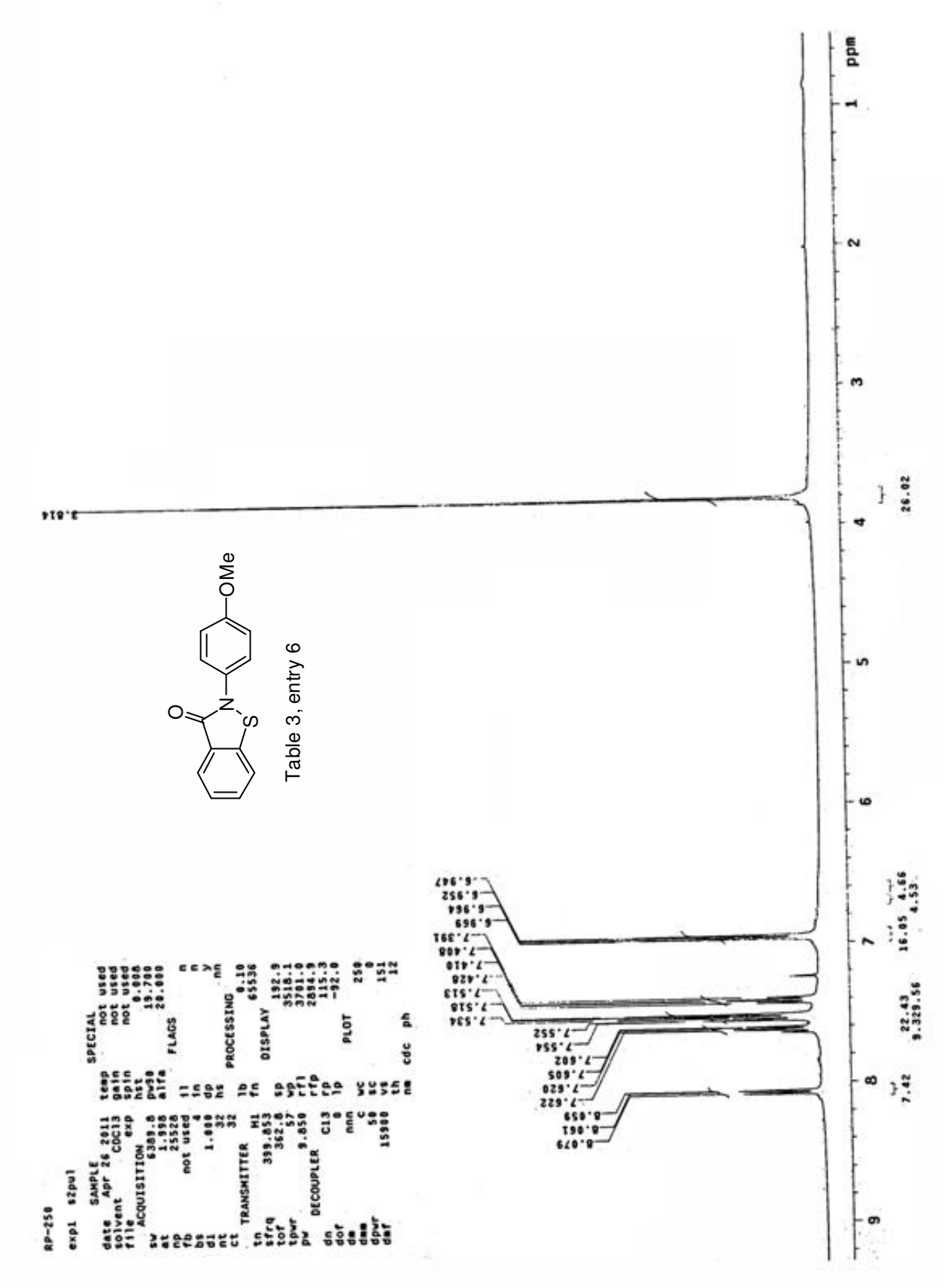
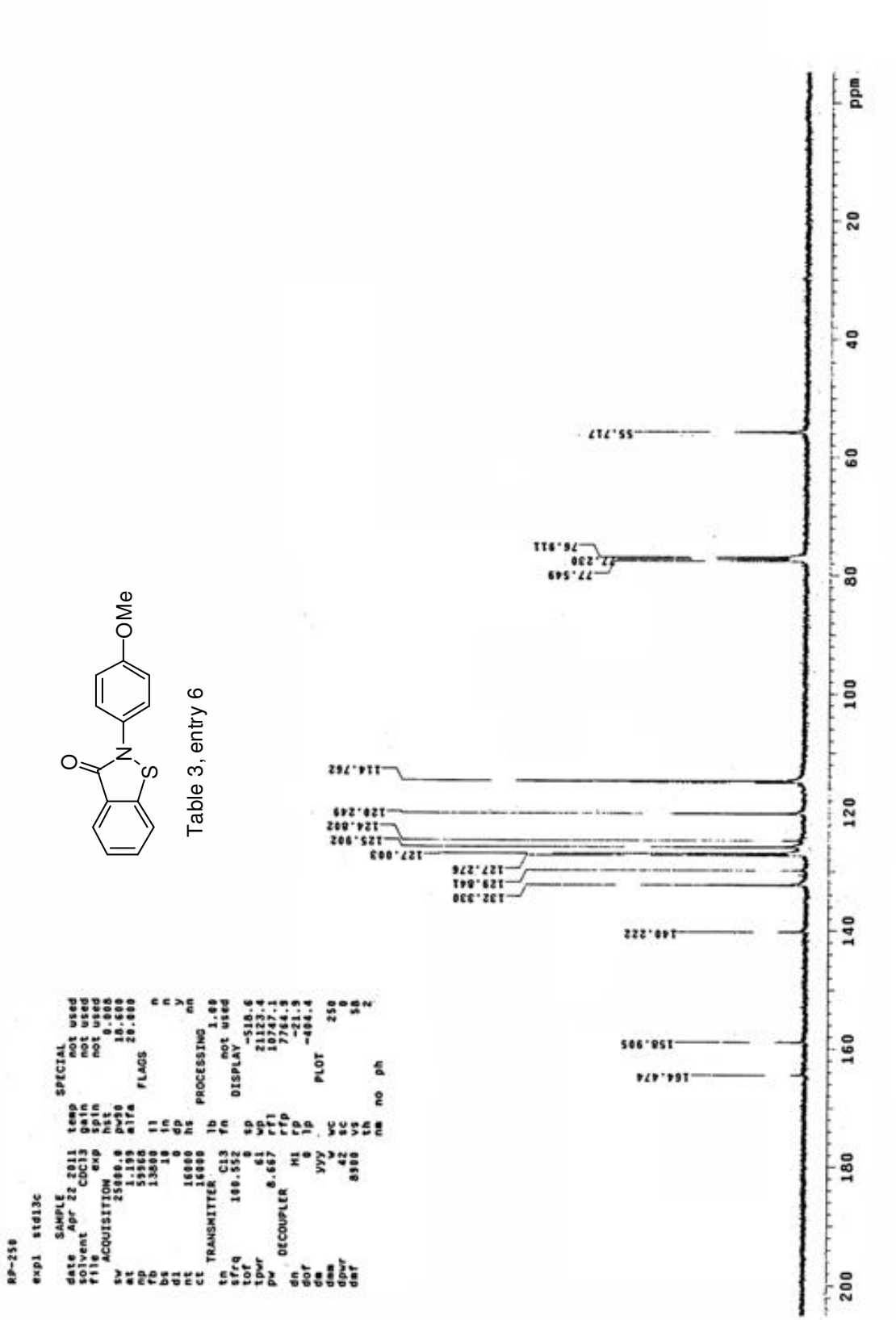








Chapter 5

One-Pot Conversion of 2-Halobenzamides to Benzo[*d*]isothiazol-3(2*H*)-one-1-oxides

5.1 Introduction

1,2-Benzoisothiazoles possess various types of biological activities such as antisecretory and reduction of the sugar level in blood.[1-2] Benzothiazol-3-one-1-oxides are important components of various pharmaceuticals and medicinally significant compounds (Figure 1).[3] Therefore, considerable effort has been made on the development of synthetic methods for the formation of these compounds from the readily accessible substrate precursors.

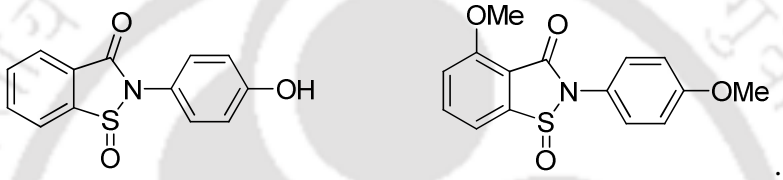
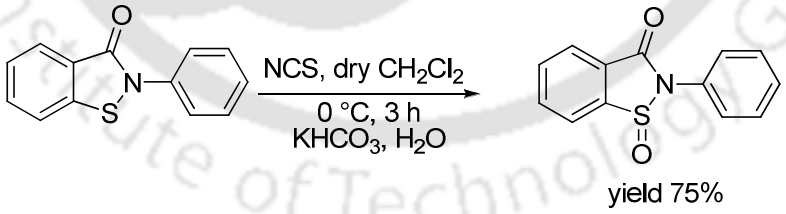


Figure 1. Examples of some medicinally important benzo[*d*]isothiazol-3(2*H*)-one-1-oxides.

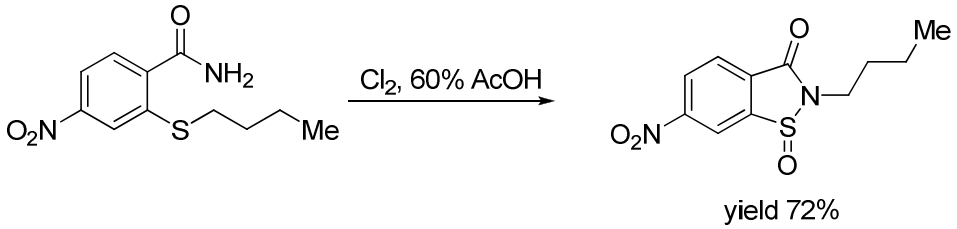
5.2 Classical Synthesis of *N*-Substituted Benzo[*d*]isothiazol-3(2*H*)-one-1-oxides

Nakanishi and co-workers synthesized *N*-substituted benzo[*d*]isothiazol-3(2*H*)-one-1-oxides by treatment of *N*-substituted benzo[*d*]isothiazol-3(2*H*)-one with *N*-chlorosuccimide (NCS) in dry dichloromethane (Scheme 1).[6a]



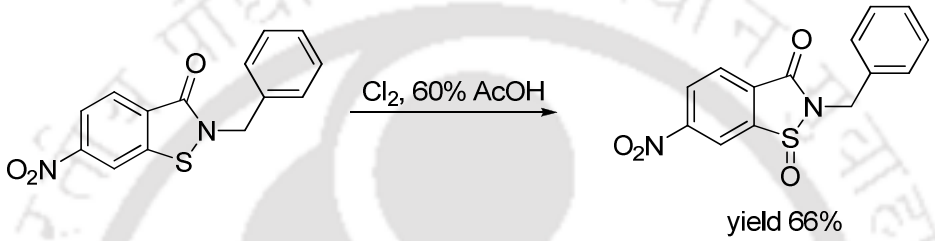
Scheme 1

Zlotin and co-workers demonstrated the synthesis of *N*-substituted-6-nitro benzo[*d*]isothiazol-3(2*H*)-one-1-oxides by passing chlorine gas in a solution of 2-(alkylthio)-4-nitrobenzamides in 60% acetic acid (Scheme 2).[6b]



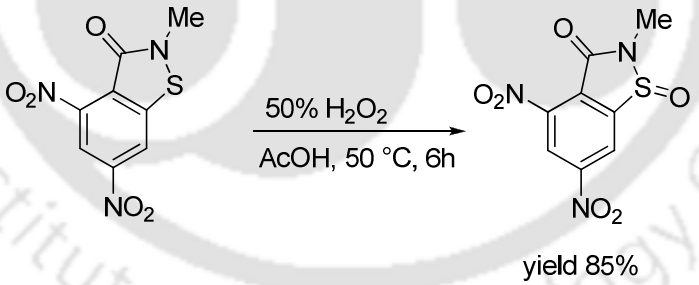
Scheme 2

They also showed the synthesis of the *N*-substituted-6-nitro benzo[*d*]isothiazol-3(2*H*)-one-1-oxides from the corresponding benzo[*d*]isothiazol-3(2*H*)-ones (Scheme 3).[6c]



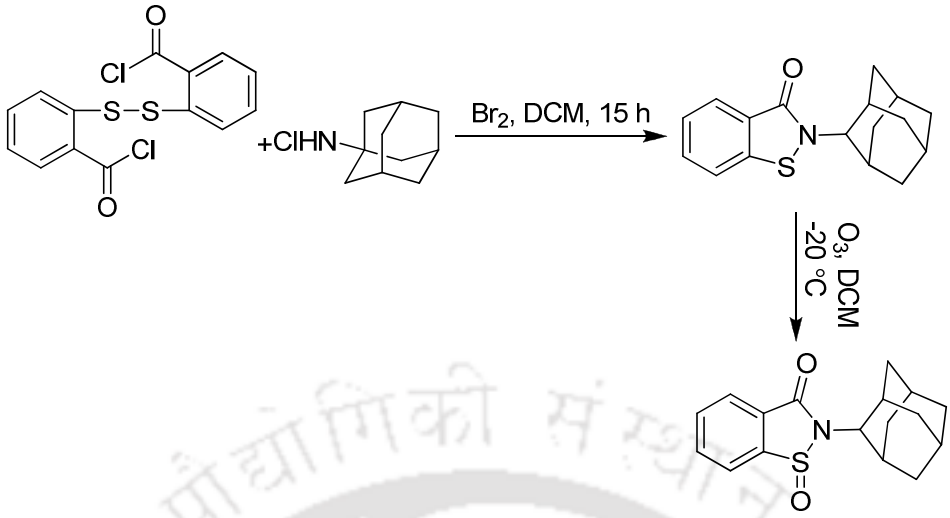
Scheme 3

Later, the same group developed a strategy for the synthesis of 4,6-dinitrobenzo[*d*]isothiazol-3(2*H*)-one-1-oxide by treating the corresponding 4,6-dinitrobenzo[*d*]isothiazol-3(2*H*)-one with 50% H_2O_2 (Scheme 4).[6d]



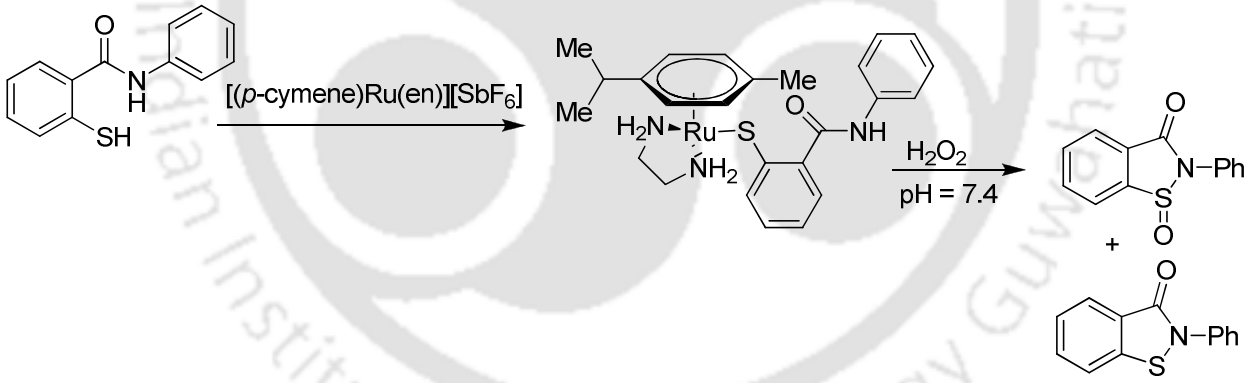
Scheme 4

Kamigata and co-workers synthesized *N*-admantyl benzo[*d*]isothiazol-3(2*H*)-one, which was then oxidized to *N*-admantyl benzo[*d*]isothiazol-3(2*H*)-one-1-oxide by treatment with ozone in dichloromethane (Scheme 5).[6e]



Scheme 5

Sadler and co-workers demonstrated the synthesis of *N*- phenylbenzo[*d*]isothiazol-3(2*H*)-one-1-oxide along with *N*-phenylbenzo[*d*]isothiazol-3(2*H*)-one by treating 2-mercapto-*N*-phenyl-benzamide with a ruthenium complex followed by treatment with hydrogen peroxide (Scheme 6).[6f]



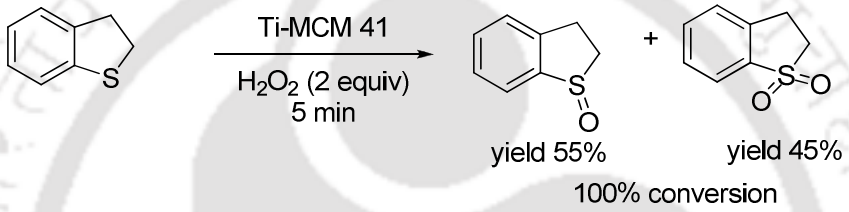
Scheme 6

5.3 Titanium-Catalyzed Oxidation of Sulfides

Titanium catalyzed oxidation of sulfides to sulfoxides is a well known and highly utilized reaction.[5,6] In the presence of hydrogen peroxide as oxidant, the reaction becomes even more attractive due to the fact that hydrogen peroxide generates only water as a byproduct.[6,7] However, there is a problem of overoxidation the sulfides to the corresponding sulfones. This over-oxidation can be avoided by suitably modifying the catalyst or the reaction conditions or the

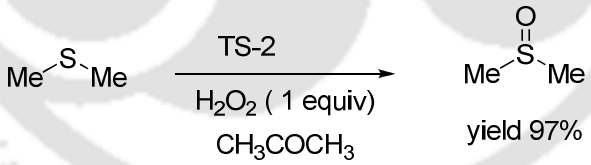
use of a suitable oxidant. A few examples of oxidation of sulfides using titanium based catalysts is noted below.

Titanium containing zeolites have been widely used for oxidation of alkyl aryl sulfides to their corresponding sulfoxides. A wide range of these catalysts such as TS-1,[8] TS-2,[8a, 9] Ti-b,[8b, 10] Ti-MCM-41 (Ti-M41),[11] Ti-HMS[8b] and Ti-MMM[12] show good catalytic properties in a range of mild selective oxidations of sulfides by the use of aqueous hydrogen peroxide. Cojocariu and co-workers oxidized phenyl methyl sulfide to the corresponding sulfoxide by using hydrogen peroxide as oxidant in the presence of Ti-MCM-41 (Scheme 7).[13]In this case, the amount of sulfone increased on prolonging the reaction time.



Scheme 7

Similarly, Reddy and co-workers utilized titanium silicate TS-2 as a catalyst for the oxidation of alkyl alkyl sulfides to their corresponding sulfoxides in the presence of dilute (26%) hydrogen peroxide as oxidant (Scheme 8).[14]

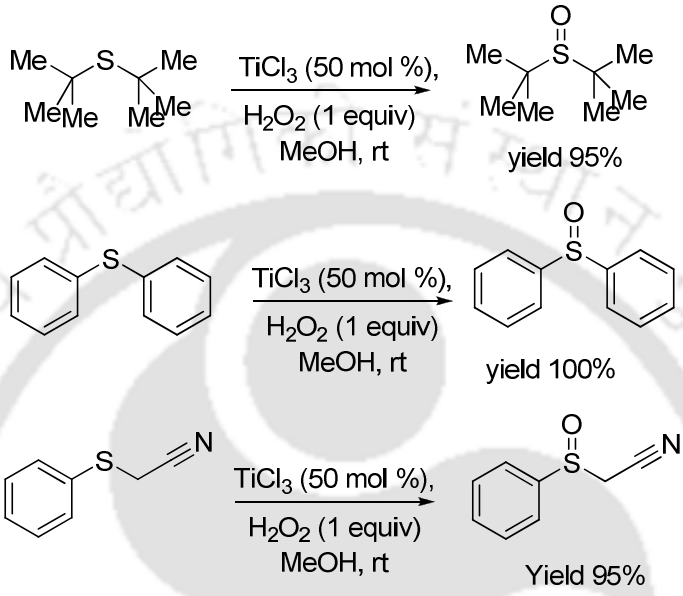


Scheme 8

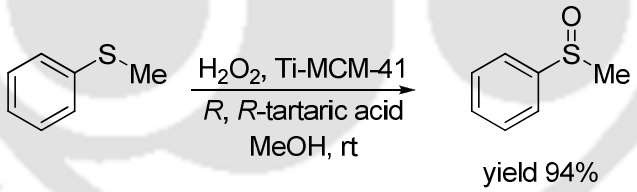
Titanium trichloride ($TiCl_3$) was successfully used as a catalyst for the hydrogen peroxide oxidation of sulfides by Oae and co-workers.[15] The oxidation reactions were carried out in methanol at room temperature (Scheme 9).

Oxidation of the thioanisole by H_2O_2 on Ti-MCM-41(Ti-M41) in various solvents and with or without a chiral modifier was studied by Iwamoto and co-workers.[11b] They observed that, when methanol was used as the solvent in the oxidation of thioanisole without the chiral modifier, the sulfoxide was obtained with a yield of 28 and 9% ee. Application of (*R*,*R*)-tartaric acid allowed the sulfoxide synthesis with a much higher yield (94%) (Scheme 10).

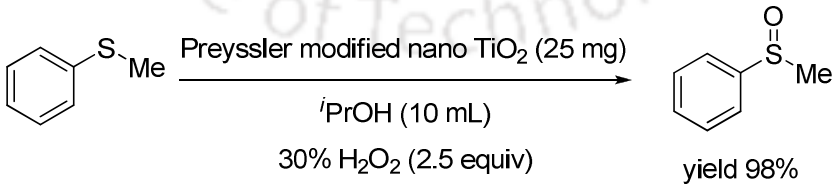
Shiri and co-workers employed Preyssler-type heteropoly acid modified nano sized TiO_2 for the oxidation of alkyl aryl sulfides to give the corresponding alkyl aryl sulfoxides. The reaction is selective and provides the products with high yield (Scheme 11).[16] However, the use of unmodified nano sized TiO_2 led to the exclusive formation of the corresponding sulfone.



Scheme 9



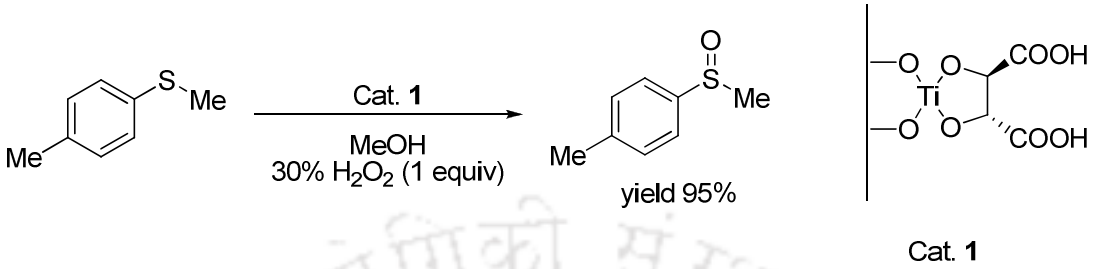
Scheme 10



Scheme 11

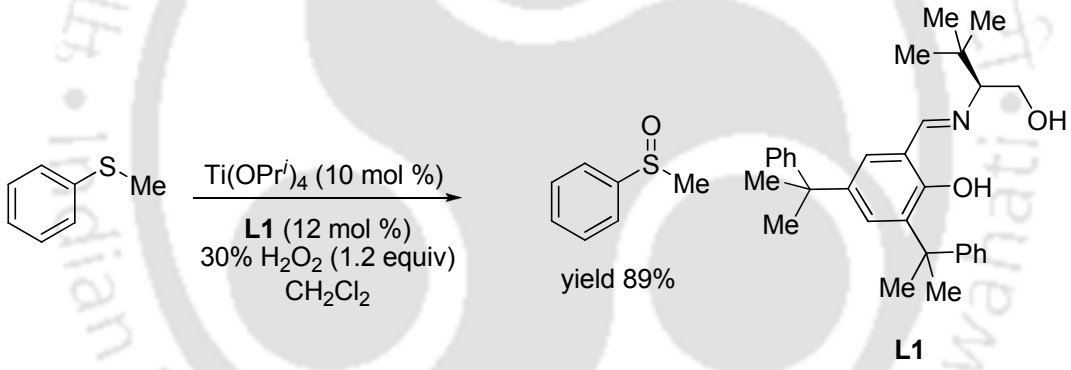
$Ti(O^iPr)_4$ is widely used as a catalyst for oxidation of sulfides.[17] Thus, Mayoral and co-workers demonstrated the use of $Ti(OPr^i)_4$ as a catalyst for the oxidation of sulfides to sulfoxides. After

some optimization studies using various oxidants, they used $Ti(O^iPr)_4$ supported on silica as a catalyst for the oxidation of alkyl aryl sulfides to their corresponding sulfoxides in good yields and selectivity.(Scheme 12).[18]



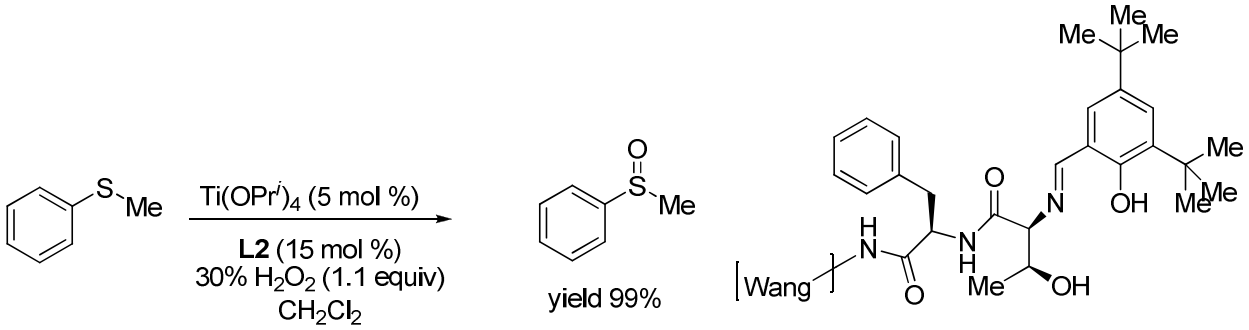
Scheme 12

Yang and co-workers employed $Ti(OPr^i)_4$ along with Schiff base **L1** for the oxidation of alkyl aryl sulfides to sulfoxides in the presence of H_2O_2 as an oxidant. The reaction provides the product sulfoxides in good yield with moderate enantioselectivity (Scheme 13).[19]



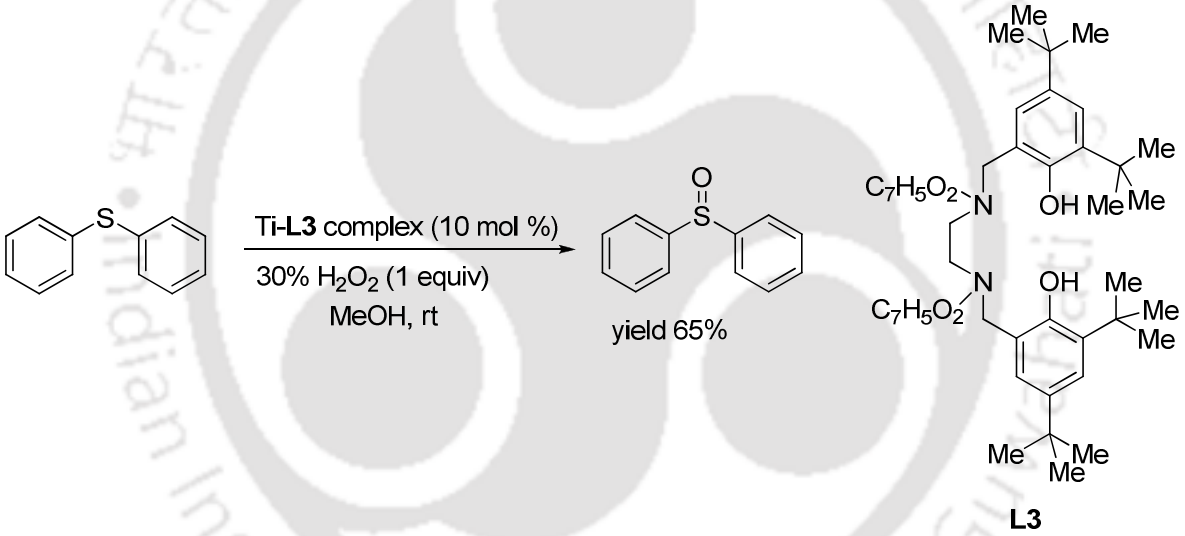
Scheme 13

Green and co-workers reported a new efficient protocol for the oxidation of various alkyl aryl sulfides by aqueous hydrogen peroxide with a titanium–ligand complex supported on Wang resin (**L2**). This protocol provides the target molecules in high yield with moderate enantioselectivity (Scheme 14). [20]



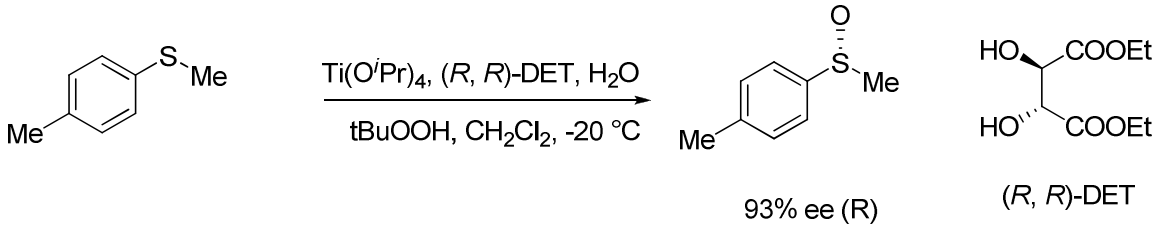
Scheme 14

Ghosh and co-workers also used a titanium based catalyst derived from Ti(OPr^i)$_4$ for the selective conversion of alkyl aryl sulfides to their corresponding sulfoxides. The reaction is highly selective and provided the products with high yields (Scheme 15).[21]

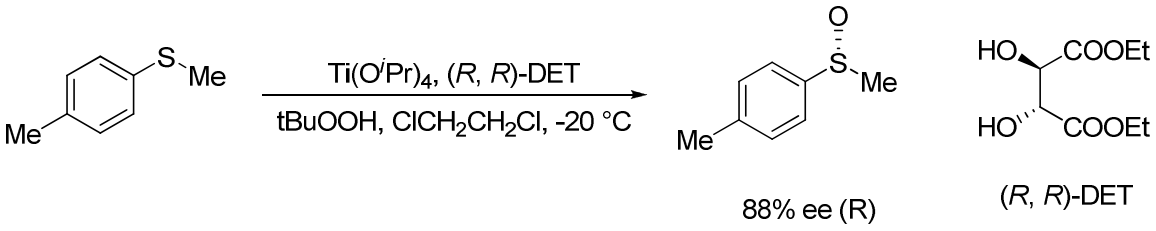


Scheme 15

Ti(^{i}PrO)$_4$ has been used in the selective oxidation of sulfides to sulfoxides.[17] The first practical and efficient oxidation method for the metal catalyzed asymmetric oxidation of sulfides was reported by Kagan and Modena independently in 1984 (Scheme 16-17).[17d-e]

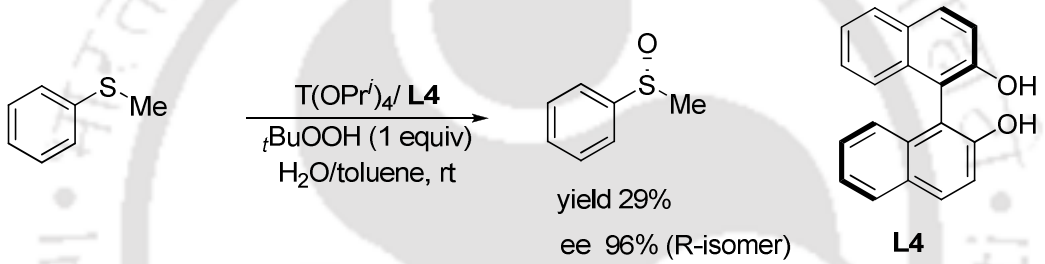


Scheme 16



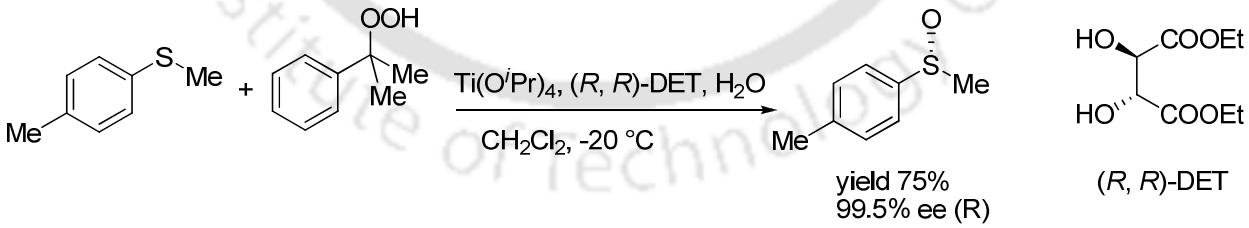
Scheme 17

An asymmetric oxidation of sulfides with high enantioselectivity has been reported using chiral titanium complex derived from (*R*)-(+)-BINOL and Ti(*i*-PrO)$_4$ (Scheme 18).[22] In this case, the authors observed athat that the reaction first proceeds by enantioselective oxidation and then kinetic resolution takes place.



Scheme 18

Kagan and co-workers have described a highly enantioselective oxidation of sulfides to sulfoxides mediated by chiral titanium complex using cumyl hydroperoxide as terminal oxidant. The ratio of Ti(O^{i}Pr)$_4$: (*R*,*R*)-DET: H$_2$O is 1:2:1 which is necessary for high ee (Scheme 19).[17b]



Scheme 19

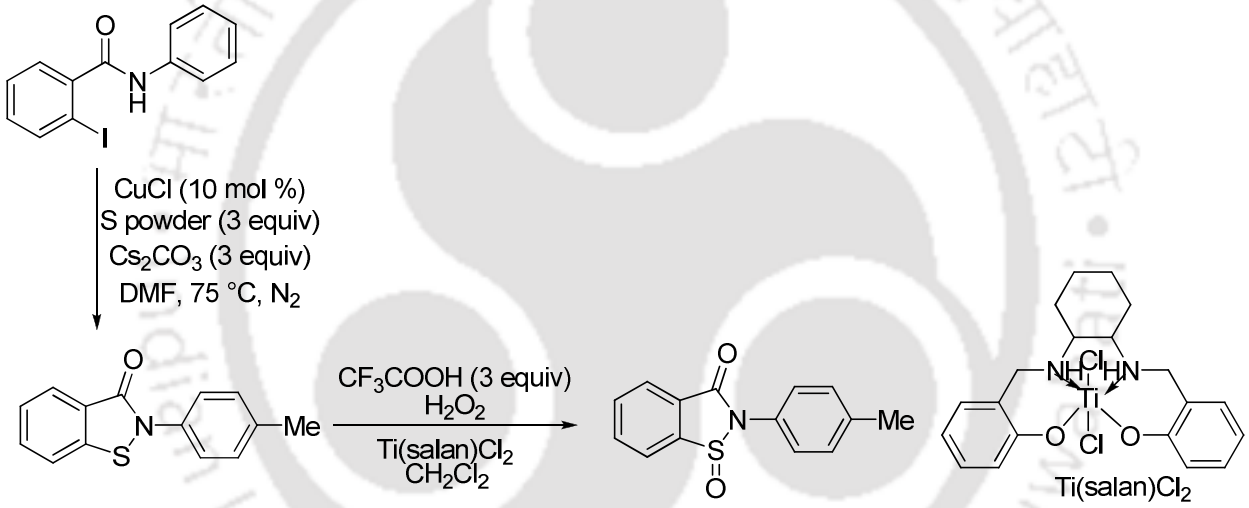
5.4 Present Study

The oxidation of alkyl aryl sulfides to the corresponding alkyl aryl sulfoxides and alkyl aryl sulfones has been studied extensively due to the importance of the products in the area of medicinal chemistry.[5] In this chapter we describe a tandem one-pot synthesis of *N*-substituted

benzo[*d*]isothiazol-3(2*H*)-one-1-oxides from the corresponding *N*-substituted-2-halobenzamides. The *N*-substituted-2-halobenzamides are first converted to the corresponding *N*-substituted benzo[*d*]isothiazol-3(2*H*)-one by using the protocol described in the last chapter which were then treated with hydrogen peroxide in the presence of Ti(salan) as catalyst.

The effect of the quantity of hydrogen peroxide and the Ti(salan) catalyst was studied on the conversion of *N*-(4-methylphenyl) benzo[*d*]isothiazol-3(2*H*)-one to its corresponding S-oxide and a 10 mol % of Ti(salan) along with 1.2 equivalents of 30% hydrogen peroxide was the optimum condition (Table 1). Under these conditions, no over oxidation of the sulfoxide to sulfone was observed.

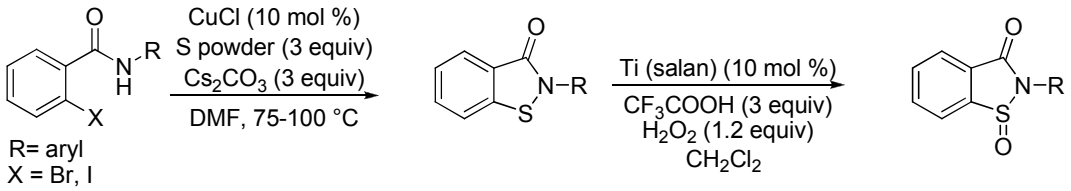
Table 1. Optimization of Reaction Conditions.

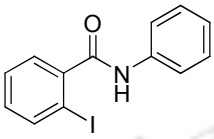
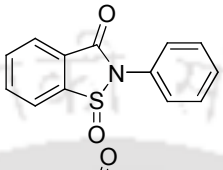
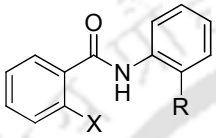
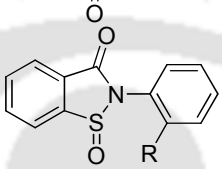
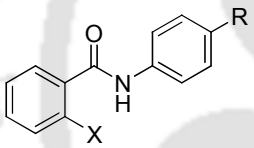
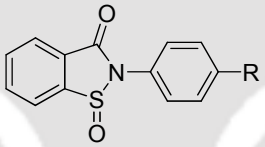
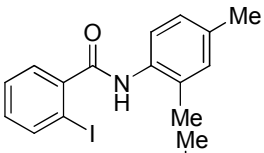
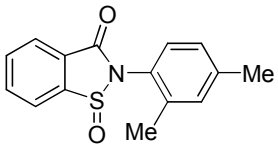
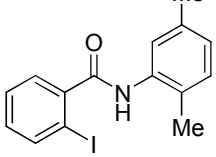
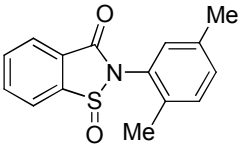


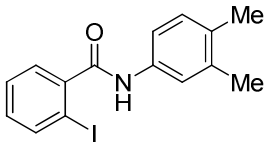
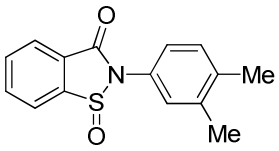
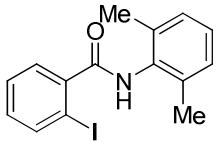
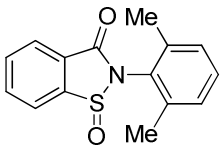
Entry	$Ti(salan)Cl_2$ (mol %)	30% H_2O_2 (equiv)	Conv (%)[a]
1	-	1.2	46
2	2.5	1.2	51
3	5	1.2	63
4	7.5	1.2	69
5	10	1.2	75

[a] *N*-(4-Methylphenyl)2-iodobenzamide (0.5 mmol), CuCl (10 mol %), sulfur powder (1.5 mmol) and K_2CO_3 (1.5 mmol) were stirred in 1 mL of DMF at 75 °C for 6 h under N_2. Then the reaction mixture was cooled and CF_3COOH (3 equiv) was added to it followed by $Ti(salan)Cl_2$ 30% H_2O_2 and CH_2Cl_2 (1 mL).

Table 2. Synthesis of *N*-Aryl Benzo[*d*]isothiazol-3(2*H*)-one-1-oxides.



Entry	Substrate	Product	Time (h)	Yield (%)[a]
1			24	80
2	 R = Cl, X = I		27	77
3	R = OMe, X = I		20	75
4	R = OMe, X = Br		34	35
5	R = Me, X = I		23	77
6	 R = Cl, X = Br		28	31
7	R = Cl, X = I		28	76
8	R = OMe, X = Br		20	35
9	R = OMe, X = I		20	82
10	R = Me, X = I		22	84
11	R = Et, X = I		22	77
12	R = ^{i}Pr, X = I		27	79
13			24	82
14			24	80

15			24	84
16			24	76

[a] *N*-Substituted-2-iodobenzamide (0.5 mmol), CuCl (10 mol %), sulfur powder (1.5 mmol) and Cs_2CO_3 (1.5 mmol) were stirred at 75-100 °C in DMF (1 mL) under N_2. The reaction mixture was then cooled and CF_3COOH (1.5 mmol) was added followed by addition of 30% H_2O_2 (3 equiv) and Ti(salan)Cl_2 (10 mol %).

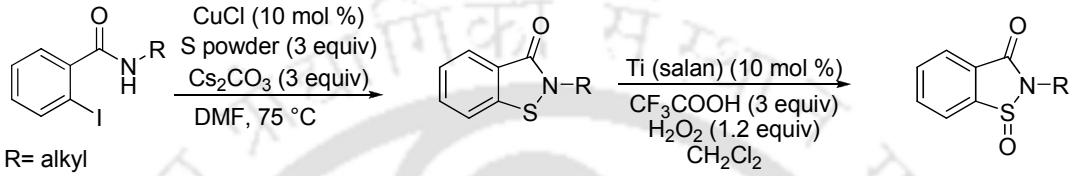
[b] Isolated yield.

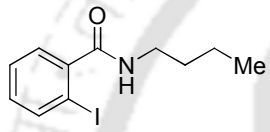
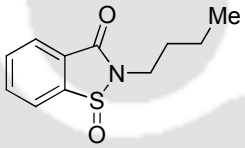
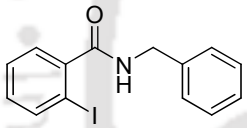
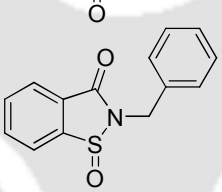
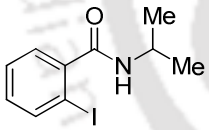
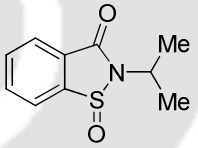
The scope of the procedure was next investigated for the synthesis of a series of *N*-aryl benzo[*d*]isothiazol-3(2*H*)-one-1-oxides from the corresponding *N*-aryl-2-halobenzamides (Table 2). Thus, *N*-phenyl 2-iodobenzamide was converted to N-phenyl benzo[*d*]isothiazol-3(2*H*)-one-1-oxide with a yield of 80% in 24 h (entry 1). Similarly, *N*-substituted 2-iodobenzamide having

N-(2-chlorophenyl) and *N*-(2-methylphenyl) substituents proceeded reactions to afford the desired products in 77% yield (entries 2 and 5). On the other hand, *N*-(2-methoxylphenyl)-2-iodobenzamide and *N*-(2-methoxylphenyl)-2-bromobenzamide underwent reaction to yield *N*-(2-methoxylphenyl)benzo[*d*]isothiazol-3(2*H*)-one-1-oxide in 75% and 35% yield, respectively (entries 3 and 4). Similarly, *N*-(4-chlorophenyl)-2-iodobenzamide and *N*-(4-methoxyphenyl)-2-iodobenzamide could be transformed to *N*-(4-chlorophenyl)benzo[*d*]isothiazol-3(2*H*)-one-1-oxide and *N*-(4-methoxylphenyl)benzo[*d*]isothiazol-3(2*H*)-one-1-oxide in 76% and 82% yield, respectively (entries 7 and 9), while *N*-(4-chlorophenyl)-2-bromobenzamide and *N*-(4-methoxyphenyl)-2-bromobenzamide gave the target products in 31% and 35% yield, respectively (entries 6 and 8). *N*-Substituted 2-iodobenzamides having *N*-(4-methylphenyl), N-(4-ethylphenyl) and N-(4-isopropylphenyl) substituents proceeded reactions to afford the desired products in 74-84% yields (entries 10-12). 2-Iodobenzamides having *N*-(2,4-dimethylphenyl)-, *N*-(2,5-dimethylphenyl), *N*-(3,4-dimethylphenyl) and *N*-(2,6-dimethylphenyl) substituents underwent reaction to afford the corresponding benzo[*d*]isothiazol-3(2*H*)-one-1-oxides in 76-84% yield (entries 12-16).

The reaction of *N*-alkyl-2-iodobenzamides was then studied (Table 3). *N*-Butyl-2-iodobenzamide and *N*-isoproyl-2-iodobenzamide could be converted to the corresponding desired products in 43% and 54% yield, respectively, while *N*-benzyl-2-iodobenzamide underwent the reaction to yield *N*-benzyl benzo[*d*]isothiazol-3(2*H*)-one-1-oxide in 45% yield (entry 2).

Table 3. Synthesis of *N*-Alkyl Benzo[*d*]isothiazol-3(2*H*)-one-1-oxides.

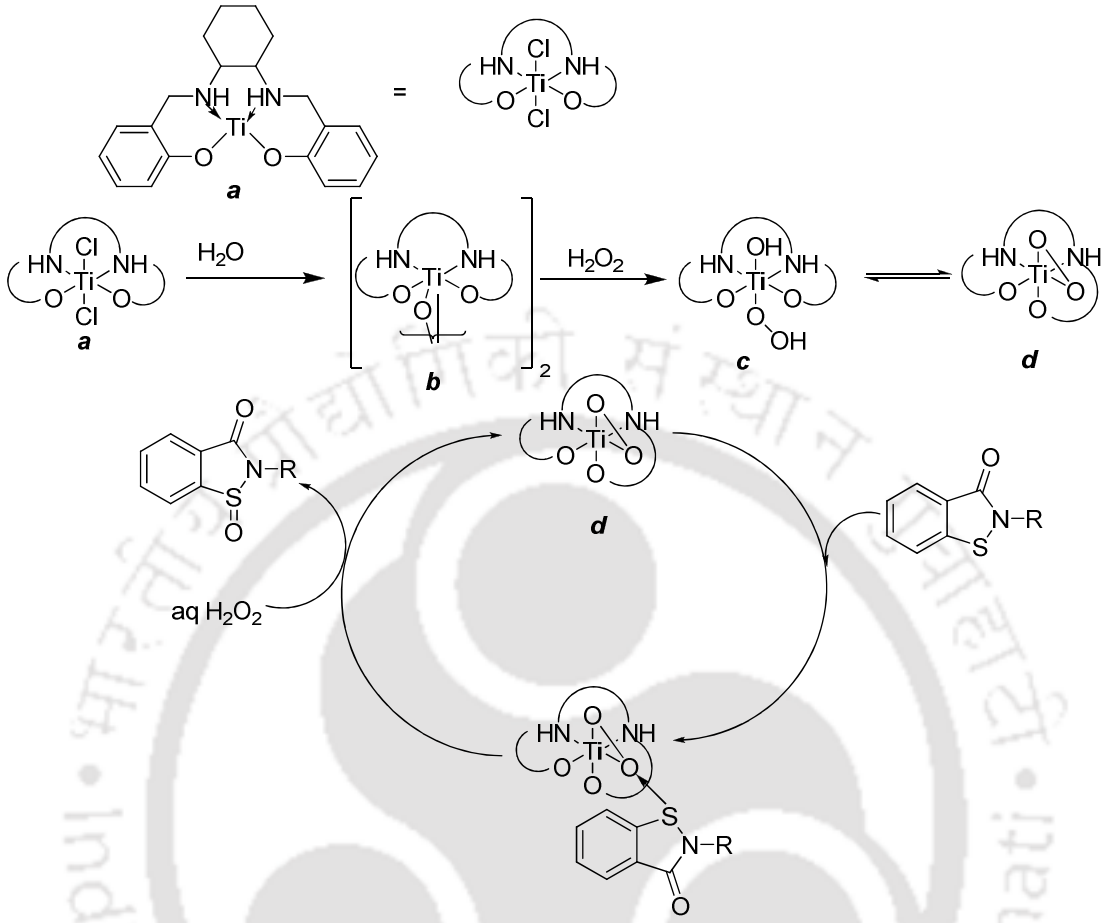


Entry	Substrate	Product	Time (h)	Yield (%)[a, b]
1			19	43
2			18	45
3			20	54

[a] *N*-Substituted-2-iodobenzamide (0.5 mmol), CuCl (10 mol %), sulfur powder (1.5 mmol) and Cs_2CO_3 (1.5 mmol) were stirred at 75-100 °C in DMF (1 mL) under N_2. The reaction mixture as then cooled and CF_3COOH (1.5 mmol) was added followed by addition of 30% H_2O_2 (1.2 equiv) and Ti(salan)Cl_2 (10 mol %).

[b] Isolated yield.

Regarding the mechanism,[23] Ti(salan) ***a*** may undergo partial hydrolysis to give ***b*** which may give rise to ***c*** by reaction with hydrogen peroxide (Scheme 17). The resultant ***c*** may exist in equilibrium with μ-oxo bridged form ***d***. Thus either ***c*** or ***d*** may act as the source of oxygen transfer thereby oxidizing the *N*-substituted benzo[*d*]isothiazol-3(2*H*)-ones to *N*-substituted benzo[*d*]isothiazol-3(2*H*)-one-1-oxides.



Scheme 5

In summary, we have devised a tandem one-pot protocol for the synthesis of *N*-substituted benzo[*d*]isothiazol-3(2*H*)-one-1-oxides from *N*-substituted 2-halobenzamides. The reaction is general and efficient and provides the target molecules in high yield.

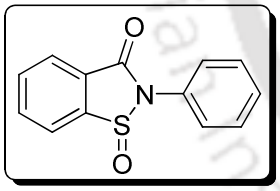
5.5 Experimental Conditions

General Information. CuCl (98%) and sulfur powder (97%) were purchased from Rankem and used without further purification. Hydrogen peroxide (30%) and trifluoroacetic acid were purchased from Merck and used without further purification. 2-Iodobenzoic acid (98%), 2-bromobenzoic acid (97%) and anilines were purchased from Aldrich. Column chromatography was performed with Rankem silica gel (60-120 mesh). The substituted 2-halobenzamides were prepared according to the reported procedures.[1]NMR (^{1}H and ^{13}C) spectra were recorded with a

Varian 400 or a Bruker Ultrashield 300 spectrometer. Melting points were determined using Buchi B-540 melting point apparatus and are uncorrected. Elemental analysis was carried out using Perkin Elmer-2400 CHNS analyzer.

General Procedure for the Synthesis of *N*-Substituted Benzo[*d*]isothiazol-3(2*H*)-one-1-oxides. An oven dried round bottom flask (10 mL) was charged with *N*-substituted 2-halobenzamide (0.5 mmol), CuCl (10 mol %), sulfur powder (1.5 mmol) and K_2CO_3 or Cs_2CO_3 (1.5 mmol) in DMF (1 mL) under nitrogen atmosphere. The resultant mixture was stirred at 75-100 °C under nitrogen balloon for the appropriate time. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. The reaction mixture was then cooled to room temperature and treated with trifluroacetic acid (1.5 mmol) followed addition of 30% H_2O_2 (1.2 equiv), dichloromethane (1 mL) and Ti(salan)Cl_2 (10 mol %). The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. The reaction mixture was then diluted with ethyl acetate (10 mL) The organic layer was separated and washed with water (3 x 5 mL) and brine (1 x 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using hexane and ethyl acetate as eluent.

Characterization Data of *N*-Substituted Benzo[*d*]isothiazol-3(2*H*)-one-1-oxides



***N*-Phenylbenzo[*d*]isothiazol-3(2*H*)-one-1-oxide (Table 2, Entry 1).**

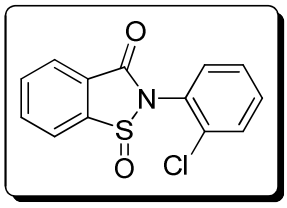
Colorless solid; yield: 80%; mp 135-136 °C (lit.[4a] 136-137 °C).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.18 (d, *J* = 8.0 Hz, 1H), 7.80-7.61 (m, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.46-7.38 (m, 2H), 7.28 (t, *J* = 7.2 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ = 164.3, 145.1, 135.0, 133.8, 132.9, 129.7, 128.5, 127.9, 126.8, 125.0.

FT-IR (KBr): 2932, 2841, 1676, 1410, 1254, 1110, 1091, 1015 cm^{-1}.

Anal. Calcd for $C_{13}H_9NOS$: C, 64.18; H, 3.73; N, 5.76; S, 13.18. Found: C, 64.21; H, 3.75; N, 5.73; S, 13.21.



***N*-(2-Chlorophenyl)benzo[*d*]isothiazol-3(2*H*)-one-1-oxide (Table 2, Entry 2).**

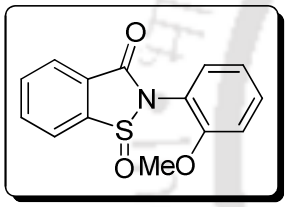
Colorless solid; yield: 31%; mp 120-121 °C

^{1}H NMR ($CDCl_3$, 400MHz) δ = 8.18 (d, *J* = 8.0 Hz, 1H), 7.96-7.29 (m, 7H).

^{13}C NMR ($CDCl_3$, 400MHz) δ = 165.4, 145.9, 134.7, 133.2, 133.4, 133.2, 129.3, 128.6, 127.2, 125.9, 124.6, 122.6, 121.1.

FT-IR (KBr): 2926, 2851, 1736, 1490, 1325, 1182, 1028 cm^{-1}.

Anal. Calcd for $C_{13}H_8ClNO_2S$: C, 56.22; H, 2.90; N, 5.04; S, 11.55 Found: C, 56.18; H, 2.93; N, 5.06; S, 11.50.



***N*-(2-Methoxyphenyl)benzo[*d*]isothiazol-3(2*H*)-one-1-oxide (Table 2, Entry 3).**

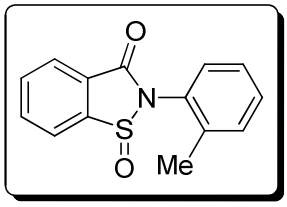
Colorless solid; yield: 75%; mp 125-126 °C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.15 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 6.8 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.40-7.35 (m, 3H), 7.03 (t, *J* = 8.0 Hz, 2H), 3.80 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 166.1, 157.7, 142.8, 132.5, 130.7, 130.3, 127.9, 124.7, 124.1, 123.9, 120.4, 111.7, 56.5.

FT-IR (KBr): 2923, 2851, 1663, 1587, 1459, 1414, 1251, 1100, 1084 cm^{-1}.

Anal. Calcd for $C_{14}H_{11}NO_3S$: C, 61.52; H, 4.06; N, 5.12; O, S, 11.73. Found: C, 61.48; H, 4.09; N, 5.10; S, 11.77.



***N*-(2-Methylphenyl)benzo[*d*]isothiazol-3(2*H*)-one-1-oxide (Table 2, Entry 5).**

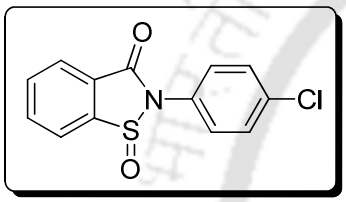
Colorless solid; yield: 77%; mp 120-121 °C

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.17 (d, *J* = 8.0 Hz, 1H), 7.73 (t, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.49 (s, 1H), 7.48-7.39 (m, 2H), 7.36 (t, *J* = 8.0 Hz, 1H), 7.07 (d, *J* = 7.6 Hz, 1H), 2.38 (s, 3H).

^{13}C NMR ($CDCl_3$, 100MHz) δ = 164.4, 140.5, 138.9, 137.0, 132.9, 128.8, 127.9, 127.3, 126.2, 125.8, 124.8, 121.7, 119.9, 21.8.

FT-IR (KBr): 2963, 2917, 1657, 1514, 1334, 1100, 1015 cm^{-1}.

Anal. Calcd for $C_{14}H_{11}NO_2S$: C, 65.35; H, 4.31; N, 5.44; S, 12.46. Found: C, 65.38; H, 4.29; N, 5.41; S, 12.43.



***N*-(4-Chlorophenyl)benzo[*d*]isothiazol-3(2*H*)-one-1-oxide (Table 2, Entry 6).**

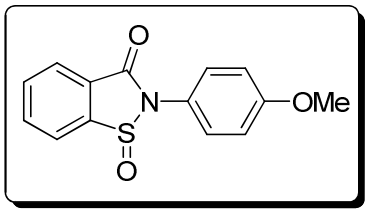
Colorless solid; yield: 31%; mp 127-128 °C (lit.[4a] 128-129 °C).

^{1}H NMR ($CDCl_3$, 400MHz) δ = 8.18 (d, *J* = 8.0 Hz, 1H), 8.06-7.59 (m, 7H).

^{13}C NMR ($CDCl_3$, 400MHz) δ = 164.4, 145.6, 134.7, 134.6, 133.4, 133.0, 129.8, 128.1, 126.2, 124.9, 124.6.

FT-IR (KBr): 2926, 2851, 1731, 1581, 1490, 1325, 1303, 1182, 1028 cm^{-1}.

Anal. Calcd for $C_{13}H_8ClNO_2S$: C, 56.22; H, 2.90; N, 5.04; S, 11.55 Found C, 56.18; H, 2.93; N, 5.06; S, 11.50.



***N*-(4-Methoxyphenyl)benzo[*d*]isothiazol-3(2*H*)-one-1-oxide (Table 2, Entry 8).**

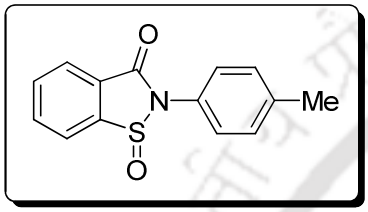
Colorless solid; yield: 35%; mp 146-147 °C (lit.[4a] 147-148 °C).

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.19 (d, *J* = 8.0 Hz, 1H), 7.73 (t, *J* = 6.8 Hz, 1H), 7.65-7.62 (m, 3H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.02 (d, *J* = 6.8 Hz, 2H), 3.81 (s, 3H)

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 164.5, 159.9, 144.9, 133.8, 132.9, 129.8, 127.9, 127.2, 126.3, 124.8, 114.9, 55.7.

FT-IR (KBr): 2923, 2854, 1720, 1591, 1331, 1267, 1100, 1095 cm^{-1}.

Anal. Calcd for $C_{14}H_{11}NO_3S$: C, 61.52; H, 4.06; N, 5.12; S, 11.73. Found: C, 61.52; H, 4.10; N, 5.15; S, 11.75.



***N*-(4-Methylphenyl)benzo[*d*]isothiazol-3(2*H*)-one-1-oxide (Table 2, Entry 10).**

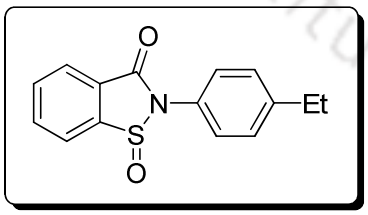
Colorless solid; yield: 84%; mp 167-168 °C (lit.[4a] 167.5-168.5 °C).

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.21 (d, *J* = 8.0 Hz, 1H), 7.87-7.63 (m, 5H), 7.21 (d, *J* = 7.6 Hz, 2H), 2.29 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 164.4, 145.1, 139.4, 138.0, 134.3, 133.4, 130.8, 130.4, 128.4, 127.3, 126.1, 124.9, 21.3.

FT-IR (KBr): 2923, 2917, 2851, 1674, 1331, 1261, 1100, 1019 cm^{-1}.

Anal. Calcd for $C_{14}H_{11}NO_2S$: C, 65.35; H, 4.31; N, 5.44; S, 12.46. Found: C, 65.31; H, 4.34; N, 5.40; S, 12.48.



***N*-(4-Ethylphenyl)benzo[*d*]isothiazol-3(2*H*)-one-1-oxide (Table 2, Entry 11).**

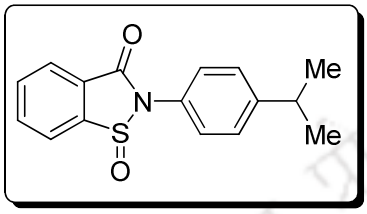
Colorless solid; yield: 77%; mp 164-165 °C

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.20 (d, *J* = 8.4 Hz, 1H), 7.73-7.52 (m, 5H), 7.39 (d, *J* = 8.0 Hz, 2H), 2.80 (q, *J* = 8.0 Hz, 2H), 1.36 (t, *J* = 8.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 164.2, 143.5, 139.9, 134.6, 132.2, 128.8, 127.1, 125.7, 124.8, 120.0, 28.5, 15.5.

FT-IR (KBr): 2923, 2917, 2851, 1614, 1331, 1251, 1120, 1019 cm^{-1}.

Anal. Calcd for $C_{15}H_{11}NO_2S$: C, 66.40; H, 4.83; N, 5.16; S, 11.82. Found: C, 66.44; H, 4.81; N, 5.11; S, 11.78.



***N*-(4-Isopropylphenyl)benzo[*d*]isothiazol-3(2*H*)-one-1-oxide (Table 2, Entry 12).**

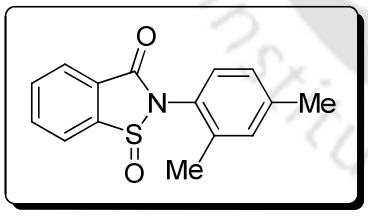
Colorless solid; yield: 79%; mp 160-161 °C

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.20 (d, *J* = 8.8 Hz, 1H), 7.73-7.50 (m, 5H), 7.42 (d, *J* = 8.0 Hz, 2H), 3.05-3.02 (m, 1H), 1.36 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 164.2, 148.1, 139.9, 134.6, 132.2, 127.4, 127.1, 125.7, 124.9, 124.8, 120.0, 33.8, 29.7, 23.9.

FT-IR (KBr): 2923, 2917, 2851, 1624, 1301, 1251, 1125, 1019 cm^{-1}.

Anal. Calcd for $C_{16}H_{15}NO_2S$: C, 67.34; H, 5.30; N, 4.91; S, 11.24. Found: C, 67.30; H, 5.34; N, 4.93; S, 11.27.



***N*-(2,4-Dimethylphenyl)benzo[*d*]isothiazol-3(2*H*)-one-1-oxide (Table 2, Entry 13).**

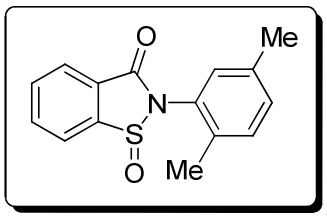
Colorless solid; yield: 80%; mp 118-119 °C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.19 (d, *J* = 8.0 Hz, 1H), 7.85- 7.51(m, 4H), 7.04 (s, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 2.26 (s, 3H), 2.15 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 164.9, 142.3, 138.5, 135.4, 133.2, 133.0, 131.3, 128.8, 127.4, 127.1, 125.2, 124.1, 21.3, 18.1.

FT-IR (KBr): 2923, 2854, 1679, 1329, 1262, 1108, 1017 cm^{-1}.

Anal. Calcd for $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83; N, 5.16; S, 11.82. Found C, 66.44; H, 4.81; N, 5.19; S, 11.79.



***N*-(2,5-Dimethylphenyl)benzo[*d*]isothiazol-3(2*H*)-one-1-oxide (Table 2, Entry 14).**

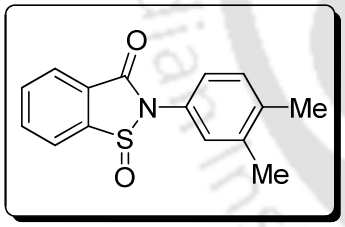
Colorless solid; yield: 82%; mp 117-118 °C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.20 (d, *J* = 8.0 Hz, 1H), 7.83- 7.63(m, 4H), 7.10 (d, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 7.6 Hz, 1H), 2.30 (s, 3H), 2.18 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 164.3, 145.3, 138.3, 135.7, 133.6, 133.3, 131.7, 127.8, 127.4, 127.1, 126.7, 124.1, 21.3, 17.8.

FT-IR (KBr): 2923, 2854, 1679, 1329, 1262, 1108, 1017 cm^{-1}.

Anal. Calcd for $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83; N, 5.16; S, 11.82. Found C, 66.42; H, 4.80; N, 5.20; S, 11.84.



***N*-(3,4-Dimethylphenyl)benzo[*d*]isothiazol-3(2*H*)-one-1-oxide (Table 2, Entry 15)**

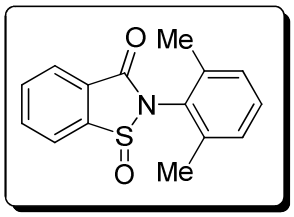
Colorless solid; yield: 84%; mp 117-118 °C.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.17 (d, *J* = 8.0 Hz, 1H), 7.83-7.50 (m, 5H), 7.19 (d, *J* = 8.0 Hz, 1H), 2.30 (s, 3H), 2.29 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.3, 142.2, 137.6, 135.4, 134.8, 132.0, 130.8, 127.8, 126.9, 125.2, 124.1, 122.5, 120.2, 20.0, 19.8.

FT-IR (KBr): 2920, 2849, 2920, 1645, 1261, 1101, 1041 cm^{-1}.

Anal. Calcd for $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83; N, 5.16; S, 11.82. Found: C, 66.45; H, 4.85; N, 5.14; S, 11.85.



***N*-(2,6-Dimethylphenyl)benzo[*d*]isothiazol-3(2*H*)-one-1-oxide (Table 2, Entry 15).**

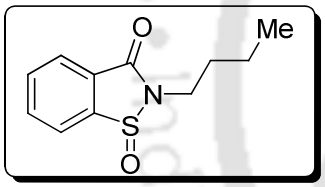
Colorless solid; yield: 76%; mp 120-121 °C

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.21 (d, *J* = 8.4 Hz, 1H), 7.81-7.62 (m, 3H), 7.21-7.18 (m, 3H), 2.26 (s, 3H), 2.12 (s, 3H);

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 164.7, 144.4, 138.9, 136.1, 133.9, 132.3, 131.6, 130.8, 129.7, 127.3, 126.1, 124.1, 120.8, 20.6, 18.4.

FT-IR(KBr): 2920, 2849, 2920, 1656, 1278, 1111, 1021 cm^{-1}.

Anal. Calcd for $C_{15}H_{13}NO_2S$: C, 66.40; H, 4.83; N, 5.16; S, 11.82. Found: C, C, 66.36; H, 4.86; N, 5.14; S, 11.79.



***N*-Butylbenzo[*d*]isothiazol-3(2*H*)-one-1-oxide (Table 3, Entry 1).**

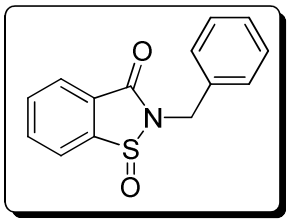
Yellow oil; yield: 43%.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.11 (d, *J* = 8.0 Hz, 1H), 7.84-7.63 (m, 3H), 3.86 (t, *J* = 7.2 Hz, 2H), 1.73(t, *J* = 7.2 Hz, 2H), 1.71-1.33 (m, 2H), 0.92 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 165.5, 143.3, 132.3, 127.1, 125.6, 125.1, 119.2, 43.8, 31.7, 19.9, 13.8.

FT-IR (neat): 2962, 2857, 1671, 1261, 1091 cm^{-1}.

Anal Calc for $C_{11}H_{13}NO_2S$: C, 59.17; H, 5.87; N, 6.27; S, 14.36. Found: C, 59.21; H, 5.83; N, 6.24; S, 14.33.



***N*-Benzylbenzo[*d*]isothiazol-3(2*H*)-one-1-oxide (Table 3, Entry 3).**

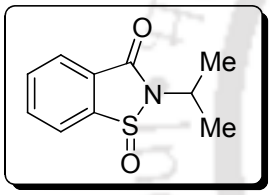
Colorless solid; yield: 45%; mp 101-102 °C

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.10 (d, *J* = 7.6 Hz, 1H), 7.76-7.29 (m, 8H), 5.01 (s, 2H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 166.1, 140.5, 136.3, 134.2, 128.9, 128.1, 127.7, 126.9, 125.3, 122.9, 120.5, 49.3.

FT-IR (KBr): 3078, 3022, 2962, 2923, 1667, 1592, 1243, 1184, 1116, 1064, 1029 cm^{-1}.

Anal Calcd for $C_{14}H_{11}NO_2S$: C, 65.35; H, 4.31; N, 5.44; S, 12.46. Found: C, 65.30; H, 4.33; N, 5.41; S, 12.46.



***N*-Isopropylbenzo[*d*]isothiazol-3(2*H*)-one-1-oxide (Table 3, Entry 3).**

Yellow oil; 54% yield.

^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.09 (d, *J* = 7.6 Hz, 1H), 7.87-7.61 (m, 3H), 5.01-4.95 (m, 1H), 1.40 (d, *J* = 6.4 Hz, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz) δ = 164.9, 146.1, 130.9, 126.4, 124.9, 124.6, 120.5, 46.1, 22.2.

FT-IR (neat): 2935, 2851, 1641, 1447, 1239, 1112, 1034 cm^{-1}.

Anal. Calcd for $C_{10}H_{11}NO_2S$: C, 57.39; H, 5.30; N, 6.69; S, 15.32. Found: C, 57.43; H, 5.28; N, 6.71; S, 15.29.

5.6 References

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RP-369b

exp1 s2pul

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ct	32	PROCESSING	
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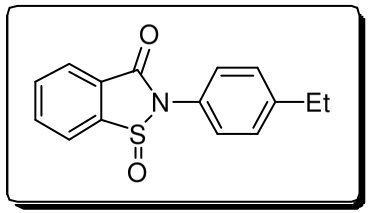
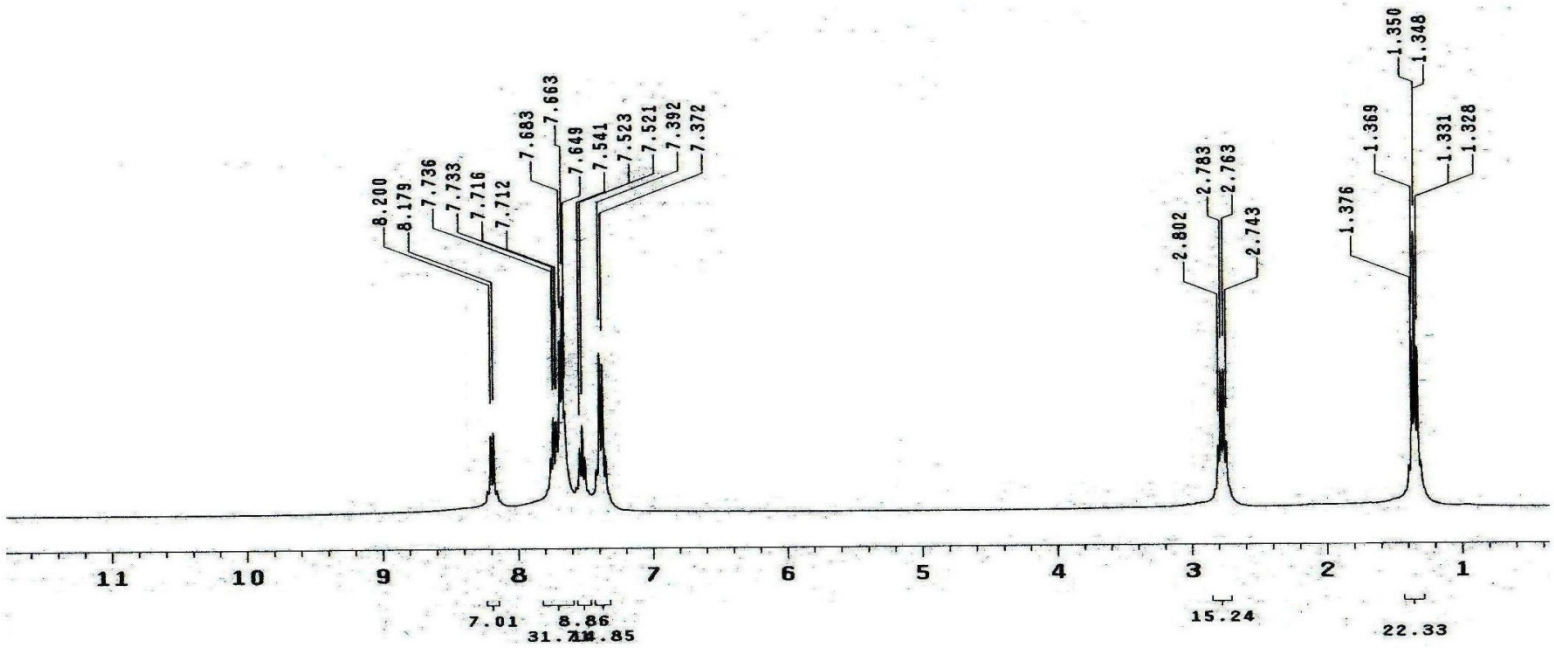
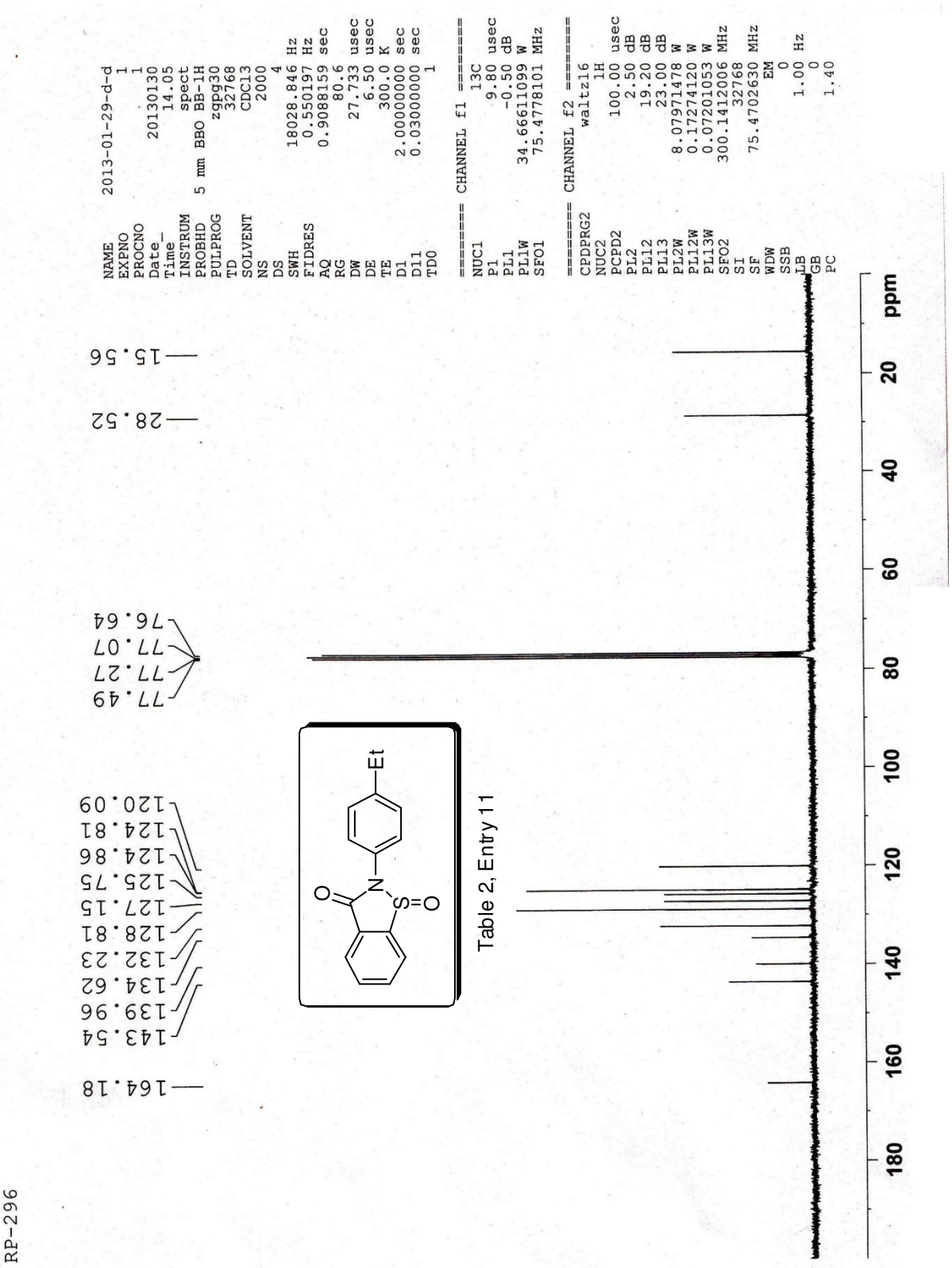
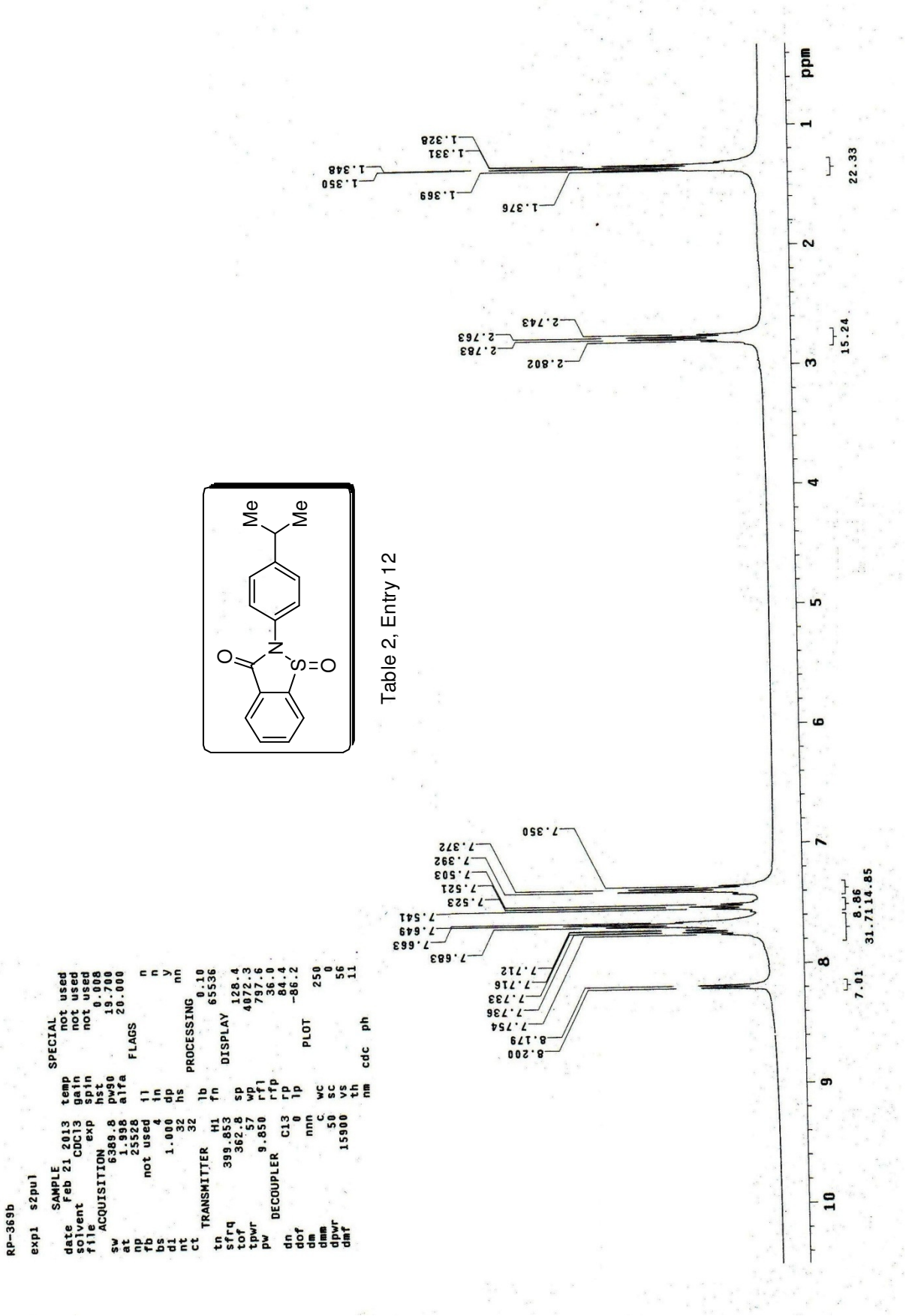
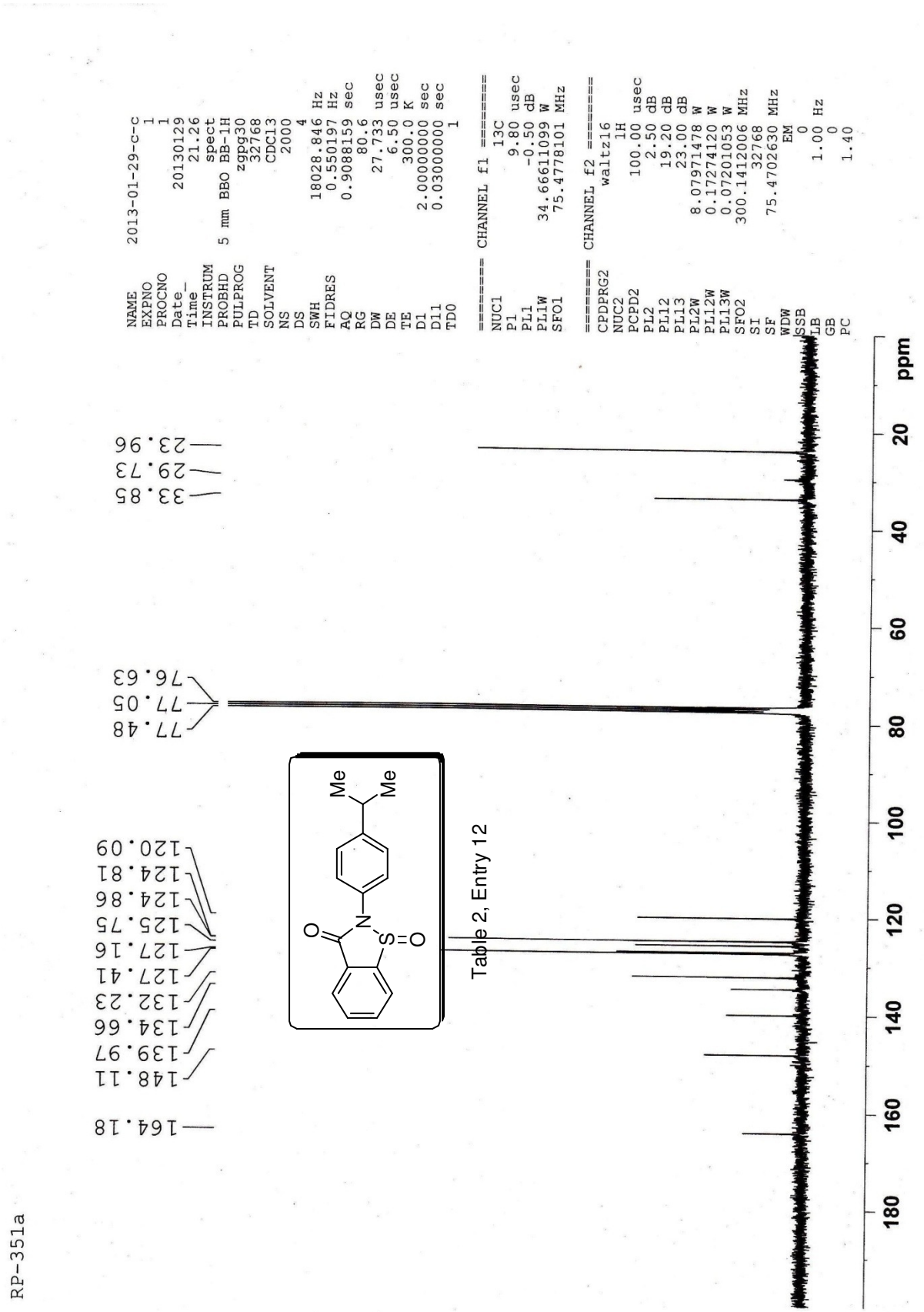


Table 2, Entry 11









Conclusions

In chapter 1, the literature survey of the copper-catalyzed *C-N*, *C-O* and *C-S* cross-coupling reactions and their mechanistic aspects are covered. The reactions have made considerable progress in the recent years.

In chapter 2, the selective hydroxylation of aryl halides with $^{n}Bu_4NOH$ is described by the combined use of CuI and 8-hydroxyquinaldine at moderate temperature. The process is efficient, general and simple to synthesis substituted phenols and avoids the use of inert conditions.

In chapter 3, the synthesis of alkyl aryl ethers has been demonstrated from aryl bromides and aryl iodides. The reaction involves the generation of phenoxides, by the protocol in chapter 1, followed by treatment with an alkyl halide. The reaction is general and efficient and provides the target molecules in high yield. Some of the protocols available previously employed copper based catalytic systems however; mostly those systems are effective catalyst only under inert conditions. Since a wide variety of compounds of biological and medicinal importance contain either phenolic OH, so we hope that this protocol may serve as an alternative route for the synthesis of those compounds.

In chapter 4, copper-catalyzed synthesis of *N*-substituted benzoisothiazol-3-ones has been demonstrated from *N*-substituted 2-halobenzamides and sulfur powder *via C-S* cross-coupling reaction followed by *N-S* bond formation. The reaction is general and synthesis of a series of compounds can be carried out in good yields.

In chapter 5, the conversion of 2-halobenzamides to benzo[*d*]isothiazol-3(2*H*)-one-1-oxides has been described. In this reaction, *N*-substituted benzoisothiazol-3-ones generated in situ using copper-catalysis (Chapter 4) is oxidized to benzo[*d*]isothiazol-3(2*H*)-one-1-oxides using titanium(IV)-salan complex in the presence of aqueous hydrogen peroxide as terminal oxidants. This protocol serves as an alternative route to this class of compounds which were previously generated from *N*-substituted benzoisothiazol-3-ones as the substrate precursor.

List of Publications

1. Reusable Cu_2O-Nanoparticles Catalyzed Amidation of Aryl Iodides
   S. Jammi, S. Krishnamoorthy, P. Saha, D. S. Kundu, S. Sakthivel, Md A. Ali, **R. Paul** and T. Punniyamurthy, *Synlett* **2009**, 3323.

2. Ligand-Free Copper-Catalyzed Synthesis of Substituted Benzimidazoles, 2-Aminobenzimidazoles, 2-Aminobenzothiazoles, and Benzoxazoles
   P. Saha, T. Ramana, N. Purkait, Md A. Ali, **R. Paul** and T. Punniyamurthy, *J. Org. Chem.* **2009**, *74*, 8.

3. Copper-Catalyzed Selective Hydroxylation of Aryl Halides with Tetrabutylammonium Hydroxide: Synthesis of Phenols and Alkyl Aryl Ethers
   R. Paul, Md A. Ali and T. Punniyamurthy, *Synthesis*, **2010**, 4268
   .
4. Copper-Catalyzed One-Pot Synthesis of *N*-Substituted Benzo[*d*]isothiazol-3(2*H*)-ones via C-S/N-S Bond Formation
   R. Paul and T. Punniyamurthy, *RSC Adv.* **2012**, *2*, 7057.

Conferences

1. Copper-Catalyzed Selective Hydroxylation of Aryl Halides with Tetrabutylammonium Hydroxide: Synthesis of Phenols and Alkyl Aryl Ethers
   R. Paul, Md A. Ali and T. Punniyamurthy, Frontiers in Chemical Sciences 2010, Indian Institute of Technology Guwahati, December 3-4 2010.

2. Copper-Catalyzed One-Pot Synthesis of *N*-Substituted Benzo[*d*]isothiazol-3(2*H*)-ones via C-S/N-S Bond Formation
   R. Paul and T. Punniyamurthy, Frontiers in Chemical Sciences 2012, Indian Institute of Technology Guwahati, December 11-12 2012.