Studies Toward Metal-Free Synthesis of Benzofuzed Azoles Using Hypervalent Iodine

A Thesis Submitted
in Partial Fulfillment of the Requirements
for the Degree of

DOCTOR OF PHILOSOPHY

by

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Dedicated

To

My Family

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
October 2015

Santhosh Kumar Alla

CERTIFICATE

This is to certify that Mr. Santhosh Kumar Alla has been working under my supervision since July 2010. I am forwarding his thesis entitled "*Studies Toward Metal-Free Synthesis of Benzofuzed Azoles Using Hypervalent Iodine*" 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
October 2015

Prof. Tharmalingam Punniyamurthy
Supervisor

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Santhosh Kumar Alla

LIST OF ABBREVIATIONS

ac	acetyl	HFIP	1,1,1,3,3,3-hexafluoro-2-propanol
acac	acetylacetone	IR	infrared
BINAM	1,1′-Binaphthyl-2,2′-diamine	*m*CPBA	*meta*-chloroperbenzoic acid
Bn	benzyl	mp	melting point
bpy	2,2'-bipyridine	Ms	methanesulfonyl
BTF	benzotrifluoride	MS	molecular sieves
Bu	butyl	m/z	mass to charge ratio
DABCO	1,4-diazabicyclo[2.2.2]octane	NMP	*N*-methyl-2-pyrrolidone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene	NMR	nuclear magnetic resonance
DCE	1,2-dichloroethane	ORTEP	oak ridge thermal ellipsoid plot
DCM	dichloromethane	Pr	propyl
DME	1,2-dimethoxyethane	*p*TSA	*p*-toluenesulfonic acid
DMF	*N*,*N*-dimethylformamide	rt	room temperature
DMEDA	*N*,*N*'-dimethylethylenediamine	SCE	saturated calomel electrode
dmgH	dimethylglyoxime	TBAB	tetra-*n*-butylammonium bromide
DMSO	dimethylsulfoxide	TBHP	*tert*-butyl hydroperoxide
dr	diastereomeric ratio	Tf	trifluoromethanesulfonyl
EDG	electron donating group	TFA	trifluoroacetic acid
ee	enantiomeric excess	TFE	2,2,2-trifluoroethanol
EWG	electron wthdrawing group	THF	Tetrahydrofuran

TLC	thin layer chromatography	TMS	trimethylsilyl
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylenediamine	TMTU	tetramethylthiourea
TMHD	2,2,6,6-tetramethyl-3,5-heptanedione	Ts	*p*-toluenesulfonyl

Abbreviations for intensities of ^{1}H-NMR signals

s	singlet	t	triplet
d	doublet	q	quartet
dd	doublet of doublet	m	multiplet
ddd	doublet of doublet of doublet	Hz	Hertz
dt	doublet of triplet		
MHz	Mega-Hertz		

Abstract

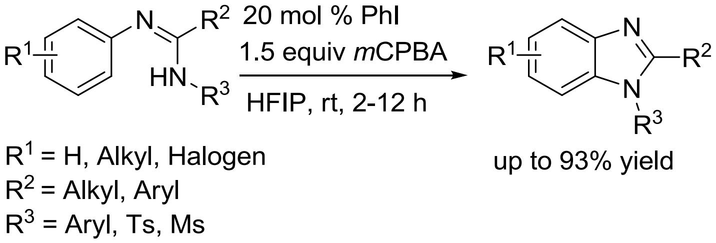
The research work presented in this thesis has been divided into five chapters. The first chapter focuses on the recent developments in hypervalent iodine chemistry. The second chapter describes iodobenzene catalyzed synthesis of substituted benzimidazoles using *m*CPBA as a terminal oxidant. The third and fourth chapters present the synthesis of substituted benzoxazoles and benzothiazoles using 1-iodo-4-nitrobenzene in the presence of oxone as an oxidant. The last chapter deals with the oxidative *C-N* bond formation of *N*,*N'*-diarylureas for the synthesis of substituted benzimidazol-2-ones using phenyliodine bis(trifluoroacetate).

Chapter 1. Recent Developments in Hypervalent Iodine Chemistry

Hypervalent compounds are those containing a main group element (Group V-VIII) with more than an octet of electrons in its valence shell. The bonding in hypervalent compounds was explained by three-center-four-electron (3c-4e) bond and they are named according to Martin-Arduengo designation. Hypervalent iodine compounds owing to their mild and selective oxidizing properties are used to a great extent in synthetic organic chemistry for the construction of carbon-carbon and carbon-heteroatom bonds. In recent years, many research groups have focused on the catalytic utilization of these reagents by developing new catalytic processes where the iodine(III) species was generated *in situ* using catalytic amount of iodoarenes and a stoichiometric oxidant.

Chapter 2. Iodobenzene Catalyzed C-H Amination of *N*-Substituted Amidines Using *m*-Chloroperbenzoic Acid

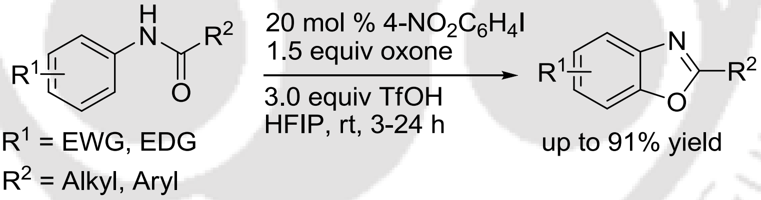
Benzimidazoles are an important class of heterocyclic compounds found in a wide variety of medicinally important molecules. This chapter presents iodobenzene catalyzed synthesis of substituted benzimidazoles from *N*,*N′*-bis(aryl)amidines and N^1-Phenyl-N^2-(4-methylbenze- ne/methylsulfonyl)amidines *via* oxidative C-H amination in the presence of *m*CPBA as a terminal oxidant at room temperature in HFIP as solvent (Scheme 1).



Scheme 1. Synthesis of Substituted Benzimidazoles

Chapter 3. Iodobenzene Catalyzed Synthesis of Benzoxazoles Using Oxone *via C-O* Bond Formation

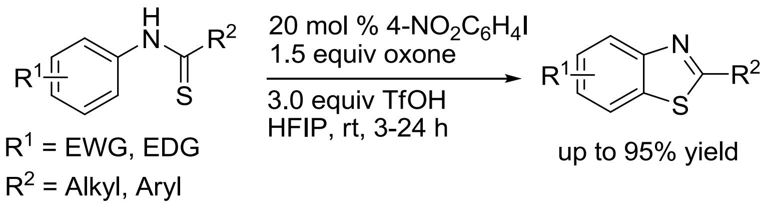
Benzoxazoles constitute a prominent class of heterocycles possessing important medicinal properties and are a privileged structural units in a diverse range of natural products and synthetic drugs with wide applications. This chapter describes a metal-free, 1-iodo-4-nitrobenzene catalyzed synthesis of 2-arylbenzoxazoles from anilides in the presence of environmentally benign oxone as a terminal oxidant at room temperature. The reaction proceeds *via* an oxidative C-H functionalization/*C-O* bond formation providing the desired products in good yields. This protocol can readily be extended for the construction of 2-alkylbenzoxazoles (Scheme 2).



Scheme 2. Synthesis of Substituted Benzoxazoles

Chapter 4. Iodobenzene Catalyzed Synthesis of Benzothiazoles Using Oxone *via C-S* Bond Formation

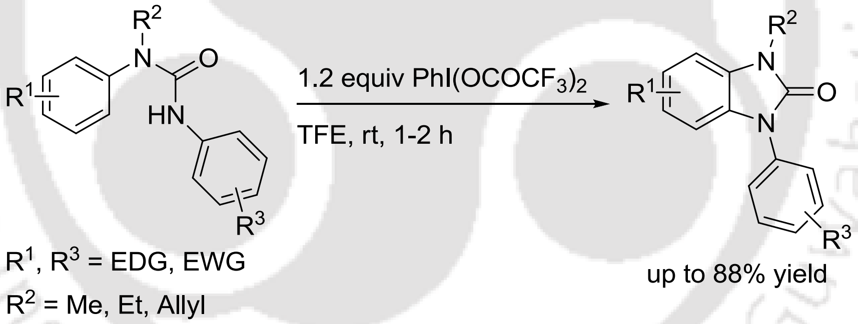
The construction of benzothiazole structural motifs have been a topic of immense interest in recent years due to their presence in a number of natural products and biologically active compounds and they are used as drugs for several diseases such as tumors, diabetes and inflammatory diseases. The present method uses 1-iodo-4-nitrobenzene as catalyst to synthesize substituted benzothiazoles from aryl/alkylthioanilides in the presence of environmentally benign oxone as a terminal oxidant at room temperature. The scope of the reaction was carried out with different aryl/alkylthioanilides derived from corresponding anilides to give desired products in good yields (Scheme 3).



Scheme 3. Synthesis of Substituted Benzothiazoles

Chapter 5. Hypervalent Iodine Mediated Synthesis of Benzimidazol-2-ones

Benzimidazol-2-ones are found in a wide variety of natural products and have attracted considerable interest due to their wide spectrum of biological activity. A metal-free synthesis of substituted benzimidazol-2-ones from *N,N'*-diarylureas using PhI(OCOCF$_3$)$_2$ at room temperature in TFE as solvent has been described in this chapter (Scheme 4).



Scheme 4. Synthesis of Benzimidazol-2-one Derivatives

Contents

Chapter I

Recent Developments in Hypervalent Iodine Chemistry

1.1. Iodine

Iodine is a chemical element with symbol **I** and atomic number 53. Its name reflects the crystalline, lustrous, deep purple color of resublimed crystalline iodine and was first isolated from the ash of seaweed by the French chemist Bernard Courtois in 1811.[1] Iodine is an essential trace element for humans and plays a vital role in many biological organisms. It belongs to the main group, p-block elements, group 17, fifth row element with the electron configuration $[Kr]d^{10}s^2p^5$, having seven electrons in its valence shell. Therefore, the preferred oxidation state of iodine is –1, however, because it is the largest, most polarizable and most electropositive of the group 17 elements, it forms stable polycoordinate, multivalent compounds with relatively weak bonds to electronegative groups or elements such as oxygen, sulfur, nitrogen or a halide.[2]

1.2. Hypervalent Compounds

Compounds containing an element from main group (Group V-VIII) having more than an octet of electrons in its valence shell are termed as hypervalent compounds.[3] These compounds were first described as hypervalent by Jeremy I. Musher in 1969 in his review titled “The Chemistry of Hypervalent Molecules”.[4]

1.3. Hypervalent Bonding

In principle, there are two possible explanations to account for the ability of the main group element in hypervalent compounds to accommodate expanded octet:

(i) By the formation of dsp^3 or d^2sp^3 hybrid orbitals by hybridization of higher energy d orbitals

(ii) By the formation of a new type of highly ionic orbital without the involvement of d orbitals, i.e. involvement of three-center-four-electron (3c-4e) bond.

Investigations carried out on bonding in hypervalent compounds by Schleyer led to the rejection of the hybridization concept.[5] The contribution of *d*-orbitals to hypervalent bonds seems not to be fundamental, since the energy gap between *sp*- and *d*-orbitals in main group elements is too large to allow hybridization. Thus, the concept of a 3c-4e bond has been accepted to explain hypervalent bonding.

In 1951, Pimentel and Rundel proposed the idea of three-center-four-electron (3c-4e) bond using molecular orbital theory.[6] According to the fundamental description of this 3c-4e bond in hypervalent compounds, one pair of bonding electrons from the central atom is delocalized to the two substituents (ligands), whereby the central atom bears a positive charge and the two monovalent ligands share the corresponding negative charge.

According to this hypervalent model, the bonding in iodine(III) molecules, RIL_2 can be explained as follows. The interaction of the doubly occupied $5p_z$ orbital of the central iodine atom and the half-filled one orbital from each of the apical two ligands L results in three molecular orbitals: bonding, nonbonding and antibonding (Figure 1). The two lower energy molecular orbitals, bonding and nonbonding are occupied. The filled nonbonding molecular orbital has a node at central iodine and this induces polarity into the hypervalent bond with a partial positive charge on the central iodine atom and partial negative charge on the axial ligands. The highest electron density is localized at the ends of the 3c-4e-bond axis, hence the more electronegative ligands prefers to occupy the apical position. The carbon substituent R is bound by a normal two-electron covalent bond and the overall geometry of molecule RIL_2 is a distorted trigonal bipyramid with two elongated I-L apical bonds and the least electronegative carbon ligand R and both electron pairs reside in equatorial positions.

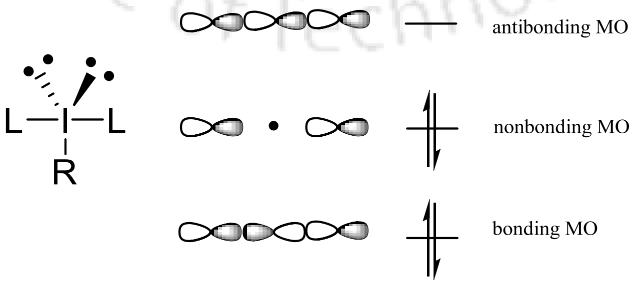


Figure 1. Molecular Orbital Description of the Three-Center-Four-Electron Bond in Iodine (III) Molecules, RIL_2.

1.4. Nomenclature of Hypervalent Compounds

Hypervalent compounds are conveniently named according to N-X-L nomenclature (Martin-Arduengo designation),[7] where 'N' denotes the number of electrons formally assigned to the valence shell of the central hypervalent atom, 'X' is the identity of central atom and 'L' describes the number of ligands on the central atom.

According to IUPAC rules, compounds with nonstandard bonding numbers are designated by lambda notation, the symbol λ^n is used to indicate any heteroatom in nonstandard valence states (n) in a formally neutral compound. Thus, H_3I is called as λ^3-iodane and H_5I as λ^5-iodane. The most common iodine(III), $ArIL_2$ is named as aryl-λ^3-iodane and iodine(V), $ArIL_4$ as aryl-λ^5-iodane. Names and abbreviations of some hypervalent iodine compounds are given in Table 1.

1.5. General Reactivity of Hypervalent Iodine

The chemistry of iodine(III) compounds is comparable to that of transition metals and in general, reactions of hypervalent iodine reagents are discussed in three main types of reactions (Figure 2).

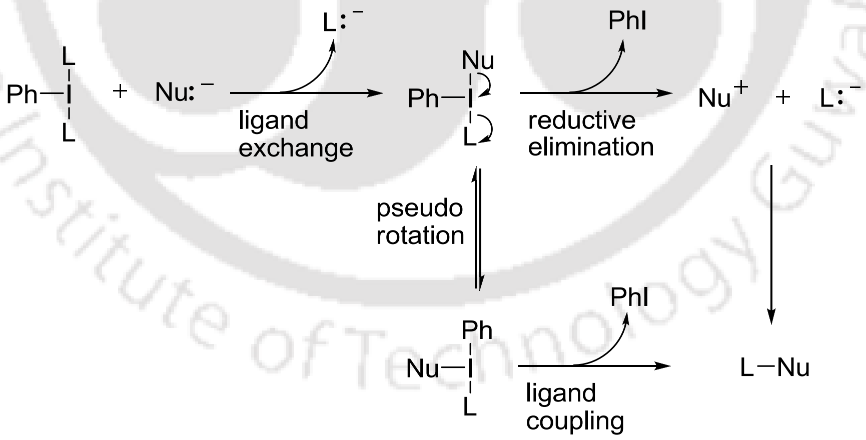
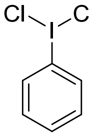
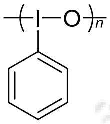
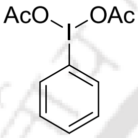
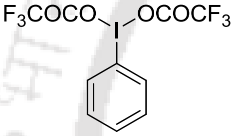
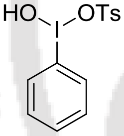
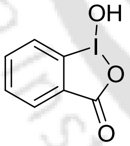
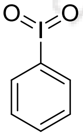
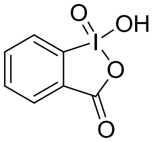
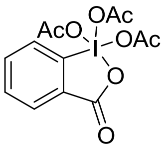


Figure 2. Description of the Reactions of Iodine(III) with Nucleophiles.

Ligand Exchange: The strongly electrophilic nature of the iodine makes it susceptible to the initial exchange of ligands on it with external nucleophiles (Nu:$^-$).

Table 1. List of Some Common Hypervalent Iodine Compounds

S. No.	Polyvalent Iodine	IUPAC Name	Common Names	Abbreviation
1		(Dichloroiodo)benzene	Iodobenzene dichloride Phenyliodine dichloride	IBD
2		Iodosylbenzene	Iodosobenzene	IDB
3		(Diacetoxyiodo)benzene	Phenyliodine diacetate	DIB PIDA
4		[Bis(trifluoroacetoxy) iodo]benzene	Iodobenzene bis(trifluoroacetate) Phenyliodine bis(trifluoroacetate)	BTI PIFA
5		[Hydroxy(4-methylphenyl sulfonyloxy)iodo]benzene	[Hydroxy(tolsyloxy)iodo] benzene Koser's reagent	HTIB
6		1-Hydroxy-1*H*-1λ^3-benzo[*d*][1, 2]iodoxol-3-one	2-Iodosobenzoic acid 2-Iodosylbenzoic acid	IBA
7		Iodylbenzene	Iodoxybenzene	
8		1-Hydroxy-1-oxo-1*H*-1λ^5-benzo[*d*][1,2]iodoxol-3-one	2-Iodoxybenzoic acid	IBX
9		1,1,1-Triacetoxy-1*H*-1λ^5-benzo[*d*][1,2]iodoxol-3-one	Dess–Martin periodinane	DMP

Reductive Elimination: The second step includes reductive elimination of iodobenzene. This step is a highly energetically favorable process, since the leaving group ability of phenyliodonio group, –I(Ph)L is about 10^6 times better than the triflate.[8] This step results in Nu^+, which can participate in variety of reactions including nucleophilic substitution, rearrangement, fragmentation, α-elimination or β-elimination.

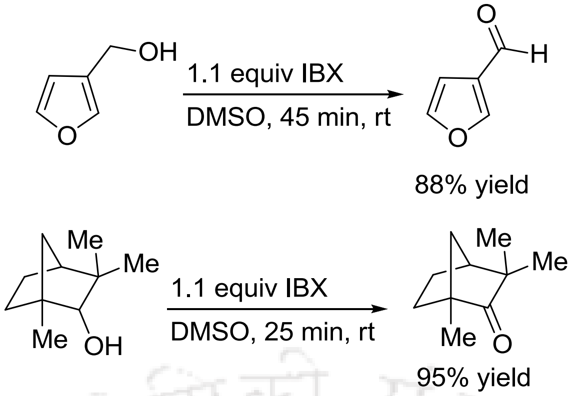
Ligand Coupling: The ligand coupling pathway requires initial pseudo rotation to bring ligands L and Nu to apical and equatorial positions favorable for coupling. Ligand coupling usually occurs in the reactions of iodonium salts as a concerted process.

1.6. Transformations Using Hypervalent Iodide Reagents

Over the past two decades there has been an unprecedented development in the use of polyvalent iodine compounds in synthetic organic chemistry. This impressive growing interest is due to their mild and selective oxidizing properties combined with their low toxicity, ready availability and easy handling. Extensive studies on the use of hypervalent iodine reagents have provided the incentive of finding a milder and more convenient strategies to carry out a wide range of organic transformations, which is clearly evident by the large number of publications in this area.[9] Hypervalent iodine compounds mediates/catalyze various oxidation reactions, in this section, a brief summary on the recent research on synthetic applications of hypervalent iodine compounds with more emphasis on the carbon-carbon and carbon-heteroatom bonds formation is outlined.

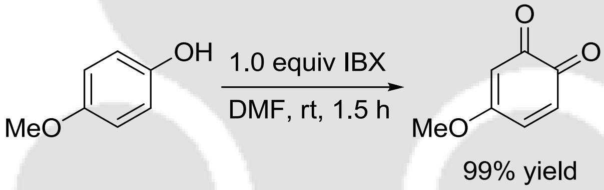
1.6.1. Oxidation of Alcohols, Phenols and Aromatic Compounds

The oxidation of an alcoholic group to a carbonyl moiety is a valuable transformation in organic chemistry. Several methods are available for this transformation, using a number of reagents, including a variety of hypervalent iodines.[10] Among them, IBX was widely explored as a mild and chemoselective reagent for alcohol oxidation. IBX oxidizes primary alcohols to the corresponding aldehydes in DMSO at room temperature without over oxidation to the acids. Sterically hindered alcohols are also easily oxidized at room temperature in high yields (Scheme 1).[10a]



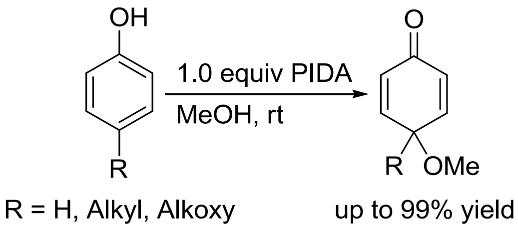
Scheme 1. Oxidation of Alcohols

Pettus and co-workers reported a regioselective oxidation of electron-rich phenols to *o*-quinones with IBX in DMF at room temperature (Scheme 2).[10c] Under these conditions, phenols without electron donating substituents and those containing electron withdrawing groups such as -C(O)R, -CHO, and -NO_2 failed to undergo oxidation.



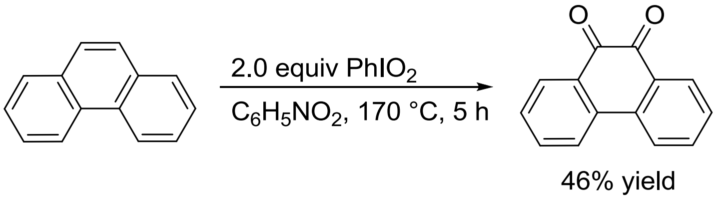
Scheme 2. Oxidation of Phenols

Further, PIDA has been applied successfully for the oxidation of phenols in methanol at room temperature (Scheme 3).[10d] The reaction of 4-alkyl phenols and 4-alkoxy phenols with 1.0 equivalent of PIDA afforded 4-alkyl-4-methoxycyclohexadienones and 4,4-dialkoxycyclohexadienones (quinone ketals), respectively. Reaction of *p*-unsubstituted phenols with 2.0 equivalents of PIDA also resulted in quinone ketals.



Scheme 3. Synthesis of Quinone Ketals by Oxidation of Phenols

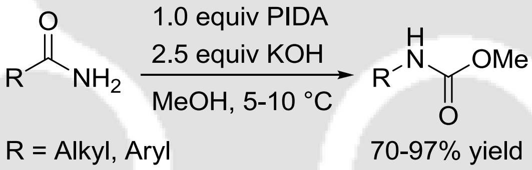
Iodoxybenzene is used for oxidizing activated C–H bonds. Reaction of phenanthrene with iodoxybenzene in nitrobenzene at 170 °C results in phenanthrenequinone (Scheme 4).[10e]



Scheme 4. Oxidation of Aromatic Compounds

1.6.2. Oxidative Rearrangements

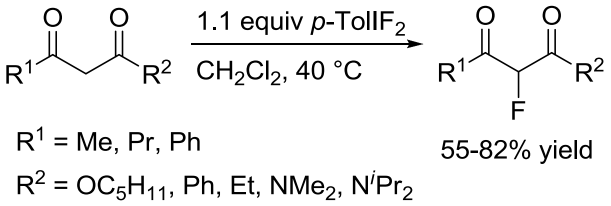
Hypervalent iodine reagents are well known for their application in cationic rearrangements and fragmentation reactions. They are particularly important as oxidants for the Hofmann-type rearrangements. For example, PIDA has been employed effectively for the Hofmann-type rearrangement for the preparation of methyl carbamates from primary alkyl- and arylcarboxamides (Scheme 5).[10i]



Scheme 5. Synthesis of Methyl Carbamates by Hofmann Rearrangement

1.6.3. Fluorination

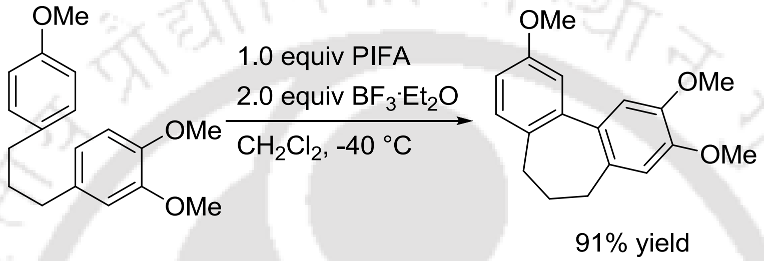
Direct fluorination of C-H bonds can be achieved using *p*-iodotoluene difluoride, *p*-TolIF$_2$. For example, the α-fluorination of β-dicarbonyl compounds has been demonstrated by Hara and co-workers using *p*-TolIF$_2$. The reagent enables monofluorinated products from β-ketoesters, β-ketoamides and β-diketones in good yields under mild conditions (Scheme 6).[10j]



Scheme 6. α-Fluorination of β-Dicarbonyl Compounds

1.6.4. Carbon-Carbon and Carbon-Heteroatom Bonds Formation

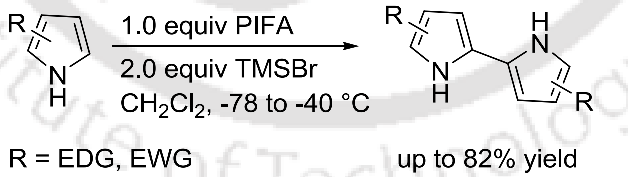
In the last two decades, a highly promising hypervalent iodine(III) mediated protocols for the formation of carbon-carbon and carbon-heteroatom bonds have been developed. For example, a hypervalent iodine(III) induced intramolecular direct C-C biaryl coupling reaction of phenol ether derivatives was developed by Kita and co-workers using PIFA in combination with $BF_3{\cdot}Et_2O$ (Scheme 7).[11a] The reaction was carried out at -40 °C in DCM solvent and affords the coupling products in good yields.



Scheme 7. Iodine(III) Induced C-C coupling

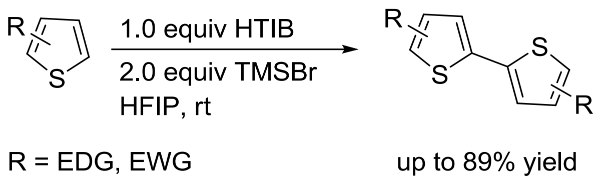
1.6.4.1. Carbon-Carbon Bond Formation

Kita and co-workers have demonstrated PIFA mediated unprecedented, selective oxidative coupling reaction of pyrroles to give α-linked bipyrroles in the presence of bromotrimethylsilane (TMSBr) as Lewis acid. The reaction condition is also efficient for the coupling of indoles (Scheme 8).[11b]



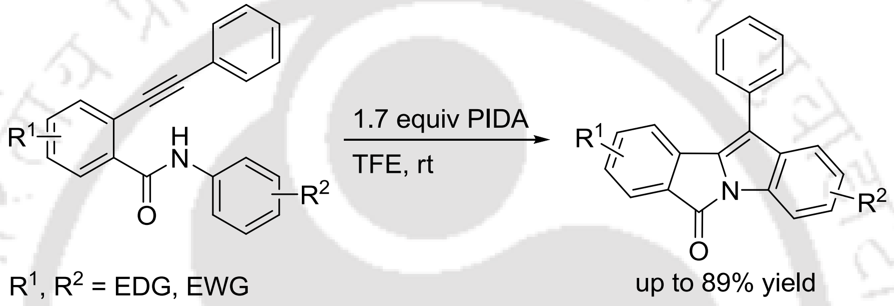
Scheme 8. Synthesis of Bipyrroles

The same group has extended this direct oxidative biaryl coupling reaction towards the synthesis of bithiophenes by the oxidative coupling of thiophenes (Scheme 9).[11c] This coupling reaction is accomplished using HTIB and TMSBr in HFIP at room temperature. The reaction involves a iodonium intermediate generated *in situ* from thiophenes and the iodine(III) reagent.



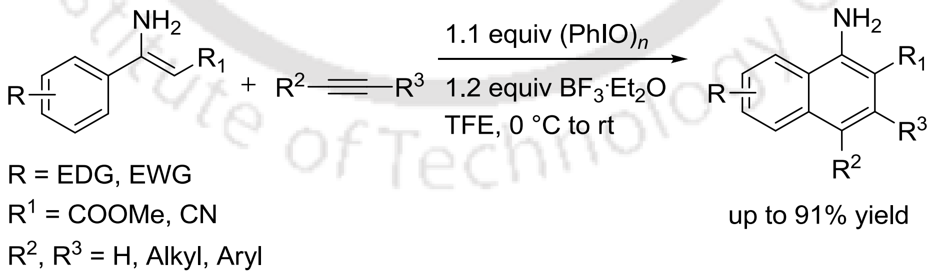
Scheme 9. Synthesis of Bithiophenes

Phenyliodine diacetate has been used for a regio- and chemoselective intramolecular cascade oxidative cyclization of 2-(1-arylethynyl)benzamides to afford 11-aryl-6*H*-isoindolo[2,1-*a*]indol-6-ones at room temperature in good to excellent yields (Scheme 10).[11d]



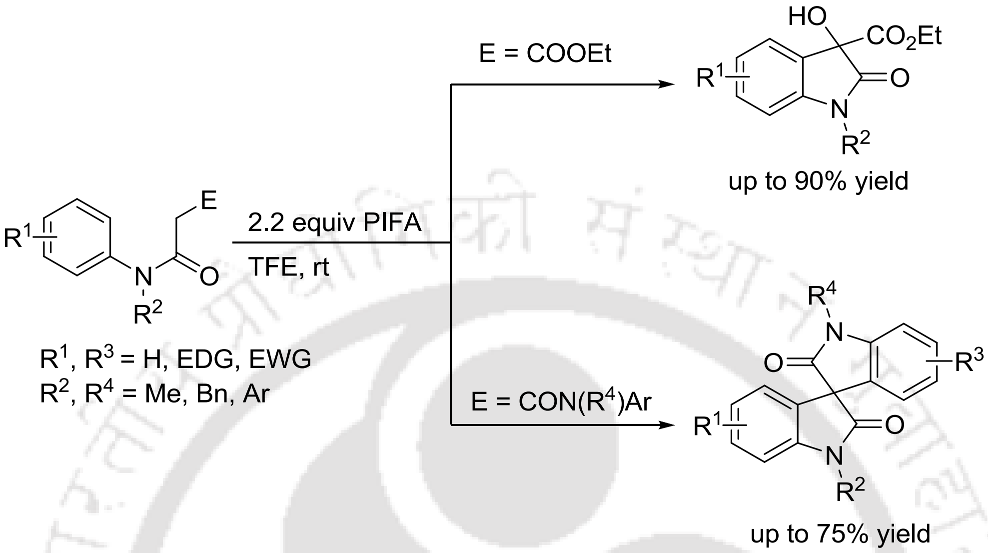
Scheme 10. Metal-Free Synthesis of Indolones

Iodine(III) reagents have been employed for benzannulation reaction. Iodosobenzene along with $BF_3 \cdot Et_2O$ mediated the benzannulation reaction between enamines and alkynes to afford 1-amino-2-naphthalenecarboxylic acid derivatives. The reaction is efficient with broad substrate scope and good functional group tolerance (Scheme 11).[11e]



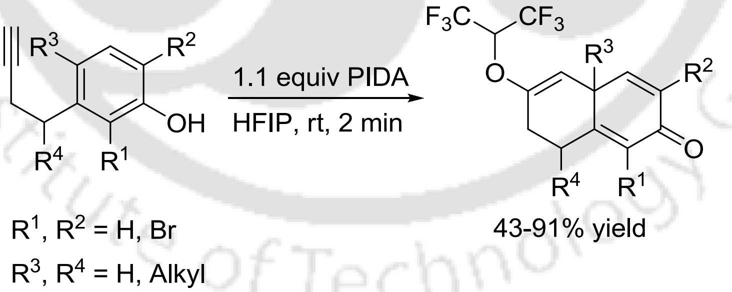
Scheme 11. Iodosobenzene Mediated Benzannulation Reaction

Zhao and co-workers have developed a metal-free oxidative C(sp^2) C(sp^3) bond formation, followed by oxidative hydroxylation or spirocyclizationprotocol for the synthesis of 3-hydroxy-2-oxindoles and spirooxindoles. The reaction of PIFA with anilides (E = COOEt) resulted in 3-hydroxy-2-oxindole derivatives, while anilides with E = CON(R^4)Ar led to the formation of spirooxindoles (Scheme 12).[11f]



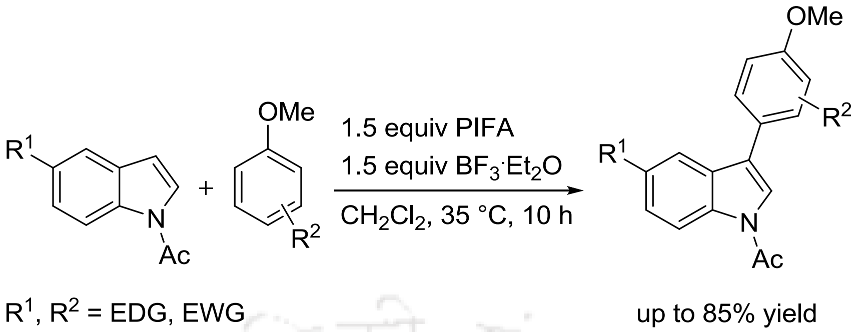
Scheme 12. Synthesis of 3-Hydroxy-2-oxindoles and Spirooxindoles

Canesi and co-workers reported oxidative cyclization process for the synthesis of bicyclic and tricyclic products starting from phenols. The reaction proceeds *via* a cationic intermediate formed by the reaction of the starting precursor with PIDA (Scheme 13).[11g]



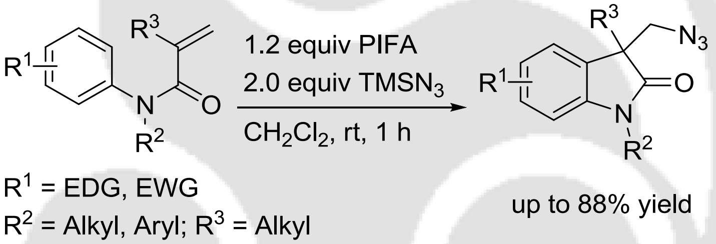
Scheme 13. PIDA Mediated Synthesis of Bicyclic and Tricyclic Products

The construction of *C-C* bond at 3rd position of *N*-acetylindoles has been successfully demonstrated by Gu and co-workers. The reaction of *N*-acetylindoles with anisoles in the presence of PIFA/$BF_3 \cdot Et_2O$ provides C-3 aryl indoles in good regioselectivity (Scheme 14).[11h]



Scheme 14. C-3 Arylation of *N*-Acetylindoles with Anisoles

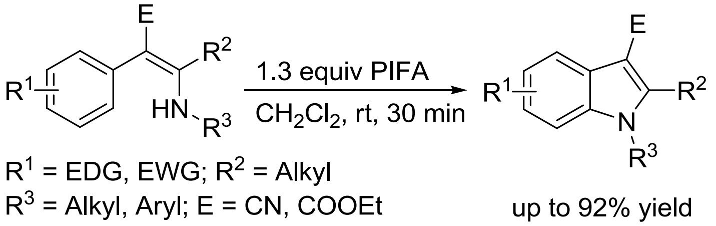
Antonchick and co-workers demonstrated a metal-free protocol employing PIFA for azidoarylation of alkenes leading to 2-oxindoles (Scheme 15).[11i] The reaction features the formation of *C-C* and *C-N* bonds initiated by the addition of azidyl radical.



Scheme 15. Synthesis of Functionalized 2-Oxindoles

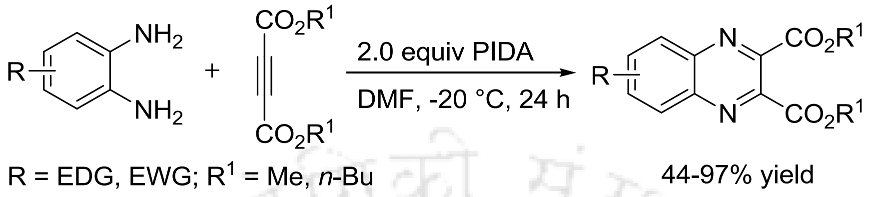
1.6.4.2. Carbon-Nitrogen Bond Formation

Zhao and co-workers have demonstrated a metal-free protocol for the synthesis of substituted *N*-arylated and *N*-alkylated indole derivatives *via* PIFA mediated intramolecular C-H amination at room temperature (Scheme 16).[12a]



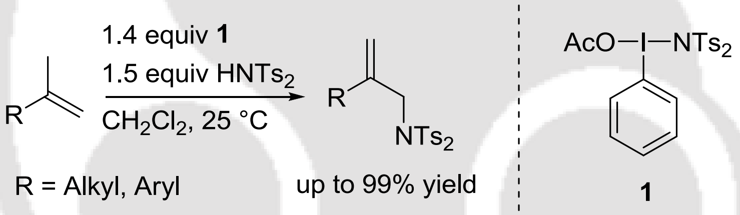
Scheme 16. Synthesis of *N*-Substituted Indoles *via* PIFA Promoted C-H Activation

Phenyliodine diacetate (PIDA) is used for the synthesis of quinoxalines by [4+2] oxidative annulation of *o*-phenylenediamines and electron-deficient alkynes in DMF at -20 °C (Scheme 17).[12b] The reaction was efficient and the desired products were obtained in good yields.



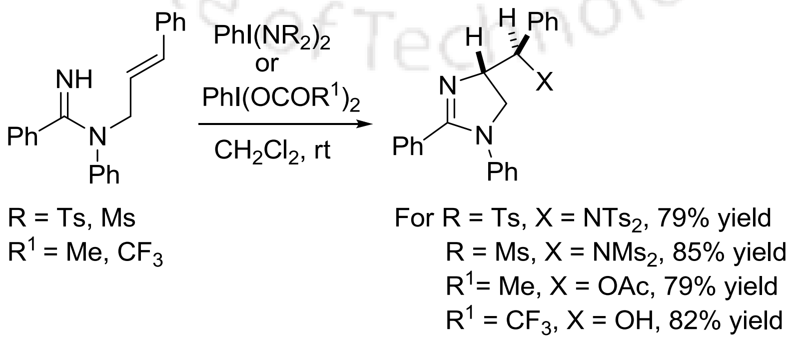
Scheme 17. Metal-Free Oxidative Annulation of *o*-Phenylenediamines and Alkynes

Muniz and co-workers have reported a metal-free intermolecular allylic amination using bistosylimide as a nitrogen source in the presence of hypervalent iodine **1**. The reaction proceeds under mild conditions, and a range of substituents and functional groups were tolerated (Scheme 18).[12c]



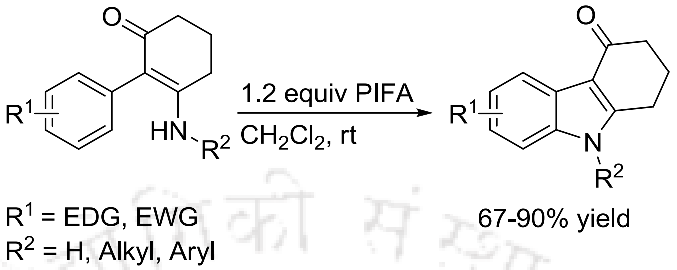
Scheme 18. Metal-Free Allylic Amination

Chiba and co-workers demonstrated a diastereoselective anti-aminooxygenation and anti-diamination of alkenes with amidines by hypervalent iodine(III) reagents, $PhI(OCOR)_2$ and $PhI(NMs_2)_2$, respectively (Scheme 19).[12d]



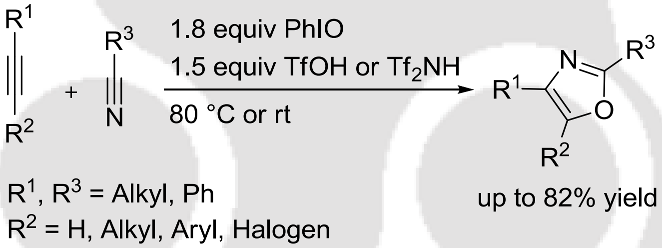
Scheme 19. Metal-Free Diamination and Aminooxygenation

A metal-free oxidative amination of aromatic C-H bond of enaminones has been demonstrated in the presence of PIFA, leading to the formation of carbazolone derivatives. This method was also used for the synthesis of 3-acetylindoles derivatives (Scheme 20).[12e]



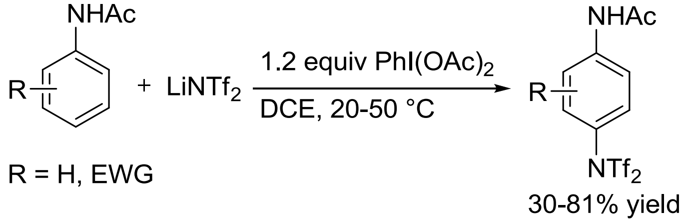
Scheme 20. Synthesis of Carbazolones from Enaminones

Saito and co-workers accomplished [2+2+1] annulation of alkynes, nitriles and *O*-atoms for the regioselective synthesis of 2,4-disubstituted and 2,4,5-trisubstituted oxazoles. This annulation was achieved by the use of iodosobenzene (PhIO) with TfOH at 80 °C or Tf_2NH at room temperature (Scheme 21).[12f]



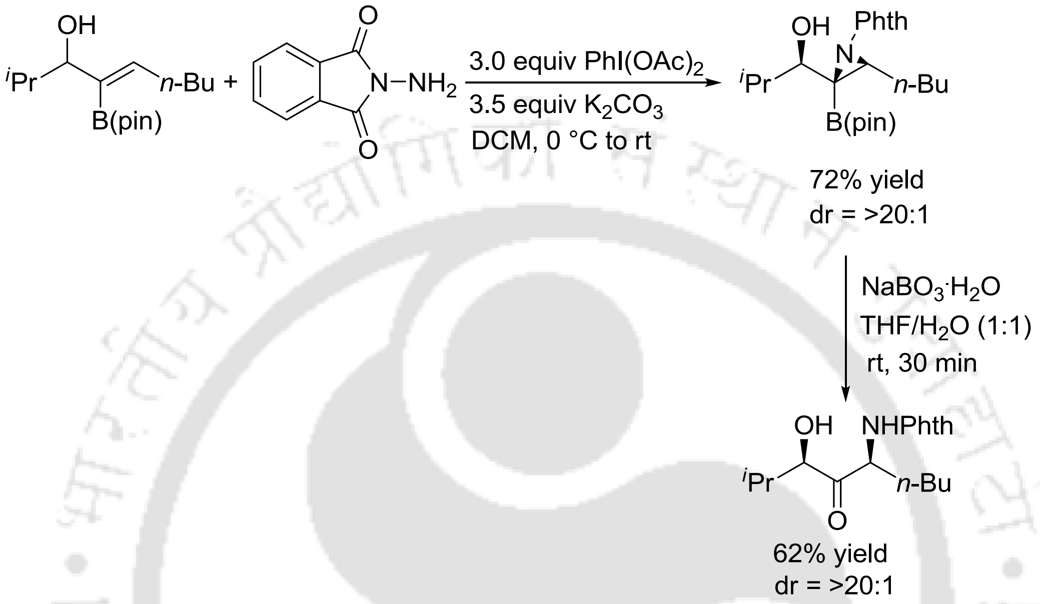
Scheme 21. Metal-Free Synthesis of 2,4-Disubstituted and 2,4,5-Trisubstituted Oxazoles

Iodine(III) reagent, PIDA, enables direct nucleophilic regioselective imidation of acetanilides. Treatment of acetanilide with lithium triflimide (as the nitrogen source) in DCE resulted in an exclusive amination at the *para* position of the acetanilide (Scheme 22).[12g]



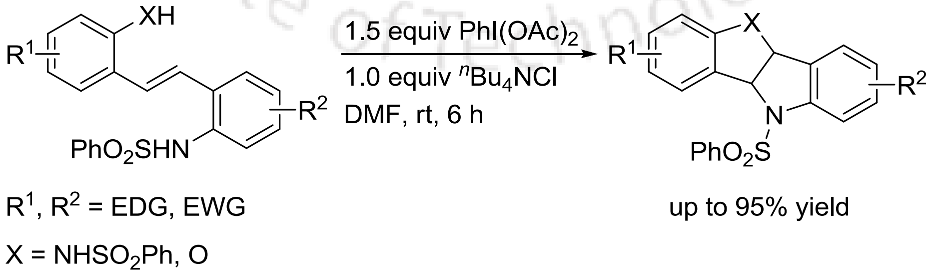
Scheme 22. *p*-Imidation of Acetanilide Derivatives

Walsh and co-workers reported aziridination of 2-B(pin)-substituted allylic alcohols with *N*-aminophthalimide in the presence of $PhI(OAc)_2$ in DCM to give *syn*-B(pin)-substituted hydroxyaziridines in good yields (Scheme 23).[12h] Oxidation of the aziridine B-C bond enables generation of *syn*-1,3-aminohydroxy-2-ketones with high diastereoselectivity.



Scheme 23. Diastereoselective Aziridazation of B(pin)-Susbstituted Allylic Alcohols

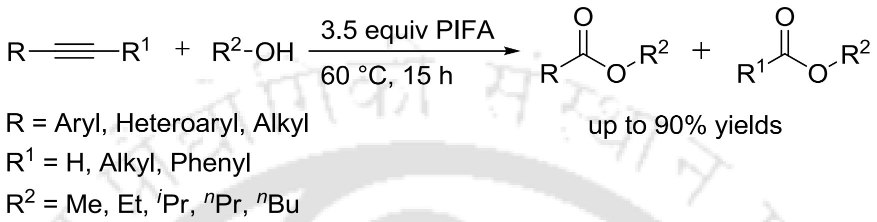
An efficient method for the synthesis of bisindolines has been developed *via* an intramolecular oxidative diamination of olefins at room temperature using PIDA and a halide additive (Scheme 24).[12i] The reaction protocol is effective to synthesize various bisindoline derivatives with broad substrate scope under mild conditions. The protocol was also successfully extended to aminohydroxylation.



Scheme 24. Intramolecular Diamination/Aminohydroxylation of Olefins

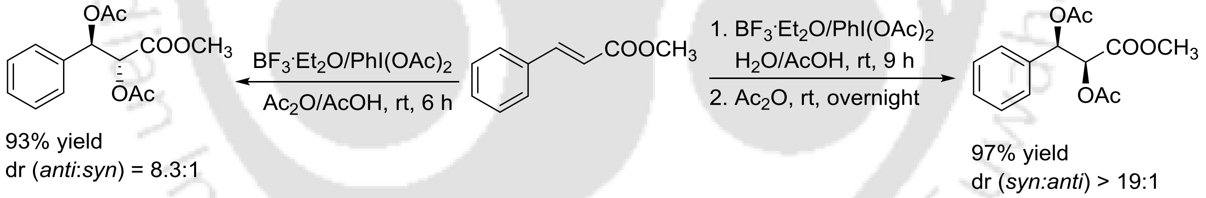
1.6.4.3. Carbon-Oxygen Bond Formation

Alkynes undergo esterification with alcohols under mild conditions using PIFA *via* C-C triple bond cleavage (Scheme 25).[13a] The reaction exhibits good functional group tolerance and broad substrate scope. The reaction proceed *via* hydroxyethanones and ethanediones as intermediates.



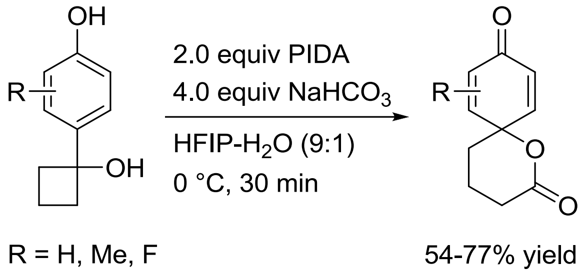
Scheme 25. PIFA Mediated Esterification of Alkynes with Alcohols

Li and co-workers have developed selective *syn* and *anti* diacetoxylations of alkenes using a $PhI(OAc)_2/BF_3{\cdot}Et_2O$ system in the presence and absence of water, respectively. The reaction works well at room temperature furnishing the desired products in good to excellent yields and diastereoselectivity (Scheme 26).[13b]

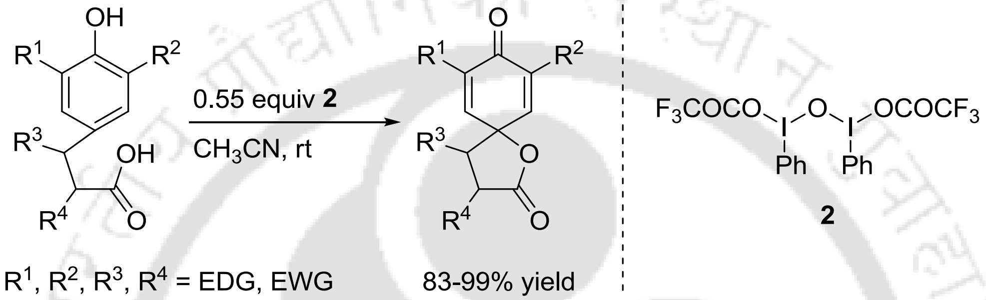


Scheme 26. Diastereoselective Diacetoxylations of Alkenes

Kita and co-workers synthesized spiro cyclohexadienone lactones by a domino reaction of 1-(*p*-hydroxyaryl)cyclobutanols with PIDA in HFIP-H_2O (Scheme 27).[13c] They further displayed the oxidizing behavior of oxo-bridged hypervalent iodine(III) trifluoroacetate **2** in oxidative cyclization of phenols involving a carbon–oxygen bond formation to produce spirocyclized cyclohexadienones. This iodine reagent could serve as a promising alternative to PIDA and PIFA to bring out phenolic oxidations (Scheme 28).[13d]

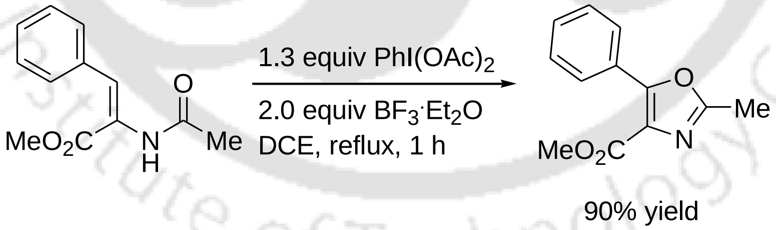


Scheme 27. Synthesis of Spiro Cyclohexadienone Lactones



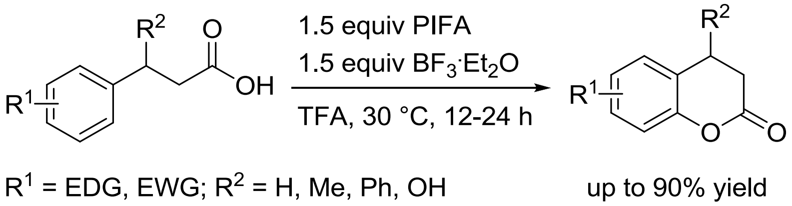
Scheme 28. Oxidative Cyclization of Phenols Leading to Spirocyclized Cyclohexadienones

The synthesis of oxazole derivatives was reported by Zhao and co-workers *via* $PhI(OAc)_2$-mediated intramolecular *C-O* bond formation of enamides (Scheme 29).[13e] The reaction condition involves the use of $PhI(OAc)_2$ along with $BF_3{\cdot}Et_2O$ in DCE under reflux condition.



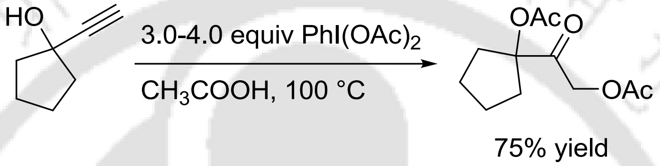
Scheme 29. Metal-Free Synthesis of Oxazole Derivatives

Gu and co-workers observed the oxidative cyclization of 3-arylpropionic acids into the corresponding 3,4-dihydrocoumarins by treatment with stoichiometric amount of PIFA or oxone and $BF_3{\cdot}Et_2O$ in trifluoroacetic acid at 30 °C (Scheme 30).[13f]



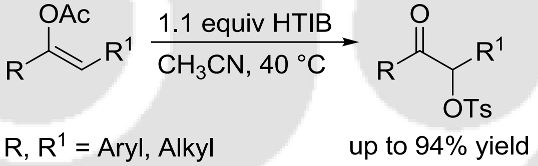
Scheme 30. Synthesis of 3,4-Dihydrocoumarins Derivatives by Oxidative Cyclization

Mo and Su have repoted a metal-free protocol to access *α*,*α′*-diacetoxy ketones from ethynylcarbinols through oxidation by PhI(OAc)$_2$ (Scheme 31).[13g]



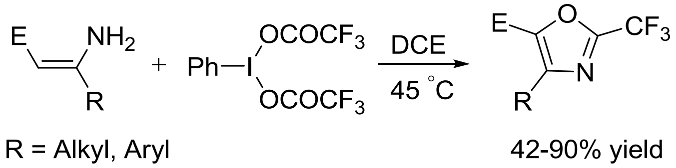
Scheme 31. Synthesis of Oxidative α,α′-Diacetoxy Ketones from Ethynylcarbinols

Legault and co-workers have used HTIB for the conversion of enol esters to *α*-tosyloxy ketones in acetonitrile at 40 °C. The reaction is well applicable for aromatic, aliphatic and cyclic enol esters (Scheme 32).[13h]



Scheme 32. Oxidative Conversion of Enol Esters to *α*-Tosyloxy Ketones

Zhao and co-workers have synthesized 4,5-disubstituted-2-(trifluoromethyl)oxazoles by the treatment of *β*-monosubstituted enamines with PIFA (Scheme 33).[13i] The reaction takes place *via* the oxidative *β*-trifluoroacetoxylation of the enamine followed by subsequent intramolecular cyclization.

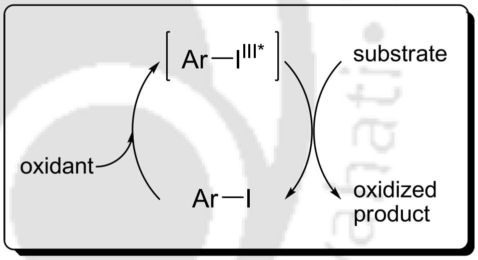


Scheme 33. Synthesis of Functionalized Oxazoles from Enamines

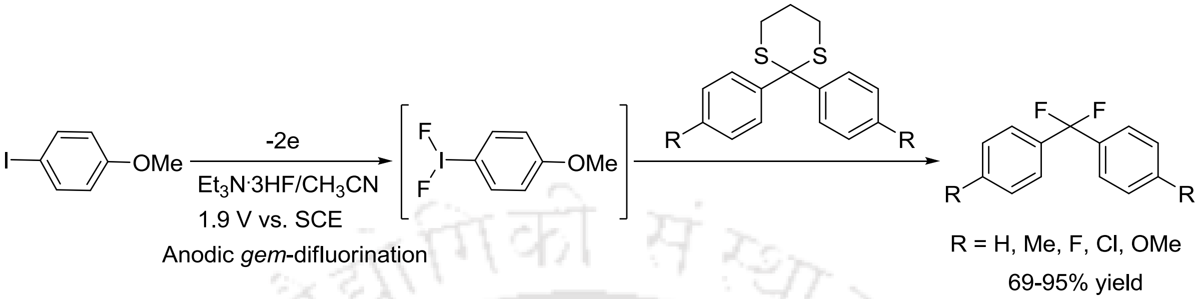
1.7. Catalytic Carbon-Carbon and Carbon-Heteroatom Bonds Formation

Hypervalent iodine reagents served a paramount purpose in bringing out various oxidations and in the synthesis of various functionalized oxygen, nitrogen and sulfur containing heterocycles. Though these reagents are considered to be safe, effective and environmentally benign alternative to transition metals, their stoichiometric or excess use in reactions is always accompanied by the co-liberation of equimolar amounts of iodoarenes together with the desired oxidation products, which creates a difficulty in the purification process and also waste disposal problem in large scale synthesis. Also, these reagents have to be prepared before performing the reaction, hence, an alternative catalytic process is highly desirable, aiming at mimicking the reaction sequence of transition metal catalyzed reactions, where a metal was used in catalytic amounts together with an oxidant. Accordingly, many research groups have focused on this catalytic version using only catalytic amounts of iodoarene and a stoichiometric oxidant.[14]

In the catalytic process, the desired transformation is achieved by using iodine(I) containing compound in catalytic amount together with a stoichiometric oxidant. The oxidant generates the hypervalent iodine(III) species *in situ*, which leads the reaction giving the oxidation product accompanied by the liberation of iodine(I), which is reoxidized to iodine(III) by the oxidant.

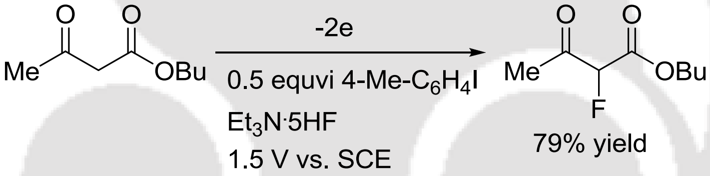


The key to achieve an efficient catalytic cycle of hypervalent iodine compounds is the careful selection of the oxidant. The oxidant must be capable of oxidizing ArI to I(III), and also should be inert to both the starting substrates and the products of successful catalytic reactions or the regeneration of I(III) should be considerably faster than the rates of any undesired substrates/products decomposition and other side reactions.[14b] In 1994, it was T. Fuchigami who laid the foundation for bringing this catalytic cycle into reality. In his initial study of electrosynthesis of hypervalent iodobenzene difluorides, he subjected different substituted iodobenzenes to anodic oxidation in the presence of $Et_3N{\cdot}3HF$ in anhydrous acetonitrile and found *p*-methoxyiodobenzenes provided the desired hypervalent difluoride at a positive potential (1.9 V vs SCE). Later, the electrolytic solution containing *p*-methoxyiodobenzene difluoride was used for *gem*-difluorination of various dithioketals (Scheme 34).[15a,b]



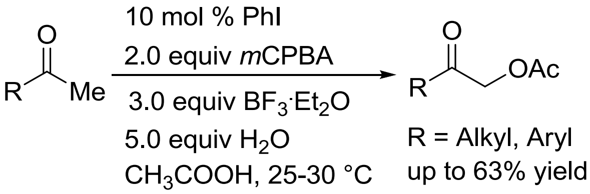
Scheme 34. Electrosynthesis of *gem*-Difluorides

Later, Hara and co-workers have demonstrated electrochemical oxidation of *p*-iodotoluene in the presence of $Et_3N·5HF$ at a potential (1.5 V vs SCE) to *p*-iodotoluene difluoride and its subsequent use for *α*-fluorination of *β*-dicarbonyl compounds (Scheme 35).[15c]



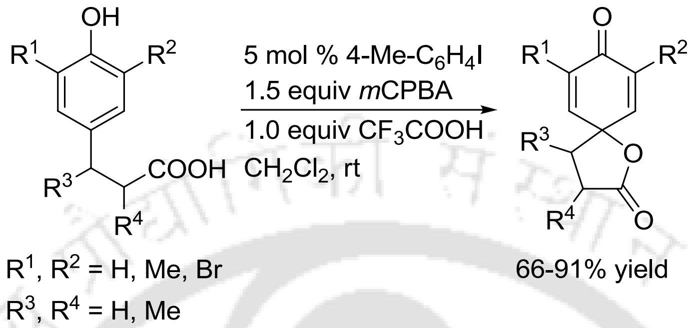
Scheme 35. *α*-Fluorination of *β*-Dicarbonyl compounds

A major breakthrough in this area came in 2005 when Ochiai and co-workers demonstrated the use of *m*CPBA as an effective oxidant for the oxidation of iodoarene to active iodine(III) species. The method involves the *α*-oxidation of ketones by the *in situ* generated hypervalent iodanes by the oxidation of a catalytic amount of iodobenzene with *m*CPBA in the presence of $BF_3·Et_2O$ (Scheme 36).[16a]



Scheme 36. Catalytic α-oxidation of Ketones Using Iodobenzene

Soon after, Kita and co-workers reported iodine(III) catalyzed oxidative spirocyclization reaction of phenols using *m*CPBA as an oxidant (Scheme 37).[16b] A variety of suitably substituted phenols underwent cyclization to give the spirocyclized products in good yields and in short reaction times.

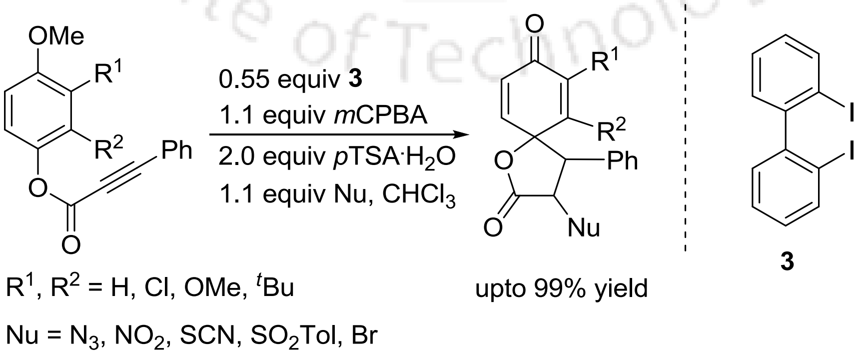


Scheme 37. Catalytic Spirocyclization of Phenols

Later, there is a diverse and fascinating progress in developing new ways of *in situ* oxidation of iodoarenes by organic and inorganic oxidants such as *m*CPBA, peracetic acid, oxone, H_2O_2, etc., and their utilization in bringing out various new organic transformations under metal-free conditions.

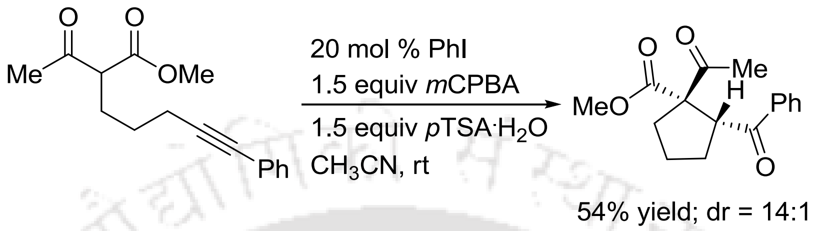
1.7.1. Carbon-Carbon Bond Formation

Kita and co-workers have reported a straight forward, one-pot strategy for the synthesis of functionalized cyclohexadienone-type spirocyclic compounds by the spirocyclization reaction of aryl alkynes using catalyst **3** in the presence of *m*CPBA and *p*TSA·H_2O (Scheme 38).[17a] A variety of nucleophiles were incorporated into the final spirocyclized product.



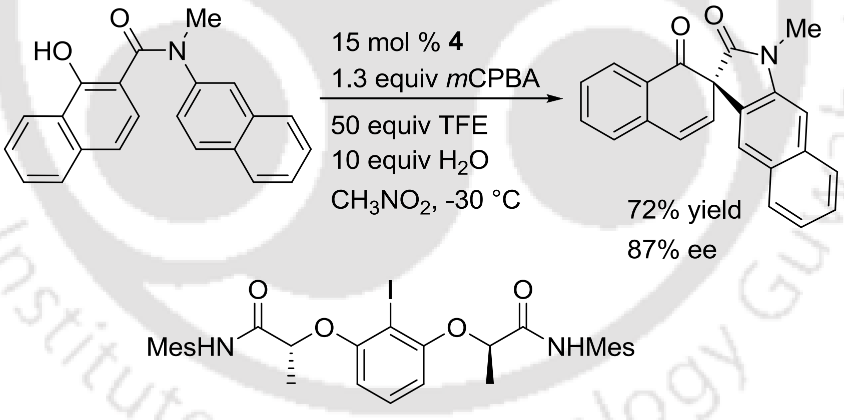
Scheme 38. Synthesis of Functionalized Spirocyclic Compounds

The use of catalytic iodobenzene was explored by Moran and co-workers in the 5-*exo*-*dig* cyclization of δ-alkynyl β-ketoesters, resulting in the diastereoselective formation of cyclopentane derivatives. This oxidative cyclization was carried out with iodobenzene in the presence of *m*CPBA and *p*TSA·H_2O in acetonitrile at room temperature (Scheme 39).[17b]



Scheme 39. Iodobenzene Catalyzed 5-*exo*-*dig* Cyclization

Gong and co-workers reported the first enantioselective dearomatizative spirocyclization of 1-hydroxy-*N*-aryl-2-naphthamide derivatives by chiral organoiodine catalyst **4** to give access to spirooxindoles in good yields with high to excellent levels of enantioselectivity (Scheme 40).[17c]



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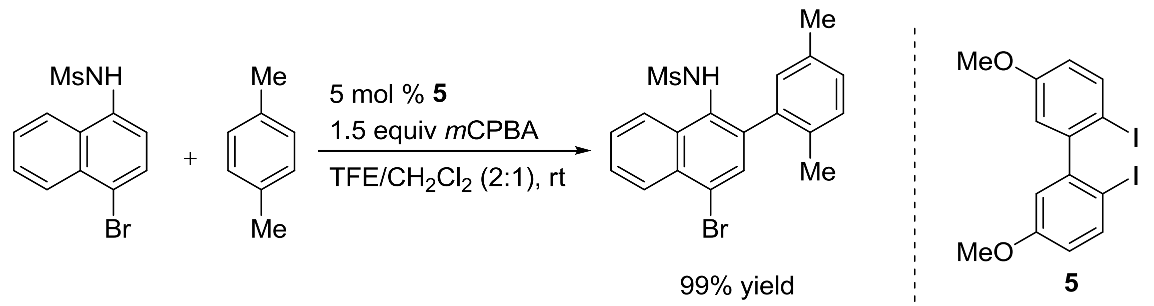
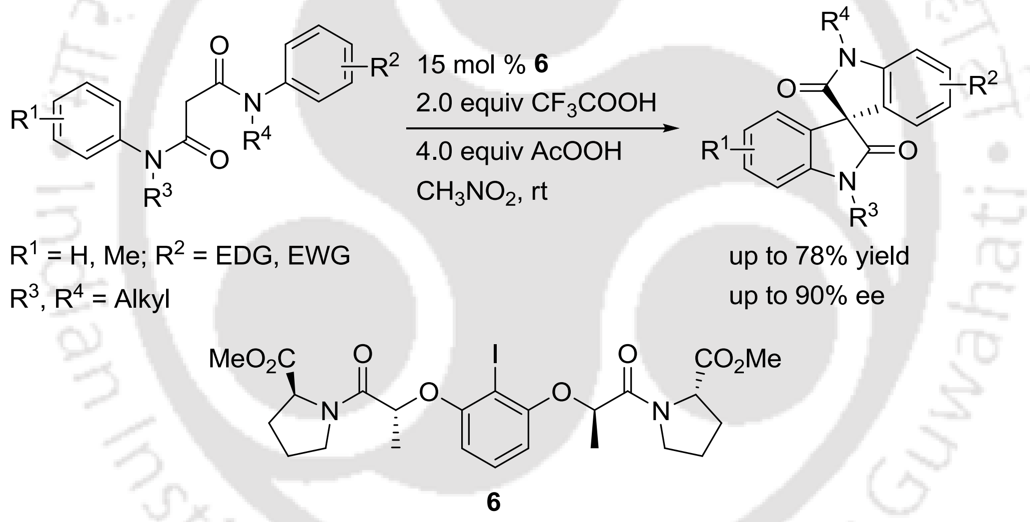
Scheme 40. Synthesis of Chiral Spirooxindole Derivatives

An organocatalytic oxidative cross-biaryl-coupling was presented by Kita and co-workers. The *C*-*C* coupling of *N*-methanesulfonyl anilides with aromatic hydrocarbons was achieved using catalytic 2,2′-diiodobiphenyl catalyst **5** together with *m*CPBA in TFE/CH_2Cl_2 at room temperature (Scheme 41).[17d]



Scheme 41. Organocatalytic Oxidative Cross-Biaryl-Coupling

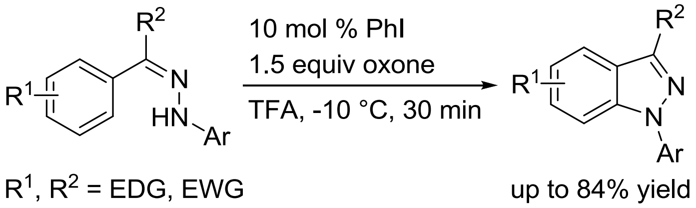
An asymmetric *C-C* bond formation reaction *via* an organocatalytic oxidative coupling reaction of N^1,N^3-diphenylmalonamides using a chiral organoiodine compound **6** as catalyst was reported (Scheme 42).[17e] The reaction involves stereoselective functionalization of four C-H bonds to give spirooxindoles with high levels of enantioselectivity.



Scheme 42. Asymmetric *C-C* Bond Formation Using Chiral Organoiodine Compound

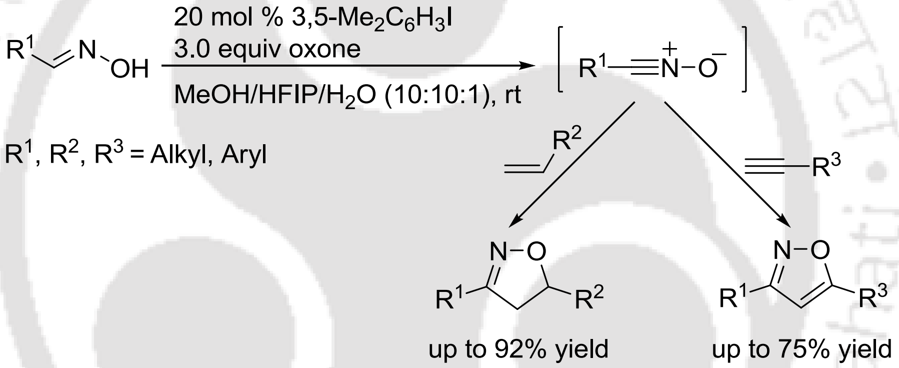
1.7.2. Carbon-Nitrogen Bond Formation

Tanimori and co-workers have reported a metal-free protocol for the synthesis of *N*-arylsubstituted 1*H*-indazole derivatives from hydrazones *via* a catalytic hypervalent iodine cycle. The intramolecular C–H amination of hydrazones using 10 mol % iodobenzene in the presence of oxone as an oxidant in trifluoroacetic acid afforded 1*H*-indazoles in moderate to good yields (Scheme 43).[18a]



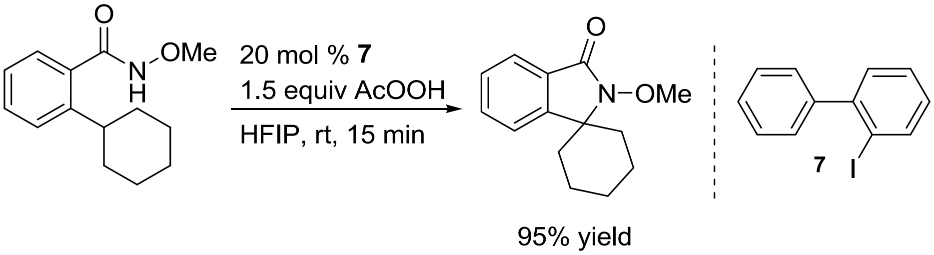
Scheme 43. Iodobenzene Catalyzed Synthesis of Substituted 1*H*-indazoles

Zhdankin and co-workers reported the synthesis of isoxazolines and isoxazoles by cyclization of aldoxime and alkene or alkyne. In this reaction, active iodine(III) species was generated from 1-iodo-3,5-dimethylbenzene and oxone (Scheme 44).[18b] This iodine(III) species oxidizes aldoxime to nitrile oxide, which reacts with alkenes and alkynes to give the corresponding isoxazolines and isoxazoles in moderate to good yields.



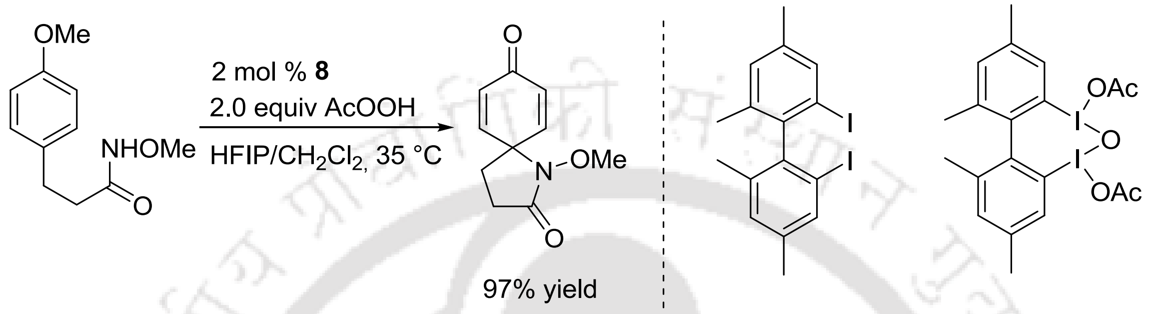
Scheme 44. Metal-free Synthesis of Isoxazolines and Isoxazoles

A new strategy was devised by Shi and co-workers for synthesis of γ-lactams through an intramolecular tertiary C−H amination using iodoarene **7** as catalyst and *m*CPBA as oxidant under mild reaction conditions. The reaction proceeds *via* formation of an iodonium cationic intermediate (Scheme 45).[18c]



Scheme 45. Iodoarene Catalyzed C-H Amination of sp^3 C-H Bond

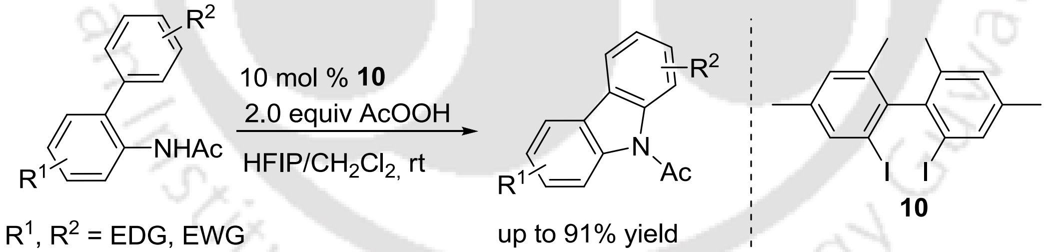
In continuation of their efforts towards developing new transformations using hypervalent iodine, Kita and co-workers demonstrated the *in situ* generation of µ-oxo-bridged reactive hypervalent iodine species **9** from its bis(iodoarene) precursor **8** and its efficient use as green organocatalyst for the synthesis of spirocyclized amides in the presence of peracetic acid as an oxidant (scheme 46).[18d]



8 **9**

Scheme 46. Metal-Free Synthesis of Spirolactams

Antonchick and co-workers reported an atom-economical organocatalytic protocol for the preparation of carbazoles through oxidative *C-N* bond formation (Scheme 47).[18e] The reaction conditions involve 10 mol % 2,2′-diiodobiphenyl catalyst **10** and peracetic acid as an oxidant in HFIP/CH_2Cl_2 at room temperature.



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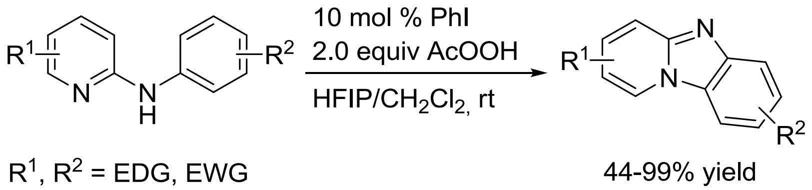
Scheme 47. Organocatalytic Synthesis of Carbazoles Using Iodoarene

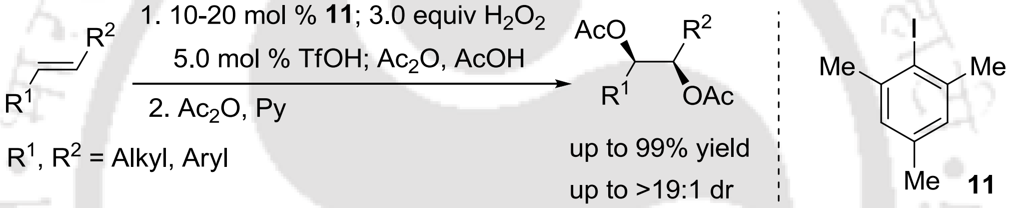
Oxidative cycloamination of *N*-aryl-2-aminopyridines was described by Zhu and co-workers for the synthesis of pyrido[1,2-*a*]benzimidazoles. They made use of iodobenzene and peracetic acid for the *in situ* generation of iodine(III) species, which catalyzes the *C-N* bond formation reaction affording the desired products in good to excellent yields (Scheme 48).[18f] This catalytic system is also effective for the conversion of *N*-arylamidines to 1*H*-benzo[*d*]imidazoles.



Scheme 48. Synthesis of Pyrido[1,2-*a*]benzimidazoles by Oxidative Cycloamination

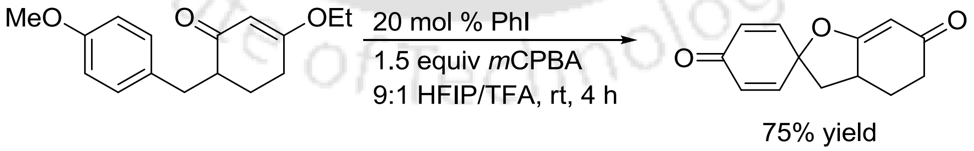
1.7.3. Carbon-Oxygen Bond Formation

Metal-free *syn* diacetoxylation of alkenes was proposed by Li and co-workers using aryl iodide **11** as catalyst. This method is operationally simple and a variety of electron-rich as well as electron-deficient alkenes undergo the reaction to afford the diacetoxylation products with high diastereoselectivity (Scheme 49).[19a]



Scheme 49. Metal-Free *syn* Diacetoxylation of Alkenes

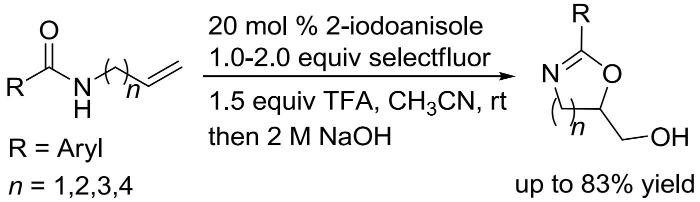
Hutt and co-workers reported iodobenzene catalyzed oxidative cyclization of vinylogous esters bearing *para* or *meta*-methoxy benzyl groups for the synthesis of spirofurans. They used iodobenzene together with *m*CPBA as a co-oxidant in HFIP/TFA at room temperature. The reaction is also compatible for the synthesis of benzopyrans (Scheme 50).[19b]



Scheme 50. Synthesis of Spirofurans

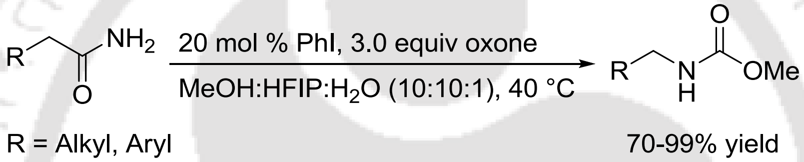
Moran and co-workers showed the synthesis of five-, six-, and seven-membered rings with a range of substitutions by the oxidative cyclization of *N*-alkenylamides catalyzed by 2-

iodoanisole. Selectfluor is used as an oxidant along with TFA in CH_3CN at room temperature (Scheme 51).[19c]



Scheme 51. Oxidative Cyclization of Unsaturated Amides

Zhdankin and co-workers showed the preparation of methyl carbamates from carboxamides ((Scheme 52).[19d] The reaction involves a catalytic use of iodobenzene together with oxone in MeOH-HFIP-H_2O at 40 °C.



Scheme 52. Synthesis of Methyl Carbamates by Hofmann Rearrangement

In conclusion, both stoichiometric and catalytic hypervalent iodine reactions are powerful and versatile tools for the synthesis various functionalized oxygen, nitrogen and sulfur containing heterocycles. These metal-free reactions occur under mild conditions and at ambient temperatures. Furthermore, enantioselective reactions can also be carried out using chiral iodoarenes. Moreover, these reactions are also involved in the fascinating and elegant syntheses of complex polycylic skeletons of natural and unnatural biologically active molecules.

1.8. References

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Chapter II

Iodobenzene Catalyzed C-H Amination of *N*-Substituted Amidines Using *m*-Chloroperbenzoic Acid

Heterocyclic compounds are core units of numerous biologically active complex natural products,[1] pharmaceuticals[2] as well as in material sciences.[3] As a result, over the years many studies have been devoted to the synthesis of heterocyclic frameworks through carbon-carbon and carbon-heteroatom bonds formation.[4-6] Transition metal catalyzed cross-coupling and C-H activation methods are among the diverse synthetic strategies and most prevalent toward heterocyclic compound synthesis.[7] In particular, the functionalization of traditionally inert C-H bonds offers an efficient, atom-economical and straightforward pathway by obviating the need for prior functionalization in starting precursors. The developments of metal-free protocols as cost-effective and environmentally benign alternatives are still needed. Intramolecular C-H functionalization/cyclization using hypervalent iodine reagents provides an elegant approach toward the metal-free synthesis of heterocycles.[8] In this chapter, we describe a new iodobenzene-catalyzed C-H amination of *N*-Substituted amidines using *m*-chloroperbenzoic acid as an oxidant for the synthesis of functionalized benzimidazoles at room temperature. This process involves oxidative C–H functionalization and *C–N* bond formation.

Benzimidazoles are an important class of heterocyclic compounds found in a wide variety of medicinally important molecules and got immense applications in therapeutic and biological sciences (Figure 1).[9] These applications include Nek2 inhibitor,[10a] Lck inhibitor,[10b] neuropeptide YY1 receptor antagonist,[10c] poly(ADP-ribose)polymerase (PARP) inhibitor,[10d] factor Xa (FXa) inhibitor,[10e] 5-lipoxygenase inhibitor,[10f] *N*-methyl-D-aspartate (NMDA) antagonist[10g] and nonpeptide thrombin inhibitor.[10h] Furthermore, they exhibit several other pharmacological activities such as anti-inflammatory, analgesic, antimicrobial, antidiabetic, antiviral, antifungal and antiparasitic applications.[11] They have also been used as synthetic intermediates for the preparation of dyes and high-temperature resistance polymers.[12] Thus, search for new simple and general synthetic routes for the construction of functionalized benzimidazoles continues to be of tremendous interest.

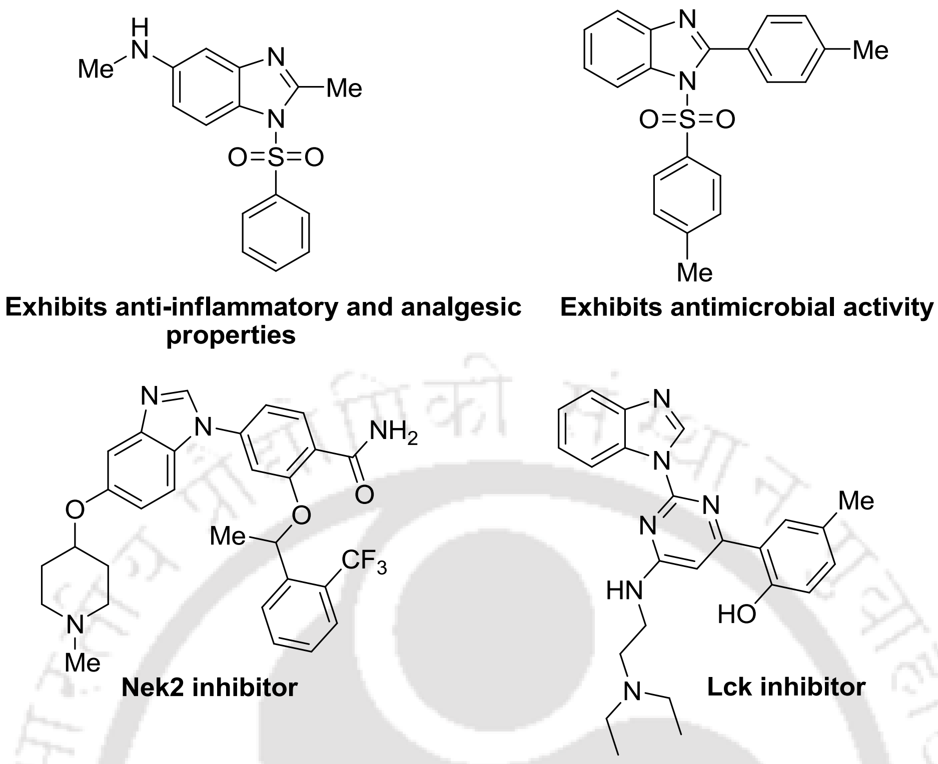
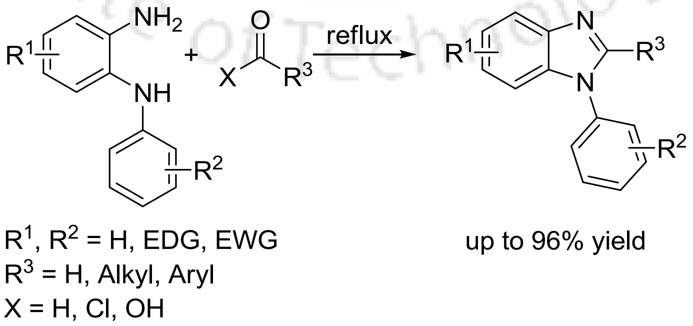


Figure 1. Examples of some biologically active compounds

2.1. Strategies for Synthesis of Benzimidazoles

2.1.1. Conventional Methods

Over the years, the classical method that has been used to build this class of heterocycles involves the condensation of benzene-1,2-diamine with carboxylic acids or its equivalent followed by oxidative cyclization (Scheme 1).[13] *o*-Nitroanilines can be used as a substitute for 1,2-diaminoarene derivatives under reductive conditions. However, these methods often



Scheme 1. Classical Methods of Synthesis of Benzimidazoles

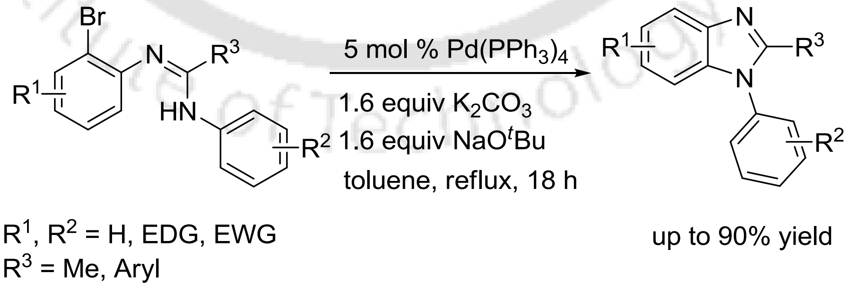
suffer from drawbacks of unavailability of suitably substituted substrate precursors, lack of regioselectivity and requirement of harsh reaction conditions, such as involvement of strong acid in combination with elevated temperatures. Significant attention has thus been focused in designing more convenient strategies to synthesize these target heterocyclic frameworks under relatively milder conditions.

2.1.2. Cross-Coupling Reactions

The cross coupling reactions using transition metals are well established methods for the formation of carbon-nitrogen bonds and so to synthesize nitrogen containing heterocycles. This concept has enabled to overcome the aforementioned drawbacks associated with classical methods, developing milder and efficient protocols for the synthesis of substituted benzimidazoles for the past few years. The most prevalent and widely used metals in *C- N* cross coupling reactions for the synthesis of substituted benzimidazoles are palladium, copper, cobalt and nickel.

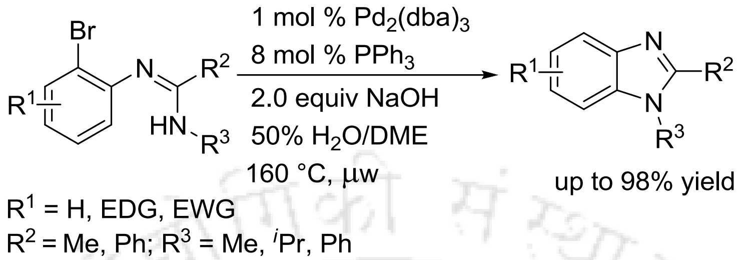
2.1.2.1. Palladium Catalyzed Synthesis of Benzimidazoles

Palladium catalyzed oxidative cyclization reactions represents an important approach for preparing heterocyclic compounds. Brain and co-workers described the synthesis of substituted benzimidazoles through a palladium(0) catalyzed intramolecular *C-N* cross coupling reaction of (*o*-bromophenyl)amidines. The reaction was carried out using $Pd(PPh_3)_4$, K_2CO_3 and NaO^{t}Bu in refluxing toluene for 18 h (Scheme 2).[14a]



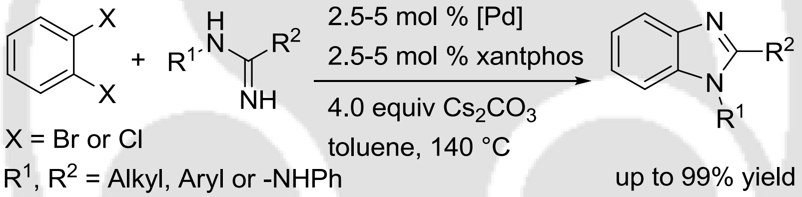
Scheme 2. Palladium Catalyzed Synthesis of 1,2-Disubstituted Benzimidazoles

Later, they have modified the procedure to avoid the necessity of the NaO^{t}Bu/K_2CO_3 and to make the purification process much easier and even to carry out the reaction at low catalyst loadings and shorten reaction times. The modification involves the use of microwave conditions in combination with palladium complex as a catalyst in the presence of triphenylphosphine and NaOH in aqueous DME (Scheme 3).[14b]



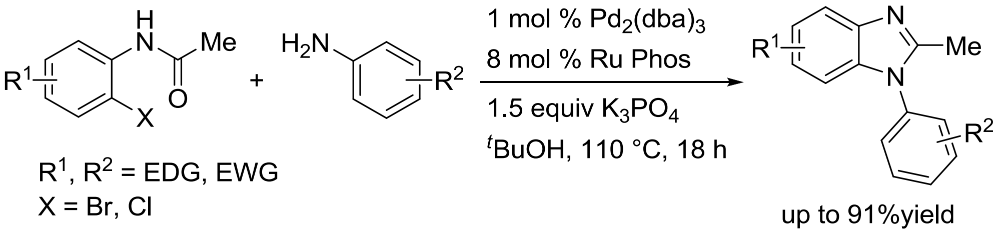
Scheme 3. Synthesis of Substituted Benzimidazoles Under Microwave Conditions

Treatment of *N*-substituted amidines with 1,2-dihaloarenes in the presence of palladium catalyst provided 1,2-disubstituted benzimidazoles by a regiospecific two fold amination as shown in Scheme 4.[14c]



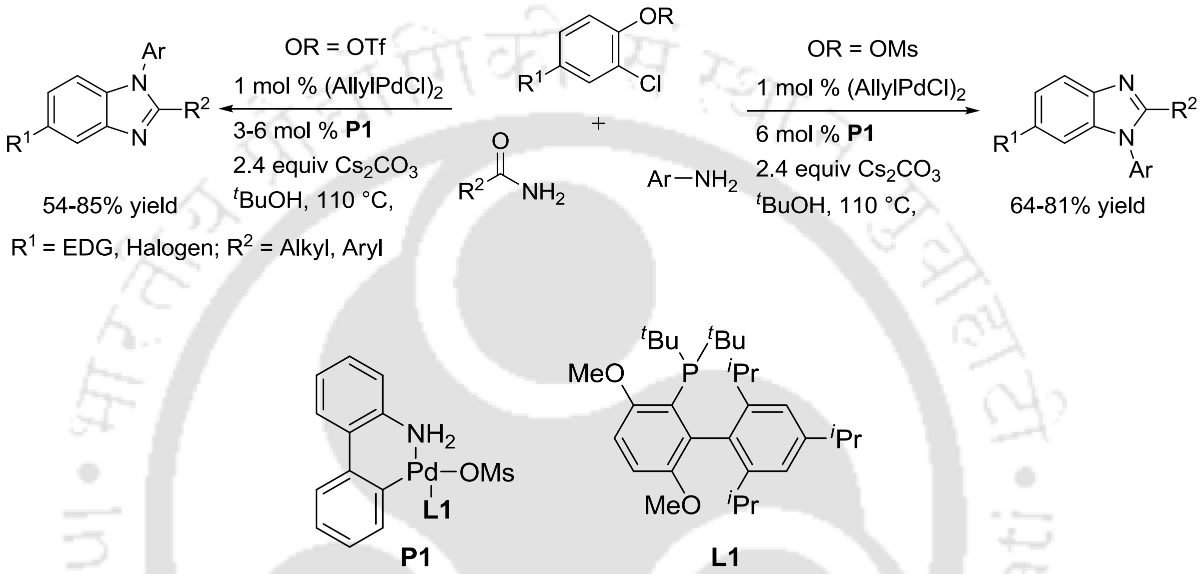
Scheme 4. Palladium Catalyzed Twofold Amination of 1,2-Dihaloarenes

Buchwald and co-workers have developed a method for the synthesis of *N*-aryl benzimidazoles *via* palladium catalyzed cascade amination of *o*-haloanilides and various substituted anilines, followed by condensation. This method allows the preparation of a variety of *N*-aryl benzimidazoles in regioisomerically pure form with good functional group tolerance (Scheme 5).[14d]



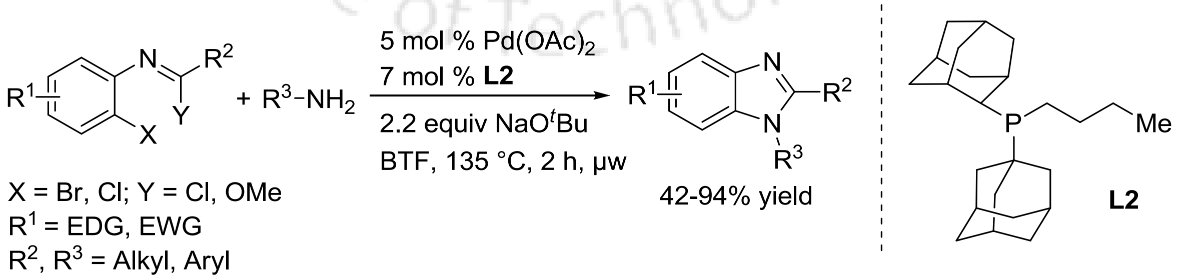
Scheme 5. Palladium Catalyzed Regiospecific Synthesis of *N*-Aryl Benzimidazoles

The same group has reported a cascade palladium catalytic system for regio- and chemoselective construction of benzimidazoles by intermolecular amination and amidation reactions of 2-chloroaryl sulfonates (or halides) using *tert*-BuBrettPhos ligand **L1** (Scheme 6).[14e] In this reaction, it was observed that different 2-chloroaryl sulfonates (triflate versus mesylate) can be reacted under very similar reaction conditions to exclusively afford the opposite regioisomeric heterocycles.



Scheme 6. Palladium Catalyzed Regio- and Chemoselective Synthesis of Substituted Benzimidazoles

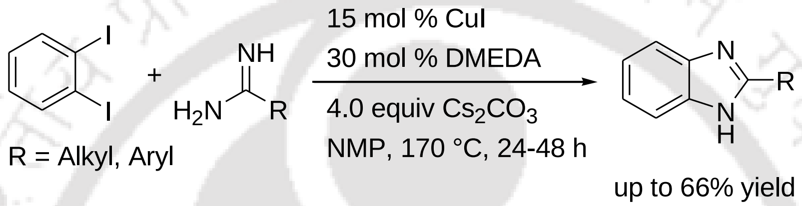
Willis and co-workers have demonstrated the use of *N*-(*o*-halophenyl)imidoyl chlorides and the corresponding imidates as suitable precursors for the synthesis of substituted benzimidazoles using $Pd(OAc)_2$ with phosphorus ligand **L2** (Scheme 7).[14f]



Scheme 7. Palladium Catalyzed Synthesis of Substituted Benzimidazoles

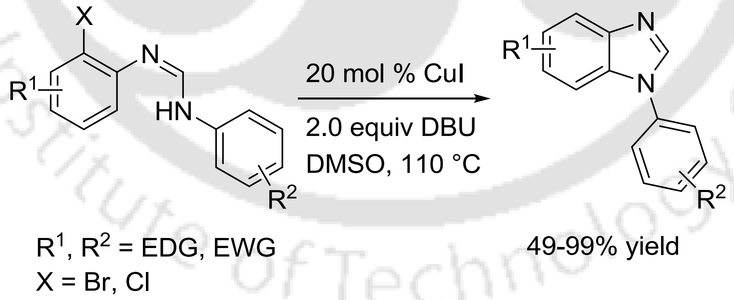
2.1.2.2. Copper Catalyzed Synthesis of Benzimidazoles

Copper catalysts are convenient to use in cross-coupling reactions, owing to their less-toxic nature, more stability and are well suited for synthesis of various substituted benzimidazoles. Deng and co-workers have synthesized 1,2-disubstituted benzimidazoles from amidines through tandem inter- and intramolecular *C-N* cross-coupling reaction. CuI in combination with DMEDA as ligand has been used as an efficient catalytic system for this transformation (Scheme 8).[15a]



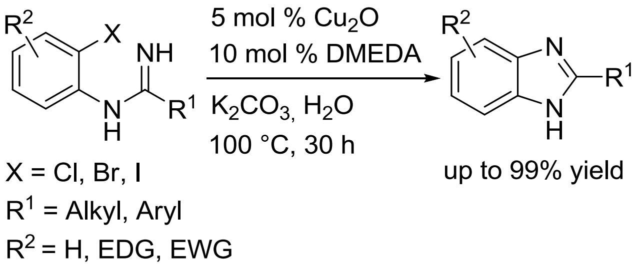
Scheme 8. Synthesis of Substituted Benzimadazoles from 1,2-Dihaloarenes

Glorius and co-workers reported an intramolecular arylation of formamidines to afford 2-unsubstituted *N*-arylbenzimidazoles in the presence of copper(I) catalyst. This protocol is very effective in accessing a library of *N*-aryl benzimidazoles with sterically demanding aromatic groups on the nitrogen atom (Scheme 9).[15b]



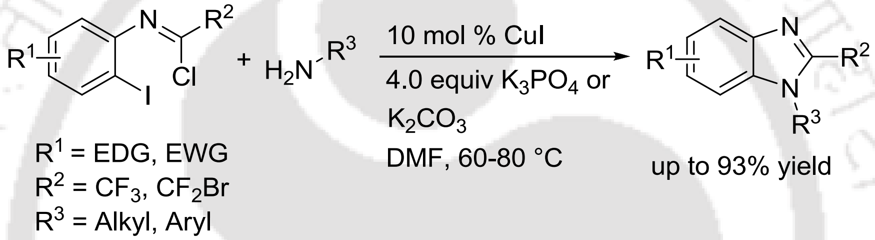
Scheme 9. Synthesis of *N*-Aryl Benzimidazoles

In a similar fashion, Cu_2O with DMEDA has been employed by Peng and co-workers for intramolecular *N*-arylation of (*o*-haloaryl)amidines to afford benzimidazole derivatives with environmentally benign water as solvent, which makes this methodology highly valuable from both environmental and economical points of view. (Scheme 10).[15c]



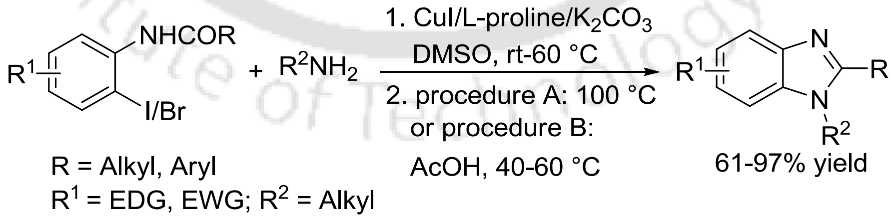
Scheme 10. Copper-Catalyzed Synthesis of Benzimidazoles in Water

Direct synthesis of 2-fluoroalkyl benzimidazoles *via* a tandem *C-N* cross coupling reaction was accomplished by the reaction of fluorinated imidoylchlorides with primary amines in the presence of CuI and K_3PO_4 or K_2CO_3 in DMF solvent (Scheme 11).[15d]



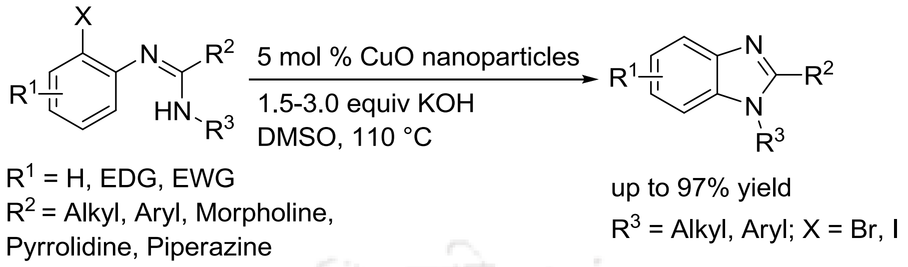
Scheme 11. Synthesis of 2-Fluoroalkyl Benzimidazoles

Ma and co-workers investigated the *ortho*-substituent effect of NHCOR group on copper-catalyzed aryl amination of 2-haloacetanilides to afford *ortho*-aminoanilides and further 1,2-disubstituted benzimidazoles were achieved in one-pot through an intramolecular condensation/cyclization route in moderate to high yields (Scheme 12).[15e]



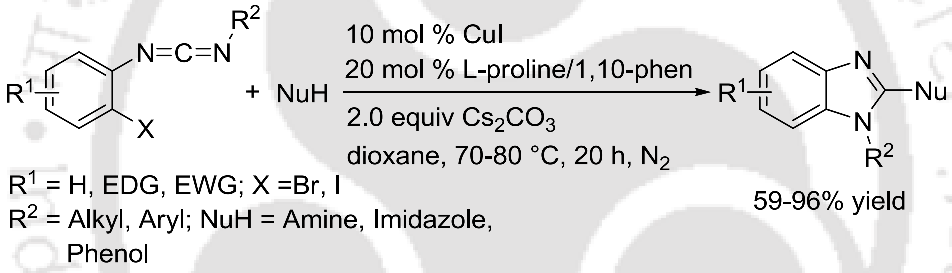
Scheme 12. *Ortho*-Substituent Assisted Synthesis of Benzimidazoles

Our group reported the use of copper(II) oxide nanoparticles in the synthesis of *N*-aryl benzimidazoles and 2-aminobenzimidazoles *via* an intramolecular cyclization of 2-bromoarylamidine derivatives in DMSO under air. The reactions are simple, general, and efficient and the catalyst can be recovered and recycled without loss of activity (Scheme 13).[15f]



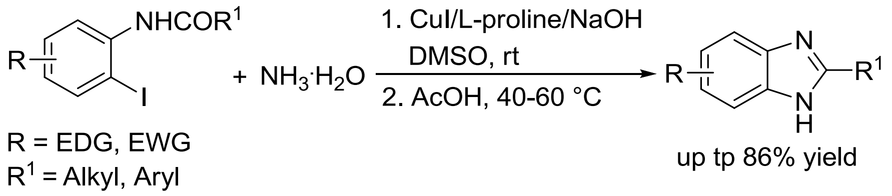
Scheme 13. Synthesis of Substituted Benzimidazoles Using Recyclable CuO Nanoparticles

N-Substituted 2-heterobenzimidazoles have been prepared in good yield through a Cu(I)-catalyzed cascade intermolecular addition/intramolecular *C*-*N* coupling process between *o*-haloarylcarbodiimides and *N*- or *O*-nucleophiles (Scheme 14).[15g]



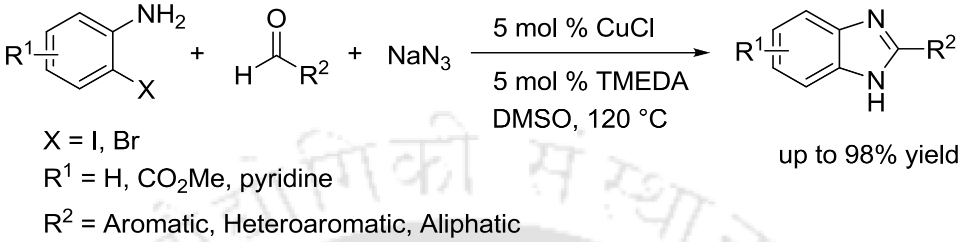
Scheme 14. Synthesis of *N*-substituted 2-heterobenzimidazoles

Ma and co-workers have developed a method for the synthesis of 2-substituted 1*H*-benzimidazoles through CuI/L-proline catalyzed coupling of 2-iodoanilides with aqueous ammonia and subsequent additive cyclization. A wide range of functional groups were tolerated under these reaction conditions, providing the desired heterocycles with great diversity (Scheme 15).[15h]



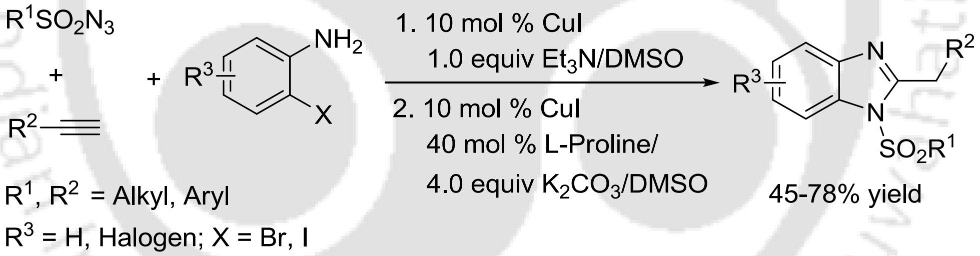
Scheme 15. Synthesis of 2-substituted 1*H*-benzimidazoles

A one-pot, three-component reaction of 2-haloanilines, aldehydes and NaN_3 by copper catalysis was described for the efficient synthesis of 2-substituted 1*H*-benzimidazoles. The reaction conditions involve the use of 5 mol % of CuCl and 5 mol % of TMEDA in DMSO at 120 °C (Scheme 16).[15i]



Scheme 16. Copper-Catalyzed One-Pot, Three-Component Synthesis of Benzimidazoles

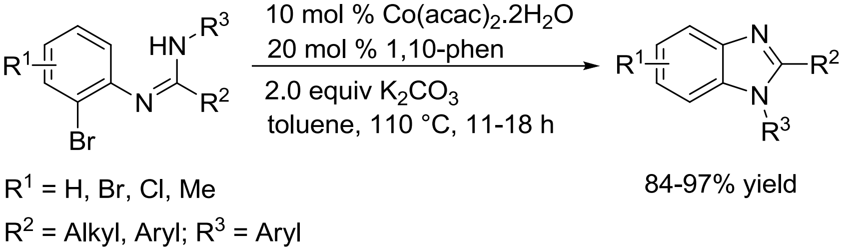
Another one pot, three-component reaction was reported by Wang and co-workers for the synthesis of 2-substituted 1-sulfonylbenzimidazoles. Cascade reaction of sulfonyl azides, alkynes and 2-bromoanilines using a catalytic amount of CuI afforded benzimidazoles in moderate to good yields (Scheme 17).[15j]



Scheme 17. Three-Component Synthesis of 2-Substituted 1-Sulfonylbenzimidazoles

2.1.2.3. Cobalt Catalyzed Synthesis of Benzimidazoles

Cobalt-salts have also been used for *C–N* cross-coupling reaction for synthesis of substituted benzimidazoles. As an example, our group has reported a cobalt(II)-complex catalyzed intramolecular *C-N* cross-coupling of *o*-haloarylamidines to afford benzimidazoles in the presence of K_2CO_3 at moderate temperature.. The reaction is efficient and the desired products were obtained in good yield (Scheme 18).[16]



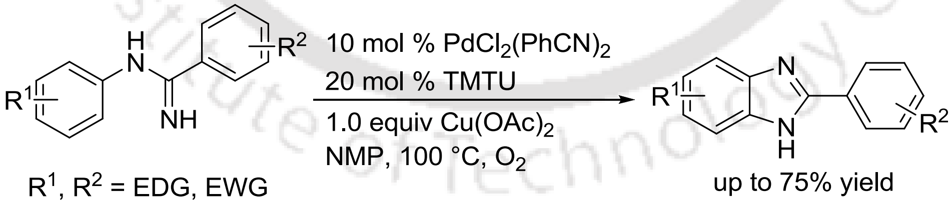
Scheme 18. Cobalt-Catalyzed Intramolecular Cyclization of 2-Haloarylamidines

2.1.3. C-H Functionalization Reactions

The C-H functionalization reactions, in consideration of achieving atom-economical processes alternative to cross-coupling reactions, hold a prominent place in organic chemistry. This strategy has been used for the synthesis of substituted benzimidazoles through Pd- and Cu- catalyzed reactions.

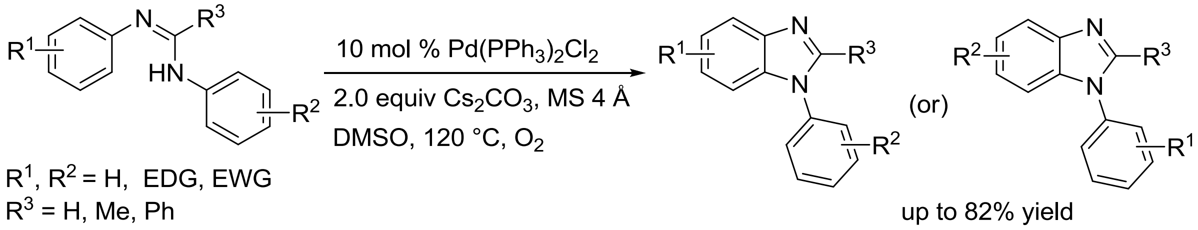
2.1.3.1. Palladium Catalyzed Synthesis of Benzimidazoles

Shi and co-workers have demonstrated a Pd(II)-catalyzed intramolecular C-H amination of *N*-arylbenzimidamides for straightforward synthesis of 1*H*-benzo[*d*]imidazoles. The reaction was carried out with $PdCl_2(PhCN)_2$ in the presence of TMTU and $Cu(OAc)_2$ in *N*-methyl-2-pyrrolidone (NMP) as solvent. The reaction intermediates involves a palladacycle monomer or dimer. TMTU was used to promote the catalytic efficiency of the Pd(II) catalyzed C-H activation. (Scheme 19).[17a]



Scheme 19. Palladium Catalyzed Synthesis of Benzimidazoles by C-H Functionalization

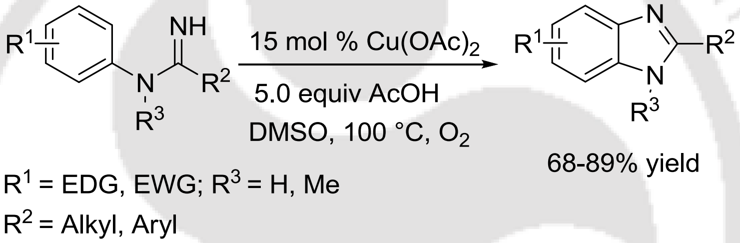
Our group has reported the synthesis of 2-unsubstituted and 2-substituted *N*-aryl benzimidazoles by palladium catalyzed aerobic oxidative C-H amination (Scheme 20).[17b]



Scheme 20. Synthesis of 2-Unsubstituted and 2-Substituted *N*-Aryl benzimidazoles

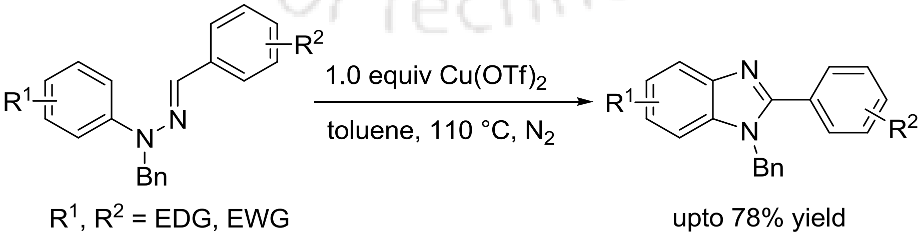
2.1.3.2. Copper Catalyzed Synthesis of Benzimidazoles

Buchwald and co-workers reported an efficient $Cu(OAc)_2$ catalyzed intramolecular C-H functionalization/*C-N* bond formation protocol for the synthesis of suitably substituted benzimidazoles from amidines in good to very good yields (Scheme 21).[18a]



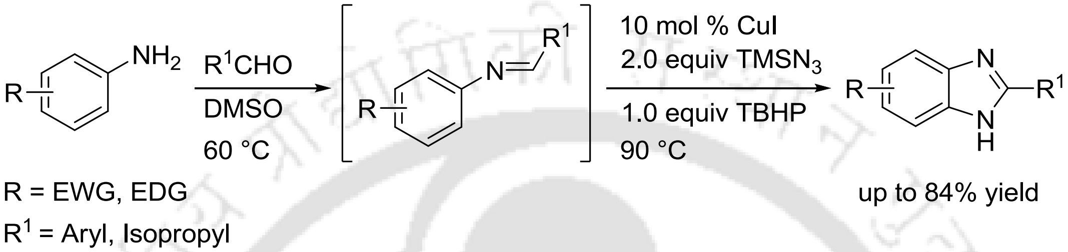
Scheme 21. Copper Catalyzed Synthesis of Benzimidazoles by C-H Functionalization

Our group has developed a new method for the transformation of *N*-benzyl bisarylhydrazones to 2-aryl-*N*-benzylbenzimidazoles. This reaction involves a copper(II)-mediated cascade C-H functionalization followed by *C-N* bond formation under neutral conditions (Scheme 22).[18b] In this reaction, the substrates having electron-withdrawing groups have exhibited greater reactivity in comparison to those bearing electron-donating groups.



Scheme 22. Copper Mediated Rearrangement of *N*-benzyl Bisarylhydrazones for the Synthesis of Benzimidazoles

Recently, we reported a one-pot synthesis of substituted benzimidazoles starting from aryl amines, aldehydes and azides. The reaction involves chelation of the copper catalyst to the imine, followed by *ortho* C-H azidation and subsequent cyclization to give benzimidazoles. The use of inexpensive copper catalysts, the commercially available starting materials and the broad substrate scope are significant practical advantages of this method (Scheme 23).[18c]

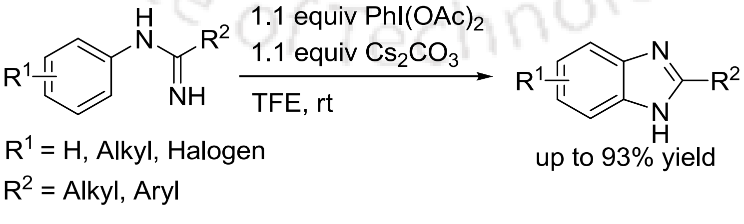


Scheme 23. Copper Catalyzed Synthesis of 1*H*-benzo[*d*]imidazole *via* C-H Azidation

2.1.4. Hypervalent Iodine Mediated Synthesis of Benzimidazoles

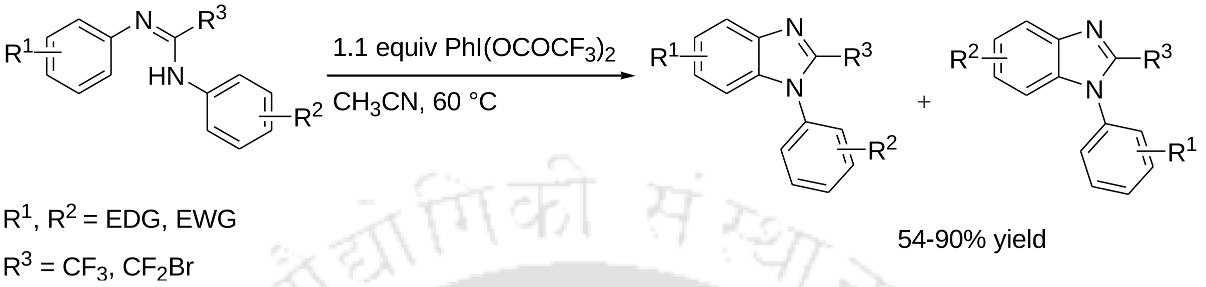
Cross-coupling and C-H functionalization reactions catalyzed by transition metals are very effective under relatively milder conditions compared to the classical methods, but the high cost and toxicity of some of the metal salts restrict their practical utility on a larger scale process. Hence, new routes for the construction of the benzimidazole structural framework under metal-free conditions using hypervalent iodine reagent were developed.

Zhu and co-workers have developed a method for the construction of 2-substituted benzimidazoles through PIDA mediated intramolecular oxidative imidation of aromatic C-H bonds of readily available *N*-arylamidines (Scheme 24).[19a]



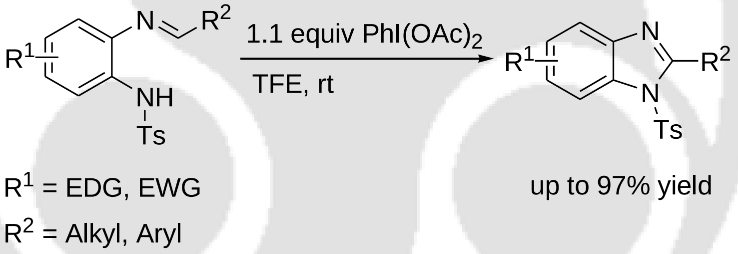
Scheme 24. PIDA Mediated Synthesis of 2-Substituted Benzimidazoles

A process for the synthesis of *N*-aryl or *N*-alkyl 2-fluoro-methylbenzimidazoles has been developed by Wu and co-workers from *N*,*N'*-disubstituted ethanimidamides by oxidative cyclization with phenyliodine bis(trifluoroacetate) (Scheme 25).[19b]



Scheme 25. Synthesis of Substituted Benzimidazoles by Oxidative C-H Amination

Mal group has developed transition metal-free, $PhI(OAc)_2$ mediated C(sp^2)-H amidation at room temperature, resulting in functionalized benzimidazoles in good to excellent yields (Scheme 26).[19c]

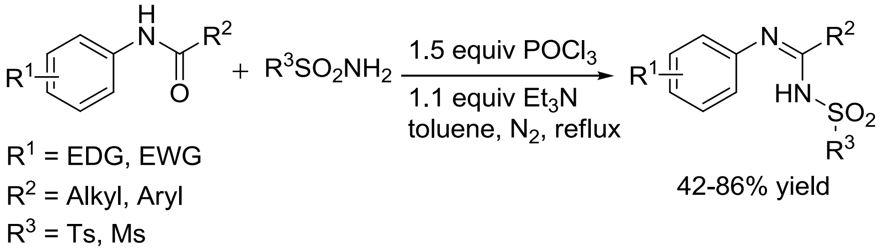


Scheme 26. Metal-Free Synthesis of Substituted Benzimidazoles

2.2. Present Study

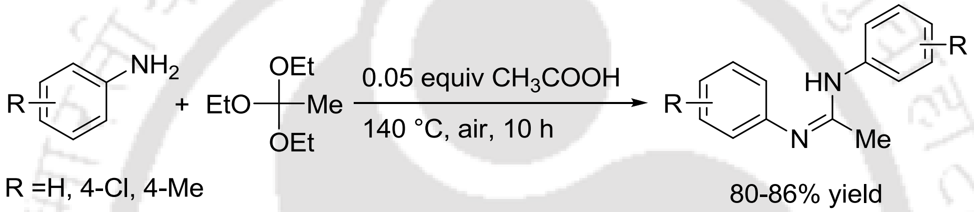
We have studied the synthesis of 2-substituted *N*-sulfonyl benzimidazoles and *N*-aryl benzimidazoles from *N''*-aryl-*N'*-tosyl/*N'*-methylsulfonylamidines and *N*,*N'*-bis(aryl)amidines *via* iodobenzene-catalyzed C–H functionalization strategy.

Synthesis of *N*-Phenyl-*N'*-sulfonylamidines (1a-r). The cyclization precursors, *N*-phenyl-*N'*-sulfonyl amidines were prepared by heating sulfonamides with the corresponding amides, $POCl_3$ and Et_3N in toluene for 2-5 h (Scheme 27).[14a]



Scheme 27. Synthesis of *N*-Phenyl-*N′*-sulfonylamidines

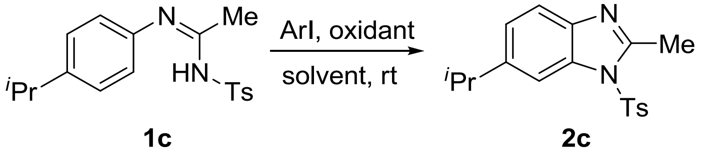
Synthesis of *N,N′*-Diarylacetamidines (1s-u). *N,N′*-Diarylacetamidines have been synthesized by heating anilines with triethyl orthoacetate in the presence of small amount of glacial acetic acid for 10 h at 140 °C (Scheme 28).[17b]



Scheme 28. Synthesis of *N,N′*-diarylacetamidines

The cyclization of amidines was optimized using (*Z*)-*N″*-4-isopropylphenyl-*N′*-tosylacetamidine **1c** as a model substrate (Table 1). Treating the substrate **1c** with stoichiometric amounts of hypervalent iodine reagents $PhI(OAc)_2$ and PhIO resulted in the formation of the desired benzimidazole in 68 and 66% conversions, respectively (entries 1-2). Reaction of the substrate **1c** with 20 mol % of iodobenzene and 1.5 equiv of *m*CPBA as an oxidant in 0.5 mL of CH_2Cl_2 for 12 hours at room temperature did not afford the target benzimidazole **2c** (entry 3). Further optimization with various solvents such as MeOH, DME, DMSO, DMF and CF_3COOH proved unsuccessful (entries 4-8). However, to our delight, **1c** readily cyclized to give the target benzimidazole **2c** in 76% conversion using 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as solvent (entry 9). Employing various substituted iodoarenes gave inferior results (entries 10-11). In addition, sreening with oxidants such as *tert*-butyl hydroperoxide (TBHP), H_2O_2, $K_2S_2O_8$ and oxone were not successful (entries 12-15). Lowering the quantity of iodobenzene to 10 mol % led to the product formation in 53% conversion (entry 16).

Table 1. Optimization of Reaction Conditions[a]

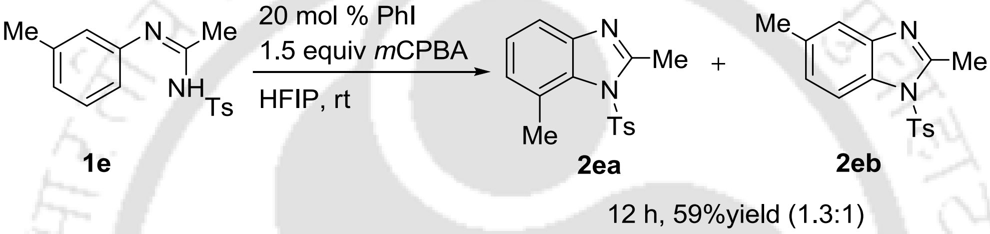


entry	Ar	oxidant	solvent	conversion (%)[b]
1	-	$PhI(OAc)_2$	HFIP	68
2	-	PhIO	HFIP	66
3	C_6H_5	*m*CPBA	DCM	n.d.
4	C_6H_5	*m*CPBA	MeOH	n.d.
5	C_6H_5	*m*CPBA	DME	n.d.
6	C_6H_5	*m*CPBA	DMSO	n.d.
7	C_6H_5	*m*CPBA	DMF	n.d.
8	C_6H_5	*m*CPBA	CF_3COOH	trace
9	$\mathbf{C_6H_5}$	***m*CPBA**	**HFIP**	**76**
10	4-OMe-C_6H_4	*m*CPBA	HFIP	33
11	4-Me-C_6H_4	*m*CPBA	HFIP	55
12	C_6H_5	TBHP	HFIP	n.d.
13	C_6H_5	H_2O_2	HFIP	trace
14	C_6H_5	$K_2S_2O_8$	HFIP	n.d.
15	C_6H_5	Oxone	HFIP	n.d.
16[c]	C_6H_5	*m*CPBA	HFIP	53
17	-	*m*CPBA	HFIP	n.d.

[a] **1c** (0.5 mmol), aryl iodide (20 mol %), oxidant (1.5 equiv), solvent (1 mL), rt, 12 h. [b] Determined by ^1H NMR. [c] Iodobenzene (10 mol %) used.

Control experiment confirmed that without iodobenzene, the formation of the product **2c** was not observed (entry 17).

With the optimized conditions, the scope of the procedure with a series of substituted amidines was next studied (Table 2). (*Z*)-*N''*-Phenyl-*N'*-tosylacetamidine **1a** proceeded reaction to give 2-methyl-1-tosyl-1*H*-benzo[*d*]imidaozle **2a** in 68% yield. Similarly, (*Z*)-*N''*-aryl-*N'*-tosylacetamidines **1b**, **1d** and **1f-g** with R' having 2-methyl, 4-methyl, 3,4-dimethyl and 3,5-dimethyl substituents underwent cyclization to give the corresponding substituted benzimidazoles **2b**, **2d** and **2f-g** in 59-64% yields, while the substrates **1h-j** bearing halogen substituents such as 2-bromo, 4-chloro and 4-fluoro gave the target products **2h-j** in 42-91% yields. In contrast, the substrate **1k** with R' having 4-nitro substituent showed no reaction and the starting material was recovered intact. (*Z*)-*N''*-(naphthalen-4-yl)-*N'*-tosylacetamidine **1l** could cyclize to give the target heterocycle **2l** in 34% yield. In case of the substrate **1e**, a 1.3:1 mixture of regioisomers **2ea** and **2eb** was obtined in 59% yield (Scheme 29).

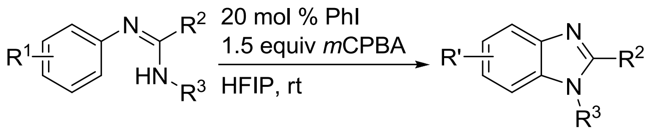


Scheme 29. Reaction of *meta* Substituted Amidine

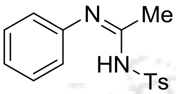
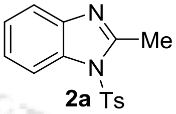
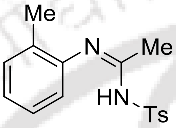
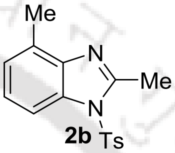
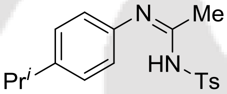
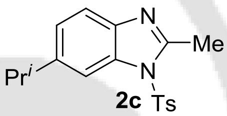
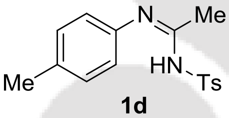
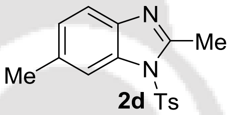
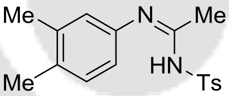
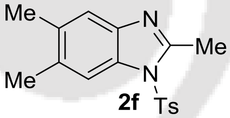
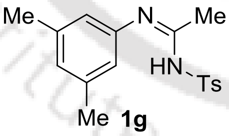
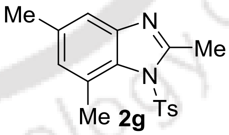
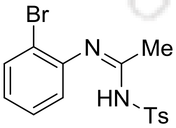
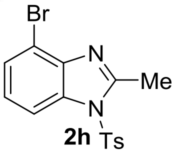
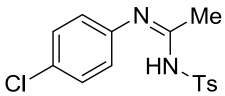
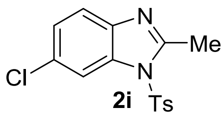
The reaction of the amidines with R^2 having alkyl, aryl and vinyl substituents was next studied. The procedure was general and the reaction proceeded to give the target heterocycles in moderate to high yield. The substrates **1m-o** having R^2 with alkyl groups, ethyl, *n*-pentyl and *tert*-butyl exhibited greater reactivity compared to that bearing phenyl and styryl substituents **1p-q** affording the corresponding heterocyles **2m-q** in 58-90% yields.

Finally, the cyclization of different *N'*-substituted acetamidines was studied. As above, the cyclization of the substrates *N'*-methylsulfonyl acetamidine **1r** and *N'*-aryl acetamidines **1s-u** could be accomplished to provide the corresponding benzimidazoles **2r-u** in 56-93% yields. The substrate with electron withdrawing substituent **1t** exhibited enhanced reactivity compared to that bearing electron donating group **1u**. In contrary, *N'*-unsubstituted and *N'*-cyclohexyl acetamidines **1v-w** showed no reaction and the starting materials were recovered intact.

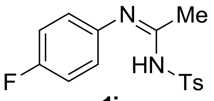
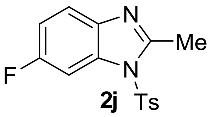
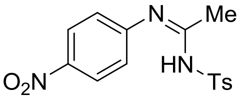
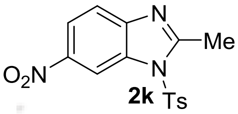
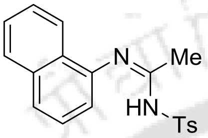
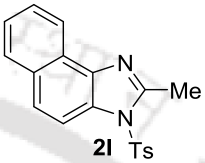
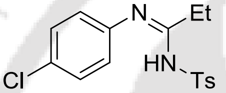
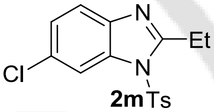
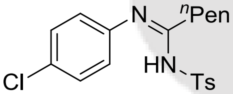
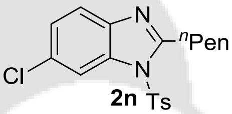
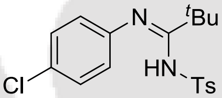
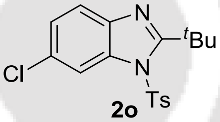
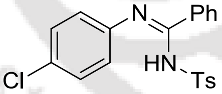
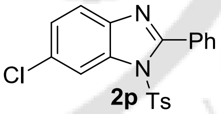
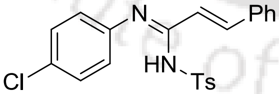
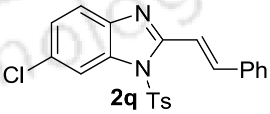
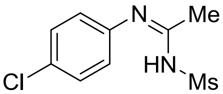
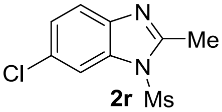
Table 2. Reaction of *N'*-Aryl Substituted Amidines[a]



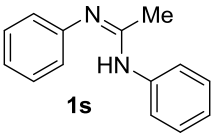
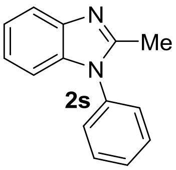
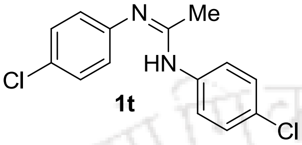
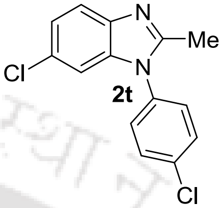
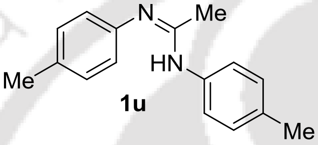
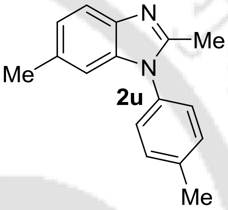
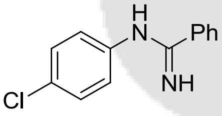
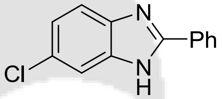
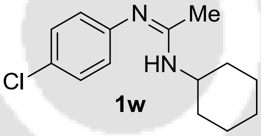
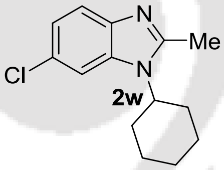
1a-d, f-w **2a-d, f-w**

entry	substrate	time (h)	product	yield (%)[c]
1	 **1a**	12	 **2a**	68
2	 **1b**	12	 **2b**	63[b]
3	 **1c**	12	 **2c**	63
4	 **1d**	12	 **2d**	59
5	 **1f**	12	 **2f**	60
6	 **1g**	12	 **2g**	64
7	 **1h**	12	 **2h**	42[b]
8	 **1i**	2	 **2i**	91

Continued........

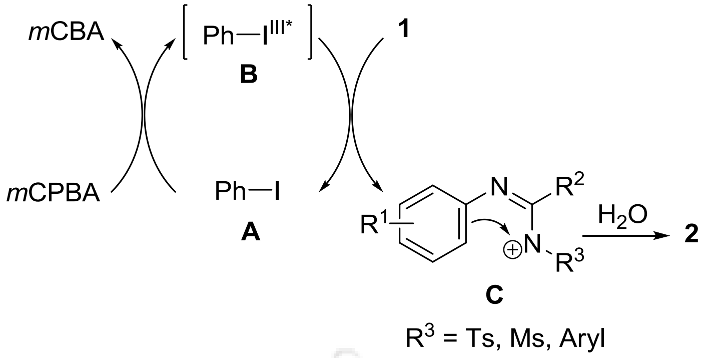
entry	substrate	time (h)	product	yield (%)
9	 **1j**	12	 **2j**	78
10	 **1k**	12	 **2k**	0
11	 **1l**	12	 **2l**	34
12	 **1m**	5	 **2m**	90
13	 **1n**	5	 **2n**	87
14	 **1o**	5	 **2o**	82
15	 **1p**	12	 **2p**	63
16	 **1q**	12	 **2q**	58
17	 **1r**	12	 **2r**	56

Continued........

entry	substrate	time (h)	product	yield (%)
18	 **1s**	12	 **2s**	72
19	 **1t**	2	 **2t**	93
20	 **1u**	12	 **2u**	64
21	 **1v**	12	 **2v**	0
22	 **1w**	12	 **2w**	0

[a] Substrates **1a-d, 1f-w** (0.5 mmol), iodobenzene (20 mol %), *m*CPBA (1.5 equiv), HFIP (1 mL), rt. [b] Iodobenzene (40 mol %) used. [c] Isolated yield.

A putative reaction mechanism is shown in Scheme 30. The oxidation of iodobenzene **A** using *m*CPBA may give the active hypervalent iodine(III) species[21a] that could react with **1** to generate nitrenium ion **C**.[8m,21b] The nucleophilic arene attacks to the nitrenium ion may lead to the formation of the target benzimidazoles, accompanied by the liberation of iodobenzene **A**, which could be reoxidized to **B** by *m*CPBA.



Scheme 30. Proposed Catalytic Cycle

Finally, the stucture was further confirmed by X-ray analysis of 6-chloro-2-methyl-1-tosyl-1*H*-benzo[*d*]imidazole **2i** (Figure 2).

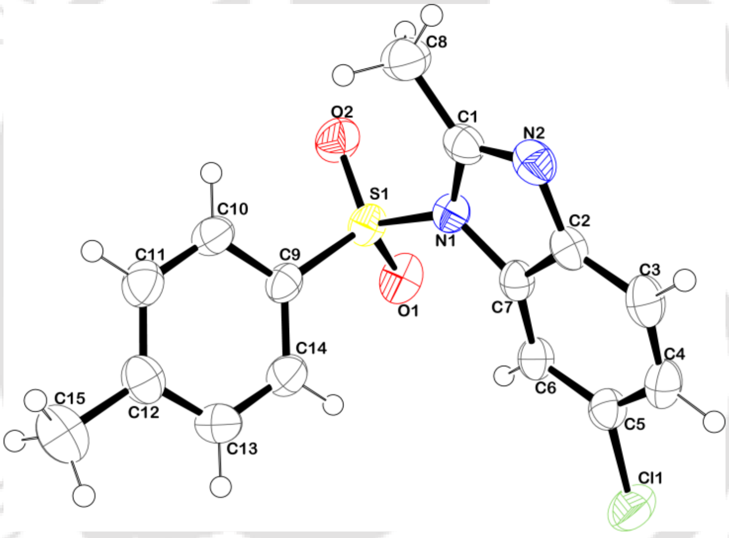


Figure 2. ORTEP diagram of 6-chloro-2-methyl-1-tosyl-1*H*-benzo[*d*]imidazole **2i**.

In summary, we have developed a new protocol for the synthesis of 2-substituted *N*-sulfonyl benzimidazoles and *N*-aryl benzimidazoles using iodobenzene as catalyst in the presence of *m*CPBA as a terminal oxidant at room temperature. The reaction is simple and general to afford the target products in moderate to good yield.

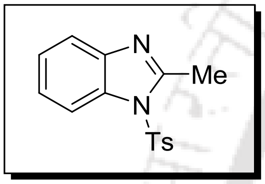
2.3. Experimental Section

2.3.1. General Information: Anilines, toluene-4-sulphonamide, *m*CPBA (ca. 77 wt%), 1,1,1,3,3,3-hexafloro-2-propanol were purchased from Aldrich and were used as received. Phosphorous oxychloride and methanesulfonamide was purchased from Avra synthesis. PhIO was prepared according to reported procedure.[21c] Purification of the reaction products was carried out by column chromatography using Rankem silica gel (60-120 mesh). Analytical TLC was performed on Merck silica gel G/GF 254 plate. NMR spectra were recorded on DRX-400 Varian spectrometer and Bruker Ultrashield^{TM} 300 using $CDCl_3$ as solvent and Me_4Si as 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. FT-IR spectra were recorded using Perkin Elmer IR spectrometer. Elemental analysis were recorded using Perkin Elmer CHNS analyzer. Mass spectra were recorded on a Waters Q-Tof Premier mass spectrometer. X-Ray data were collected on a Bruker SMART APEX equipped with a CCD area detector using Mo/Kα radiation. The structures were solved by direct method using *SHELLX-97* (Gottingen, Germany).

2.3.2. General Procedure for Cyclization of Substituted Amidines using PhIO/ PhI(OAc)$_2$ in HFIP. To a stirred solution of amidine (0.5 mmol, 1.0 equiv) in HFIP (1 mL) was added PhIO/PhI(OAc)$_2$ (0.5 mmol, 1.0 equiv) at room temperature under air. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. After 12 h, the resulting solution was extracted with ethyl acetate (3 x 10 mL) and H_2O (3 x 5 mL), later washed with brine (2 x 5 mL). Drying over Na_2SO_4 and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane and ethyl acetate as eluent to give analytically pure 6-isopropyl-2-methyl-1-tosyl-1*H*-benzo[*d*]imidazole**.**

2.3.3. General Procedure for Iodobenzene Catalyzed Synthesis of Substituted Benzimidazoles 2a-w. *m*CPBA (1.5 equiv) was added to a stirred solution of amidine **1** (0.5 mmol, 1.0 equiv) and iodobenzene (20 mol %) in HFIP (1 mL) at room temperature under air. The mixture was stirred and the progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. After the appropriate time, saturated $NaHCO_3$ (5 mL) was added to the reaction mixture. The resulting solution was extracted with ethyl acetate (3 x 10 mL) and washed with brine (2 x 5 mL). Drying over Na_2SO_4 and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using n-hexane and ethyl acetate as eluent to afford analytically pure *N*-substituted benzimidazoles.

2.4. Characterization Data of Substituted Benzimidazoles 2a-w



2-Methyl-1-tosyl-1*H*-benzo[*d*]imidazole 2a. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane $R_f = 0.60$; white solid; yield 68%.

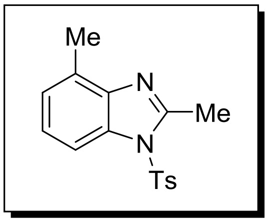
Mp: 113-115 °C (lit.[11c] mp 117 °C).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01-7.99 (m, 1H), 7.79 (d, J = 8.4 Hz, 2H), 7.61-7.59 (m, 1H), 7.33-7.26 (m, 4H), 2.79 (s, 3H), 2.37 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 146.0, 141.9, 135.4, 133.2, 130.3, 126.8, 124.7, 124.6, 119.7, 113.5, 21.6, 16.9.

FT-IR (KBr) 3105, 2963, 1597, 1546, 1427, 1372, 1247, 1188, 1172, 1088, 1053, 1015 cm^{-1}.

Anal. Calcd. for $C_{15}H_{14}N_2O_2S$: C, 62.92; H, 4.93; N, 9.78; S, 11.20. Found: C, 63.04; H, 4.91; N, 9.73; S, 11.16.



2,4-Dimethyl-1-tosyl-1*H*-benzo[*d*]imidazole 2b. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane $R_f = 0.36$; white solid; yield 63%.

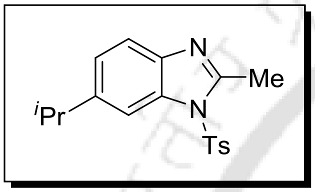
Mp: 91-93 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.78 (d, *J* = 8.4 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 2H), 7.20-7.13 (m, 3H), 7.05 (d, *J* = 7.6 Hz, 1H), 2.75 (s, 3H), 2.49 (s, 3H), 2.29 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 150.7, 146.0, 141.1, 135.7, 133.0, 130.4, 129.8, 126.9, 125.4, 124.7, 111.1, 21.8, 17.1, 16.7.

FT-IR (KBr) 2920, 2888, 1547, 1425, 1377, 1334, 1276, 1186, 1143, 1090, 1051 cm^{-1}.

Anal. Calcd. for $C_{16}H_{16}N_2O_2S$: C, 63.98; H, 5.37; N, 9.33; S, 10.67. Found: C, 64.13; H, 5.35; N, 9.27; S, 10.63.



6-Isopropyl-2-methyl-1-tosyl-1*H*-benzo[*d*]imidazole 2c. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R$_f$ = 0.60; brown solid; yield 63%.

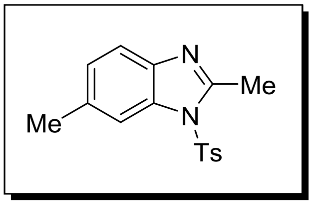
Mp: 105-107 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.84 (d, *J* = 1.6 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.19 (dd, *J* = 8.0 Hz, 1.2 Hz, 1H), 3.06-3.02 (m, 1H), 2.76 (s, 3H), 2.36 (s, 3H), 1.30 (d, *J* = 6.8 Hz, 6H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 150.8, 146.0, 145.8, 140.2, 135.4, 133.3, 130.1, 126.7, 123.3, 119.2, 111.0, 34.5, 24.3, 21.4, 16.8.

FT-IR (KBr) 2952, 2865, 1612, 1592, 1553, 1458, 1437, 1370, 1312, 1260, 1181, 1130, 1087, 1058, 1037, 1010 cm^{-1}.

Anal. Calcd. for $C_{18}H_{20}N_2O_2S$: C, 65.83; H, 6.14; N, 8.53; S, 9.76. Found: C, 65.97; H, 6.13; N, 8.47; S, 9.71.



2,6-Dimethyl-1-tosyl-1*H*-benzo[*d*]imidazole 2d. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R$_f$ = 0.54; brown solid; yield 59%.

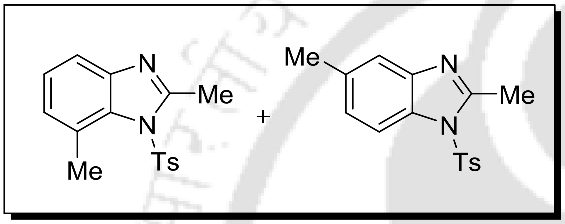
Mp: 102-104 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80-7.76 (m, 3H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 1H), 2.75 (s, 3H), 2.48 (s, 3H), 2.36 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 145.9, 140.0, 135.6, 134.9, 133.5, 130.3, 126.7, 126.0, 119.1, 113.5, 22.0, 21.6, 16.9.

FT-IR (KBr) 3031, 2922, 1613, 1594, 1551, 1454, 1370, 1263, 1187, 1159, 1089, 1048, 1012 cm^{-1}.

Anal. Calcd. for $C_{16}H_{16}N_2O_2S$: C, 63.98; H, 5.37; N, 9.33; S, 10.67. Found: C, 64.11; H, 5.36; N, 9.26; S, 10.61.



2,7-Dimethyl-1-tosyl-1*H*-benzo[*d*]imidazole 2ea and 2,5-Dimethyl-1-tosyl-1*H*-benzo[*d*]imidazole 2eb. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.42; white solid; yield 59%.

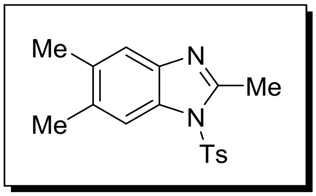
Mp: 70-72 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.41 (s, 1H), 7.29-7.26 (m, 4H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.17-7.14 (m, 1H),), 7.05 (d, *J* = 7.2 Hz, 1H), 2.89 (s, 3H), 2.79 (s, 3H), 2.49 (s, 3H), 2.43 (s, 3H), 2.40 (s, 3H), 2.38 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 151.5, 146.0, 145.4, 143.2, 142.2, 137.2, 135.6, 134.6, 133.1, 131.2, 130.3, 128.9, 126.8, 126.2, 126.1, 125.0, 124.7, 119.7, 117.8, 113.1, 21.9, 21.7, 21.4, 18.9, 16.9.

FT-IR (KBr) 3047, 2923, 2853, 1918, 1739, 1648, 1594, 1542, 1491, 1427, 1372, 1352, 1294, 1258, 1213, 1173, 1089, 1055, 1036, 1014 cm^{-1}.

Anal. Calcd. for $C_{16}H_{16}N_2O_2S$: C, 63.98; H, 5.37; N, 9.33; S, 10.67. Found: C, 64.12; H, 5.35; N, 9.27; S, 10.63.



2,5,6-Trimethyl-1-tosyl-1*H*-benzo[*d*]imidazole 2f. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane $R_f = 0.50$; white solid; yield 60%.

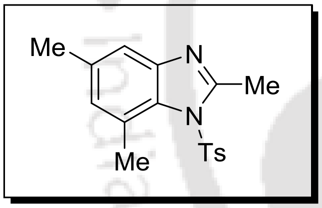
Mp: 145-147 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77-7.75 (m, 3H), 7.34 (s, 1H), 7.26 (d, *J* = 8.4 Hz, 2H), 2.73 (s, 3H), 2.37 (s, 3H), 2.36 (s, 3H), 2.30 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 145.9, 140.5, 135.8, 133.9, 133.6, 131.7, 130.3, 126.8, 119.9, 113.8, 21.7, 20.7, 20.2, 16.9.

FT-IR (KBr) 2919, 1596, 1549, 1463, 1376, 1278, 1225, 1188, 1174, 1123, 1090, 1040 cm^{-1}.

Anal. Calcd. for $C_{17}H_{18}N_2O_2S$: C, 64.94; H, 5.77; N, 8.91; S, 10.20. Found: C, 65.08; H, 5.76; N, 8.85; S, 10.15.



2,5,7-Trimethyl-1-tosyl-1*H*-benzo[*d*]imidazole 2g. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane $R_f = 0.42$; brown solid; yield 64%.

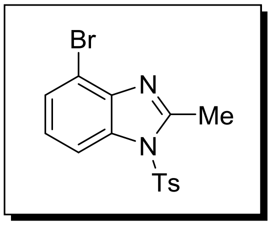
Mp: 66-68 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.4 Hz, 2H), 7.28-7.26 (m, 3H), 6.87 (s, 1H), 2.86 (s, 3H), 2.45 (s, 3H), 2.39 (s, 3H), 2.36 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 145.3, 143.7, 137.2, 134.8, 131.1, 130.3, 130.2, 126.2, 124.2, 117.8, 21.8, 21.7, 21.1, 18.9.

FT-IR (KBr) 3047, 2922, 1595, 1556, 1459, 1357, 1249, 1186, 1176, 1086, 1037 cm^{-1}.

Anal. Calcd. for $C_{17}H_{18}N_2O_2S$: C, 64.94; H, 5.77; N, 8.91; S, 10.20. Found: C, 65.07; H, 5.75; N, 8.86; S, 10.15.



4-Bromo-2-methyl-1-tosyl-1*H*-benzo[*d*]imidazole 2h. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane $R_f = 0.70$; white solid; yield 42%.

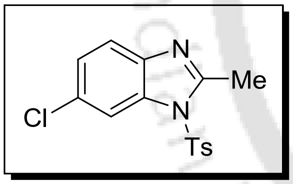
Mp: 171-172 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 8.4 Hz, 0.8 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.49 (dd, *J* = 8.0 Hz, 0.8 Hz, 1H), 7.28 (d, *J*= 8.0 Hz, 2H), 7.21(t, *J* = 8.0 Hz, 1H), 2.82 (s, 3H), 2.37 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 152.3, 146.4, 139.9, 134.9, 133.6, 130.3, 127.7, 126.8, 125.6, 112.6, 21.7, 17.0.

FT-IR (KBr) 2922, 2853, 1731, 1589, 1553, 1472, 1383, 1269, 1142, 1087, 1024 cm^{-1}.

Anal. Calcd. for $C_{15}H_{13}BrN_2O_2S$: C, 49.33; H, 3.59; N, 7.67; S, 8.78. Found: C, 49.47; H, 3.57; N, 7.61; S, 8.73.



6-Chloro-2-methyl-1-tosyl-1*H*-benzo[*d*]imidazole 2i. Analytical TLC on silica gel, 3:7 ethyl acetate/ hexane $R_f = 0.54$; white solid; yield 91%.

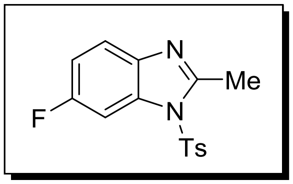
Mp: 140-142 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 2.0 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.29 (dd, *J* = 8.8 Hz, 2.0 Hz, 1H), 2.76 (s, 3H), 2.39 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 152.1, 146.4, 140.5, 135.1, 133.8, 130.54, 130.5, 126.9, 125.2, 120.4, 113.7, 21.7, 16.9.

FT-IR (KBr) 3072, 2913, 1610, 1597, 1545, 1431, 1375, 1271, 1189, 1172, 1090, 1045, 1002 cm^{-1}.

Anal. Calcd. for $C_{15}H_{13}ClN_2O_2S$: C, 56.16; H, 4.08; N, 8.73; S, 10.00. Found: C, 56.29; H, 4.06; N, 8.66; S, 9.97.



6-Fluoro-2-methyl-tosyl-1*H*-benzo[*d*]imidazole 2j. Analytical TLC on silica gel, 3:7 ethyl acetate/ hexane $R_f = 0.50$; white solid; yield 78%.

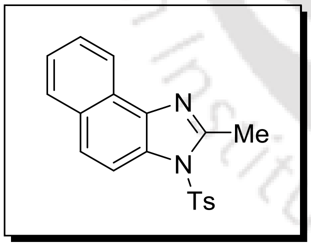
Mp: 95-97 °C.

^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.4 Hz, 2H), 7.75 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 7.54 (dd, *J* = 8.8 Hz, 4.8 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.06-7.01 (m, 1H), 2.75 (s, 3H), 2.38 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 161.7, 159.3, 151.9, 146.4, 138.3, 135.2, 133.6, 133.4, 130.5, 127.0, 120.5, 120.4, 112.9, 112.6, 101.3, 101.0, 21.8, 17.0.

FT-IR (KBr) 3075, 2917, 1619, 1597, 1553, 1477, 1376, 1272, 1175, 1143, 1119, 1045, 1002 cm^{-1}.

Anal. Calcd. for $C_{15}H_{13}FN_2O_2S$: C, 59.20; H, 4.31; N, 9.20; S, 10.54. Found: 59.32; H, 4.30; N, 9.15; S, 10.50.



2-Methyl-3-tosyl-3*H*-naphtho[1,2-*d*]imidazole 2l. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane $R_f = 0.80$; white solid; yield 34%.

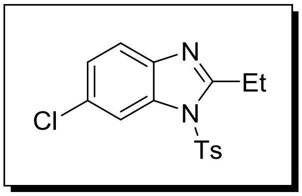
Mp: 107-109 °C.

^1H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, *J* = 8.0 Hz, 1H), 8.18 (d, *J* = 9.2 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 2H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.62-7.58 (m, 1H), 7.52-7.48 (m, 1H), 7.26-7.24 (m, 2H), 2.90 (s, 3H), 2.35 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 149.8, 146.1, 137.4, 135.3, 131.0, 130.3, 129.6, 128.1, 126.9, 126.7, 126.0, 125.5, 125.4, 121.9, 112.9, 21.5, 16.9.

FT-IR (KBr) 3058, 2922, 1594, 1540, 1370, 1261, 1188, 1171, 1115, 1085, 1066, 1009 cm^{-1}.

Anal. Calcd.. for $C_{19}H_{16}N_2O_2S$: C, 67.84; H, 4.79; N, 8.33; S, 9.53. Found: C, 67.94; H, 4.78; N, 8.29; S, 9.49.



6-Chloro-2-ethyl-1-tosyl-1*H*-benzo[*d*]imidazole 2m. Analytical TLC on silica gel, 3:7 ethyl acetate/ hexane R$_f$ = 0.60; white solid; yield 90%.

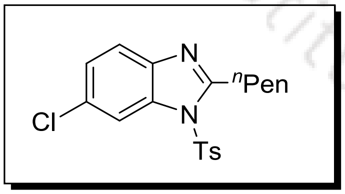
Mp: 123-125 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.05 (d, *J* = 2.0 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.56 (d, *J* = 8.8 Hz, 1H), 7.30-7.26 (m, 3H), 3.14 (q, *J* = 7.2 Hz, 2H), 2.38 (s, 3H), 1.42 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 156.9, 146.3, 140.6, 135.2, 133.9, 130.5, 130.4, 126.8, 125.1, 120.5, 113.8, 23.3, 21.6, 11.5.

FT-IR (KBr) 2981, 2935, 1613, 1597, 1460, 1369, 1292, 1232, 1186, 1089, 1041 cm^{-1}.

Anal. Calcd. for $C_{16}H_{15}ClN_2O_2S$: C, 57.40; H, 4.52; N, 8.37; S, 9.58. Found: C, 57.53; H, 4.51; N, 8.31; S, 9.54.



6-Chloro-2-*n*-Pentyl-1-tosyl-1*H*-benzo[*d*]imidazole 2n. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R$_f$ = 0.74; white solid; yield 87%.

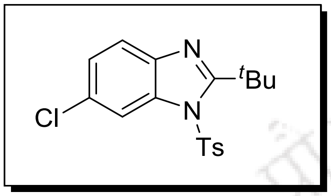
Mp: 147-149 °C.

^{1}H NMR (400 MHz, CDCl$_3$) δ 8.04 (d, *J* = 2.0 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.30-7.26 (m, 3H), 3.08 (t, *J* = 7.6 Hz, 2H), 2.38 (s, 3H), 1.86-1.82 (m, 2H), 1.40-1.33 (m, 4H), 0.90 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 146.4, 140.7, 135.5, 133.9, 130.6, 130.5, 126.9, 125.3, 120.6, 114.0, 31.7, 29.9, 27.4, 22.5, 21.8, 14.1.

FT-IR (KBr) 2950, 2866, 1597, 1544, 1494, 1461, 1374, 1267, 1195, 1158, 1090, 1035 cm^{-1}.

Anal. Calcd. for $C_{19}H_{21}ClN_2O_2S$: C, 60.55; H, 5.62; N, 7.43; S, 8.51. Found: C, 60.67; H, 5.61; N, 7.38; S, 8.47.



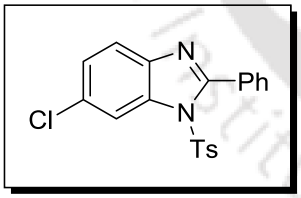
2-*tert*-Butyl-6-chloro-1-tosyl-1*H*-benzo[*d*]imidazole 2o. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.86; brown liquid; yield 82%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 2.0 Hz, 1H), 7.61 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 8.8 Hz, 1H), 7.25-7.22 (m, 3H), 2.36 (s, 3H), 1.61 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6, 145.7, 139.5, 136.5, 135.6, 130.9, 130.3, 126.6, 125.3, 121.0, 115.0, 37.3, 30.2, 21.8.

FT-IR (neat) 2972, 2928, 1596, 1524, 1453, 1377, 1276, 1193, 1180, 1086, 1070, 1010 cm^{-1}.

Anal. Calcd. for $C_{18}H_{19}ClN_2O_2S$: C, 59.58; H, 5.28; N, 7.72; S, 8.84. Found C, 59.72; H, 5.26; N, 7.67; S, 8.79.



6-Chloro-2-phenyl-1-tosyl-1*H*-benzo[*d*]imidazole 2p. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.55; white solid; yield 63%.

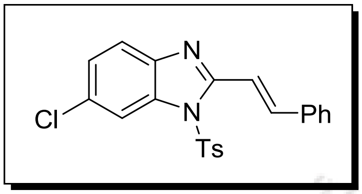
Mp: 157-159 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 1.6 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.55-7.52 (m, 3H), 7.45-7.42 (m, 2H), 7.36 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 7.29 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 2.32 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 146.1, 141.2, 134.7, 134.5, 131.2, 130.8, 130.7, 129.8, 129.6, 127.7, 127.0, 125.9, 121.1, 115.3, 21.6.

FT-IR (KBr) 3120, 2360, 1895, 1607, 1531, 1465, 1452, 1365, 1325, 1264, 1188, 1176, 1070, 1004 cm^{-1}.

Anal. Calcd. for $C_{20}H_{15}ClN_2O_2S$: C, 62.74; H, 3.95; N, 7.32; S, 8.38. Found: C, 62.87; H, 3.93; N, 7.27; S, 8.34.



6-Chloro-2-styryl-1-tosyl-1*H*-benzo[*d*]imidazole 2q. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.70; white solid; yield 58%.

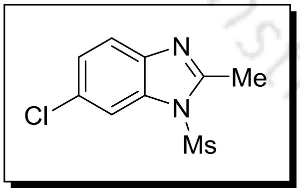
Mp: 130-132 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 2.0 Hz, 1H), 7.89 (d, *J* = 3.6 Hz, 2H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.66 (d, *J* = 7.6 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 1H),7.46-7.40 (m, 3H), 7.34 (dd, *J* = 8.4 Hz, 2.0 Hz, 1H), 7.27-7.25 (m, 2H), 2.36 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 146.4, 141.5, 140.5, 135.8, 135.2, 133.9, 130.9, 130.5, 129.9, 129.1, 127.9, 127.0, 126.1, 120.7, 114.3, 114.1, 21.8.

FT-IR (KBr) 2924, 1624, 1594, 1493, 1452, 1373, 1274, 1161, 1088, 1043 cm^{-1}.

Anal. Calcd. for $C_{22}H_{17}ClN_2O_2S$: C, 64.62; H, 4.19; N, 6.85; S, 7.84. Found: C, 64.78; H, 4.17; N, 6.79; S, 7.79.



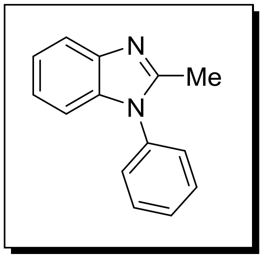
6-Chloro-2-methyl-1-(methylsulfonyl)-1*H*-benzo[*d*]imidazole 2r. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.40; white solid; yield 56%.

Mp: 104-106 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 2.0 Hz, 1H), 7.58 (d, *J* = 8.8 Hz, 1H), 7.32 (dd, *J* = 8.4 Hz, 1.6 Hz, 1H), 3.23 (s, 3H), 2.77 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 140.5, 133.4, 130.7, 125.5, 120.6, 113.3, 42.3, 16.8.

FT-IR (KBr) 3012, 2930, 1613, 1556, 1461, 1434, 1357, 1330, 1278, 1161, 1048, 1009 cm^{-1}. Anal. Calcd. for $C_9H_9ClN_2O_2S$: C, 44.18; H, 3.71; N, 11.45; S, 13.10. Found C, 44.30; H, 3.70; N, 11.40; S, 13.06.



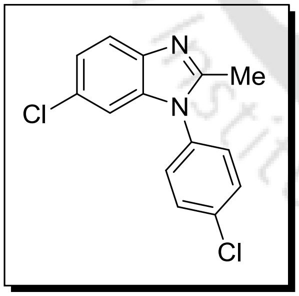
2-Methyl-1-phenyl-1*H*-benzo[*d*]imidazole 2s. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane $R_f = 0.20$; yellow liquid; yield 72%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.6 Hz, 1H), 7.59 (t, *J* = 7.2 Hz, 2H), 7.53 (d, *J* = 6.8 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 2H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.21 (t, *J* = 8.0 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 2.51 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5, 142.4, 136.4, 135.9, 129.9, 128.8, 127.0, 122.4, 119.9, 118.8, 110.0, 14.0.

FT-IR (neat) 3056, 2956, 2923, 1672, 1597, 1499, 1457, 1395, 1324, 1287, 1248, 1181, 1016 cm^{-1}.

Anal. Calcd. for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.83; H, 5.78; N, 13.39.



6-Chloro-1-(4-chlorophenyl)-2-methyl-1*H*-benzo[*d*]imidazole 2t. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane $R_f = 0.40$; brown solid: yield 93%.

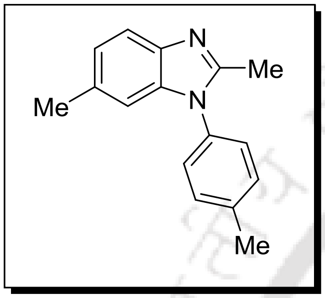
Mp: 109-111 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.8 Hz, 1H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.29 (d, *J* = 8.8 Hz, 2H), 7.22 (dd, *J* = 8.8 Hz, 2.0 Hz, 1H), 7.06 (d, *J* = 1.6 Hz, 1H), 2.46 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 152.2, 141.0, 136.7, 135.2, 133.9, 130.4, 128.6, 128.3, 123.2, 119.9, 109.9, 14.3.

FT-IR (KBr) 3091, 3026, 1686, 1613, 1524, 1497, 1389, 1307, 1294, 1201, 1188, 1091, 1061 cm^{-1}.

Anal. Calcd. for $C_{14}H_{10}Cl_2N_2$: C, 60.67; H, 3.64; N, 10.11. Found: C, 60.77; H, 3.62; N, 10.05.



2,6-Dimethyl-1-(4-methylphenyl)-1*H*-benzo[*d*]imidazole 2u. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane $R_f = 0.40$; yellow liquid; yield 64%.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.61 (d, *J* = 8.4 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 2H), 7.26-7.22 (m, 2H), 7.08 (d, *J* = 8.0 Hz, 1H), 6.90 (s, 1H), 2.473 (s, 3H), 2.47 (s, 3H), 2.40 (s, 3H).

^{13}C NMR (75 MHz, CDCl$_3$) δ 151.2, 140.5, 138.8, 136.8, 133.5, 132.4, 130.5, 126.9, 123.7, 118.4, 109.9, 21.7, 21.3, 14.3.

FT-IR (neat) 3035, 2967, 2922, 2862, 1626, 1515, 1484, 1448, 1318, 1257, 1212, 1108, 1010 cm^{-1}.

Anal. Calcd. for $C_{16}H_{16}N_2$: C, 81.32; H, 6.82; N, 11.85. Found: C, 81.42; H, 6.80; N, 11.77.

2.5. References

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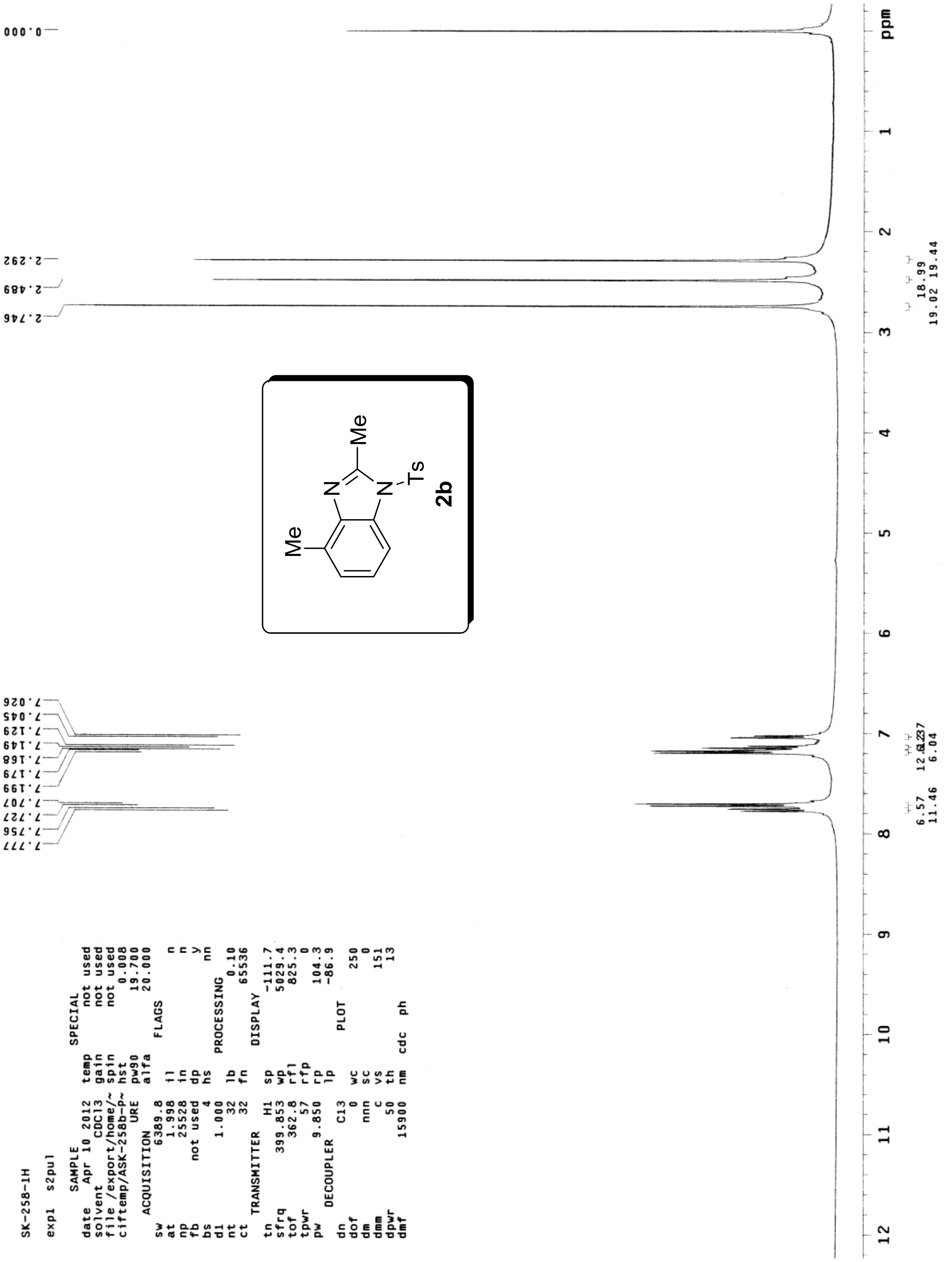
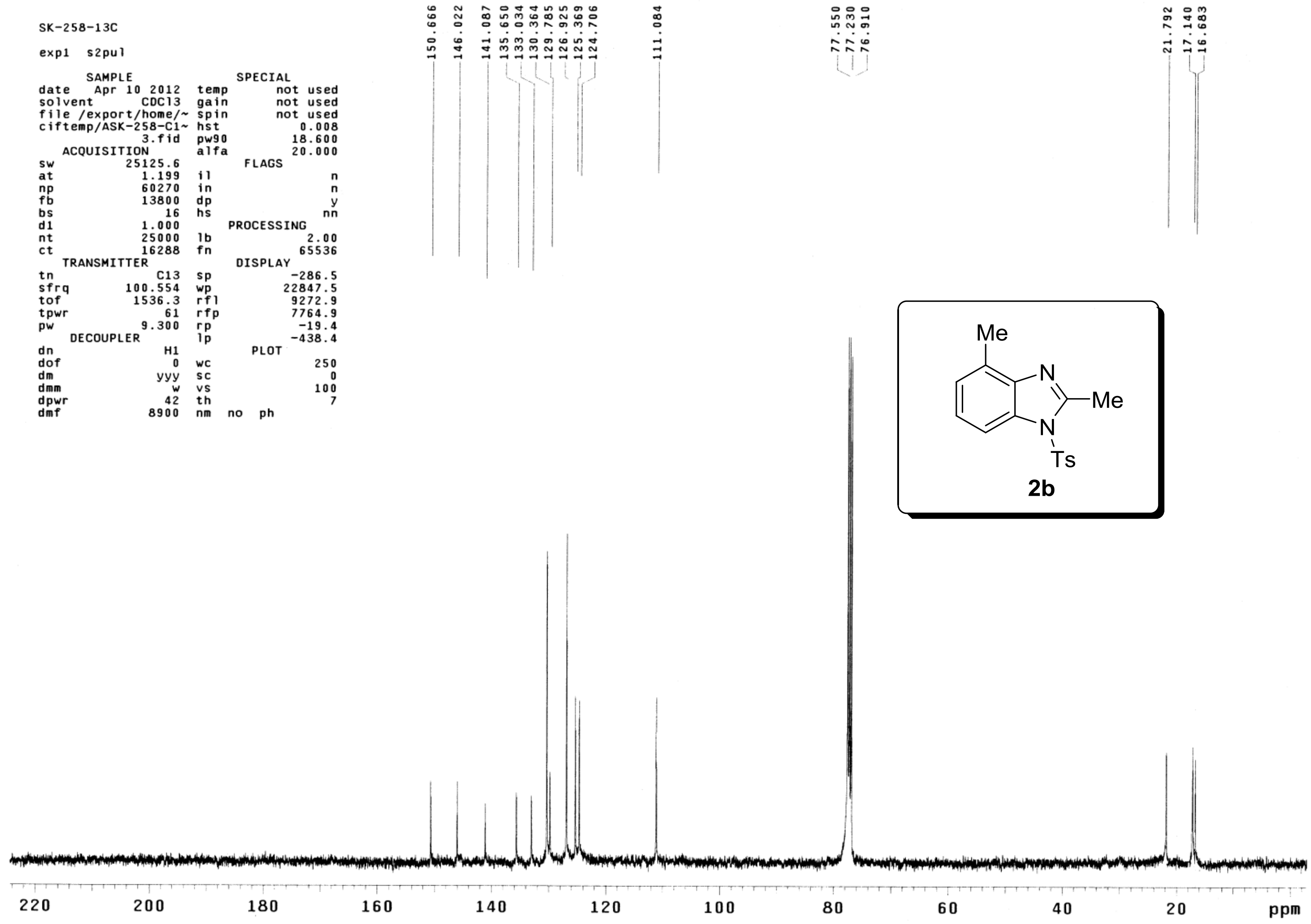
Crystal Data and Structure Refinement for 2i at 296(2) K

Identification code	2i	
Empirical formula	$C_{15}H_{13}ClN_2O_2S$	
Formula weight	320.78	
Temperature	296 (2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c Loop xyz 'x, y, z' '-x, y+1/2, -z+1/2' '-x, -y, -z' 'x, -y-1/2, z-1/2'	
Unit cell dimensions	*a* = 14.7051 (5) Å	α(°)=90.00
	b = 12.7004 (4) Å	β(°)=102.019 (2)
	c = 7.9795 (2) Å	γ(°)=90.00
Volume	1457.59 (8) $Å^3$	
Z	4	
Density (calculated)	1.462 Mg/m^3	
Absorption coefficient	0.410 mm^{-1}	
F(000)	664.0	
Crystal size	0.30 x 0.18 x 0.12 mm	
Theta range for data collection	1.42 to 24.99 °	
Index ranges	-16<=h<=16, -13<=k<=14, -9<=l<=9	
Reflections collected	2420	
Independent reflections	2130 [R (int) = 0.0819]	
Completeness to theta = 24.99°	97.7 %	
Absorption correction	None	
Max. and min. transmission	0.941and 0.923	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2420 / 0 /192	
Goodness-of-fit on F^2	0.891	
Final R indices [I>2sigma (I)]	$R1$ = 0.0397, $wR2$ = 0.1152	
R indices (all data)	$R1$ = 0.0450, $wR2$ = 0.1204	

2.6. Selected Spectra



2b



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solvent      CDCl3  gain       not used
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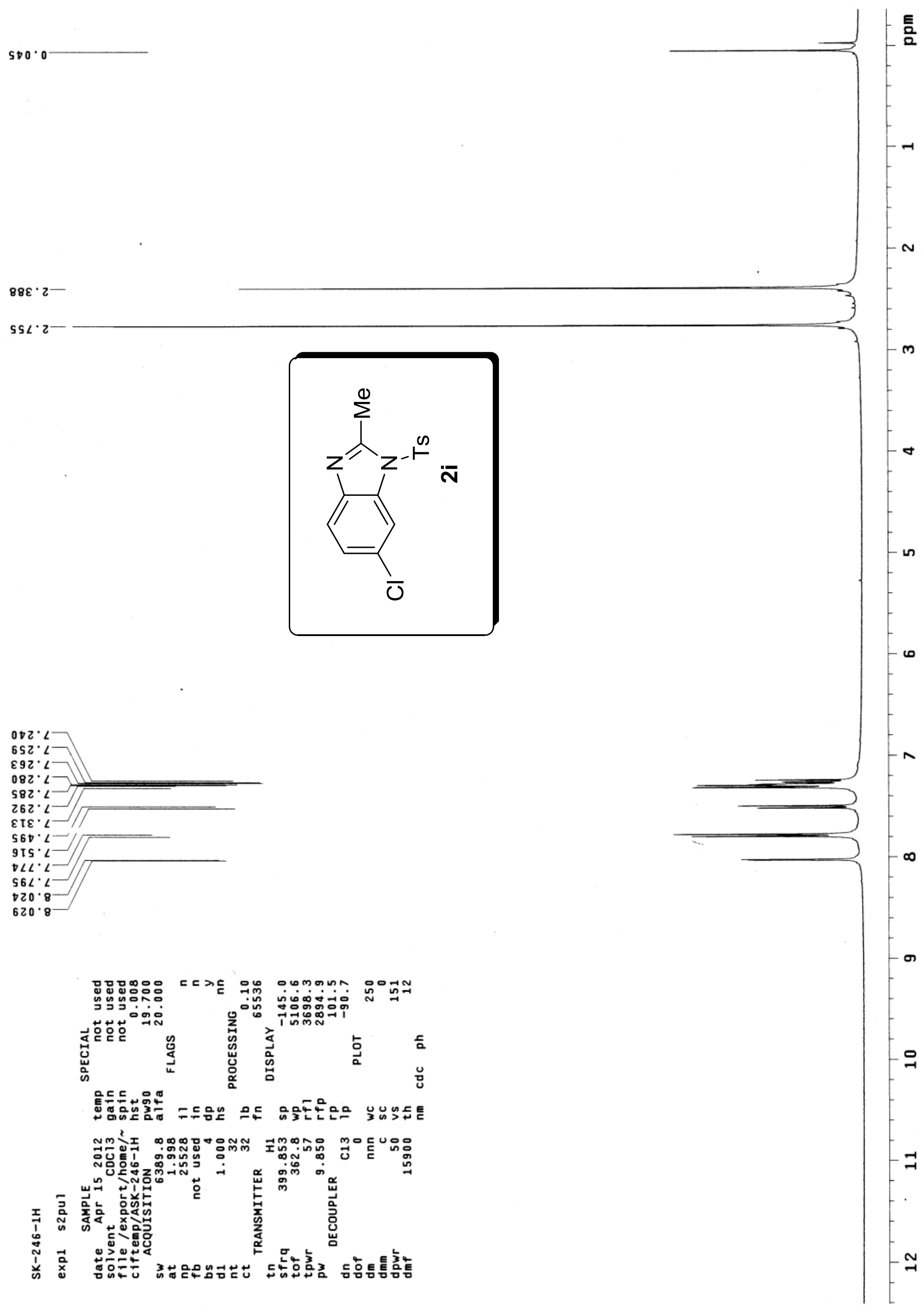
ciftemp/ASK-258-C1~ hst           0.008
             3.fid  pw90         18.600
   ACQUISITION      alfa         20.000
sw         25125.6          FLAGS
at           1.199  il                n
np           60270  in                n
fb           13800  dp                y
bs              16  hs               nn
d1           1.000        PROCESSING
nt           25000  lb             2.00
ct           16288  fn            65536
   TRANSMITTER              DISPLAY
tn             C13  sp           -286.5
sfrq       100.554  wp          22847.5
tof         1536.3  rfl          9272.9
tpwr            61  rfp          7764.9
pw           9.300  rp            -19.4
    DECOUPLER       lp           -438.4
dn              H1          PLOT
dof              0  wc              250
dm             yyy  sc                0
dmm              w  vs              100
dpwr            42  th                7
dmf           8900  nm  no  ph
```

2b



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solvent       CDCl3  gain       not used
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ciftemp/ASK-246-1H  hst           0.008
    ACQUISITION     pw90         19.700
sw           6389.8  alfa         20.000
at            1.998          FLAGS
np            25528  il               n
fb         not used  in               n
bs                4  dp               y
d1            1.000  hs              nn
nt               32        PROCESSING
ct               32  lb            0.10
    TRANSMITTER      fn           65536
tn               H1          DISPLAY
sfrq        399.853  sp          -145.0
tof           362.8  wp          5106.6
tpwr             57  rfl         3698.3
pw            9.850  rfp         2894.9
     DECOUPLER       rp           101.5
dn              C13  lp           -90.7
dof               0           PLOT
dm              nnn  wc             250
dmm               c  sc               0
dpwr             50  vs             151
dmf           15900  th              12
                     nm  cdc  ph
```
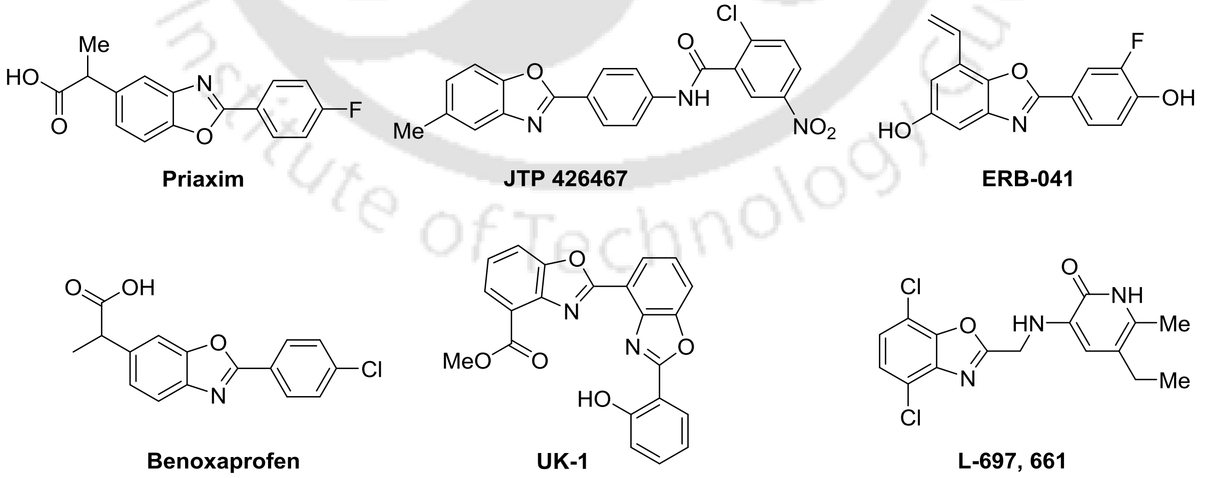


16.866
21.701
76.910
77.230
77.550
113.708
120.427
125.239
126.894
130.464
130.540
133.774
135.093
140.546
146.418
152.093
Me
N
N
Ts
Cl
2i
ppm
20
40
60
80
100
120
140
160
180
200
220
SK-246-13C
exp1 s2pul
SAMPLE
date Apr 16 2012
solvent CDCl3
file exp
ACQUISITION
sw 25125.6
at 1.199
np 60270
fb 13800
bs 16
d1 1.000
nt 6000
ct 4192
TRANSMITTER
tn C13
sfrq 100.554
tof 1536.3
tpwr 61
pw 9.300
DECOUPLER
dn H1
dof 0
dm yyy
dmm w
dpwr 42
dmf 8900
SPECIAL
temp not used
gain not used
spin not used
hst 0.008
pw90 18.600
alfa 20.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 2.00
fn 65536
DISPLAY
sp -396.1
wp 23243.1
rfl 9282.8
rfp 7764.9
rp -60.9
lp -341.5
PLOT
wc 250
sc 0
vs 100
th 11
nm no ph

Chapter III

Iodobenzene Catalyzed Synthesis of Benzoxazoles Using Oxone *via C-O* Bond Formation

Benzoxazoles constitutes a prominent class of heterocycles possessing important medicinal properties and is a privileged structural feature in a diverse range of natural products and synthetic drug molecules with wide applications.[1] For examples, benzoxazole scaffold is found in a range of cytotoxic naturally occurring compounds, such as AJI9561,[2a] salvianen,[2b] UK-1[2c] and antimicrobacterial pseudopteroxazole.[2d] Recent medicinal chemistry applications of benzoxazoles include HIV reverse transcriptase inhibitor L-697,661,[3a] orexin-1 receptor antagonist SB-334867,[3b] estrogen receptor-β agonist ERB-041,[3c] 5-HT3 receptor agonist,[3d] selective peroxisome proliferator-activated receptor γ antagonist JTP-426467,[3e] anticancer agent NSC-693638[1b] and potent anti-inflammatory benoxaprofen.[3f] In addition, benzoxazoles could be used as upregulators of utrophin production for the treatment of Duchenne Muscular Dystrophy (DMD).[3g] Furthermore, benzoxazoles are used as herbicides, like Fenoxaprop ethyl[4a] and also got wide applications as fluorescent whitening dyes such as bisbenzoxazolyl ethylenes and arenes,[4b] sensors for metals,[4c] photoluminescent dyes[4d] and electronic devices.[4e] These properties makes benzoxazoles highly valuable and subsequently several strategies were developed for their synthesis.


Priaxim

JTP 426467

ERB-041

Benoxaprofen

UK-1

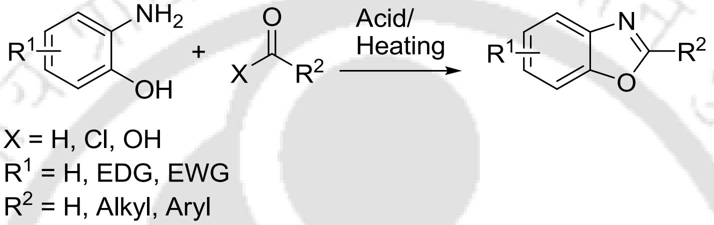
L-697, 661

Figure 1. Examples of Some Biologically Active and Medicinally Significant Compounds

3.1. Strategies for Synthesis of Benzoxazoles

3.1.1. Traditional Methods

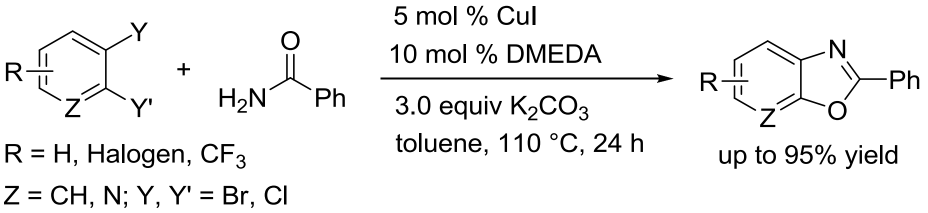
Traditional methods for the synthesis of benzoxazole framework include the condensation of *o*-aminophenols with carboxylic acid or aldehydes, followed by oxidative cyclization using strong acids or with the use of stoichiometric amount of oxidant (Scheme 1).[5] The requirement of harsh reaction conditions such as use of strong acids and elevated temperature (~210 °C)[6] cause safety concerns and makes these processes limited in their use.



Scheme 1. Classical Methods for Synthesis of Benzoxazole Derivatives

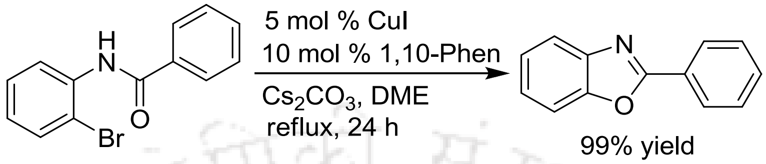
3.1.2. Cross-Coupling Reactions

Transitional-metal promoted/catalyzed transformations are well established towards carbon-carbon and carbon-oxygen bonds formation, enabling to develop protocols for the synthesis of heterocyclic compounds under relatively milder reaction conditions. Over the past few decades, the cross coupling reactions have become a reliable synthetic strategy for the synthesis of various benzoxazole derivatives. For example, Glorius and co-workers first reported a route for the synthesis of benzoxazoles from readily available primary amides and *o*-dihalobenzene (Scheme 2).[7a] The domino inter- and intramolecular *C–N* and *C–O* cross-coupling reactions of *o*-dihalobenzene with primary amides in the presence of CuI in combination with DMEDA provided the target benzoxazoles in good yields.



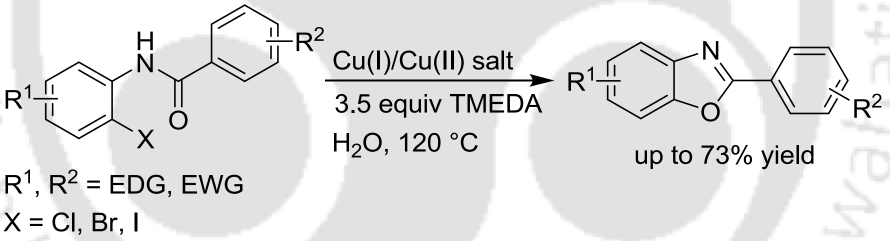
Scheme 2. Cross-Coupling of *o*-dihalobenzene with Primary Amides Under Cu Catalysis

A copper catalyzed intramolecular *C-O* bond formation strategy has been employed for the synthesis of benzoxazoles by Batey and co-workers (Scheme 3).[7b-c] Here, the cyclization of *o*-haloanilides was carried out using CuI/1,10-phenanthroline in the presence of Cs_2CO_3 in DME under reflux to afford a library of benzoxazoles in good yields.



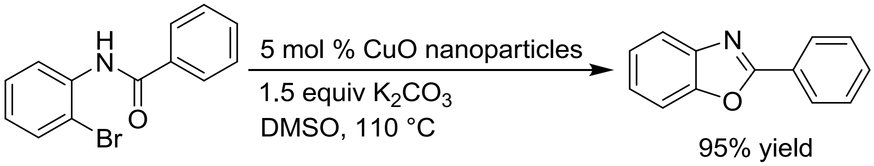
Scheme 3. Copper-Catalyzed Synthesis of Benzoxazoles form *o*-haloanilides

Dominguez group has demonstrated the use of water as a solvent in the synthesis of benzoxazoles through an intramolecular *O*-arylation of *o*-halobenzanilides using copper catalysis. The reaction involves the use of catalytic amount of copper salt along with TMEDA in water at 120 °C. In this reaction, *o*-bromo- and *o*-chlorobenzanilides gave better results compared to *o*-iodobenzanilides (Scheme 4).[7d]



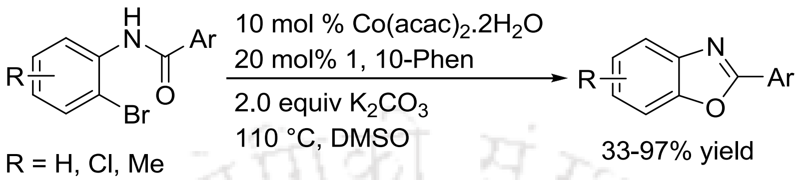
Scheme 4. Copper-Catalyzed Synthesis of Benzoxazoles in Water

We have developed a simple, general and efficient protocol for the synthesis of 2-aryl and 2-alkylbenzoxazoles from *o*-halobenzanilides using catalytic copper(II) oxide nanoparticles under ligand free conditions (Scheme 5).[7e-f] The reaction scope is viable for a variety of substituents and also the catalyst can be recovered and recycled without loss of activity.



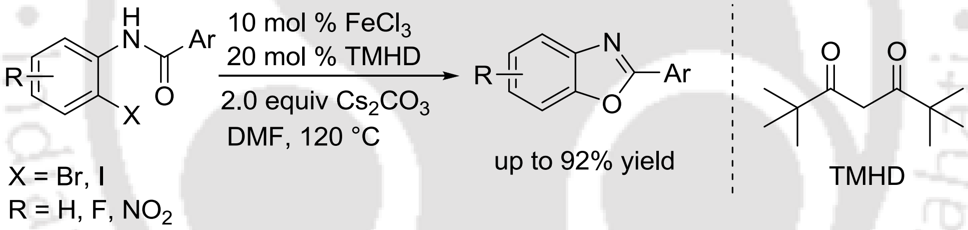
Scheme 5. Ligand-Free Copper-Catalyzed Synthesis of Substituted Benzoxazoles

We have further emphasised the value of cross-coupling reactions for the synthesis of benzoxazoles. The intramolecular *C–O* cross-coupling of *N*-(2-bromophenyl)benzamides was achieved using cobalt(II) complex in presence of K_2CO_3 at moderate temperature to afford substituted benzoxazoles (Scheme 6).[7g]



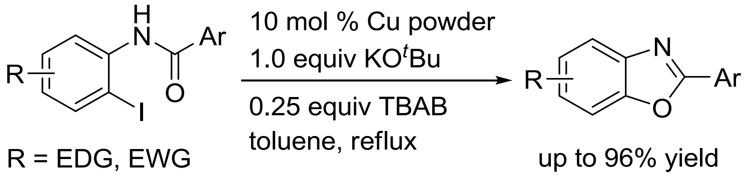
Scheme 6. Cobalt-Catalyzed Intramolecular Cross-Coupling of 2-Haloarylanilides

Bolm and co-workers reported an iron-catalyzed intramolecular *O*-arylation of 2-haloanilides for the synthesis of benzoxazole derivatives (Scheme 7).[7h] In this protocol, environmentally benign $FeCl_3$ was used as a catalyst in combination with TMHD to bring out the cyclization.



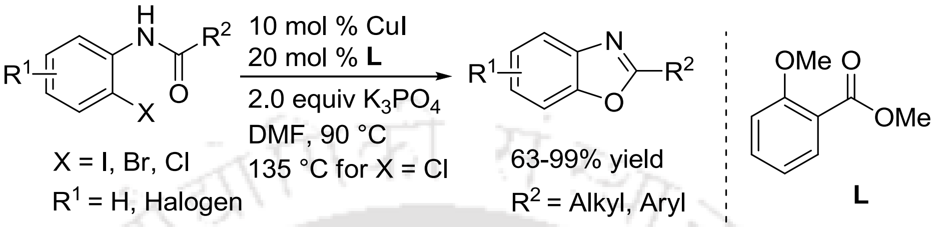
Scheme 7. Iron-Catalyzed Intramolecular *O*-Arylation of 2-Haloanilides

An intramolecular *C–O* cross-coupling reaction of *ortho*-iodoanilides, catalyzed by copper powder was developed by Ray and co-workers in the presence of potassium *tert*-butoxide and TBAB under ligand free conditions (Scheme 8).[7i] The scope of this protocol is only limited to anilides having electron donating substituents.



Scheme 8. Copper Powder Catalyzed Intramolecular *C–O* Cross-Coupling Reaction

Xie and co-workers have demonstrated the preparation of 2-substituted benzoxazoles from *N*-(2-iodo/bromo/chlorophenyl)benzamides *via* Cu-catalyzed intramolecular cyclization coupling reaction using methyl 2-methoxybenzoate **L** as the ligand under mild reaction conditions (Scheme 9).[7j]



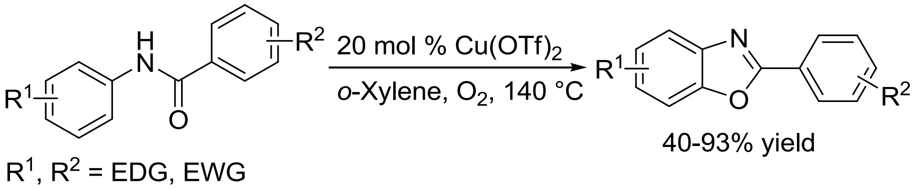
Scheme 9. CuI Catalyzed Synthesis of Benzoxazoles

Alternatively, a direct C-H functionalization and *C-C* bond formation of benzoxazoles with aryl iodides also result in the corresponding 2-substituted benzoxazoles. Dougulis and co-workers have developed a protocol for the synthesis of 2-arylbenzoxazoles by the coupling of unsubstituted benzoxazoles and aryl iodides using CuI as a catalyst and lithium *tert*-butoxide as a base in DMF at 140 °C (Scheme 10).[7k]

Scheme 10. Copper-Catalyzed Arylation of Benzoxazoles

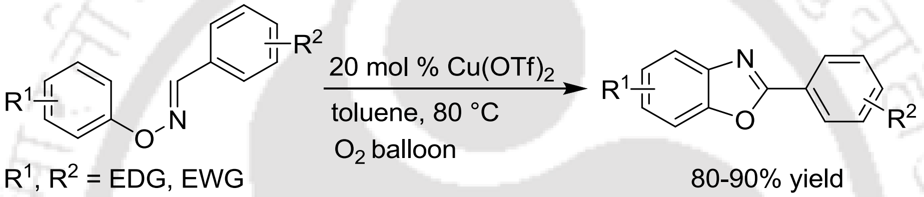
3.1.3. C–H Functionalization Reactions

Direct C–H functionalization facilitates the transformation of C-H bonds to *C-O* bonds, and thus remains as a ubiquitous strategy to develop economical and environmentally friendly protocols for synthesis of substituted benzoxazoles. Recently, the use of transition metal as active catalysts for this purpose has been reported. For example, Nagasawa and co-workers have synthesized 2-arylbenzoxazoles by intramolecular oxidative C–H functionalization/*C–O* bond formation of benzanilides using Cu(OTf)$_2$ as a catalyst in *o*-xylene at 140 °C under oxygen atmosphere (Scheme 11).[8a]



Scheme 11. Copper-Catalyzed Synthesis of Benzoxazoles by C-H Functionalization

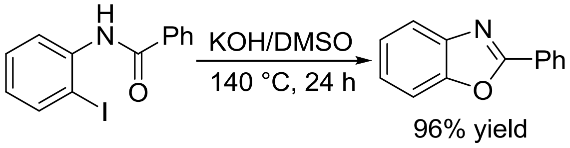
We have demonstrated a copper(II)-catalyzed rearrangement of bisaryloxime ethers to substituted 2-arylbenzoxazoles (Scheme 12).[8b-c] The reaction involves a cascade C-H functionalization and *C-N*/*C-O* bonds formation in the presence of Cu(OTf)$_2$ in toluene at 80 °C using molecular oxygen yielding benzoxazoles in good yields.



Scheme 12. Benzoxazole Synthesis *via* Rearrangement of Bisaryloxime Ethers

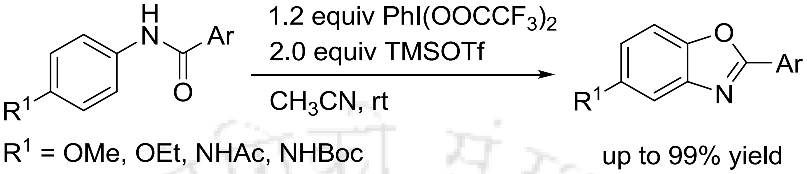
3.1.4. Metal-Free Protocols

In addition to transition metal catalyzed cross-coupling and C-H functionalization reactions, major progress has been made to develop metal-free protocols for the synthesis of benzoxazoles. For example, Chang and Bolm have described the formation of *C-O*, C-*S* and C-*N* bonds by the reaction of aryl halides with various sulfur-, oxygen- and nitrogen based nucleophiles under transition-metal free conditions. They made use of *in situ* superbase, made from KOH/DMSO to accomplish this transformation. Intramolecular *O*-arylations of *N*-(2-iodophenyl)benzamide under the reaction conditions of KOH/DMSO at 140 °C afforded 2-phenylbenzoxazole in 96% yield (Scheme 13).[9a]



Scheme 13. Metal-Free Synthesis of Benzoxazoles

Yu and co-workers have developed a method for the construction of substituted benzoxazoles by intramolecular oxidative *C-O* bond formation of anilides using phenyliodine bis(trifluoroacetate) and TMSOTf (Scheme 14).[9b] These reaction conditions are limited to only electron rich *N*-phenyl benzamides.

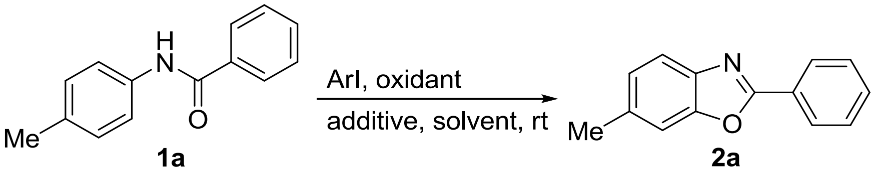


Scheme 14. Hypervalent Iodine Mediated Synthesis of Benzoxazoles

3.2. Present Study

We have developed a metal-free protocol for the synthesis of 2-aryl/alkyl benzoxazoles from benzanilides *via* 1-iodo-4-nitrobenzene catalyzed C-H functionalization/*C-O* bond formation using oxone as an oxidant. Initially, the optimization of the reaction conditions was studied using *N*-*p*-tolylbenzamide **1a** as a model substrate in the presence of different aryl iodides, terminal oxidants, additives and solvents at room temperature (Table 1). The reaction of substrate **1a**, iodobenzene (0.2 equiv) and oxone (1.5 equiv) in HFIP (hexafluoro-2-propanol) at room temperature for 12 h resulted in the formation of the target benzoxazole **2a** with 5% conversion (entry 1). The addition of TfOH (3.0 equiv) led to increase the product **2a** formation to 37%, whereas $BF_3{\cdot}Et_2O$ and TMSOTf gave **2a** with 24 and 25% conversions, respectively (entries 2-4). In contrast, *p*$TSA{\cdot}H_2O$ showed no effect and the starting material was recovered intact (entry 5). In a set of oxidants screened, oxone afforded superior results than $NaBO_3{\cdot}4H_2O$, *m*CPBA, $Na_2S_2O_8$ and 30% H_2O_2 (entries 6-9). In addition, screening with different catalysts revealed that iodobenzene with 4-nitro substituent exhibited greater reactivity leading to **2a** in 93% conversion (entry 10). In contrast, iodobenzene with electron donating substituents (4-methyl and 4-methoxy) gave inferior results, whereas 2-iodobenzoic acid yielded **2a** in 31% conversion (entries 11-13). Solvent screening experiments showed that best results were obtained using HFIP (entries 14-16). Lowering the amount of either aryl iodide (10 mol %) or oxidant (1 equiv) or additive (2 equiv) led to the product formation in <72% conversion (entries 17-20). Furthermore, the screening of the oxidants, $NaBO_3{\cdot}4H_2O$, *m*CPBA, $Na_2S_2O_8$ and 30% H_2O_2 with 1-iodo-4-nitrobenzene led to inferior

Table 1. Optimization of the Reaction Conditions[a]



entry	ArI (20 mol %)	oxidant (1.5 equiv)	additive (3.0 equiv)	solvent	conv. (%)[b]
1	PhI	oxone	-	HFIP	5
2	PhI	oxone	TfOH	HFIP	37
3	PhI	oxone	$BF_3\cdot Et_2O$	HFIP	24
4	PhI	oxone	TMSOTf	HFIP	25
5	PhI	oxone	*p*TSA·H_2O	HFIP	n.d.
6	PhI	$NaBO_3\cdot 4H_2O$	TfOH	HFIP	4
7	PhI	30% H_2O_2	TfOH	HFIP	2
8	PhI	$Na_2S_2O_8$	TfOH	HFIP	10
9	PhI	*m*CPBA	TfOH	HFIP	23
10	**4-$NO_2C_6H_4I$**	**oxone**	**TfOH**	**HFIP**	**93**
11	4-MeC_6H_4I	oxone	TfOH	HFIP	17
12	4-$OMeC_6H_4I$	oxone	TfOH	HFIP	5
13	2-IC_6H_4COOH	oxone	TfOH	HFIP	31
14	4-$NO_2C_6H_4I$	oxone	TfOH	CH_2Cl_2	5
15	4-$NO_2C_6H_4I$	oxone	TfOH	THF	n.d.
16	4-$NO_2C_6H_4I$	oxone	TfOH	toluene	n.d.
17	4-$NO_2C_6H_4I$	oxone	TfOH	HFIP	63[c]
18	4-$NO_2C_6H_4I$	oxone	TfOH	HFIP	35[d]
19	4-$NO_2C_6H_4I$	oxone	TfOH	HFIP	70[e]
20	4-$NO_2C_6H_4I$	oxone	TfOH	HFIP	72[f]
21	4-$NO_2C_6H_4I$	$NaBO_3\cdot 4H_2O$	TfOH	HFIP	12
22	4-$NO_2C_6H_4I$	30% H_2O_2	TfOH	HFIP	7

Continued....

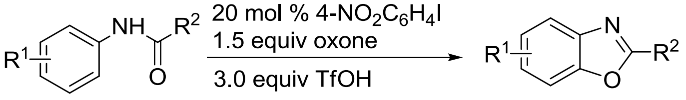
23	4-$NO_2C_6H_4I$	$Na_2S_2O_8$	TfOH	HFIP	12
24	4-$NO_2C_6H_4I$	*m*CPBA	TfOH	HFIP	43
25	-	oxone	TfOH	HFIP	n.d.
26	4-$NO_2C_6H_4I$	oxone	-	HFIP	9

[a] Reaction conditions: **1a** (0.25 mmol), ArI (20 mol %), oxidant (0.37 mmol), additive (0.75 mmol), solvent (1.5 mL), rt, 12 h. [b] Determined by 400 MHz ^{1}H NMR spectroscopy. [c] Oxone (0.25 mmol) was used. [d] TfOH (0.25 mmol) was used. [e] TfOH (0.5 mmol) was used. [f] 4-$NO_2C_6H_4I$ (10 mol %) was used. n.d. = not detected.

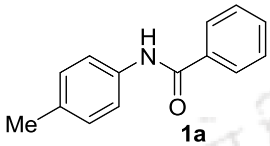
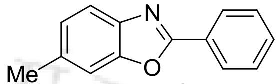
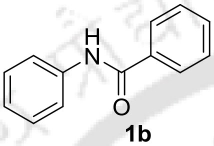
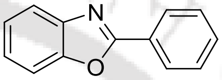
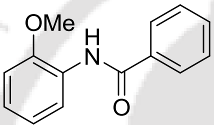
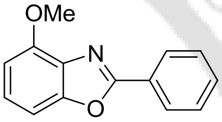
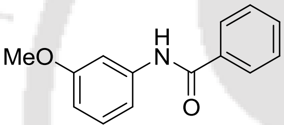
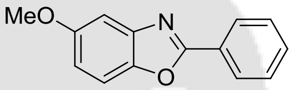
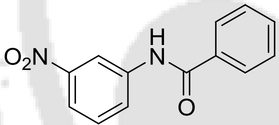
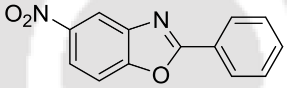
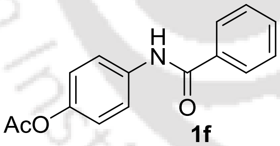
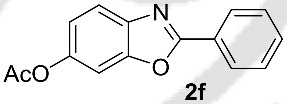
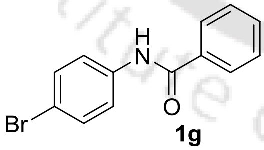
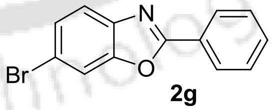
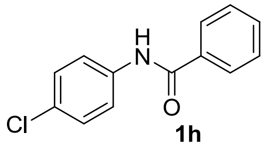
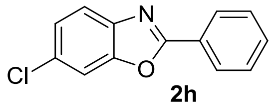
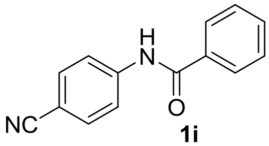
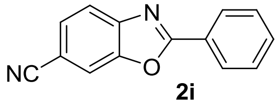
results (entries 21-24). Control experiments confirmed that in the absence of aryl iodide, no reaction was observed and the starting material was recovered intact (entry 25). Finally, the reaction using 1-iodo-4-nitrobenzene without TfOH as an additive yielded **2a** in 9% conversion (entry 26).

To explore the scope and functional group compatibility of this protocol, a series of alkyl/arylanilides were subjected to the optimized reaction conditions (Table 2). First, the reactivity of unsubstituted arylanilide and the substrates with electron withdrawing and donating groups in the anilide aryl ring were tested. The reaction of *N*-phenylbenzamide **1b** afforded benzoxazole **2b** in 12% yield. A similar result was observed with the substrate **1c** having 2-methoxy substituent. The substrate **1d** with 3-methoxy group underwent decomposition, while **1e** substituted with 3-nitro group failed to react and the starting material was recovered intact. However, the substrates **1g-h, 1k** and **1m** with 4-bromo, 4-chloro, 4-fluoro and 4-methoxy substituents readily underwent reaction to furnish the corresponding substituted benzoxazoles **2g-h**, **2k** and **2m** in 77-91% yields. The substrates **1i**, **1j** and **1o** having electron withdrawing 4-cyano, 4-ester and 4-trifuloromethyl groups were less reactive, giving the benzoxazoles **2i**, **2j** and **2o** in 14-25% yields. Furthermore, the substrate **1f** with 4-acetoxy group underwent hydrolysis, while **1l** and **1n** having 4-keto and 4-nitro substituents showed no reaction and the starting materials were recovered. These results indicate the involvement of an electrophilic aromatic substitution process in the cyclization reaction. Furthermore, the reaction of the substrate **1p** with 2,4-dimethyl substituents provided the corresponding benzoxazole **2p** in 70% yield. These results suggest that the regioselectivity of the cyclization depends on the arene substituents.

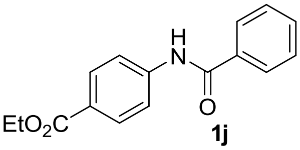
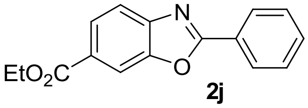
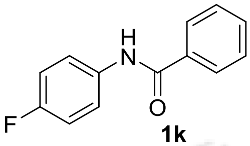
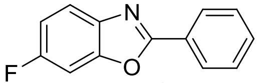
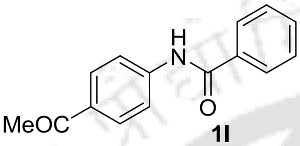
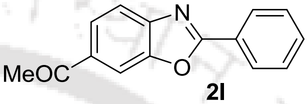
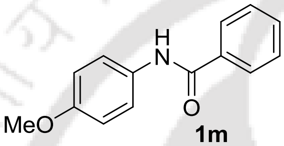
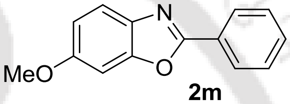
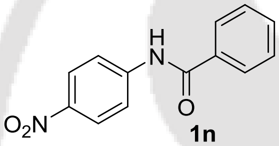
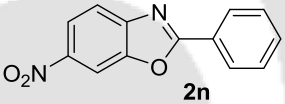
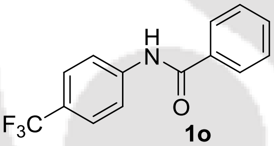
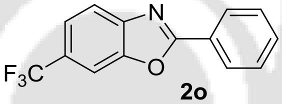
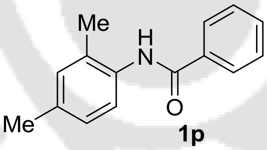
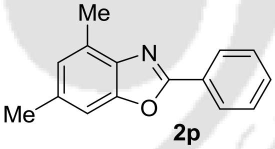
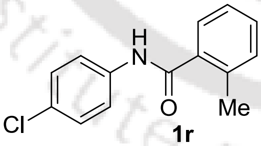
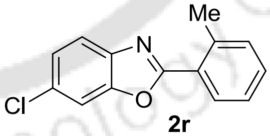
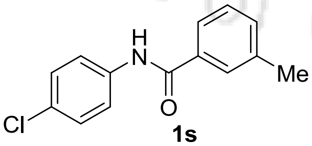
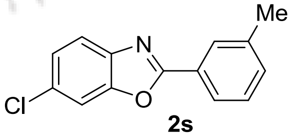
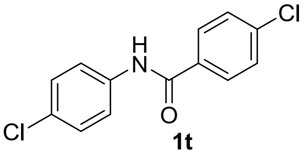
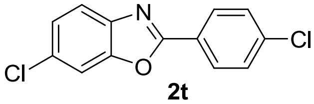
Table 2. 1-Iodo-4-nitrobenzene Catalyzed Synthesis of Benzoxazoles with Oxone[a]



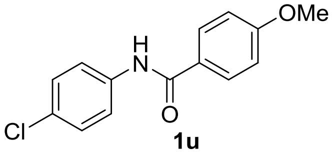
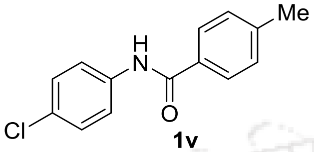
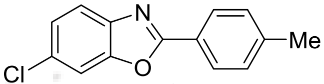
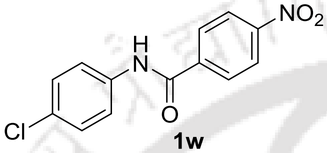
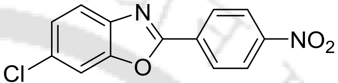
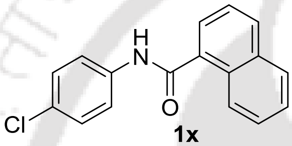
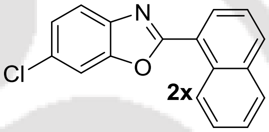
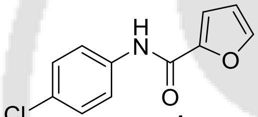
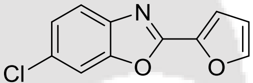
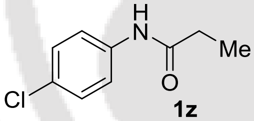
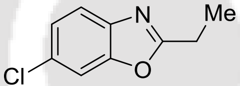
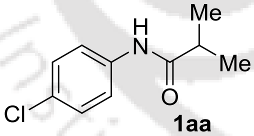
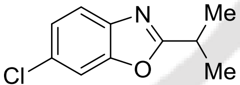
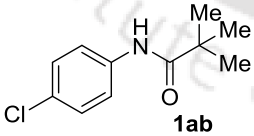
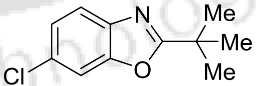
1a-p,1r-ab → **2a-p, 2r-ab**

entry	substrate	time (h)	product	yield (%)
1	 **1a**	12	 **2a**	88
2	 **1b**	48	 **2b**	12
3	 **1c**	48	 **2c**	15
4	 **1d**	48	 **2d**	decomposition
5	 **1e**	48	 **2e**	0
6	 **1f**	1	 **2f**	0
7	 **1g**	12	 **2g**	88
8	 **1h**	3	 **2h**	91
9	 **1i**	48	 **2i**	19

Continued......

entry	substrate	time (h)	product	yield (%)
10	 **1j**	48	 **2j**	14
11	 **1k**	5	 **2k**	77
12	 **1l**	48	 **2l**	0
13	 **1m**	12	 **2m**	82
14	 **1n**	12	 **2n**	0
15	 **1o**	48	 **2o**	25
16	 **1p**	12	 **2p**	70
17	 **1r**	12	 **2r**	91
18	 **1s**	12	 **2s**	84
19	 **1t**	12	 **2t**	89

Continued......

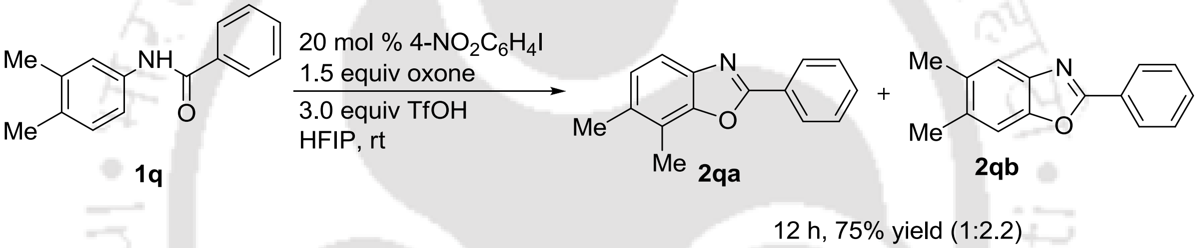
entry	substrate	time (h)	product	yield (%)
20	 **1u**	12	 **2u**	81
21	 **1v**	12	 **2v**	82
22	 **1w**	24	 **2w**	81
23	 **1x**	12	 **2x**	70
24	 **1y**	8	 **2y**	90
25	 **1z**	12	 **2z**	63
26	 **1aa**	20	 **2aa**	80
27	 **1ab**	24	 **2ab**	45

[a] Reaction conditions: **1a-p, 1r-ab** (0.36 mmol), 1-iodo-4-nitrobenzene (20 mol %), oxone (0.54 mmol), TfOH (1.08 mmol), HFIP (2.5 mL), rt.

Next, the reactions of the substrates having electron donating and withdrawing groups in the amide aryl ring were studied. In general, these substrates smoothly underwent reaction with good yields. For examples, the reactions of the substrates **1r-w** with 2-methyl, 3-methyl, 4-chloro, 4-methoxy, 4-methyl and 4-nitro substituents gave the corresponding 2-

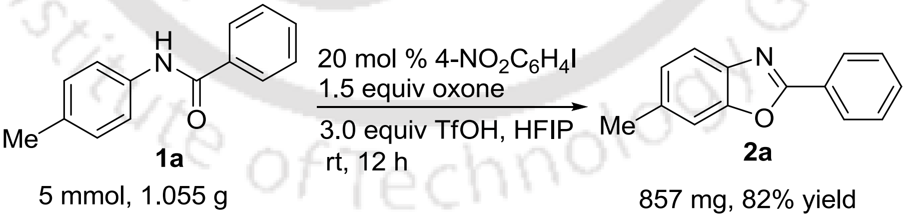
arylbenzoxazoles **2r-w** in 81-91% yields. Similarly, the substrates **1x-y** bearing 1-naphthyl and 2-furyl substituents at 2nd position proceeded reaction to give the corresponding benzoxazoles **2x** and **2y** in 70 and 90% yields, respectively. Then, the reaction conditions were further investigated for the synthesis of 2-alkylbenzoxazoles. Interestingly, the reactions took place to furnish the desired 2-alkylbenzoxazoles with moderate to good yields. For example, the substrates **1z, 1aa** and **1ab** with R^2 = ethyl, isopropyl and *tert*-butyl substituents could be converted to give the benzoxazoles **2z, 2aa** and **2ab** in 63, 80 and 45% yields, respectively.

The substrate **1q** having 3,4-dimethyl substituents afforded a 1:2.2 mixture of 6,7-dimethyl-2-phenylbenzoxazole **2qa** and 5,6-dimethyl-2-phenylbenzoxazole **2qb** in 75% yield (Scheme15).



Scheme 15. Reaction of 3,4-Dimethyl Substituted Benzanilide

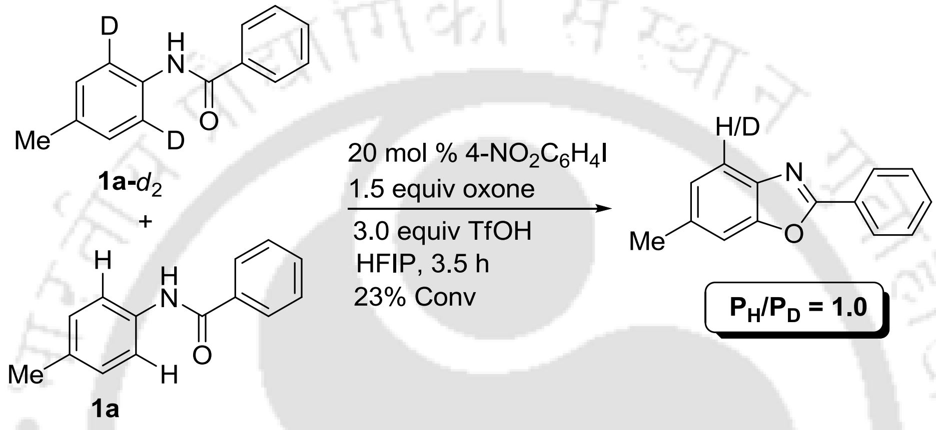
The reaction was scaled up with 1.055 g of **1a** as a representative example (Scheme 16). The reaction readily occurred to furnish the desired 2-arylbenzoxazole **2a** in 82% yield.



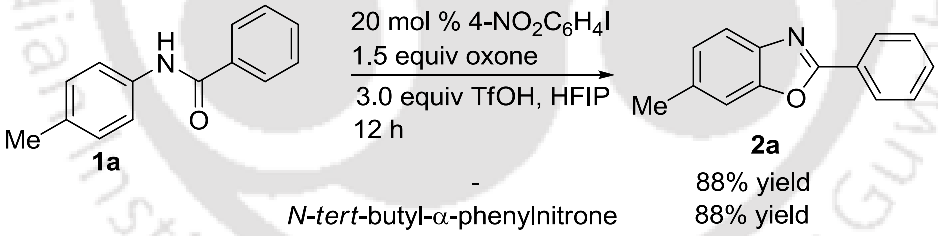
Scheme 16. Gram Scale Synthesis

To investigate the reaction kinetics, an intermolecular competitive reaction between equimolar amounts of **1a**-d_2 and **1a** was conducted under the typical reaction conditions. At 23% conversion, the reaction revealed an intermolecular kinetic isotopic effect P_H/P_D = 1.0, which suggests that the C-H bond breaking step was not involved in the rate-determining step (Scheme 17).[10]

Then, the application of radical scavenger for I^{III} species, *N*-*tert*-butyl-α-phenylnitrone,[11a] was studied. However, the radical scavenger did not affect the reaction, and the target 2-arylbenzoxazole **2a** was obtained in 88% yield (Scheme 18). This result reveals that the radical was not involved in the cyclization process.

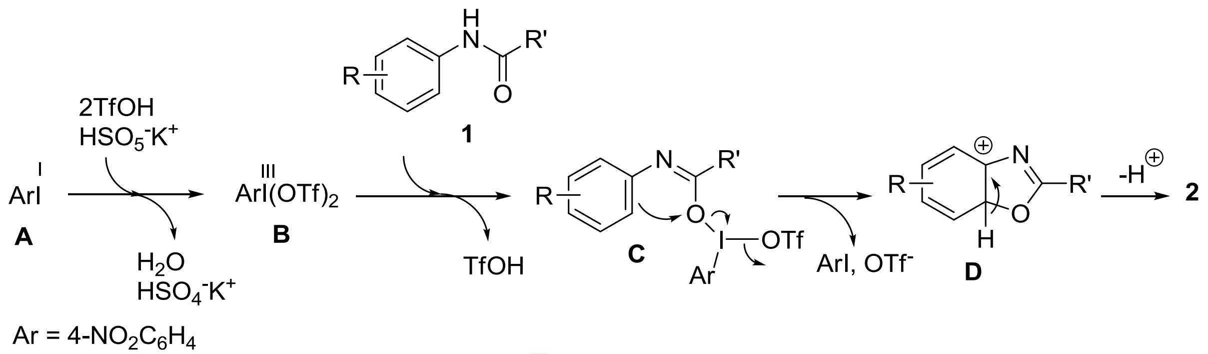


Scheme 17. Intermolecular Kinetic Isotope Experiment



Scheme 18. Radical Scavenger Experiment with *N*-*tert*-Butyl-α-phenylnitrone

Thus, the reaction of aryl iodide **A** with TfOH and oxone can generate an active hypervalent iodine(III) species, $ArI(OTf)_2$ **B**,[11b,c] that can catalyze the oxidative cyclization of the substrate **1** to give an intermediate **C**, which could be stabilized by HFIP.[11d,e] Intramolecular cyclization of **C** can give the cationic intermediate **D,** accompanied by the liberation of iodobenzene **A,** which could be reoxidized to **B.** The intermediate **D** can furnish the target product **2** by aromatization (Scheme 19).



Shcheme 19. Proposed Catalytic Cycle

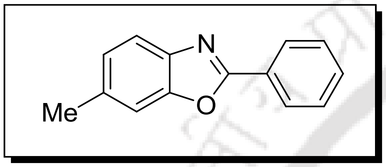
In conclusion, we have developed a general method for the synthesis of substituted benzoxazoles using 1-iodo-4-nitrobenzene as a catalyst in high yield. The advantages of this procedure includes no use of toxic metals and the reaction can be performed at room temperature with good compatibility for variety of substituents.

3.3. Experimental Section

3.3.1. General Information. All chemicals and solvents were purchased from commercial suppliers and were used as received. Substituted anilides were prepared from anilines and acid chlorides.[12] Purification of the reaction products was carried out by column chromatography using silica gel (230-400 mesh). Analytical TLC was performed on silica gel G/GF 254 plate. NMR spectra were recorded on DRX-400 Varian spectrometer and Bruker Avance III 600 spectrometer using $CDCl_3$ as solvent and Me_4Si as 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. FT-IR spectra were recorded using Perkin Elmer IR spectrometer. Elemental analysis were recorded using Perkin Elmer CHNS analyzer. Mass spectra were recorded on a Waters Q-Tof Premier mass spectrometer.

3.3.2. General Procedure for 1-Iodo-4-nitrobenzene Catalyzed Synthesis of Substituted Benzoxazoles 2a-ab: Oxone (1.5 equiv) was added to a stirred solution of anilide (0.36 mmol, 1.0 equiv), 1-iodo-4-nitrobenzene (20 mol %) and triflic acid (3.0 equiv) in HFIP (2.5 mL) at room temperature under air. The mixture was stirred and the progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. The reaction mixture was then treated with saturated $Na_2S_2O_3$ (1 mL) and $NaHCO_3$ (1 mL) solutions. The resultant mixture was extracted using ethyl acetate (3 x 10 mL) and washed with brine (2 x 5 mL) and water (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 to afford analytically pure substituted benzoxazoles.

3.4. Characterization Data of Substituted Benzoxazoles 2a-ab



6-Methyl-2-phenylbenzo[*d*]oxazole 2a. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.54; white solid; 66 mg, yield 88%.

Mp: 91-92 °C (lit.[7b] mp 93 °C).

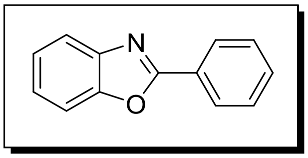
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23-8.21 (m, 2H), 7.63 (d, J = 8.4 Hz, 1H), 7.51-7.50 (m, 3H), 7.37 (s, 1H), 7.16 (d, J = 8.4 Hz, 1H), 2.49 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.3, 150.8, 139.8, 135.2, 131.0, 128.6, 127.25, 127.2, 125.6, 119.1, 110.5, 21.5.

FT-IR (KBr) 3054, 2919, 1647, 1615, 1554, 1482, 1448, 1337, 1247, 1173, 1126, 1052, 1021 cm^{-1}.

Anal. Calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.29; H, 5.32; N, 6.73.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{11}NOH$ 210.0913, found 210.0922.



2-Phenylbenzo[*d*]oxazole 2b. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.62; white solid; 8.0 mg, yield 12%.

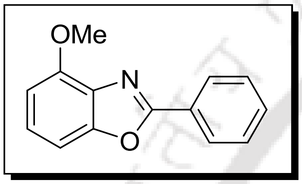
Mp: 102-103 °C (lit.[8a] mp 102 °C).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26-8.24 (m, 2H), 7.78-7.75 (m, 1H), 7.59-7.56 (m, 1H), 7.53-7.51 (m, 3H), 7.35-7.33 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.1, 150.9, 142.2, 131.6, 129.0, 127.7, 127.3, 125.2, 124.7, 120.1, 110.7.

FT-IR (KBr) 3063, 2920, 1722, 1615, 1550, 1448, 1345, 1284, 1239, 1194, 1145, 1104, 1055, 1022, 1002 cm^{-1}.

Anal. Calcd for $C_{13}H_9NO$: C, 79.98; H, 4.65; N, 7.17. Found: C, 79.92; H, 4.66; N, 7.21. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_9NOH$ 196.0757, found 196.0759.



4-Methoxy-2-phenylbenzo[*d*]oxazole 2c. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.46$; white solid; 12 mg, yield 15%.

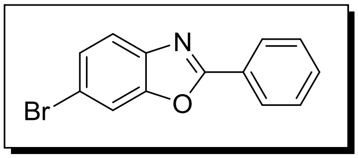
Mp: 65-66 °C (lit.^{8a} mp 67 °C).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31-8.29 (m, 2H), 7.52-7.50 (m, 3H), 7.31-7.26 (m, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 4.07 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 152.4, 151.8, 132.0, 131.5, 129.0, 127.8, 127.4, 125.9, 106.2, 103.6, 56.4.

FT-IR (KBr) 3066, 2960, 1625, 1510, 1486, 1445, 1428, 1355, 1322, 1269, 1240, 1097, 1056, 1019 cm^{-1}.

Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.71; H, 4.90; N, 6.17. HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{11}NO_2H$ 226.0863, found 226.0859.



6-Bromo-2-phenylbenzo[*d*]oxazole 2g. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.60$; white solid; 87 mg, yield 88%.

Mp: 96-97 °C (lit.^{8a} mp 95 °C).

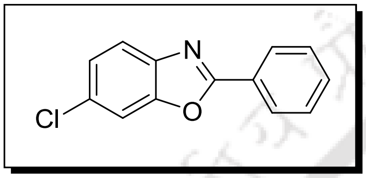
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23-8.20 (m, 2H), 7.74 (d, *J* = 1.6 Hz, 1H), 7.63 (d, *J* = 8.8 Hz, 1H), 7.55-7.50 (m, 3H), 7.48 (dd, *J* = 8.4 Hz, 2.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 151.5, 141.6, 132.1, 129.2, 128.3, 127.9, 126.9, 121.2, 118.2, 114.4.

FT-IR (KBr) 2960, 1638, 1557, 1506, 1449, 1422, 1328, 1257, 1041 cm^{-1}.

Anal. Calcd for $C_{13}H_8BrNO$: C, 56.96; H, 2.94; N, 5.11.Found: C, 57.04; H, 2.92; N, 5.07.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_8BrNOH$ 273.9862, found 273.9860.



6-Chloro-2-phenylbenzo[*d*]oxazole 2h. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.63; white solid; 75 mg, yield 91%.

Mp: 104-105 °C (lit.[7b] mp 107 °C).

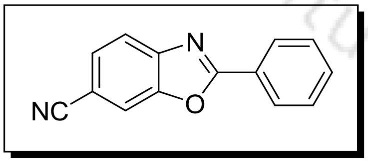
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22-8.20 (m, 2H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.58 (d, *J* = 1.6 Hz, 1H), 7.54-7.51 (m, 3H), 7.33 (dd, *J* = 8.8 Hz, 2.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 151.1, 141.1, 132.0, 130.9, 129.2, 127.9, 126.9, 125.5, 120.7, 111.4.

FT-IR (KBr) 3059, 2926, 1618, 1552, 1488, 1450, 1331, 1263, 1051, 1022 cm^{-1}.

Anal. Calcd for $C_{13}H_8ClNO$: C, 67.99; H, 3.51; N, 6.10. Found: C, 68.09; H, 3.49; N, 6.04.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_8ClNOH$ 230.0367, found 230.0367.



2-Phenylbenzo[*d*]oxazole-6-carbonitrile 2i. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.58; white solid; 15.0 mg, yield 19%.

Mp: 198-199 °C.

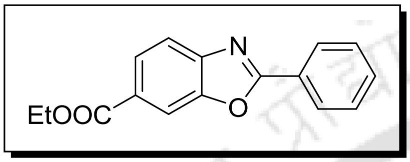
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27-8.24 (m, 2H), 7.90 (d, *J* = 0.8 Hz, 1H), 7.84 (d, *J* = 8.8 Hz, 1H), 7.65 (dd, *J* = 8.0 Hz, 1.2 Hz, 1H), 7.61-7.52 (m, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 166.3, 150.3, 146.2, 132.9, 129.4, 129.1, 128.4, 126.3, 121.2, 119.0, 115.1, 108.4.

FT-IR (KBr) 2924, 1700, 1630, 1601, 1552, 1517, 1482, 1456, 1409, 1351, 1327, 1292, 1225, 1111, 1047 cm^{-1}.

Anal. Calcd for $C_{14}H_8N_2O$: C, 76.35; H, 3.66; N, 12.72. Found: C, 76.30; H, 3.65; N, 12.76.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_8N_2OH$ 221.0709, found 221.0711.



Ethyl 2-phenylbenzo[*d*]oxazole-6-carboxylate 2j. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.46; white solid; 13 mg, yield 14%.

Mp: 76-77 °C.

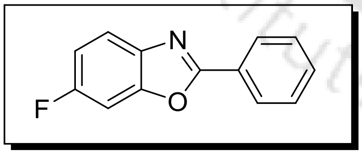
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.29-8.28 (m, 3H), 8.11 (dd, *J* = 7.8 Hz, 1.2 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.60-7.54 (m, 3H), 4.45 (q, *J* = 7.2 Hz, 2H), 1.45 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 166.4, 165.8, 150.7, 146.2, 132.4, 129.3, 128.2, 127.8, 126.9, 126.6, 119.7, 112.5, 61.5, 14.6.

FT-IR (KBr) 2980, 1713, 1614, 1582, 1476, 1447, 1431, 1365, 1346, 1318, 1292, 1262, 1226, 1187, 1051, 1020 cm^{-1}.

Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 71.85; H, 4.91; N, 5.30.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{16}H_{13}NO_3H$ 268.0968, found 268.0961.



6-Fluoro-2-phenylbenzo[*d*]oxazole 2k. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.62; white solid; 59 mg, yield 77%.

Mp: 106-107 °C (lit.[7b] mp 109 °C).

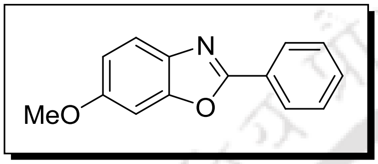
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21-8.18 (m, 2H), 7.69 (dd, *J* = 8.4 Hz, 4.8 Hz, 1H), 7.52-7.50 (m, 3H), 7.30 (dd, *J* = 7.6 Hz, 2.0 Hz, 1H), 7.11-7.06 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 162.1 (d, *J* = 242.5 Hz), 151.0 (d, *J* = 15.3 Hz), 138.6 (d, *J* = 1.6 Hz), 131.8, 129.1, 127.7, 127.1, 120.5 (d, *J* = 10.7 Hz), 112.8 (d, *J* = 24.4 Hz), 99.0 (d, *J* = 28.2 Hz).

FT-IR (KBr) 3055, 2920, 1624, 1556, 1490, 1451, 1345, 1289, 1256, 1210, 1129, 1103, 1049, 1021 cm^{-1}.

Anal. Calcd for $C_{13}H_8FNO$: C, 73.23; H, 3.78; N, 6.57. Found: C, 73.18; H, 3.77; N, 6.61.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_8FNOH$ 214.0663, found 214.0661.



6-Methoxy-2-phenylbenzo[*d*]oxazole 2m. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.54; white solid; 66 mg, yield 82%.

Mp: 78-79 °C (lit.[13a] mp 75 °C).

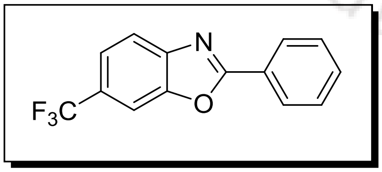
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19-8.17 (m, 2H), 7.63 (d, *J* = 9.2 Hz, 1H), 7.50-7.48 (m, 3H), 7.10 (d, *J* = 2.0 Hz, 1H), 6.95 (dd, *J* = 9.2 Hz, 2.4 Hz, 1H), 3.86 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 158.5, 151.9, 136.1, 131.3, 129.1, 127.6, 127.4, 120.2, 113.0, 95.7, 56.2.

FT-IR (KBr) 3064, 2930, 1619, 1555, 1487, 1449, 1346, 1321, 1290, 1219, 1144, 1110, 1052, 1023 cm^{-1}.

Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.60; H, 4.93; N, 6.28.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{11}NO_2H$ 226.0863, found 226.0862.



2-Phenyl-6-(trifluoromethyl)benzo[*d*]oxazole 2o. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.52; white solid; 24 mg, yield 25%.

Mp: 100-101 °C.

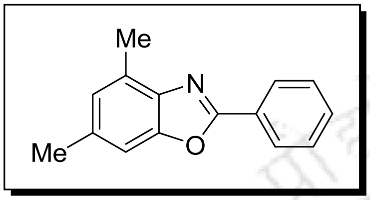
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27-8.25 (m, 2H), 7.86 (d, *J* = 9.2 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.58-7.52 (m, 3H).

^{13}C NMR (150 MHz, CDCl$_3$) δ 165.6, 150.4, 145.1, 132.5, 129.3, 128.2, 127.5, 126.7, 123.5, 122.1, 120.6, 108.7 (q, *J* = 4.5 Hz).

FT-IR (KBr) 2962, 1615, 1555, 1491, 1454, 1338, 1290, 1166, 1154, 1126, 1110, 1048 cm^{-1}.

Anal. Calcd for $C_{14}H_8F_3NO$: C, 63.88; H, 3.06; N, 5.32. Found: C, 63.94; H, 3.04; N, 5.27.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_8F_3NOH$ 264.0631, found 264.0625.



4,6-Dimethyl-2-phenylbenzo[*d*]oxazole 2p. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R$_f$ = 0.75; white solid; 56 mg, yield 70%.

Mp: 128-129 °C.

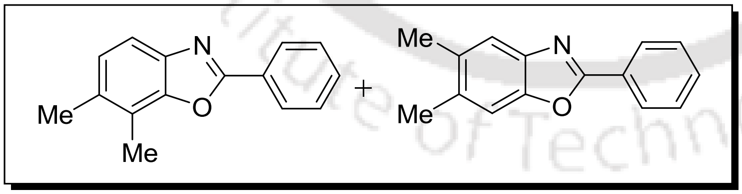
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.24-8.21 (m, 2H), 7.50-7.48 (m, 3H), 7.19 (s, 1H), 6.96 (s, 1H), 2.61 (s, 3H), 2.44 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 162.0, 151.1, 139.5, 135.3, 131.2, 130.0, 129.0, 127.8, 127.6, 126.6, 108.2, 22.0, 16.7.

FT-IR (KBr) 3059, 2922, 1614, 1554, 1489, 1447, 1337, 1291, 1264, 1224, 1069, 1049, 1019 cm^{-1}.

Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.61; H, 5.89; N, 6.31.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{13}NOH$ 224.1070, found 224.1071.



6,7-Dimethyl-2-phenylbenzo[*d*]oxazole 2qa and **5,6-Dimethyl-2-phenylbenzo[*d*]oxazole 2qb.** Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R$_f$ = 0.63; white solid; 60 mg, 75% yield.

Mp: 141-142 °C.

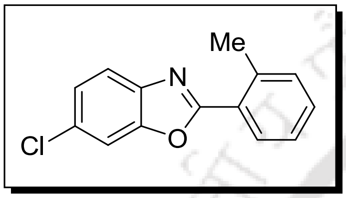
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.25-8.20 (m, 4H), 7.51-7.46 (m, 8H), 7.34 (s, 1H), 7.14 (d, *J* = 7.6 Hz, 1H), 2.48 (s, 3H), 2.39 (s, 3H), 2.37 (s, 3H), 2.35 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 162.6, 162.5, 149.6, 140.5, 139.8, 134.6, 134.0, 133.5, 131.4, 131.3, 129.1, 128.4, 128.0, 127.73, 127.7, 127.62, 127.6, 126.5, 120.2, 119.6, 116.6, 111.1, 20.8, 20.5, 19.5, 12.5.

FT-IR (KBr) 3057, 2922, 1613, 1552, 1488, 1464, 1446, 1334, 1262, 1152, 1049, 1020, 999 cm^{-1}.

Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.64; H, 5.86; N, 6.30.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{13}NOH$ 224.1070, found 224.1072.



6-Chloro-2-(*o*-tolyl)benzo[*d*]oxazole 2r. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.70$; white solid; 80 mg, yield 91%.

Mp: 89-90 °C (lit.[13b] mp 85 °C).

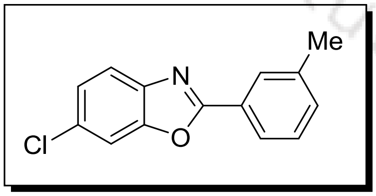
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.14 (d, J = 7.2 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.59 (d, J = 1.6 Hz, 1H), 7.41-7.39 (m, 1H), 7.35-7.31 (m, 3H), 2.78 (s, 3H).

^{13}C NMR (150 MHz, CDCl$_3$) δ 164.2, 150.7, 141.2, 139.2, 132.1, 131.4, 130.8, 130.1, 126.3, 126.0, 125.3, 120.8, 111.3, 22.4.

FT-IR (KBr) 2957, 2923, 1614, 1547, 1461, 1325, 1255, 1235, 1165, 1059, 1023 cm^{-1}.

Anal. Calcd for $C_{14}H_{10}ClNO$: C, 69.00; H, 4.14; N, 5.75. Found: C, 69.06; H, 4.12; N, 5.68.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{10}ClNOH$ 244.0524, found 244.0524.



6-Chloro-2-(*m*-tolyl)benzo[*d*]oxazole 2s. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.68$; white solid; 74 mg, yield 84%.

Mp: 98-99 °C (lit.[13b] mp 99 °C).

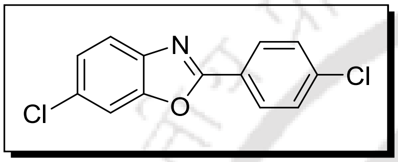
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 8.01 (d, *J* = 7.2 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.56 (d, *J* = 1.6 Hz, 1H), 7.41-7.35 (m, 2H), 7.32 (dd, *J* = 8.4 Hz, 1.6 Hz, 1H), 2.44 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 151.0, 141.1, 139.0, 132.8, 130.7, 129.0, 128.4, 126.7, 125.4, 125.0, 120.5, 111.4, 21.5.

FT-IR (KBr) 3059, 2922, 1618, 1553, 1485, 1428, 1327, 1264, 1242, 1072 cm^{-1}.

Anal. Calcd for $C_{14}H_{10}ClNO$: C, 69.00; H, 4.14; N, 5.75. Found: C, 68.95; H, 4.13; N, 5.79.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{10}ClNOH$ 244.0524, found 244.0526.



6-Chloro-2-(4-chlorophenyl)benzo[*d*]oxazole 2t. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.70; white solid; 84 mg, yield 89%.

Mp: 148-149 °C (lit.[13b] mp 148 °C).

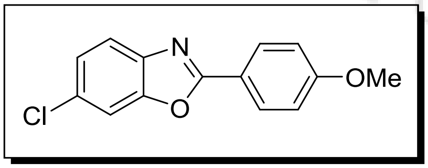
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15-8.12 (m, 2H), 7.66 (d, *J* = 8.8 Hz, 1H), 7.57 (d, *J* = 2.0 Hz, 1H), 7.50-7.47 (m, 2H), 7.34 (dd, *J* = 8.4 Hz, 1.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9, 151.1, 141.0, 138.3, 131.1, 129.5, 129.1, 125.7, 125.4, 120.7, 111.5.

FT-IR (KBr) 3064, 2923, 1616, 1594, 1551, 1482, 1460, 1403, 1328, 1282, 1260, 1230, 1109, 1090, 1047, 1010 cm^{-1}.

Anal. Calcd for $C_{13}H_7Cl_2NO$: C, 59.12; H, 2.67; N, 5.30. Found: C, 59.03; H, 2.70; N, 5.33.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_7Cl_2NOH$ 263.9977, found 263.9977.



6-Chloro-2-(4-methoxyphenyl)benzo[*d*]oxazole 2u. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.52; white solid; 76 mg, yield 81%.

Mp: 147-148 °C (lit.[13c] mp 140 °C).

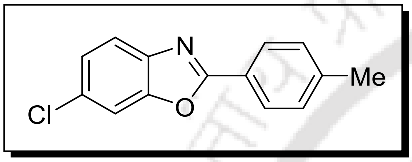
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 7.6 Hz, 2H), 7.62 (d, *J* = 8.0 Hz, 1H), 7.54 (s, 1H), 7.30 (d, *J* = 8.8 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 2H), 3.88 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 162.8, 151.1, 141.3, 130.3, 129.7, 125.3, 120.3, 119.4, 114.7, 111.3, 55.7.

FT-IR (KBr) 3073, 2924, 1621, 1602, 1505, 1454, 1440, 1333, 1263, 1257, 1177, 1055, 1024 cm^{-1}.

Anal. Calcd for $C_{14}H_{10}ClNO_2$: C, 64.75; H, 3.88; N, 5.39. Found: C, 64.82; H, 3.87; N, 5.32.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{10}ClNO_2H$ 260.0473, found 260.0473.



6-Chloro-2-*p*-tolylbenzo[*d*]oxazole 2v. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.70; white solid; 72 mg, yield 82%.

Mp: 129-130 °C (lit.[13b] mp 126 °C).

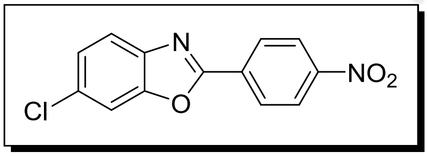
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.56 (d, *J* = 2.0 Hz, 1H), 7.32-7.29 (m, 3H), 2.42 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9, 150.8, 142.4, 140.9, 130.3, 129.7, 127.6, 125.1, 123.8, 120.2, 111.1, 21.6.

FT-IR (KBr) 2920, 2853, 1616, 1554, 1500, 1440, 1426, 1408, 1329, 1257, 1234, 1170, 1119, 1050, 1013 cm^{-1}.

Anal. Calcd for $C_{14}H_{10}ClNO$: C, 69.00; H, 4.14; N, 5.75. Found: C, 68.95; H, 4.13; N, 5.80.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{10}ClNOH$ 244.0524, found 244.0524.



6-Chloro-2-(4-nitrophenyl)benzo[*d*]oxazole 2w. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.72; white solid; 80 mg, yield 81%.

Mp: 182-183 °C.

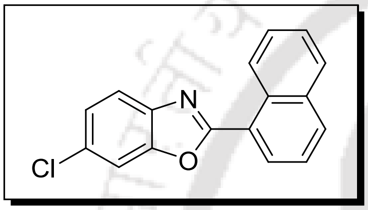
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.41-8.36 (m, 4H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.64 (d, *J* = 2.0 Hz, 1H), 7.40 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 161.5, 151.4, 150.0, 140.9, 132.5, 132.3, 128.7, 126.2, 124.4, 121.4, 111.8.

FT-IR (KBr) 3087, 1947, 1603, 1595, 1554, 1518, 1460, 1409, 1349, 1327, 1312, 1263, 1109, 1048, 1011 cm^{-1}.

Anal. Calcd for $C_{13}H_7ClN_2O_3$: C, 56.85; H, 2.57; N, 10.20. Found: C, 56.81; H, 2.56; N, 10.24.

HRMS (ESI) m/z: [M+H]$^+$ calcd for $C_{13}H_7ClN_2O_3H$ 275.0218, found 275.0216.



6-Chloro-2-(naphthalen-1-yl)benzo[*d*]oxazole 2x. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R$_f$ = 0.72; yellow solid; 70 mg, yield 70%.

Mp: 101-102 °C.

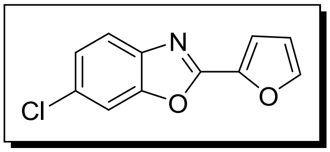
^{1}H NMR (400 MHz, CDCl$_3$) δ 9.44 (d, *J* = 8.8 Hz, 1H), 8.41 (dd, *J* = 7.6 Hz, 0.8 Hz, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.72-7.68 (m, 1H), 7.64 (d, *J* = 1.6 Hz, 1H), 7.61-7.56 (m, 2H), 7.37 (dd, *J* = 8.4 Hz, 2.0 Hz, 1H).

^{13}C NMR (150 MHz, CDCl$_3$) δ 163.6, 150.5, 141.3, 134.2, 132.9, 131.1, 130.8, 129.6, 128.9, 128.3, 126.8, 126.4, 125.4, 125.1, 123.3, 120.9, 111.4.

FT-IR (KBr) 3045, 2926, 1895, 1609, 1589, 1541, 1508, 1459, 1427, 1395, 1323, 1263, 1250, 1131, 1108, 1073, 1054, 966 cm^{-1}.

Anal. Calcd. for $C_{17}H_{10}ClNO$: C, 72.99; H, 3.60; N, 5.01. Found: C, 72.93; H, 3.62; N, 5.06.

HRMS (ESI) m/z: [M+H]$^+$ calcd for $C_{17}H_{10}ClNOH$ 280.0524, found 280.0523.



6-Chloro-2-(furan-2-yl)benzo[*d*]oxazole 2y. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.40$; pale yellow solid; 71 mg, yield 90%.

Mp: 78-79 °C.

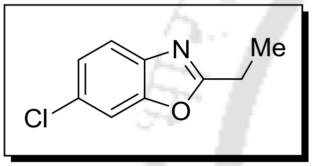
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66-7.62 (m, 2H), 7.55 (d, *J* = 2.0 Hz, 1H), 7.33 (dd, *J* = 8.4 Hz, 2.0 Hz, 1H), 7.27 (d, *J* = 3.2 Hz, 1H), 6.62-6.60 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 150.4, 146.2, 142.2, 140.6, 131.0, 125.7. 120.7, 114.9, 112.5, 111.3.

FT-IR (KBr) 3062, 3039, 1635, 1606, 1538, 1455, 1427, 1326, 1290, 1264, 1232, 1160, 1089, 1057, 1011 cm^{-1}.

Anal. Calcd for $C_{11}H_6ClNO_2$: C, 60.16; H, 2.75; N, 6.38. Found: C, 60.24; H, 2.73; N, 6.33.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{11}H_6ClNO_2H$ 220.0160, found 220.0163.



6-Chloro-2-ethylbenzo[*d*]oxazole 2z. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.50$; colorless liquid; 41 mg, yield 63%.

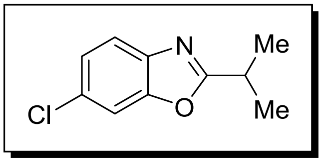
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.4 Hz, 1H), 7.47 (d, *J* = 2.0 Hz, 1H), 7.27 (dd, *J* = 8.4 Hz, 2.0 Hz, 1H), 2.96 (q, *J* = 8.0 Hz, 2H), 1.44 (t, *J* = 8.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 151.2, 140.4, 130.3, 124.9, 120.2, 111.2, 22.3, 11.0.

FT-IR (neat) 3104, 2920, 1618, 1576, 1466, 1451, 1358, 1267, 1225, 1152, 1075, 1055 cm^{-1}.

Anal. Calcd for C_9H_8ClNO: C, 59.52; H, 4.44; N, 7.71. Found: C, 59.45; H, 4.46; N, 7.74.

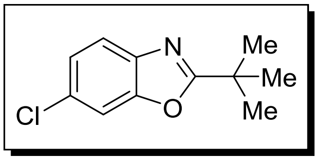
HRMS (ESI) m/z: $[M+H]^+$ calcd for C_9H_8ClNOH 182.0367, found 182.0365.



6-Chloro-2-isopropylbenzo[*d*]oxazole 2aa. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.52$; colorless liquid; 56 mg, yield 80%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.8 Hz, 1H), 7.47 (d, *J* = 2.0 Hz, 1H), 7.26-7.24 (m, 1H), 3.24-3.17 (m, 1H), 1.44 (d, *J* = 7.2 Hz, 6H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 172.2, 151.2, 140.3, 130.3, 124.9, 120.3, 111.2, 29.1, 20.4.
FT-IR (neat) 3098, 2988, 1614, 1570, 1465, 1446, 1367, 1266, 1232, 1138, 1083, 1054 cm^{-1}.
Anal. Calcd for $C_{10}H_{10}ClNO$: C, 61.39; H, 5.15; N, 7.16. Found: C, 61.46; H, 5.14; N, 7.12.
HRMS (ESI) m/z: [M+H]$^+$ calcd for $C_{10}H_{10}ClNOH$ 196.0524, found 196.0525.



2-(*tert*-butyl)-6-chlorobenzo[*d*]oxazole 2ab.[13d] Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.68$; colorless liquid; 34 mg, yield 45%.

^{1}H NMR (400 MHz, CDCl$_3$) δ 7.60 (d, *J* = 8.4 Hz, 1H), 7.50 (d, *J* = 2.0 Hz, 1H), 7.29 (dd, *J* = 8.4 Hz, 2.0 Hz, 1H), 1.49 (s, 9H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 174.4, 151.2, 140.2, 130.2, 124.8, 120.4, 111.2, 34.4, 28.6;
FT-IR (neat) 2977, 2870, 1614, 1569, 1458, 1428, 1364, 1326, 1259, 1232, 1129, 1109, 1053 cm^{-1}.

Anal. Calcd for $C_{11}H_{12}ClNO$: C, 63.01; H, 5.77; N, 6.68. Found: C, 63.07; H, 5.78; N, 6.63.
HRMS (ESI) m/z: [M+H]$^+$ calcd for $C_{11}H_{12}ClNOH$ 210.0680, found 210.0686.

3.5. References

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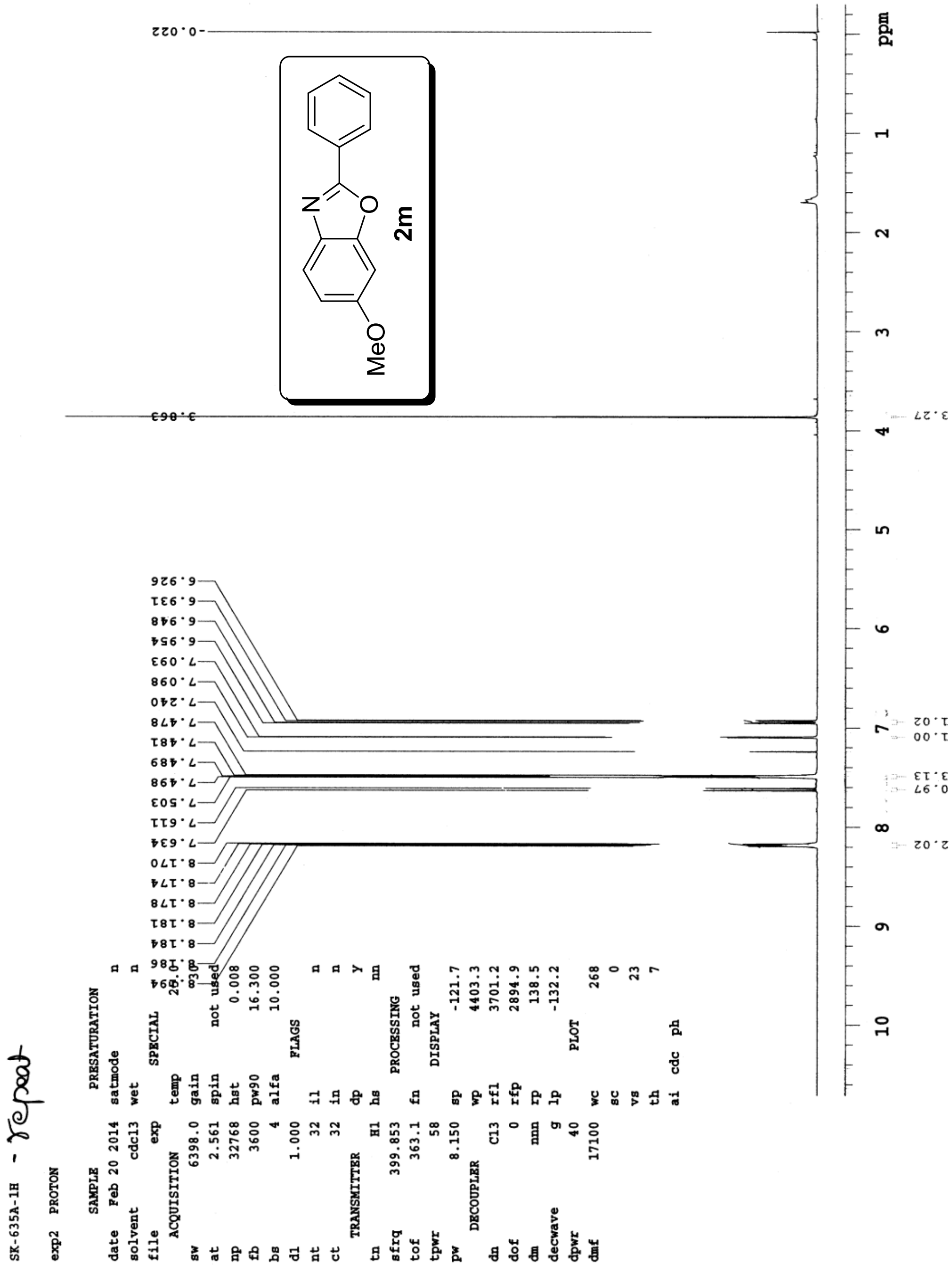
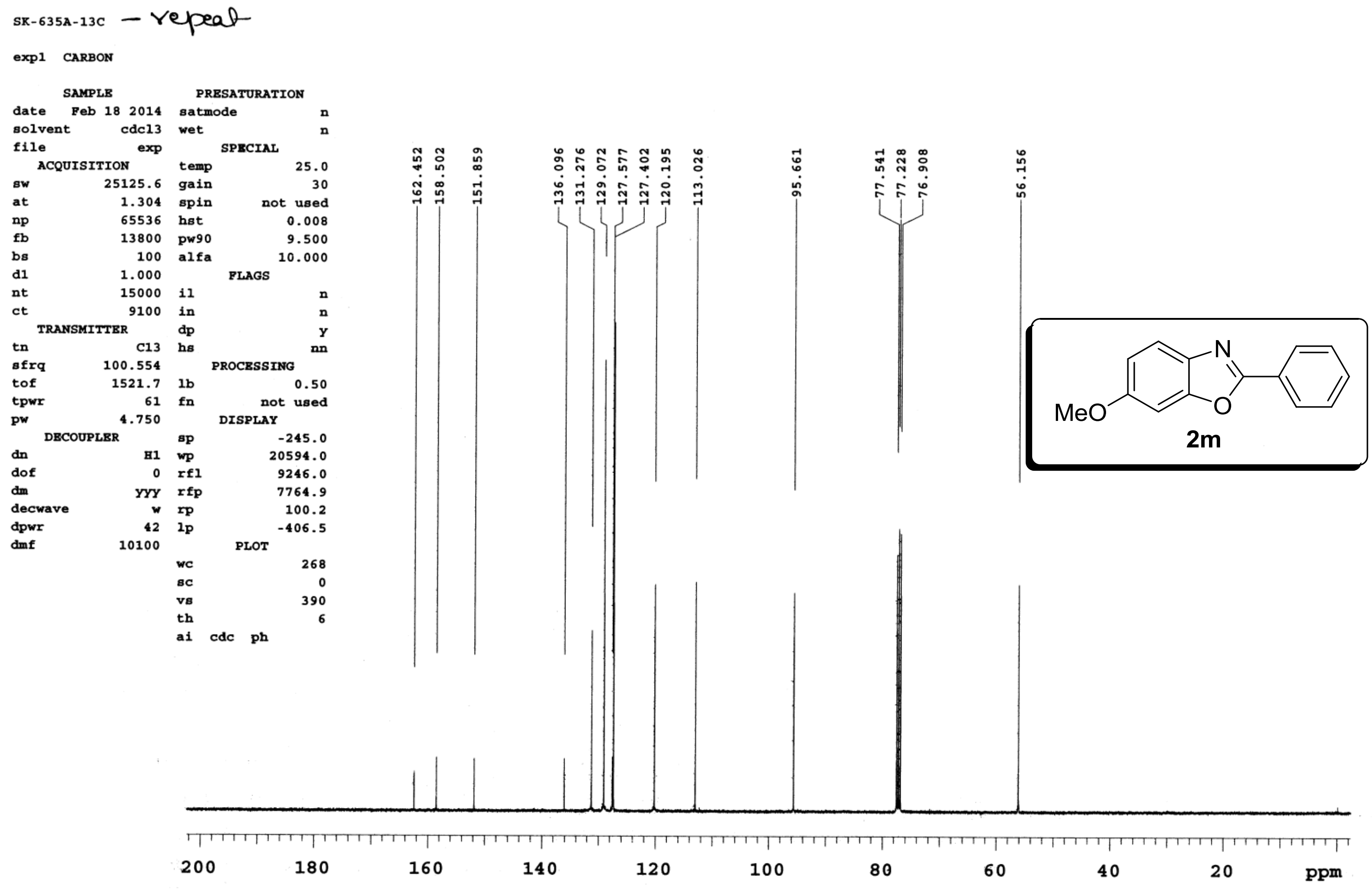
3.6. Selected Spectra





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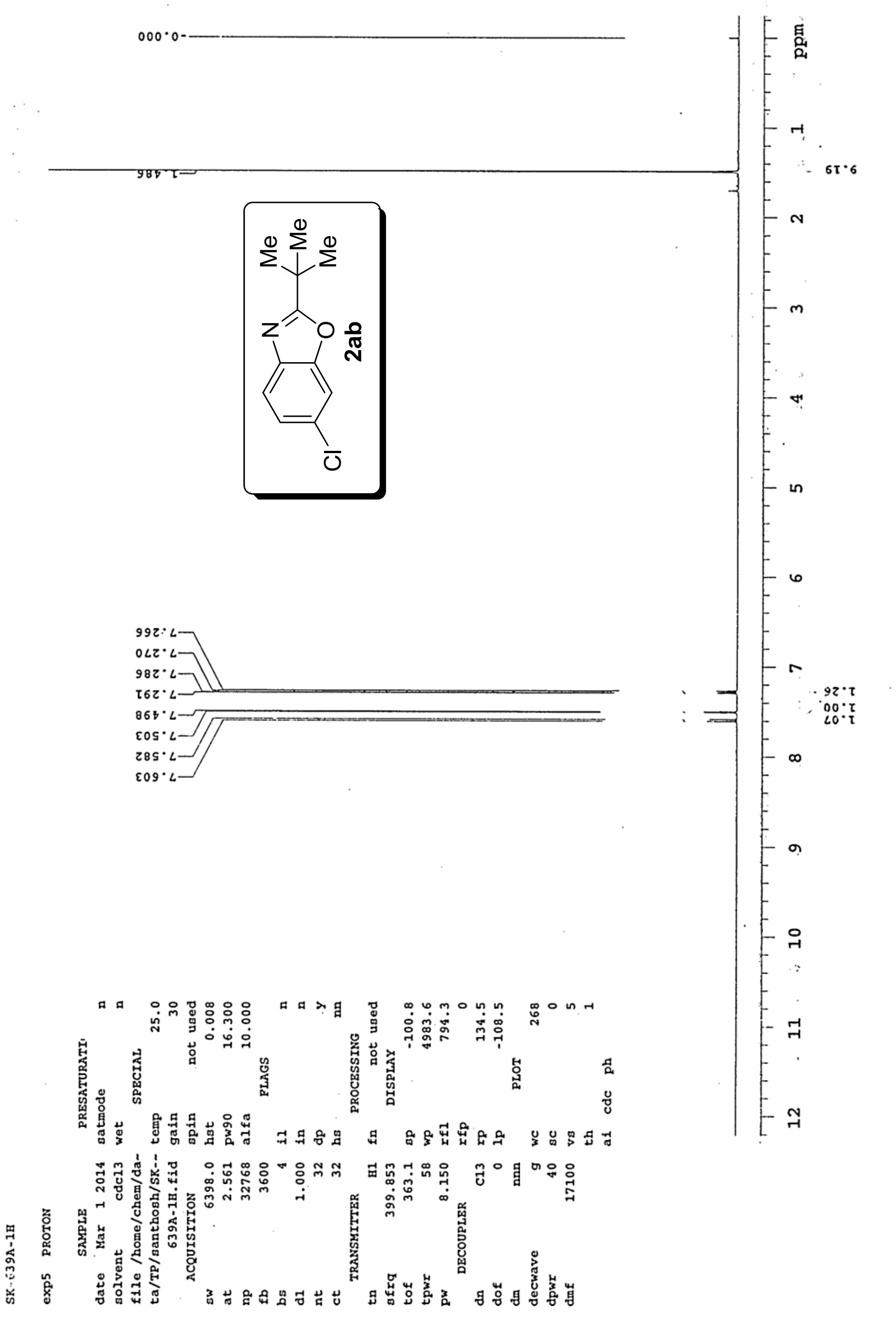
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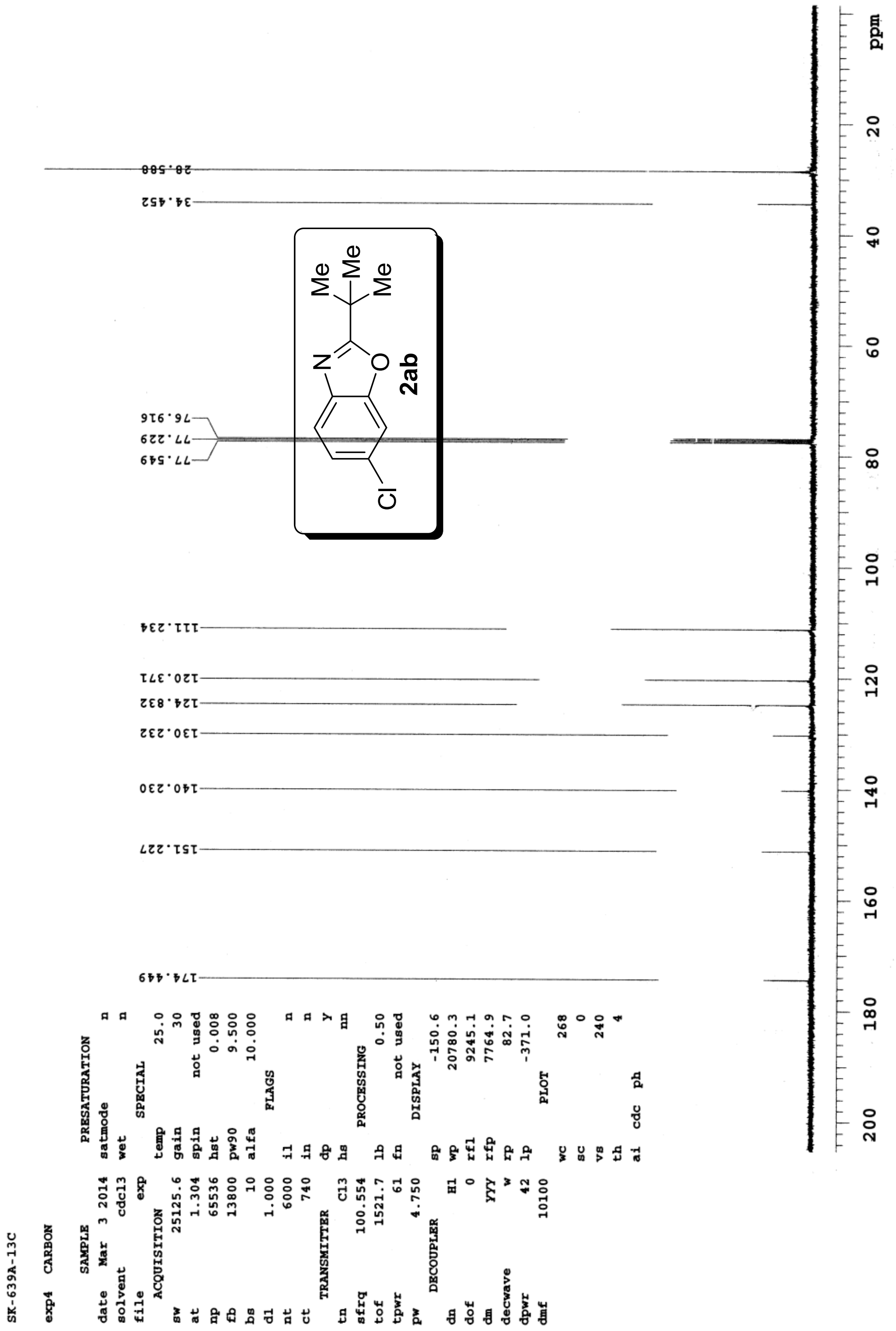
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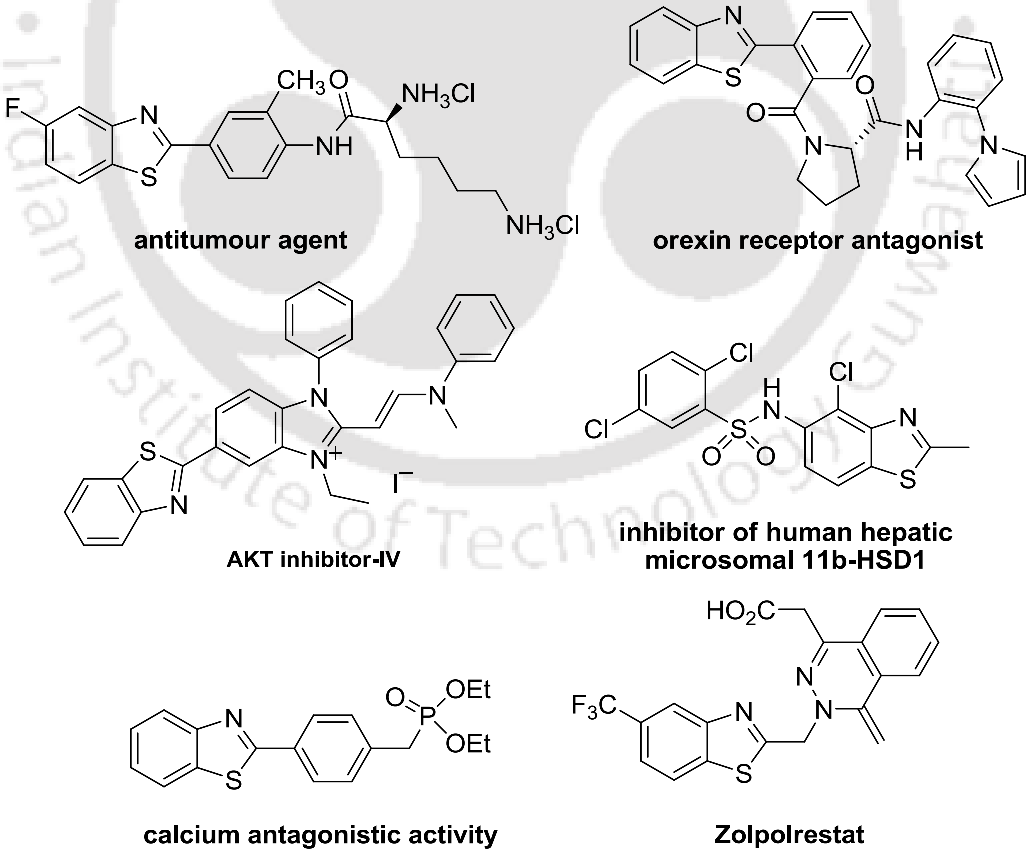
Chapter IV

Iodobenzene Catalyzed Synthesis of Benzothiazoles Using Oxone *via C-S* Bond Formation

The construction of benzothiazole structural motif remains prominent and has been a topic of immense interest in recent years, since this heterocyclic framework constitutes an integral part of many diverse natural products and biologically active compounds.[1] They have been widely utilized over the years as drugs for several diseases such as alzheimer's disease,[2a] inflammatory diseases,[2b] diabetes,[2c] tuberculosis[2d] and viral infections.[2e] The other medicinal chemistry applications of benzothiazole derivatives include antitumor,[2f] anticancer,[2g] orexin receptor antagonist,[2h] calcium antagonistic activity,[2i] AKT (protein kinase B) inhibitor-IV[2e] and inhibitors for several enzymes.[2j] Due to their diverse and important applications, the development of various synthetic strategies to access these class of compounds are highly desirable.


antitumour agent

orexin receptor antagonist

AKT inhibitor-IV

inhibitor of human hepatic microsomal 11b-HSD1

calcium antagonistic activity

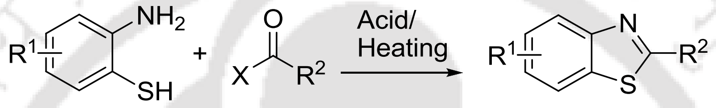
Zolpolrestat

Figure 1. Examples of some biologically active compounds

4.1. Strategies for Synthesis of Benzothiazoles

4.1.1. Classical Methods

Generally, the classical method for the construction of substituted benzothiazoles starts from the condensation of *o*-aminothiophenols with carboxylic acids or its equivalent under strong acidic condition (Scheme 1).[3] However, limitations such as harsh reaction conditions and unavailability of suitably substituted starting precursors hampers these reactions for synthesizing diverse substituted benzothiazoles. During the past several years, these problems have been overcome using cross-coupling reactions.



X = H, Cl, OH

R^1 = H, EDG, EWG

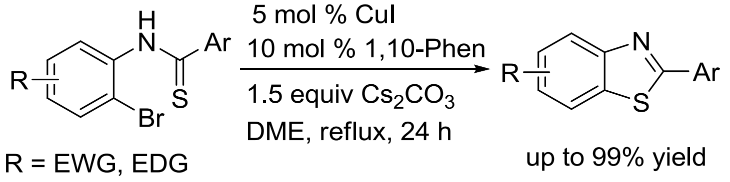
R^2 = H, Aryl, Heteroaryl

Scheme 1. Classical Methods for the Synthesis of Substituted Benzothiazoles

4.1.2. Cross-Coupling Reactions

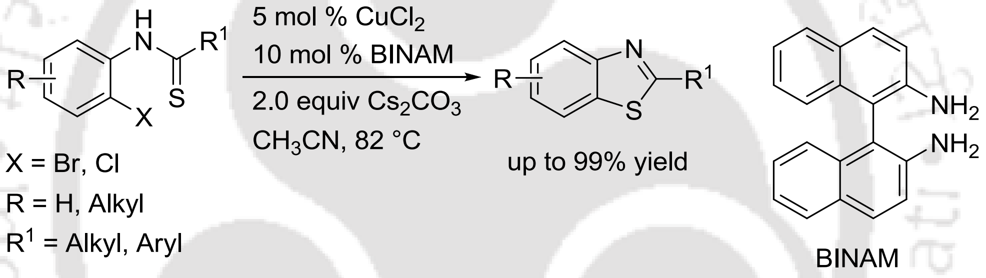
The transition metal catalyzed cross-coupling reactions are valuable tools in synthetic organic chemistry for the construction of aryl-sulfur bonds. Compared to traditional benzothiazole synthesis, this strategy offers an efficient access under milder conditions with good regioselectivity. Copper catalysis is inexpensive and less toxic compared to the other catalytic systems such as palladium. Hence, they are widely used in *C-S* cross-coupling reactions.

Batey and co-workers described a general synthesis of 2-substituted benzothiazoles from *N*-(2-bromophenyl)thiobenzamide by copper-catalyzed intramolecular *C-S* cross-coupling (Scheme 2). They used CuI along with 1,10-phenanthroline in the presence of Cs_2CO_3 in refluxing DME.[4a]



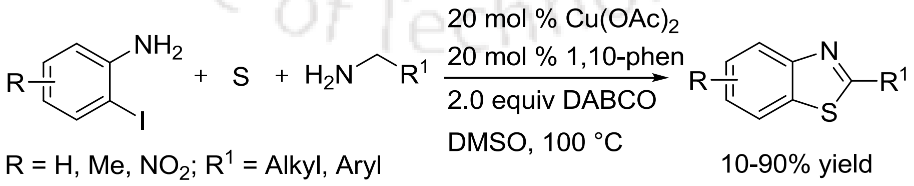
Scheme 2. Synthesis of Substituted Benzothiazoles by Cross-Coupling Reaction

In another similar cross-coupling approach, $CuCl_2$/binaphthyl amine catalytic system was used for intramolecular cyclization of *N*-(2-chloro/bromophenyl)benzothioamides for the synthesis of 2-substituted benzothiazoles. In this reaction the starting precursors having electron withdrawing, electron releasing groups and sterically hindered *ortho* substituents are well tolerated to provide the desired cross-coupled benzothiazoles in good yields. In addition, the reaction also works for 2-alkyl substituted benzothiazole synthesis (Scheme 3).[4b]



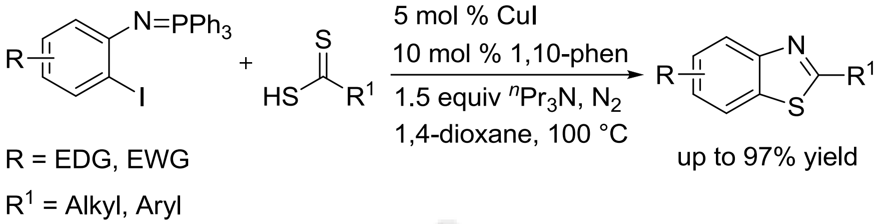
Scheme 3. Copper Catalyzed Synthesis of 2-Aryl/Alkylbenzothiazoles

Recently, a one-pot, three component procedure for the synthesis of 2-arylbenzothiazoles is reported. This protocol involves the reaction of 2-iodoanilines, benzylamines and sulfur powder in the presence of $Cu(OAc)_2$/1,10-phenanthroline along with DABCO in DMSO at 100 °C (Scheme 4).[4c]



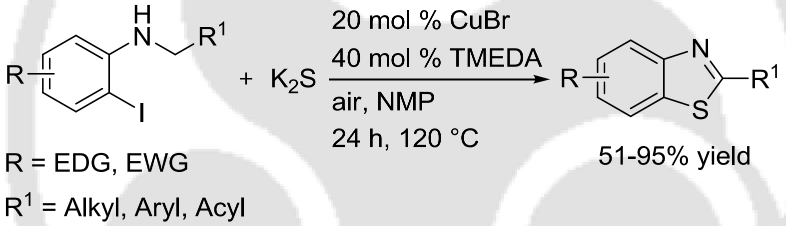
Scheme 4. Three-Component Synthesis of Benzothaizoles

Yu group reported a copper catalyzed reaction involving Ullmann-type *C*−*S* bond coupling of (2-iodophenylimino)triphenylphosphorane and thiocarboxylic acids (used as a sulfur source) with subsequent cyclization *via* Wittig condensation to afford benzothiazole derivatives in good yields (Scheme 5).[4d]



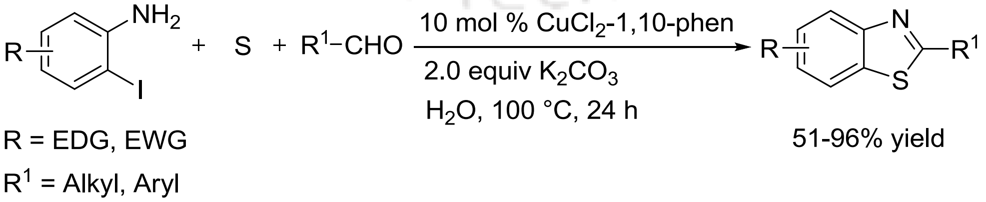
Scheme 5. Copper-Catalyzed Synthesis of Benzothiazoles Using Thiocarboxylic Acids

Potassium sulfide has been used as a sulfur source in the synthesis of benzothiazoles. The reaction of *N*-benzyl-2-iodoaniline and potassium sulfide catalyzed by CuBr/TMEDA in air resulted in double *C*–*S* bond formation *via* a traditional and an oxidative cross-coupling reaction to give the desired products in 51-95% yield (Scheme 6).[4e]



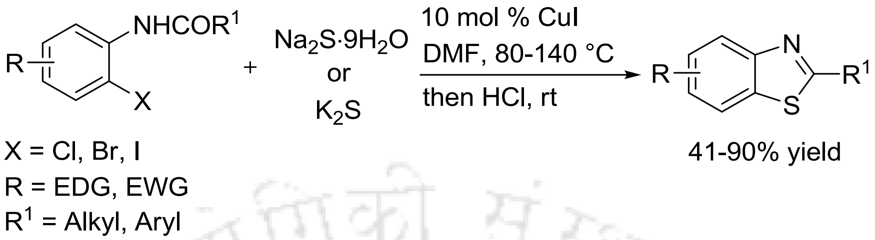
Scheme 6. Cross Coupling Synthesis of Benzothiazoles Using Molecular Oxygen as Oxidant

A one-pot, three-component reaction was presented by Zhou and co-workers for the synthesis of benzothiazoles. This catalytic system involves the use of $CuCl_2$ for the reaction of *o*-iodoaniline, aldehyde and sulfur powder in water as solvent to afford functionalized benzothiazoles (Scheme 7).[4f]



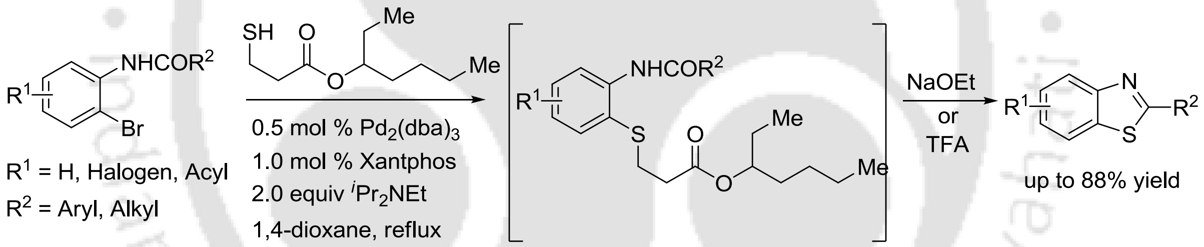
Scheme 7. Eco-Friendly Synthesis of Substituted Benzothiazoles in Water

Ma and co-workers have developed a general and mild protocol for the synthesis of -2-alkyl/arylbenzothiazoles by CuI-catalyzed coupling reaction of 2-haloanilides with metal sulfides as sulfur source in solvent DMF at 80-140 °C (Scheme 8).[4g]



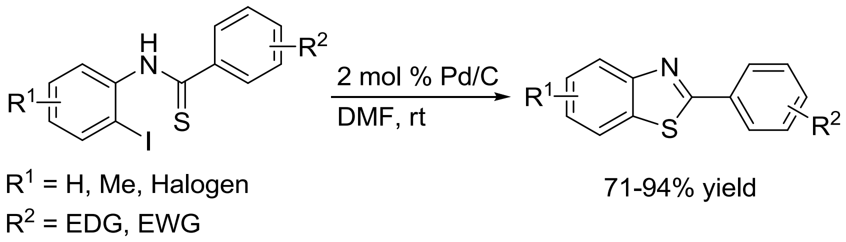
Scheme 8. Synthesis of Substituted Benzothiazoles from 2-Haloanilides

Itoh group has reported a convenient synthesis of substituted benzothiazoles from 2-bromoanilides and thiol surrogates. In this reaction, the reaction of anilides and alkyl thiolate yields sulfides that further results in benzothiazoles under basic or acidic conditions (Scheme 9).[4h]



Scheme 9. Synthesis of Benzothiazoles *via* Pd-Catalyzed Thiol Cross-Coupling

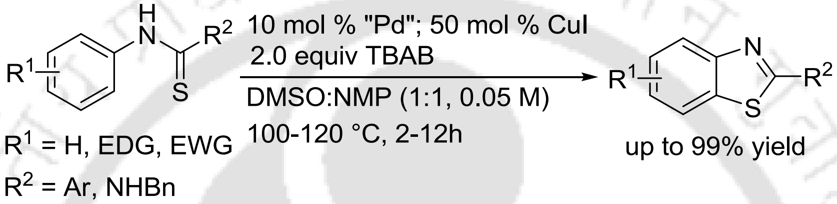
Li and co-workers have synthesized 2-substituted benzothiazoles *via* cyclization of *o*-iodothiobenzanilide derivatives using Pd/C as the catalyst at room temperature. The protocol is ligand and additive-free, high-yielding and involves very mild conditions (Scheme 10).[4i]



Scheme 10. Palladium-Catalyzed Synthesis of 2-Aryl Benzothiazoles at Room Temperature

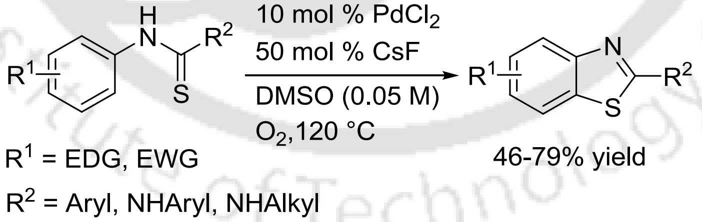
4.1.3. C–H Functionalization Reactions

Carbon-carbon and carbon-heteroatom bond formations by C–H functionalization reactions lie at the heart of the organic synthesis. Transition metal catalyzed C–H functionalization/*C-S* bond formation has been used for the synthesis of functionalized benzothiazoles. Doi and co-workers have achieved the catalytic C-H functionalization/*C-S* bond formation sequence by employing 10 mol % of Pd(II) catalyst in the presence of 50 mol % CuI and TBAB at 80-120 °C for the synthesis of 2-substituted benzothiazoles (Scheme 11).[5a]



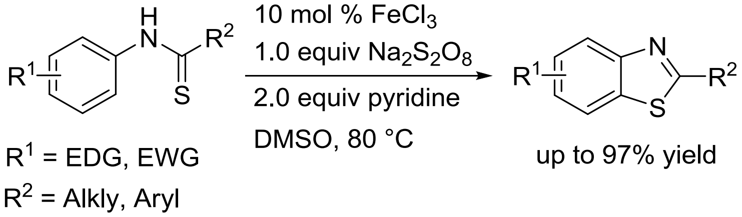
Scheme 11. Palladium Catalyzed C-H functionalization/*C-S* bond formation

They also subsequently showed palladium catalyzed cyclization of thiobenzanilides and thioureas leading to 2-aryl- and 2-aminobenzothiazoles. They were able to achieve this transformation using molecular oxygen as reoxidant and library of benzothiazoles were synthesized with good functional group compatibility (Scheme 12).[5b] In this reaction, the addition of 50 mol % of CsF greatly enhanced the outcome of the reactions.



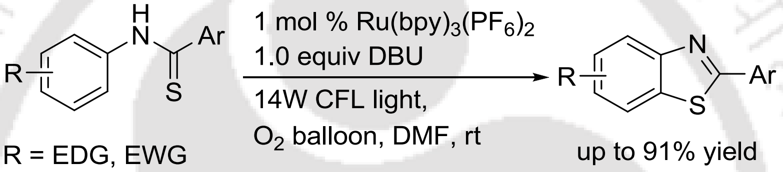
Scheme 12. Use of Molecular Oxygen in Pd-Catalyzed Synthesis of Benzothiazoles

Iron and ruthenium salts were also proved to be excellent catalysts for the synthesis of benzothiazole derivatives by C-H functionalization/*C–S* bond formation. For example, less cost iron catalyst, $FeCl_3$ was used for cyclization of thiobenzanilides in combination with $Na_2S_2O_8$ and pyridine in DMSO at 80 °C (Scheme 13).[5c]



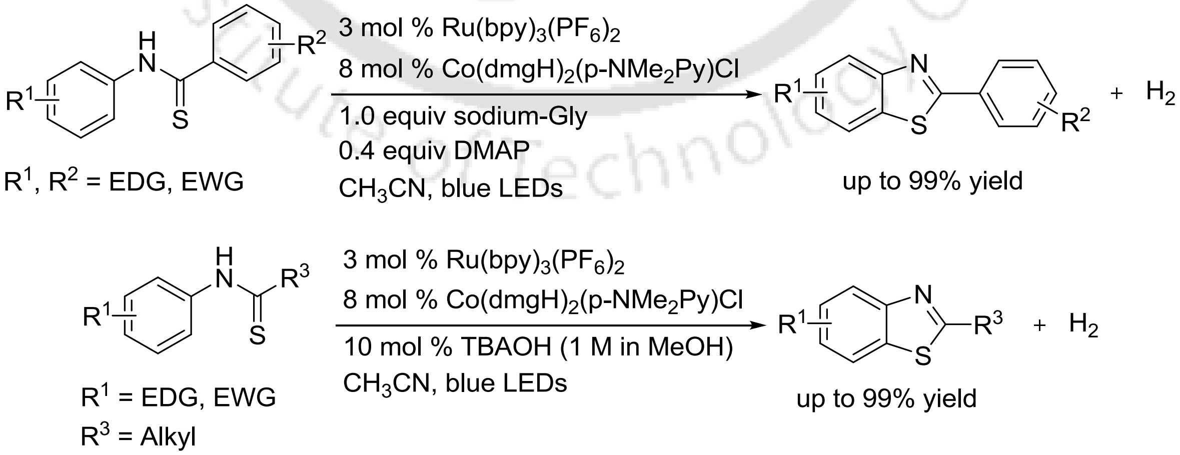
Scheme 13. Iron Catalyzed Synthesis of Benzothiazoles

Li and co-workers have accomplished 2-substituted benzothiazoles through radical cyclization of thioanilides *via* an aerobic visible-light driven photoredox catalytic system. The reaction features the use of a sensitizer, $Ru(bpy)_3(PF_6)_2$, for C-H functionalization/*C-S* bond formation with no direct metal involvement (Scheme 14).[5d]



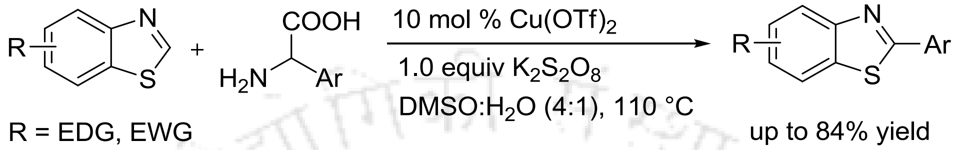
Scheme 14. An Aerobic Visible-Light Driven Synthesis of Benzothiazoles

Recently, Lei and co-workers described an external oxidant-free C−H functionalization/*C−S* bond formation reaction to form 2-arylbenzothiazoles by visible light photoredox cobalt-catalysis. Using this protocol, 2-alkylbenzothiazoles can be obtained when catalytic TBAOH was used as the base (Scheme 15).[5e]



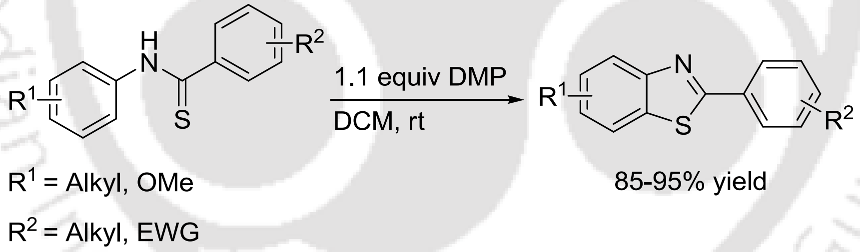
Scheme 15. A Photoredox Aromatic C−H Thiolation for Benzothiazole Synthesis

The oxidative functionalization of benzothiazoles would serve as a useful strategy towards synthesis of 2-arylbenzothiazoles. This strategy has been successful in bringing out direct oxidative coupling of benzothiazoles and phenylglycine derivatives using $Cu(OTf)_2/K_2S_2O_8$ catalytic system, resulting in array of 2-arylbenzothiazoles in moderate to good yields. (Scheme 16).[5f]



Scheme 16. Copper Catalyzed Oxidative Coupling of Benzothiazoles and Phenylglycines

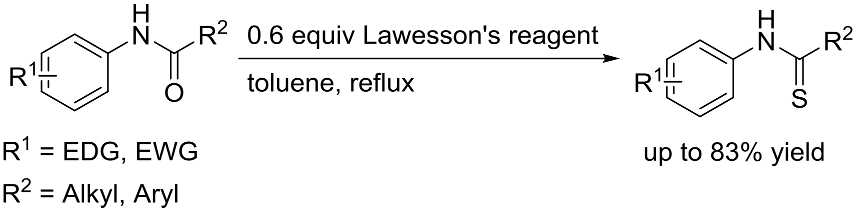
The electrophilic and mild nature of hypervalent iodine reagents makes them synthetically important for oxidative C-H functionalization reactions. These are widely used for synthesis of various heterocycles by oxidative cyclization. Dess-Martin periodinane was successfully employed by Bose and co-workers for the synthesis of electron-rich benzothiazole derivatives (Scheme 17).[6]



Scheme 17. Metal-Free Synthesis of Benzothiazoles

4.2. Present Study

Following the synthesis of substituted benzoxazoles from benzanilides using 1-iodo-4-nitrobenzene in the presence of oxone and triflic acid, we envisioned that the reaction of thiobenzanilides under similar conditions would provide access to substituted benzothiazoles. To examine this, the starting precursors, thiobenzanilides were prepared.[5a]

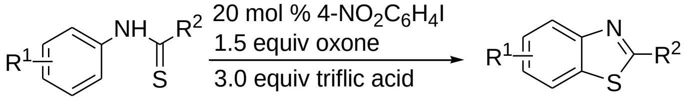


Scheme 18. Synthesis of Thiobenzanilides

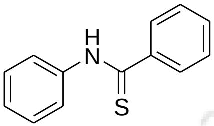
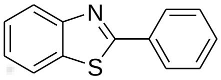
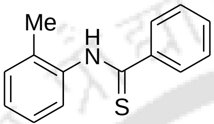
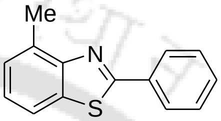
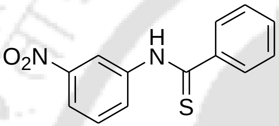
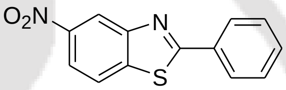
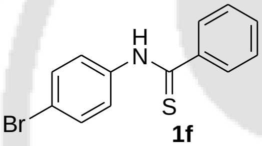
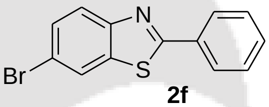
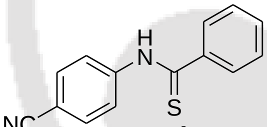
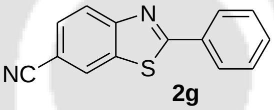
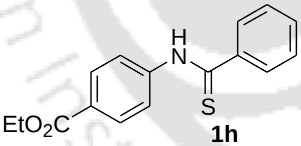
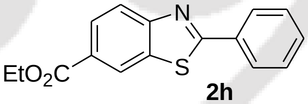
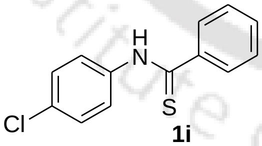
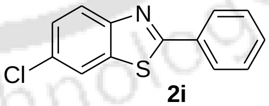
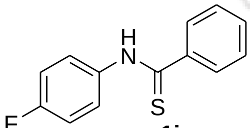
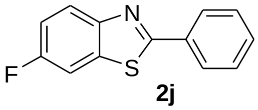
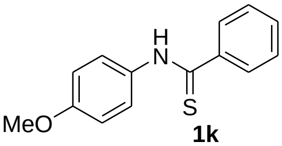
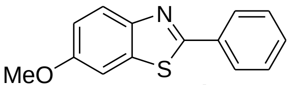
After the synthesis of starting materials, the scope and utility of the protocol used for the synthesis of benzoxazoles in chapter III was explored for the reaction of variously substituted analogue thioalkyl/arylanilides (Table 1). The reactions readily occurred to give the desired 2-alkyl/2-arylbenzothiazoles with enhanced yields. For examples, *N*-phenylthiobenzamide **1a** underwent reaction to afford 2-phenylbenzothiazole **2a** in 84% yield, while the substrate **1b** having 2-methyl substituent afforded **2b** in 41% yield. In contrast, the substrate **1e** and **1m** with 3-nitro and 4-nitro substituents showed no reaction and the starting materials were recovered intact. However, the reaction of the substrates **1f, 1i-l, 1o** and **1q** having 4-bromo, 4-chloro, 4-fluoro, 4-methoxy, 4-methyl, 2,4-dimethyl and 3,5-dichloro substituents readily occurred to give the corresponding benzothiazoles **2f**, **2i-l**, **2o** and **2q** in 61-89% yields, whereas the substrates **1g, 1h** and **1n** having 4-cyano, 4-ester and 4-trifluoromethyl substituents exhibited moderate reactivity giving the target products in 38-44% yields. On the other hand, the substrates **1r-w** containing 2-methyl, 3-methyl, 4-fluoro, 4-methoxy, 4-methyl and 4-nitro substituents in thioamide aryl ring smoothly underwent reaction to give the corresponding 2-arylbenzothiazoles **2r-w** in 86-95% yields. Likewise, the cyclization of the substrates **1x-z** having 1-naphthyl and 2-furyl substituents could be carried out to afford the corresponding benzothiazoles **2x-z** in 75-88% yields. Furthermore, this protocol was compatible for the synthesis of 2-alkylbenzothiazoles. For examples, the substrates **1aa-ab**, with R^2 = ethyl and isopropyl substituents readily cyclized to provide the desired 2-alkylbenzothiazoles **2aa** and **2ab** in 63 and 88% yields, respectively, whereas **1ac** having R^2 = *tert*-butyl underwent reaction to give the target benzothiazoles **2ac** in 81% yield.

The reaction of the substrate **1c** having 3-methoxy group afforded a 1:32 mixture of 7-methoxy-2-phenylbenzothiazole **2ca** and 5-methoxy-2-phenylbenzothiazole **2cb** in 89% yield. A similar result was obtained with the substrate **1d** having 3-methyl substituent providing a 1:3.3 mixture of 7-methyl-2-phenylbenzothiazole **2da** and 5-methyl-2-phenyl

Table 1. 1-Iodo-4-nitrobenzene Catalyzed Synthesis of Benzothiazoles with Oxone[a]



1a-b, 1e-o, 1q-ac **2a-b, 2e-o, 2q-ac**

entry	substrate	time (h)	product	yield (%)
1	 **1a**	12	 **2a**	84
2	 **1b**	12	 **2b**	41
3	 **1e**	48	 **2e**	0
4	 **1f**	12	 **2f**	89
5	 **1g**	48	 **2g**	41
6	 **1h**	48	 **2h**	38
7	 **1i**	5	 **2i**	88
8	 **1j**	12	 **2j**	83
9	 **1k**	12	 **2k**	87

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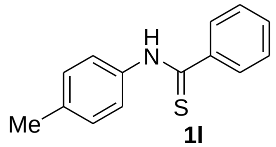
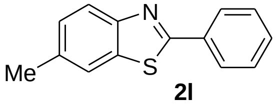
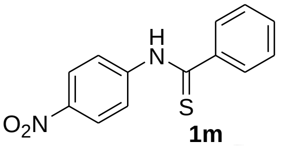
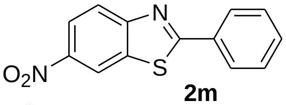
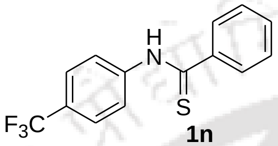
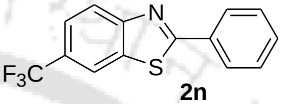
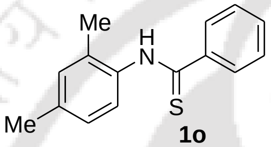
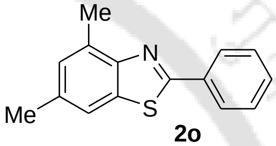
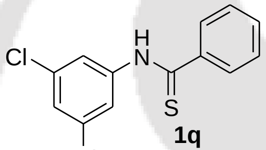
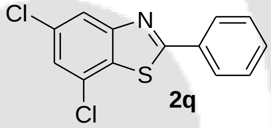
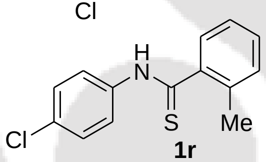
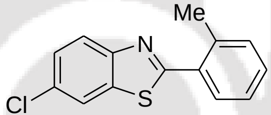
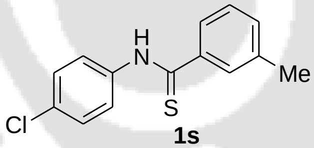
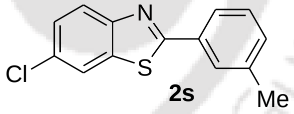
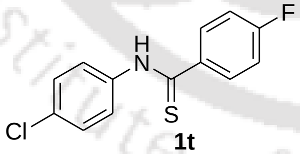
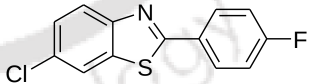
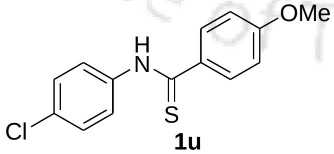
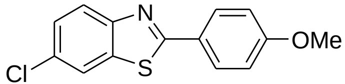
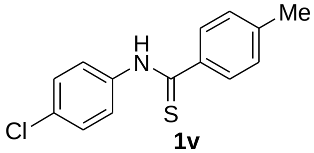
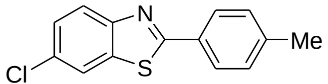
entry	substrate	time (h)	product	yield (%)
10	 **1l**	12	 **2l**	89
11	 **1m**	12	 **2m**	0
12	 **1n**	48	 **2n**	44
13	 **1o**	12	 **2o**	61
14	 **1q**	12	 **2q**	72
15	 **1r**	12	 **2r**	95
16	 **1s**	12	 **2s**	93
17	 **1t**	8	 **2t**	90
18	 **1u**	12	 **2u**	93
19	 **1v**	12	 **2v**	89

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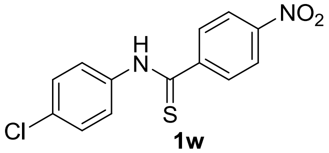
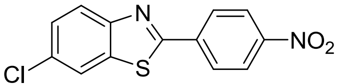
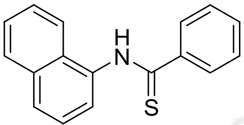
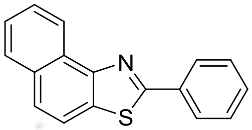
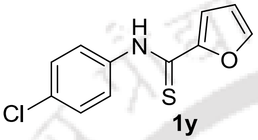
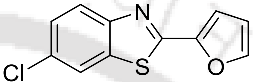
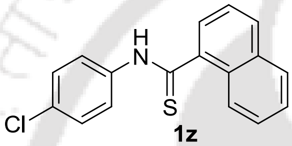
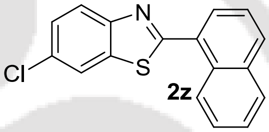
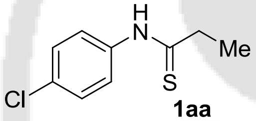
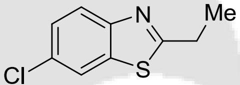
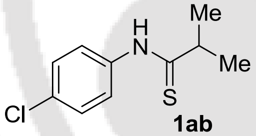
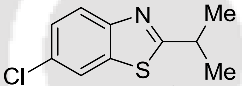
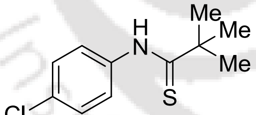
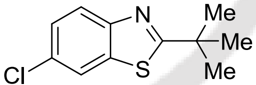
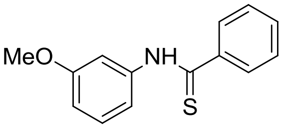
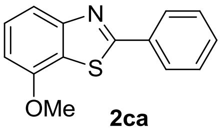
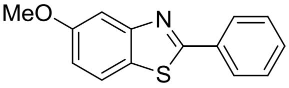
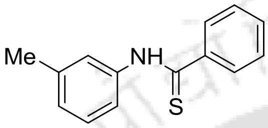
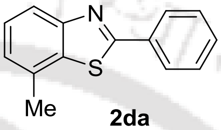
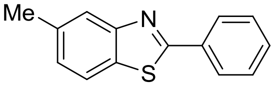
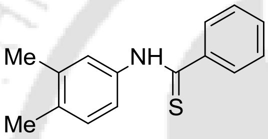
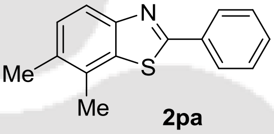
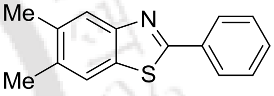
entry	substrate	time (h)	product	yield (%)
20	 **1w**	24	 **2w**	86
21	 **1x**	10	 **2x**	88
22	 **1y**	8	 **2y**	81
23	 **1z**	15	 **2z**	75
24	 **1aa**	12	 **2aa**	63
25	 **1ab**	12	 **2ab**	88
26	 **1ac**	12	 **2ac**	81

[a]Reaction conditions: **1a-b, 1e-o, 1q-ac** (0.36 mmol), 1-iodo-4-nitrobenzene (20 mol %), oxone (0.54 mmol), TfOH (1.08 mmol), HFIP (2.5 mL), rt.

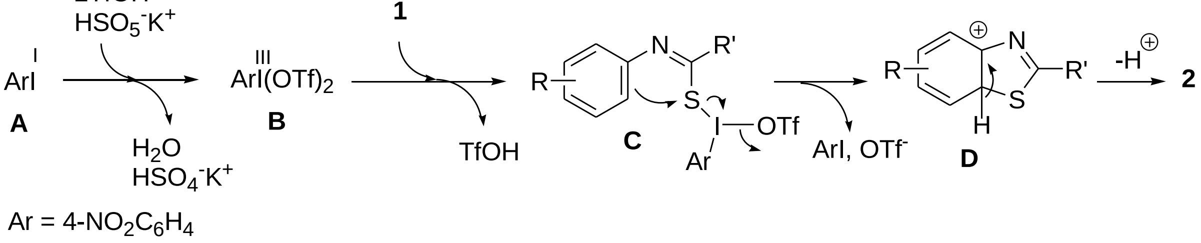
benzothiazole **2db** in 79% yield. In addition, the substrate **1p** bearing 3,4-dimethyl substituents underwent reaction to give a 1:2.4 mixture of 6,7-dimethyl-2-phenylbenzothiazole **2pa** and 5,6-dimethyl-2-phenylbenzothiazole **2pb** in 75% yield (Table 2).

Table 2. 1-Iodo-4-nitrobenzene Catalyzed Cyclization of *meta* Substituted Thioanilides[a]

entry	substrate	product
1	 **1c**	 **2ca** +  **2cb** 6 h, 89%yield (1:32)
2	 **1d**	 **2da** +  **2db** 12 h, 79%yield (1:3.3)
3	 **1p**	 **2pa** +  **2pb** 12 h, 75%yield (1:2.4)

[a]Reaction conditions: **1c-d, 1p** (0.36 mmol), 1-iodo-4-nitrobenzene (20 mol %), oxone (0.54 mmol), TfOH (1.08 mmol), HFIP (2.5 mL), rt.

A plausible mechanism can be explained as follows similar to the one given for the synthesis of benzoxazoles in chapter III. The reaction of aryl iodide **A** with TfOH and oxone can generate an active hypervalent iodine(III) species, $ArI(OTf)_2$ **B**, that could react with **1** to give an intermediate **C.** Intramolecular cyclization of **C** can give the cationic intermediate **D,** accompanied by the liberation of iodobenzene **A,** which could be reoxidized to **B.** The intermediate **D** can furnish the target products **2** by aromatization (Scheme 19).



Scheme 19. Proposed Catalytic Cycle

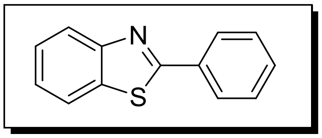
In conclusion, the synthesis of 2-aryl/alkylbenzothiazoles was demonstrated using 1-iodo-4-nitrobenzene as catalyst and oxone as an oxidant at room temperature. A wide variety of substrates undergo cyclization to give the products with high yield.

4.3. Experimental Section

4.3.1. General Information. All chemicals and solvents were purchased from commercial suppliers and were used as received. Thiobenzanilides were prepared by thionation of the corresponding anilides with Lawesson‘s reagent.[5a] Purification of the reaction products was carried out by column chromatography using silica gel (230-400 mesh). Analytical TLC was performed on silica gel G/GF 254 plate. NMR spectra were recorded on DRX-400 Varian spectrometer and Bruker Avance III 600 spectrometer using $CDCl_3$ as solvent and Me_4Si as internal standard. Chemical shifts (δ) are reported in ppm and spin-spin coupling constants (J) are given in Hz. Melting points were determined using Büchi B-540 melting point apparatus and are uncorrected. FT-IR spectra were recorded using Perkin Elmer IR spectrometer. Elemental analysis were recorded using Perkin Elmer CHNS analyzer. Mass spectra were recorded on a Waters Q-Tof Premier mass spectrometer.

4.3.2. General Procedure for 1-Iodo-4-nitrobenzene Catalyzed Synthesis of Substituted Benzothiazoles 2a-ac: Oxone (1.5 equiv) was added to a stirred solution of thioanilide (0.36 mmol, 1.0 equiv), 1-iodo-4-nitrobenzene (20 mol %) and triflic acid (3.0 equiv) in HFIP (2.5 mL) at room temperature under air. The mixture was stirred and the progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. The reaction mixture was then treated with saturated $Na_2S_2O_3$ (1 mL) and $NaHCO_3$ (1 mL) solutions. The resultant mixture was extracted using ethyl acetate (3 x 10 mL) and washed with brine (2 x 5 mL) and water (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 to afford analytically pure substituted benzothiazoles.

4.4. Characterization Data of Substituted Benzothiazoles 2a-ac



2-Phenylbenzo[*d*]thiazole 2a. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.62; white solid; 64 mg, yield 84%.

Mp: 101-102 °C (lit.[7a] mp 99 °C).

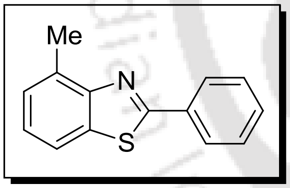
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09-8.05 (m, 3H), 7.90 (d, *J* = 7.6 Hz, 1H), 7.50-7.46 (m, 4H), 7.39-7.35 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2, 154.3, 135.2, 133.8, 131.1, 129.2, 127.7, 126.5, 125.3, 123.4, 121.8.

FT-IR (KBr) 3034, 1634, 1510, 1479, 1454, 1445, 1434, 1314, 1225, 1159, 1071, 1028 cm^{-1}.

Anal. Calcd for $C_{13}H_9NS$: C, 73.90; H, 4.29; N, 6.63; S, 15.18. Found: C, 73.99; H, 4.27; N, 6.59; S, 15.15.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_9NSH$ 212.0528, found 212.0528.



4-Methyl-2-phenylbenzo[*d*]thiazole 2b.[5d] Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.80; white solid; 33 mg, yield 41%.

Mp: 41-42 °C.

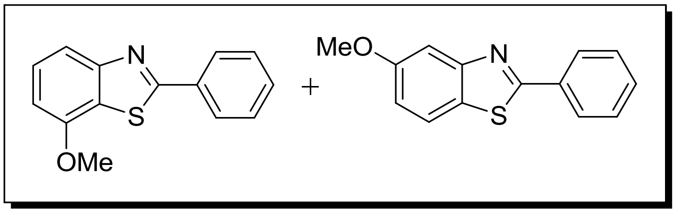
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11-8.09 (m, 2H), 7.73-7.71 (m, 1H), 7.49-7.47 (m, 3H), 7.27-7.26 (m, 2H), 2.80 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 153.7, 135.2, 134.2, 133.6, 130.9, 129.2, 127.7, 127.0, 125.3, 119.2, 18.6.

FT-IR (KBr) 3061, 2920, 1577, 1478, 1445, 1314, 1223, 1179, 1072, 970 cm^{-1}.

Anal. Calcd for $C_{14}H_{11}NS$: C, 74.63; H, 4.92; N, 6.22; S, 14.23. Found: C, 74.70; H, 4.90; N, 6.20; S, 14.20.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{11}NSH$ 226.0685, found 226.0682.



7-Methoxy-2-phenylbenzo[*d*]thiazole 2ca and **5-Methoxy-2-phenylbenzo[*d*]thiazole 2cb.** **Characterization Data for 2cb:** Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.54; white solid; 77 mg, yield 89%.

Mp: 71-72 °C (lit.[7b] mp 75 °C).

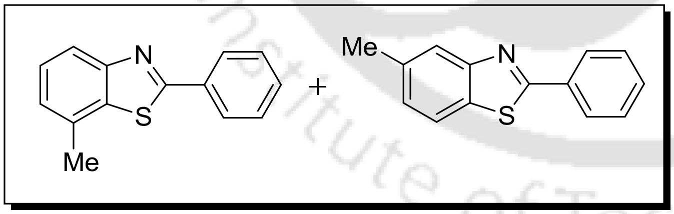
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05-8.04 (m, 2H), 7.73 (d, *J* = 8.8 Hz, 1H), 7.55 (s, 1H), 7.46 (s, 3H), 7.03 (d, *J* = 8.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 159.3, 155.6, 133.9, 131.0, 129.2, 127.6, 127.1, 122.0, 115.7, 105.7, 55.8.

FT-IR (KBr) 2936, 1601, 1558, 1465, 1430, 1329, 1279, 1248, 1160, 1139, 1076, 1025, 969 cm^{-1}.

Anal. Calcd for $C_{14}H_{11}NOS$: C, 69.68; H, 4.59; N, 5.80; S, 13.29. Found: C, 69.75; H, 4.60; N, 5.78; S, 13.25.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{11}NOSH$ 242.0634, found 242.0634.



7-Methyl-2-phenylbenzo[*d*]thiazole 2da[7c] and **5-Methyl-2-phenylbenzo[*d*]thiazole 2db.**[7d] Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.72; white solid; 64 mg, yield 79%.

Mp: 129-130 °C.

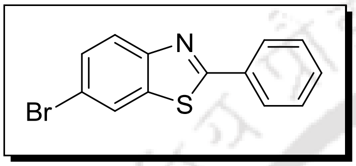
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11-8.05 (m, 3H), 7.92 (d, *J* = 8.4 Hz, 1H), 7.87 (s, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.50-7.45 (m, 7H), 7.42 (t, *J* = 7.6 Hz, 1H), 7.21-7.16 (m, 2H), 2.59 (s, 3H), 2.50 (s, 3H).

^{13}C NMR (150 MHz, CDCl$_3$) δ 168.3, 167.7, 154.7, 154.2, 136.6, 135.8, 134.0, 132.2, 131.9, 131.1, 131.0, 129.2, 129.15, 127.71, 127.7, 127.0, 126.7, 126.3, 125.6, 123.4, 121.3, 120.9, 21.7, 21.6.

FT-IR (KBr) 3066, 2921, 1601, 1502, 1476, 1441, 1313, 1276, 1230, 1152, 1071, 967 cm^{-1}.

Anal. Calcd for $C_{14}H_{11}NS$: C, 74.63; H, 4.92; N, 6.22; S, 14.23. Found: C, 74.57; H, 4.91; N, 6.26; S, 14.26.

HRMS (ESI) m/z: [M+H]$^+$ calcd for $C_{14}H_{11}NSH$ 226.0685, found 226.0686.



6-Bromo-2-phenylbenzo[*d*]thiazole 2f. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.66; white solid; 93 mg, yield 89%.

Mp: 146-147 °C (lit.[5a] mp 150 °C).

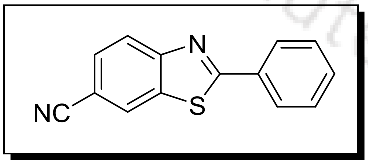
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.06-8.04 (m, 2H), 8.02 (d, *J* = 2.0 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.58 (dd, *J* = 8.8 Hz, 2.0 Hz, 1H), 7.49-7.47 (m, 3H).

^{13}C NMR (100 MHz, CDCl$_3$) δ 168.7, 153.2, 136.8, 133.3, 131.4, 130.0, 129.3, 127.7, 124.5, 124.3, 118.9.

FT-IR (KBr) 3074, 1637, 1509, 1478, 1445, 1395, 1304, 1276, 1248, 1225, 1091, 1072 cm^{-1}.

Anal. Calcd for $C_{13}H_8BrNS$: C, 53.81; H, 2.78; N, 4.83; S, 11.05. Found: C, 53.72; H, 2.80; N, 4.85; S, 11.11.

HRMS (ESI) m/z: [M+H]$^+$ calcd for $C_{13}H_8BrNSH$ 289.9634, found 289.9634.



2-Phenylbenzo[*d*]thiazole-6-carbonitrile 2g. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.64; white solid; 35 mg, yield 41%.

Mp: 193-194 °C (lit.[5a,7b] mp 195 °C).

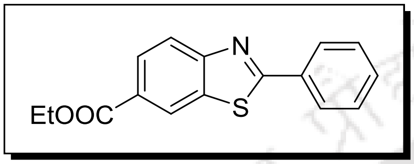
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.22 (s, 1H), 8.11-8.08 (m, 3H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.53-7.51 (m, 3H).

^{13}C NMR (150 MHz, CDCl$_3$) δ 172.5, 156.7, 135.7, 133.0, 132.3, 130.0, 129.5, 128.1, 126.6, 124.1, 118.9, 108.8.

FT-IR (KBr) 2954, 2229, 1632, 1506, 1475, 1441, 1405, 1311, 1260, 1061, 970 cm^{-1}.

Anal. Calcd for $C_{14}H_8N_2S$: C, 71.16; H, 3.41; N, 11.86; S, 13.57. Found: C, 71.24; H, 3.39; N, 11.87; S, 13.50.

HRMS (ESI) m/z: [M+H]$^+$ calcd for $C_{14}H_8N_2SH$ 237.0481, found 237.0482.



Ethyl 2-phenylbenzo[*d*]thiazole-6-carboxylate 2h. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R$_f$ = 0.56; white solid; 39 mg, yield 38%.

Mp: 192-193 °C (lit.[7b] mp 196 °C).

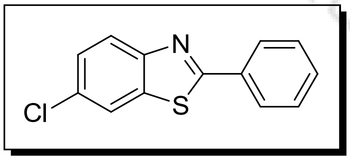
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.61 (d, *J* = 0.8 Hz, 1H), 8.17 (dd, *J* = 8.8 Hz, 1.6 Hz, 1H), 8.10-8.06 (m, 3H), 7.51-7.48 (m, 3H), 4.44 (q, *J* = 7.2 Hz, 2H), 1.44 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (150 MHz, CDCl$_3$) δ 171.5, 166.3, 157.1, 135.1, 133.4, 131.7, 129.3, 127.9, 127.7, 127.4, 123.9, 123.0, 61.4, 14.5.

FT-IR (KBr) 2975, 1708, 1684, 1628, 1506, 1477, 1441, 1408, 1390, 1325, 1273, 1226, 1133, 1056, 1030 cm^{-1}.

Anal. Calcd for $C_{16}H_{13}NO_2S$: C, 67.82; H, 4.62; N, 4.94; S, 11.32. Found: C, 67.72; H, 4.64; N, 4.98; S, 11.38.

HRMS (ESI) m/z: [M+H]$^+$ calcd for $C_{16}H_{13}NO_2SH$ 284.0740, found 284.0749.



6-Chloro-2-phenylbenzo[*d*]thiazole 2i. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R$_f$ = 0.64; white solid; 78 mg, yield 88%.

Mp: 156-157 °C (lit.[5b] mp 160 °C).

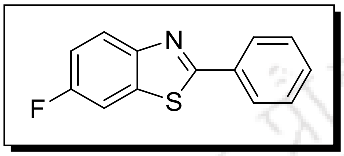
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.06-8.04 (m, 2H), 7.97 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 2.0 Hz, 1H), 7.50-7.48 (m, 3H), 7.45 (dd, *J* = 8.4 Hz, 1.6 Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 168.7, 152.9, 136.4, 133.4, 131.4, 131.3, 129.3, 127.7, 127.3, 124.1, 121.4.

FT-IR (KBr) 3076, 2923, 1587, 1545, 1479, 1438, 1306, 1246, 1224, 1104, 1072, 1053 cm^{-1}.

Anal. Calcd for $C_{13}H_8ClNS$: C, 63.54; H, 3.28; N, 5.70; S, 13.05. Found: C, 63.48; H, 3.26; N, 5.73; S, 13.09.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_8ClNSH$ 246.0139, found 246.0142.



6-Fluoro-2-phenylbenzo[*d*]thiazole 2j. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.62; white solid; 68 mg, yield 83%.

Mp: 133-134 °C (lit.[5b] mp 137 °C).

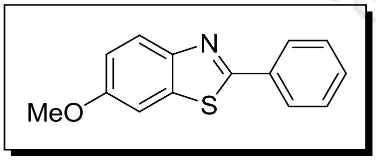
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05-8.02 (m, 2H), 8.01 (dd, *J* = 9.2 Hz, 4,8 Hz, 1H), 7.57 (dd, *J* = 7.6 Hz, 2.4 Hz, 1H), 7.49-7.47 (m, 3H), 7.23 (td, *J* = 8.8 Hz, 2.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9 (d, *J* = 3.0 Hz), 161.8 (d, *J* = 244.8 Hz), 150.9 (d, *J* = 1.5 Hz), 136.2 (d, *J* = 11.4 Hz), 133.4, 131.2, 129.2, 127.6 (d, *J* = 4.6 Hz), 124.3 (d, *J* = 9.1 Hz), 115.2 (d, *J* = 25.2 Hz), 108.1 (d, *J* = 26.6 Hz).

FT-IR (KBr) 3078, 2921, 1896, 1608, 1562, 1513, 1482, 1454, 1443, 1316, 1307, 1276, 1260, 1249, 1118, 1072, 1050, 1029 cm^{-1}.

Anal. Calcd for $C_{13}H_8FNS$: C, 68.10; H, 3.52; N, 6.11; S, 13.99. Found: C, 68.15; H, 3.51; N, 6.14; S, 13.94.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_8FNSH$ 230.0434, found 230.0438.



6-Methoxy-2-phenylbenzo[*d*]thiazole 2k. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.50; white solid; 76 mg, yield 87%.

Mp: 114-115 °C (lit.[5b] mp 116 °C).

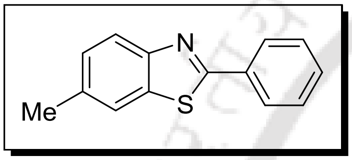
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04-8.01 (m, 2H), 7.95 (d, *J* = 8.8 Hz, 1H), 7.47-7.44 (m, 3H), 7.34 (d, *J* = 2.8 Hz, 1H), 7.09 (dd, *J* = 9.2 Hz, 2.8 Hz, 1H), 3.88 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 157.9, 148.9, 136.6, 133.9, 130.7, 129.1, 127.4, 123.9, 115.8, 104.3, 55.9.

FT-IR (KBr) 3072, 2970, 1602, 1558, 1511, 1483, 1464, 1280, 1266, 1225, 1118, 1097, 1059, 999 cm^{-1}.

Anal. Calcd for $C_{14}H_{11}NOS$: C, 69.68; H, 4.59; N, 5.80; S, 13.29. Found: C, 69.61; H, 4.60; N, 5.84; S, 13.33.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{11}NOSH$ 242.0634, found 242.0632.



6-Methyl-2-phenylbenzo[*d*]thiazole 2l. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.62; white solid; 72 mg, yield 89%.

Mp: 124-125 °C (lit.[5b] mp 126 °C).

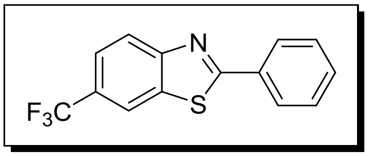
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07-8.05 (m, 2H), 7.95 (d, *J* = 8.8 Hz, 1H), 7.68 (s, 1H), 7.49-7.46 (m, 3H), 7.30-7.28 (m, 1H), 2.48 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 152.5, 135.5, 135.4, 133.9, 130.9, 129.2, 128.1, 127.6, 122.9, 121.5, 21.7.

FT-IR (KBr) 3053, 2914, 1603, 1552, 1480, 1309, 1256, 1227, 1125, 1075, 1062, 971 cm^{-1}.

Anal. Calcd for $C_{14}H_{11}NS$: C, 74.63; H, 4.92; N, 6.22; S, 14.23. Found: C, 74.73; H, 4.90; N, 6.17; S, 14.20.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{11}NSH$ 226.0685, found 226.0683.



2-Phenyl-6-(trifluoromethyl)benzo[*d*]thiazole 2n. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.52; white solid; 44 mg, yield 44%.

Mp: 157-158 °C (lit.[7a] mp 152 °C).

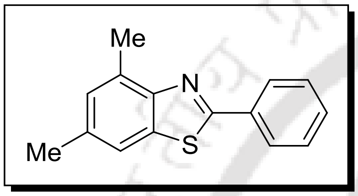
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 8.14-8.08 (m, 3H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.52-7.50 (m, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 156.3, 135.3, 133.3, 131.9, 129.4 (2C), 128.0, 123.7, 123.6, 123.5, 119.6 (q, *J* = 4.5 Hz).

FT-IR (KBr) 3036, 1512, 1482, 1461, 1415, 1320, 1252, 1225, 1167, 1109, 1086, 970 cm^{-1}.

Anal. Calcd for $C_{14}H_8F_3NS$: C, 60.21; H, 2.89; N, 5.02; S, 11.48. Found: C, 60.27; H, 2.90; N, 5.00; S, 11.44.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_8F_3NSH$ 280.0402, found 280.0406.



4,6-Dimethyl-2-phenylbenzo[*d*]thiazole (2o).[4f] Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.68; white solid; 53 mg, yield 61%.

Mp: 89-90 °C.

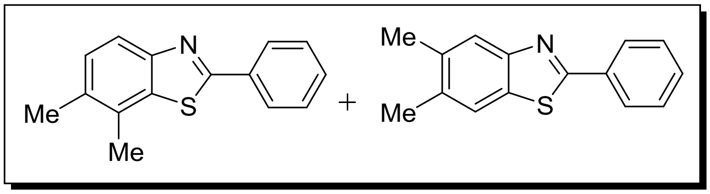
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09-8.07 (m, 2H), 7.50 (s, 1H), 7.47-7.44 (m, 3H), 7.09 (s, 1H), 2.75 (s, 3H), 2.44 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 151.9, 135.4, 135.3, 134.3, 132.9, 130.7, 129.1, 128.7, 127.6, 118.9, 21.7, 18.5.

FT-IR (KBr) 3051, 2914, 1595, 1510, 1480, 1439, 1310, 1281, 1222, 1177, 1094, 1069, 1031, 973 cm^{-1}.

Anal. Calcd for $C_{15}H_{13}NS$: C, 75.28; H, 5.47; N, 5.85; S, 13.40. Found: C, 75.36; H, 5.48; N, 5.81; S, 13.35.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{13}NSH$ 240.0841, found 240.0840.



6,7-Dimethyl-2-phenylbenzo[*d*]thiazole 2pa and **5,6-Dimethyl-2-phenylbenzo[*d*]thiazole 2pb.** Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.60; white solid; 65 mg, yield 75%.

Mp: 113-114 °C.

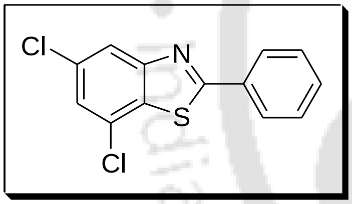
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09-8.04 (m, 4H), 7.83 (s, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.63 (s, 1H), 7.49-7.45 (m, 6H), 7.29 (d, *J* = 8.4 Hz, 1H), 2.50 (s, 3H), 2.41 (s, 3H), 2.39 (s, 3H), 2.38 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 166.8, 153.1, 152.5, 136.7, 135.7, 134.9, 134.03, 134.0, 133.1, 132.6, 131.1, 130.8, 130.76, 129.5, 129.1, 129.0, 127.5, 127.2, 123.5, 121.7, 120.4, 20.4, 20.3, 19.7, 19.4.

FT-IR (KBr) 3056, 2974, 1507, 1476, 1448, 1309, 1275, 1228, 1023, 947 cm^{-1}.

Anal. Calcd for $C_{15}H_{13}NS$: C, 75.28; H, 5.47; N, 5.85; S, 13.40. Found: C, 75.21; H, 5.49; N, 5.88; S, 13.42.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{13}NSH$ 240.0841, found 240.0841.



5,7-Dichloro-2-phenylbenzo[*d*]thiazole 2q. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.72; white solid; 73 mg, yield 72%.

Mp: 115-116 °C.

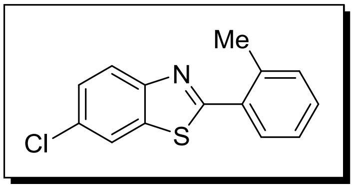
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07-8.05 (m, 2H), 7.93 (d, *J* = 1.6 Hz, 1H), 7.51-7.50 (m, 3H), 7.38 (d, *J* = 1.6 Hz, 1H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 155.1, 134.0, 133.0, 132.8, 131.9, 129.4, 127.9, 127.4, 125.3, 121.8.

FT-IR (KBr) 3060, 2921, 1570, 1537, 1507, 1441, 1424, 1379, 1262, 1098, 1067, 984 cm^{-1}.

Anal. Calcd for $C_{13}H_7Cl_2NS$: C, 55.73; H, 2.52; N, 5.00; S, 11.44. Found: C, 55.82; H, 2.51; N, 4.95; S, 11.39.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_7Cl_2NSH$ 279.9749, found 279.9749.



6-Chloro-2-(*o*-tolyl)benzo[*d*]thiazole 2r. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.68$; white solid; 89 mg, yield 95%.

Mp: 95-96 °C.

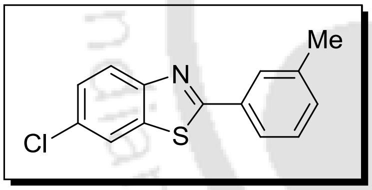
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.8 Hz, 1H), 7.89 (d, *J* = 2.0 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.46 (dd, *J* = 8.8 Hz, 2.0 Hz, 1H), 7.37-7.30 (m, 3H), 2.64 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 152.6, 137.6, 136.9, 132.8, 131.9, 131.3, 130.7, 130.5, 127.2, 126.4, 124.3, 121.2, 21.6.

FT-IR (KBr) 2924, 2853, 1604, 1591, 1480, 1441, 1382, 1305, 1220, 1100, 1050 cm^{-1}.

Anal. Calcd for $C_{14}H_{10}ClNS$: C, 64.73; H, 3.88; N, 5.39; S, 12.34. Found: C, 64.69; H, 3.90; N, 5.36; S, 12.37.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{10}ClNSH$ 260.0295, found 260.0295.



6-Chloro-2-(*m*-tolyl)benzo[*d*]thiazole 2s. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.68$; white solid; 87 mg, yield 93%.

Mp: 121-122 °C.

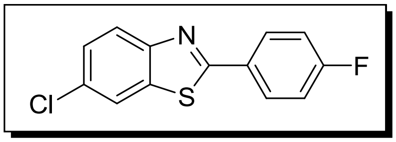
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 9.2 Hz, 1H), 7.88 (s, 1H), 7.85 (d, *J* = 2.0 Hz, 1H), 7.82 (d, *J* = 7.6 Hz, 1H), 7.44 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 7.2 Hz, 1H), 2.43 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 169.0, 152.9, 139.1, 136.4, 133.3, 132.2, 131.2, 129.2, 128.1, 127.2, 125.0, 124.0, 121.4, 21.5.

FT-IR (KBr) 3056, 2924, 1593, 1512, 1441, 1400, 1306, 1249, 1170, 1104, 1024 cm^{-1}.

Anal. Calcd for $C_{14}H_{10}ClNS$: C, 64.73; H, 3.88; N, 5.39; S, 12.34. Found: C, 64.67; H, 3.87; N, 5.43; S, 12.38.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{10}ClNSH$ 260.0295, found 260.0298.



6-Chloro-2-(4-fluorophenyl)benzo[*d*]thiazole 2t. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.68$; white solid; 85 mg, yield 90%.

Mp: 151-152 °C (lit.[7e] mp 151 °C).

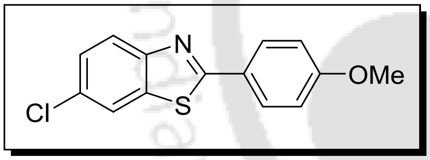
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05-8.02 (m, 2H), 7.94 (d, J = 9.2 Hz, 1H), 7.85 (d, J = 2.0 Hz, 1H), 7.44 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 7.19-7.15 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.3, 166.0, 163.5, 152.8, 136.4, 131.3, 129.8 (d, J = 9.2 Hz), 127.4, 124.1, 121.4, 116.5 (d, J = 22.1 Hz).

FT-IR (KBr) 3034, 2914, 1598, 1548, 1521, 1484, 1441, 1408, 1305, 1231, 1155, 1096, 1052, 965 cm^{-1}.

Anal. Calcd for $C_{13}H_7ClFNS$: C, 59.21; H, 2.68; N, 5.31; S, 12.16. Found: C, 59.12; H, 2.67; N, 5.35; S, 12.19.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_7ClFNSH$ 264.0045, found 264.0041.



6-Chloro-2-(4-methoxyphenyl)benzo[*d*]thiazole 2u. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.54$; white solid; 92 mg, yield 93%.

Mp: 137-138 °C (lit.[7e] mp 135 °C).

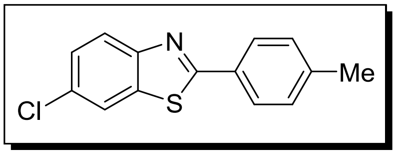
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 9.2 Hz, 2H), 7.91 (d, J = 8.8 Hz, 1H), 7.83 (d, J = 2.0 Hz, 1H), 7.42 (dd, J = 9.2 Hz, 2.4 Hz, 1H), 6.99 (d, J = 8.8 Hz, 2H), 3.87 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 162.3, 153.0, 136.2, 130.7, 129.3, 127.1, 126.2, 123.6, 121.3, 114.6, 55.7.

FT-IR (KBr) 3024, 2923, 1602, 1522, 1483, 1458, 1440, 1429, 1309, 1260, 1225, 1171, 1101, 1051, 1027, 966 cm^{-1}.

Anal. Calcd for $C_{14}H_{10}ClNOS$: C, 60.98; H, 3.66; N, 5.08; S, 11.63; Found: C, 61.07; H, 3.65; N, 5.05; S, 11.59.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{10}ClNOSH$ 276.0244, found 276.0244.



6-Chloro-2-*p*-tolylbenzo[*d*]thiazole 2v.[4e] Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.64$; white solid; 83 mg, yield 89%.

Mp: 158-159 °C.

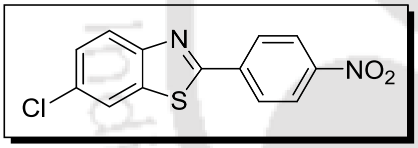
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J* = 8.0 Hz, 3H), 7.84 (d, *J* = 2.0 Hz, 1H), 7.43 (dd, *J* = 8.4 Hz, 1.6 Hz, 1H), 7.29 (d, *J* = 8.4 Hz, 2H), 2.41 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 152.9, 142.0, 136.3, 131.0, 130.7, 130.0, 127.6, 127.2, 123.9, 121.3, 21.7.

FT-IR (KBr) 2918, 1610, 1542, 1481, 1426, 1308, 1232, 1210, 1098, 1048, 962 cm^{-1}.

Anal. Calcd for $C_{14}H_{10}ClNS$: C, 64.73; H, 3.88; N, 5.39; S, 12.34; Found: C, 64.79; H, 3.86; N, 5.42; S, 12.29.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{10}ClNSH$ 260.0295, found 260.0295.



6-Chloro-2-(4-nitrophenyl)benzo[*d*]thiazole 2w. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.76$; white solid; 90 mg, yield 86%.

Mp: 208-209 °C (lit.[7f] mp 216 °C).

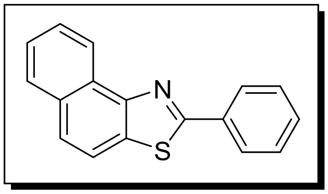
^{1}H NMR (600 MHz, DMSO-d_6) δ 8.40-8.36 (m, 5H), 8.15 (d, *J* = 8.4 Hz, 1H), 7.65 (d, *J* = 7.2 Hz, 1H).

^{13}C NMR (150 MHz, DMSO-d_6) δ 166.1, 152.2, 148.9, 137.9, 136.6, 130.9, 128.5, 127.7, 124.64, 124.6, 122.4.

FT-IR (KBr) 2920, 1684, 1653, 1597, 1518, 1403, 1346,1322, 1302, 1237, 1017, 969 cm^{-1}.

Anal. Calcd for $C_{13}H_7ClN_2O_2S$: C, 53.71; H, 2.43; N, 9.64; S, 11.03. Found: C, 53.79; H, 2.42; N, 9.61; S, 10.98.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{13}H_7ClN_2O_2SH$ 290.999, found 290.995.



2-Phenylnaphtho[1,2-*d*]thiazole 2x.[5d] Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.70; white solid; 83 mg, yield 88%.

Mp: 97-98 °C.

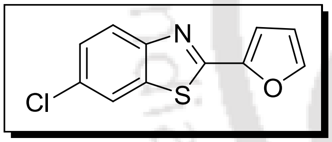
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (d, *J* = 8.4 Hz, 1H), 8.20-8.17 (m, 2H), 7.95-7.90 (m, 2H), 7.81 (d, *J* = 8.8 Hz, 1H),7.70-7.66 (m, 1H), 7.60-7.56 (m, 1H), 7.53-7.48 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 150.6, 134.2, 132.2, 131.9, 130.8, 129.2, 129.0, 128.3, 127.5, 127.1, 126.3, 126.1, 124.2, 119.2.

FT-IR (KBr) 3047, 2922, 1509, 1472, 1442, 1394, 1361, 1251, 1069, 1025, 972 cm^{-1}.

Anal. Calcd for $C_{17}H_{11}NS$: C, 78.13; H, 4.24; N, 5.36; S, 12.27. Found: C, 78.23; H, 4.23; N, 5.30; S, 12.24.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{17}H_{11}NSH$ 262.0685, found 262.0685.



6-Chloro-2-(furan-2-yl)benzo[*d*]thiazole 2y. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.48; white solid; 69 mg, yield 81%.

Mp: 115-116 °C (lit.[7e] mp 119 °C).

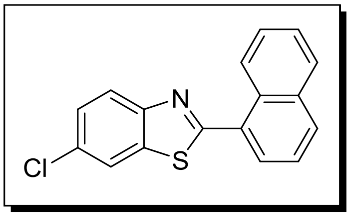
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.8 Hz, 1H), 7.84 (d, *J* = 2.0 Hz, 1H), 7.60 (d, *J* = 1.2 Hz, 1H), 7.44 (dd, *J* = 8.4 Hz, 1.6 Hz, 1H), 7.18 (d, *J* = 3.6 Hz, 1H), 6.59-6.58 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 152.5, 148.5, 145.2, 135.7, 131.2, 127.5, 123.9, 121.4, 112.8, 112.0.

FT-IR (KBr) 3131, 1600, 1578, 1548, 1502, 1470, 1435, 1304, 1281, 1250, 1222, 1132, 1099, 1077, 1019 cm^{-1}.

Anal. Calcd for $C_{11}H_6ClNOS$: C, 56.06; H, 2.57; N, 5.94; S, 13.60; Found: C, 56.00; H, 2.56; N, 5.99; S, 13.58.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{11}H_6ClNOSH$ 235.9931, found 235.9931.



6-Chloro-2-(naphthalen-1-yl)benzo[*d*]thiazole 2z. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.60$; yellow solid; 80 mg, yield 75%.

Mp: 123-124 °C.

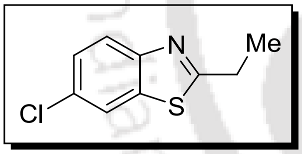
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (d, *J* = 8.8 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.93-7.90 (m, 3H), 7.62-7.48 (m, 4H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 168.4, 153.0, 136.8, 134.3, 131.62, 131.6, 130.8, 130.6, 129.7, 128.7, 128.0, 127.3, 126.8, 126.0, 125.2, 124.5, 121.2.

FT-IR (KBr) 3059, 2924, 1618, 1552, 1488, 1450, 1426, 1331, 1263, 1051, 1022 cm^{-1}.

Anal. Calcd for $C_{17}H_{10}ClNS$: C, 69.03; H, 3.41; N, 4.74; S, 10.84; Found: C, 69.11; H, 3.40; N, 4.70; S, 10.79.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{17}H_{10}ClNSH$ 296.0295, found 296.0297.



6-Chloro-2-ethylbenzo[*d*]thiazole 2aa.[7g] Analytical TLC on silica gel, 1:9 ethyl acetate/hexane $R_f = 0.58$; colourless liquid; 45 mg, yield 63%.

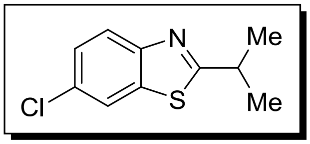
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.8 Hz, 1H), 7.79 (d, *J* = 1.6 Hz, 1H), 7.39 (dd, *J* = 8.8 Hz, 2.0 Hz, 1H), 3.14 (q, *J* = 7.6 Hz, 2H), 1.46 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 152.0, 136.5, 130.7, 126.8, 123.4, 121.3, 27.9, 13.8.

FT-IR (neat) 2968, 1592, 1519, 1441, 1400, 1301, 1270, 1169, 1096, 1049 cm^{-1}.

Anal. Calcd for C_9H_8ClNS: C, 54.68; H, 4.08; N, 7.09; S, 16.22; Found: C, 54.61; H, 4.10; N, 7.14; S, 16.20.

HRMS (ESI) m/z: $[M+H]^+$ calcd for C_9H_8ClNSH 198.0139, found 198.0139.



6-Chloro-2-isopropylbenzo[*d*]thiazole 2ab. Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.60; yellow liquid; 67 mg, yield 88%.

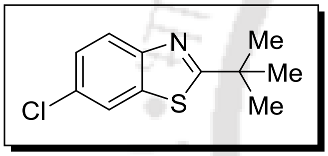
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.8 Hz, 1H), 7.80 (d, *J* = 2.0 Hz, 1H), 7.39 (dd, *J* = 9.2 Hz, 2.4 Hz, 1H), 3.40-3.36 (m, 1H), 1.46 (d, *J* = 7.2 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 179.2, 151.9, 136.1, 130.6, 126.7, 123.5, 121.3, 34.2, 22.9.

FT-IR (neat) 2968, 1592, 1517, 1463, 1443, 1310, 1298, 1265, 1100, 1037, 1001 cm^{-1}.

Anal. Calcd for $C_{10}H_{10}ClNS$: C, 56.73; H, 4.76; N, 6.62; S, 15.15. Found: C, 56.81; H, 4.74; N, 6.58; S, 15.11.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{10}H_{10}ClNSH$ 212.0295, found 212.0296.



2-(*tert*-Butyl)-6-chlorobenzo[*d*]thiazole 2ac.[7e] Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.72; colorless liquid; 66 mg, yield 81%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.8 Hz, 1H), 7.80 (d, *J* = 2.0 Hz, 1H), 7.39 (dd, *J* = 8.4 Hz, 1.6 Hz, 1H), 1.49 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 182.6, 152.0, 136.4, 130.6, 126.7, 123.6, 121.2, 38.6, 30.9.

FT-IR (neat) 2966, 1592, 1505, 1473, 1438, 1399, 1365, 1299, 1272, 1127, 1043, 1013 cm^{-1}.

Anal. Calcd for $C_{11}H_{12}ClNS$: C, 58.53; H, 5.36; N, 6.20; S, 14.20. Found: C, 58.60; H, 5.34; N, 6.17; S, 14.15.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{11}H_{12}ClNSH$ 226.0452, found 226.0447.

4.5. References

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4.6. Selected Spectra

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bs                4   alfa         10.000
d1            1.000          FLAGS
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ct               32   in                n
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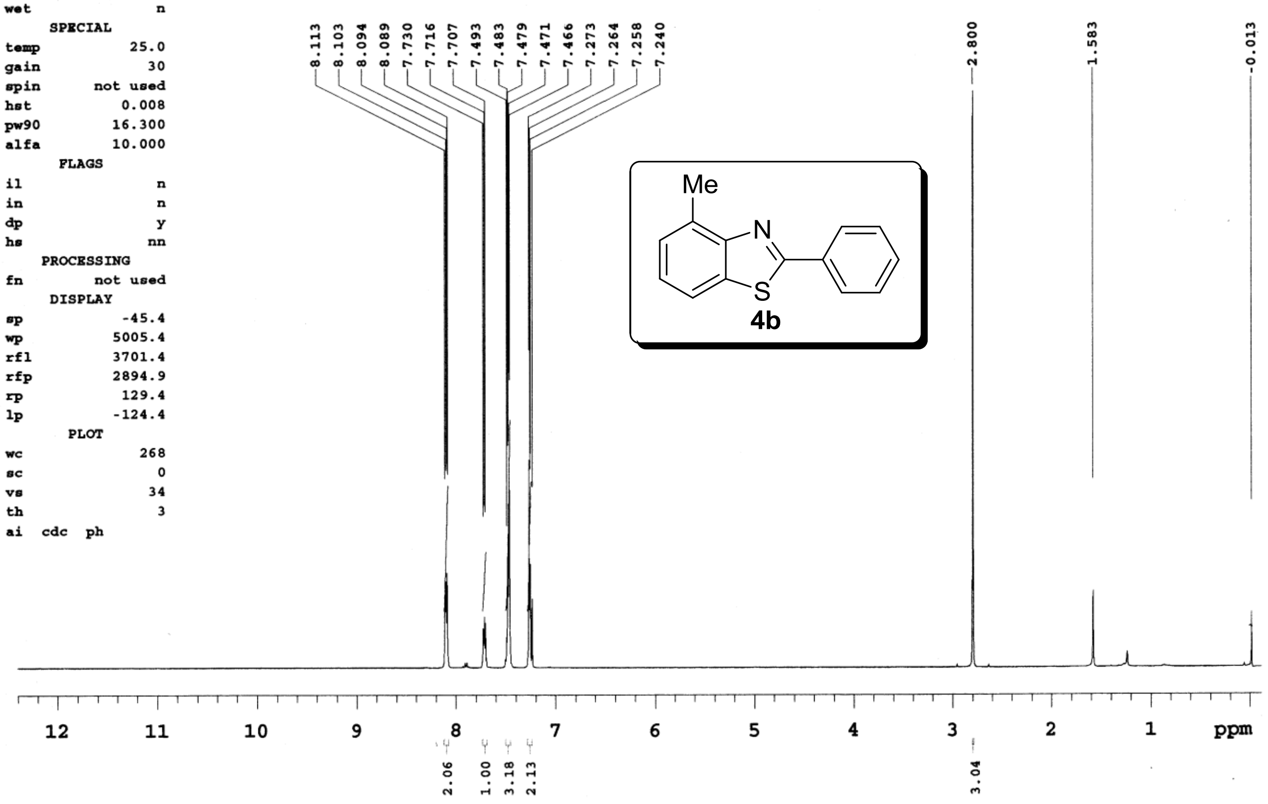

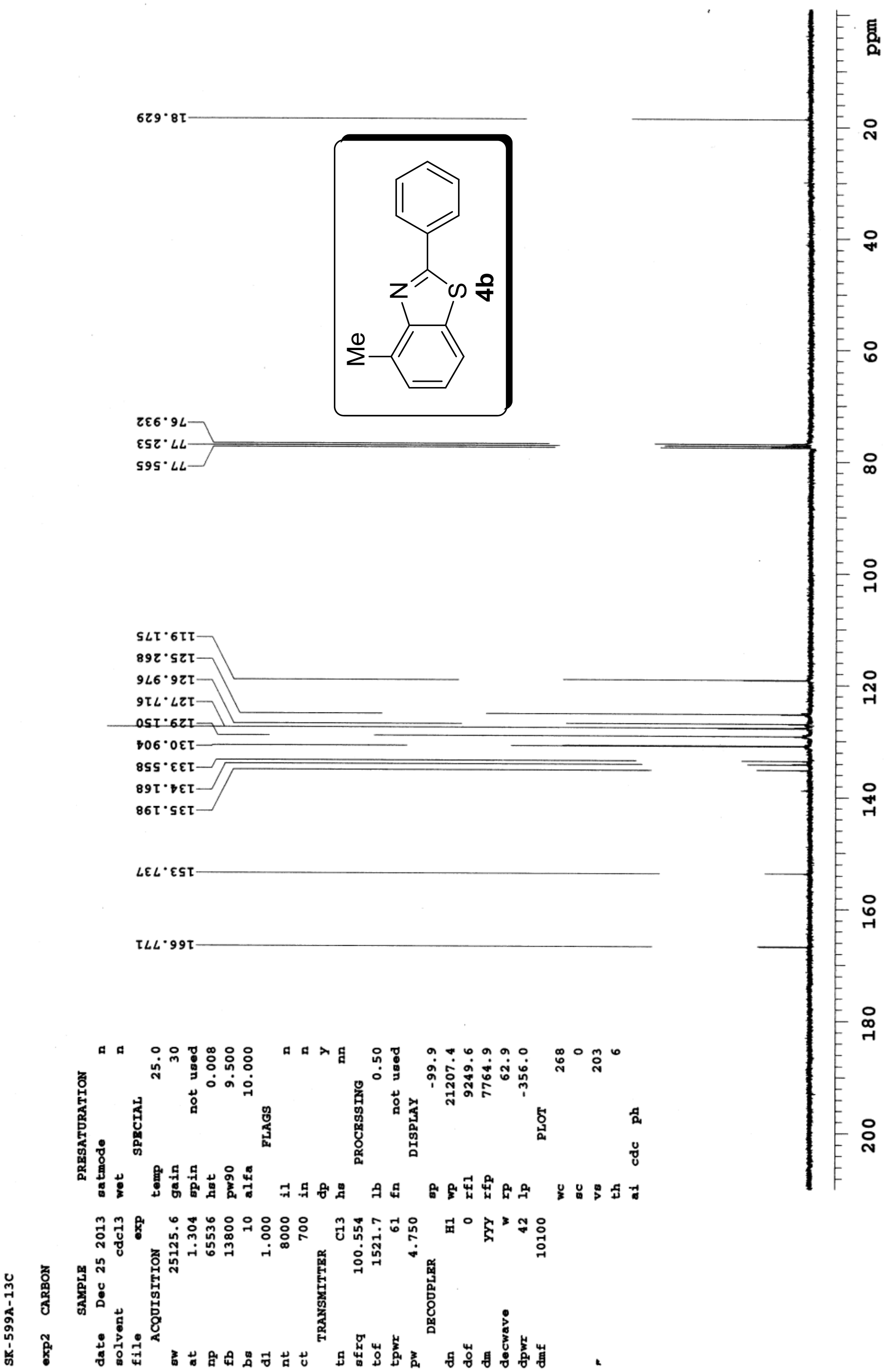
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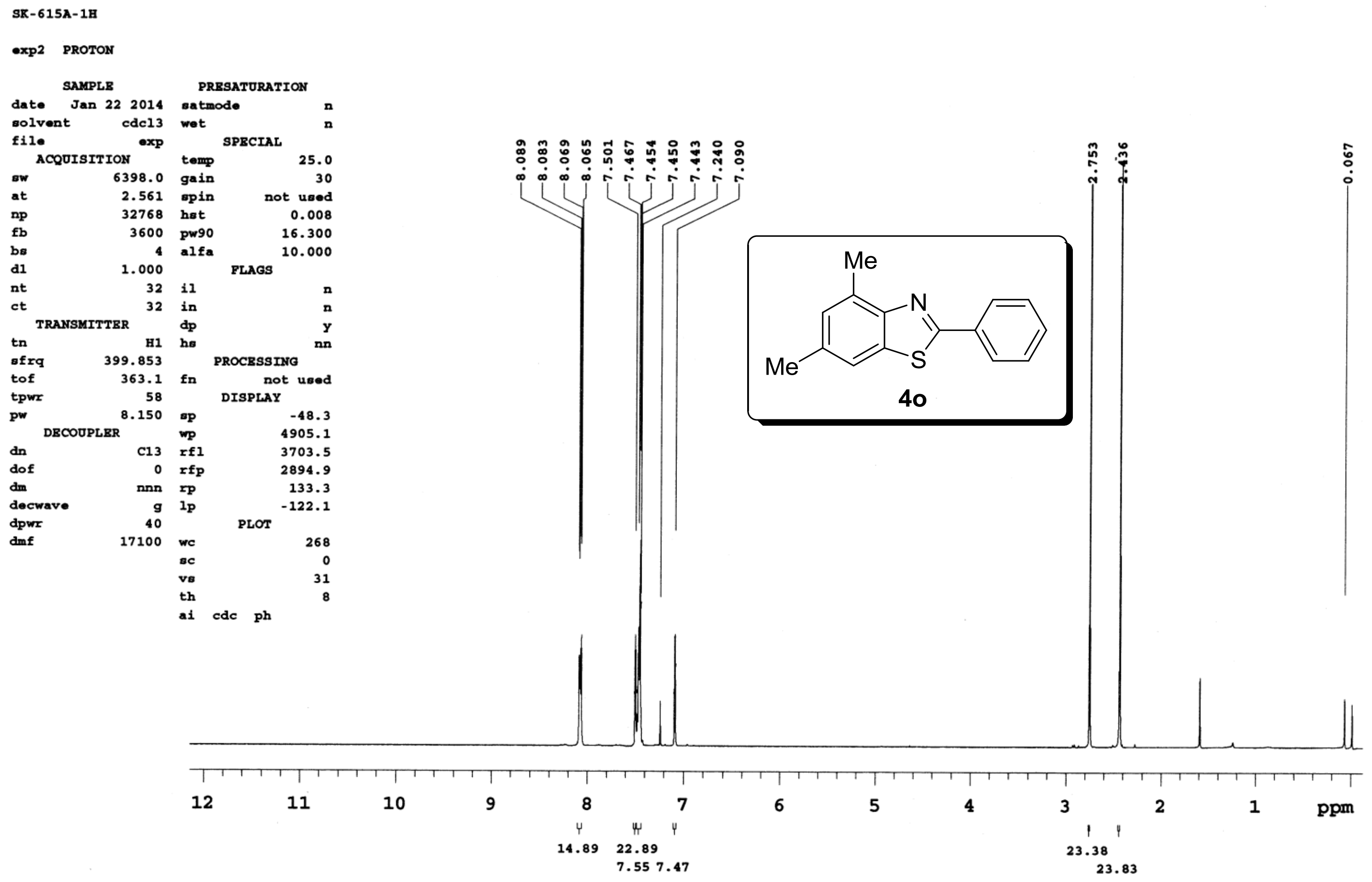

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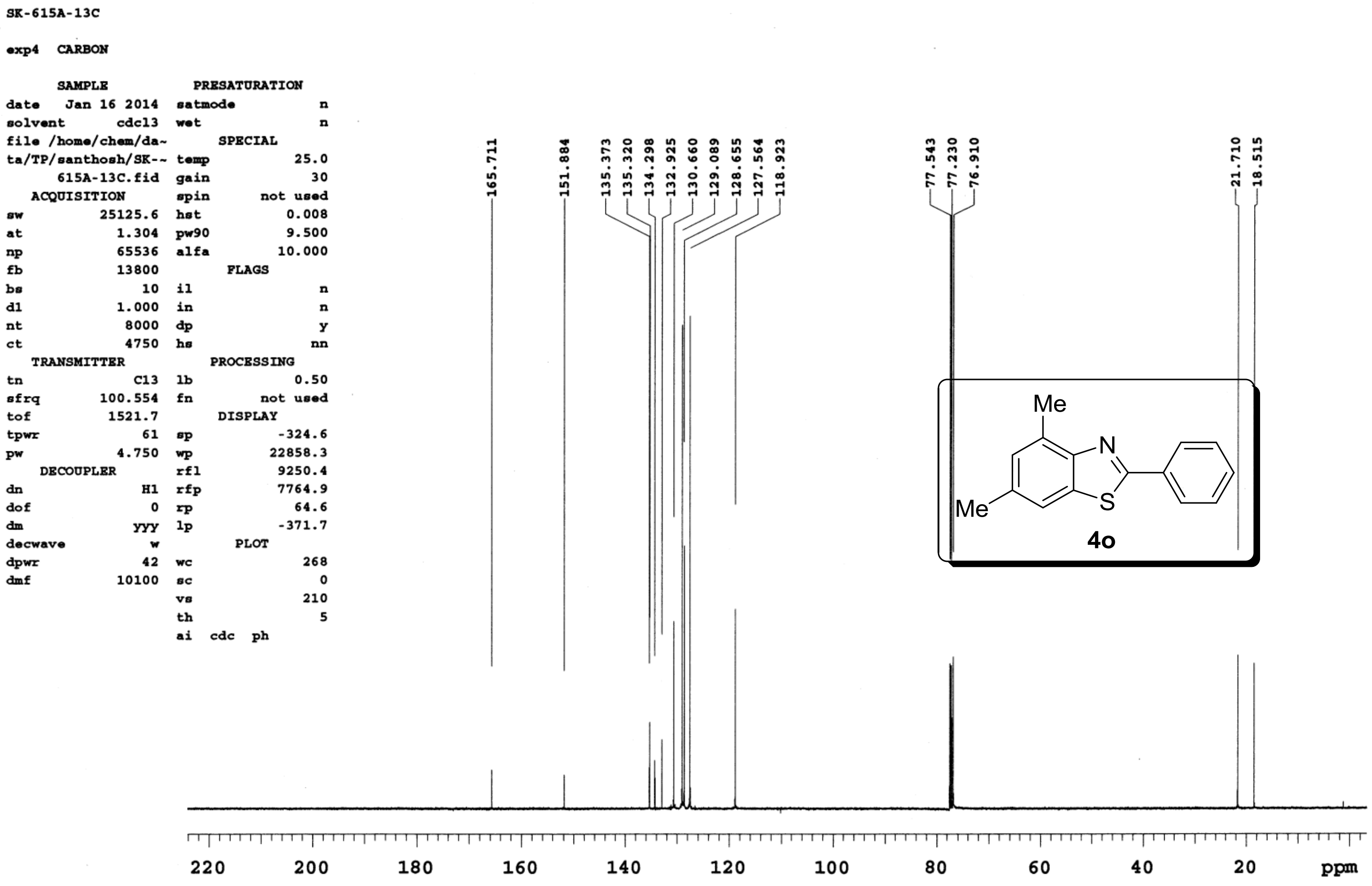

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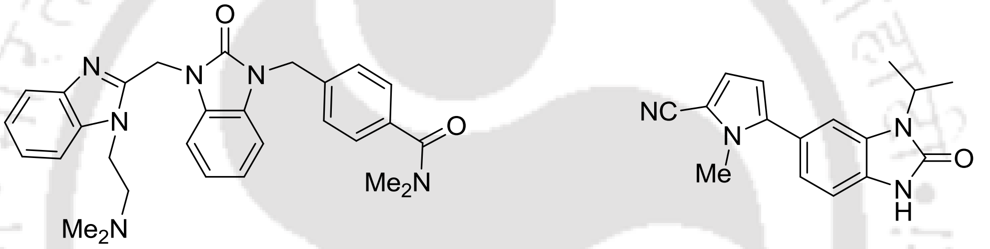
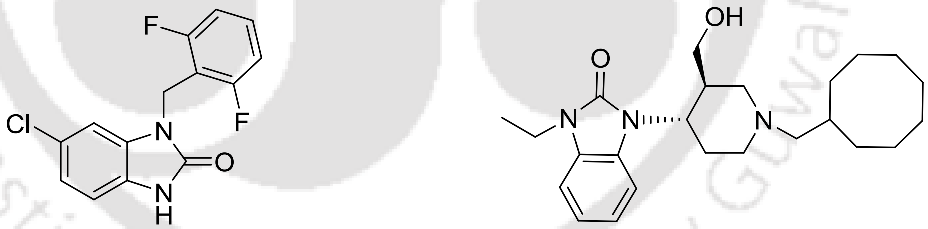
Chapter V

Hypervalent Iodine Mediated Synthesis of Benzimidazol-2-ones

Benzimidazol-2-ones are found in a wide variety of natural products and have attracted considerable interest due to their wide spectrum of biological activity. *N*-Substituted benzimidazol-2-ones and their analogues are useful pharmaceuticals such as farnesyl transferase inhibitors,[1a] progesterone receptor antagonists,[1b] inhibitors of p38 mitogen activated protein (MAP) kinase,[1c] J-113397, ORL1 antagonist,[1d] non-nucleoside HIV-1 reverse transcriptase inhibitors,[1e] respiratory syncytial virus fusion (RSV) inhibitors[1f] and K^+ channel activators[1g] (Figure 1). Syntheses of benzimidazol-2-one derivatives are thus of immense interest.



Respiratory Syncytial Virus (RSV) fusion inhibitor **Progesterone Receptor Antagonist**



HIV-1 RT Non-Nucleoside Inhibitor **J-113397**

Figure 1. Examples of some biologically active and medicinally significant compounds

5.1. Strategies for Synthesis of Benzimidazol-2-ones

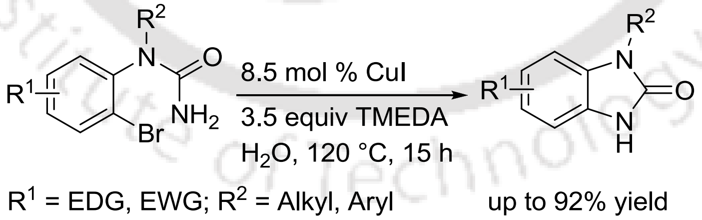
The traditional methods to access these heterocyclic compounds are highly dependent on using benzene-1,2-diamines as the key intermediates. Their subsequent cyclization to form the benzimidazolone requires the use of phosgene and triphosgene.[2] To avoid these toxic reagents and to carry out the synthesis of these heterocyclic compounds at relatively milder conditions, carbon-heteroatom cross-coupling reactions have been used.

5.1.1. Cross-Coupling Reactions

Transition metal catalyzed cross-coupling reactions stands as a powerful strategy for the synthesis of functionalized benzoxazol-2-ones. Liu and co-workers reported a CuI/DBU-catalyzed method for preparation of *N*-substituted 1,3-dihydrobenzimidazol-2-ones from *N′*-substituted *N*-(2-halophenyl)ureas. The urea undergoes cyclization in the presence of CuI and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in DMSO under microwave heating at 120 °C to provide the desired benzoxazol-2-ones in good yields (Scheme 1).[3a]

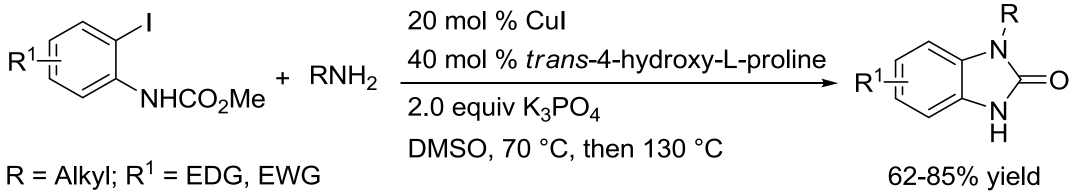
Scheme 1. Intramoecular Cyclization of *N*-(2-Halophenyl)ureas

Copper-catalyzed intramolecular *N*-arylation of ureas in water has been shown to be a convenient process for the synthesis of benzimidazol-2-ones (Scheme 2).[3b] The cyclization of N^1-substituted-2-bromoarylureas using CuI in the presence of TMEDA in water at 120 °C afforded a library of benzimidazol-2-ones derivatives.



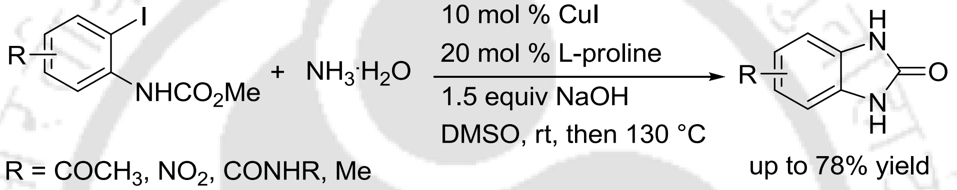
Scheme 2. Copper Catalyzed Synthesis of Benzimidazol-2-ones in Water

Ma group has developed a cascade coupling/condensative cyclization reaction of *o*-iodoarylcarbamates and amines for the synthesis of *N*-substituted 1,3-dihydrobenzimidazol-2-ones *via* a CuI/*trans*-4-hydroxy-L-proline system in the presence of K_3PO_4 in DMSO (Scheme 3).[3c]



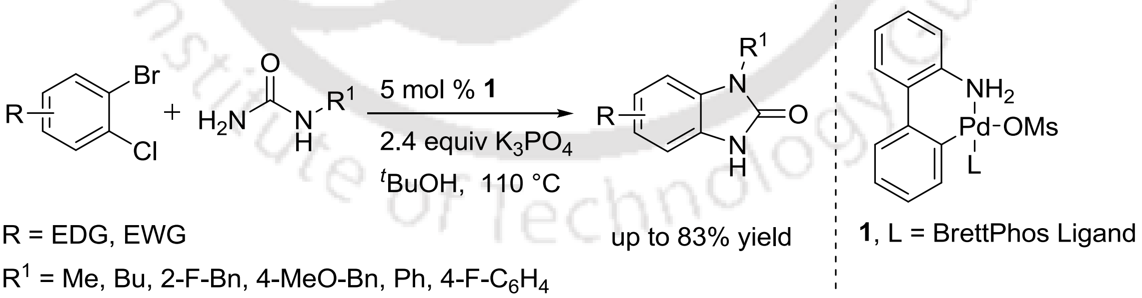
Scheme 3. Synthesis of *N*-substituted 1,3-Dihydrobenzimidazol-2-ones

The same group has further extended this method for the synthesis of 1,3-dihydrobenzimidazol-2-ones using aqueous ammonia instead of amines through a CuI/L-proline catalyzed coupling of 2-iodophenylcarbamates with ammonia in the presence of NaOH in DMSO (Scheme 4).[3d]



Scheme 4. Synthesis of 1,3-Dihydrobenzimidazol-2-ones

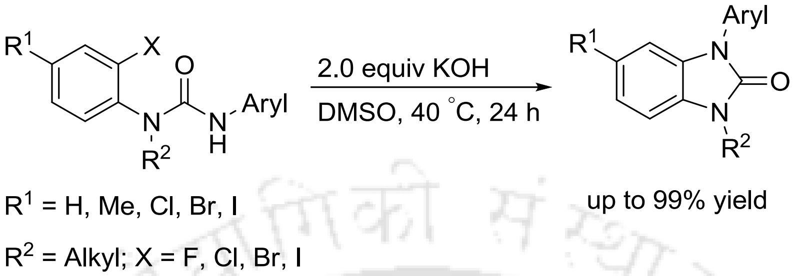
Palladium catalyzed regioselective construction of benzimidazolones *via* a cascade *C*−*N* coupling of monosubstituted ureas with substituted 1,2-dihaloaromatic compounds was demonstrated by Buchwald and co-workers (Scheme 5).[3e] In this reaction, the desired products were formed with good regioselectivity.



Scheme 5. Palladium Catalyzed Regioselective Synthesis of Benzimidazol-2-ones

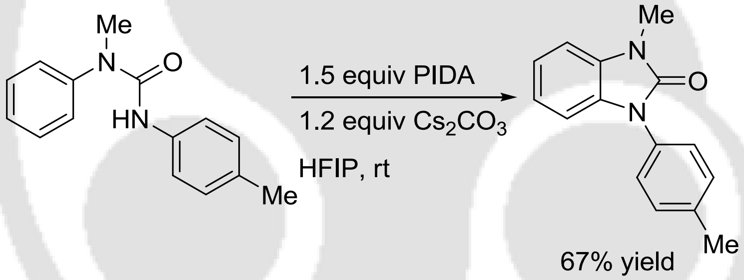
5.1.2. Metal-Free Protocols

Compared to the metal-catalyzed protocols for the synthesis of benzimidazol-2-ones, there are only fewer examples of metal-free processes. For example, Bolm and co-workers have demonstrated the use of KOH and DMSO for the intramolecular *N*-arylation of ureas to form benzimidazol-2-ones at 40 °C. Under the reaction conditions, various aryl halides show satisfying reactivity to afford the desired heterocyclic compounds (Scheme 6).[4a]



Scheme 6. Synthesis of Benzimidazol-2-ones Using KOH/DMSO

Recently, during the preparation of our manuscript, there was a report from Fu and co-workers for the synthesis of benzimidazol-2-ones using PIDA in the presence of Cs_2CO_3 (Scheme 7).[4b]

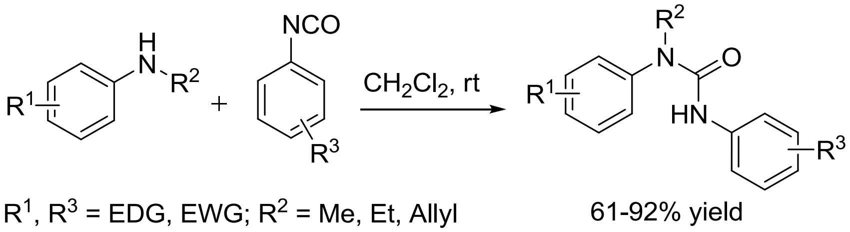


Scheme 7. Synthesis of Benzimidazol-2-ones Using PIDA

5.2. Present Study

One of the important aspects of our research studies includes the construction of heterocyclic compounds under metal-free conditions using hypervalent iodine chemistry. In the previous chapters, we have successfully described metal-free syntheses of benzimidazole, benzoxazole and benzothiazole derivatives. In this chapter, we describe PIFA mediated metal and base-free synthesis of benzimidazol-2-ones by intramolecular oxidative C-H amination of *N*,*N'*-diarylureas.

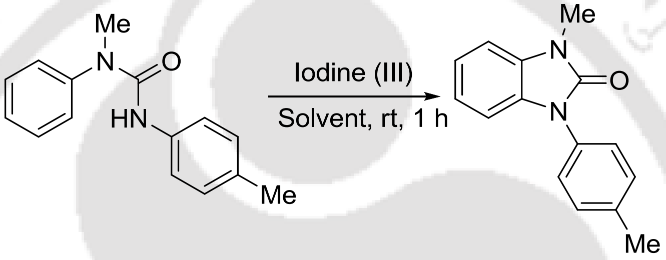
Synthesis of *N,N'*-diarylureas. *N*,*N'*-Diarylureas were prepared by the reaction of *N*-methyl anilines and isocyanates in dry CH_2Cl_2 (Scheme 8).[5]



Scheme 8. Synthesis of *N*,*N'*-diarylureas

First, the standardization of the protocol was carried out with 1-methyl-1-phenyl-3-*p*-tolyl-urea **1a** as a model substrate using PhI(OCOCF$_3$)$_2$ in different solvents at room tempera-

Table 1. Optimization of Reaction Conditions[a]



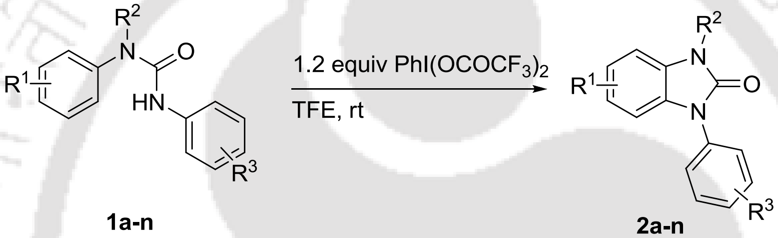
entry	iodine(III)	solvent	conversion (%)[b]
1	PhI(OCOCF$_3$)$_2$	DCM	62
2	PhI(OCOCF$_3$)$_2$	CH$_3$CN	75
3	PhI(OCOCF$_3$)$_2$	DMF	n.d.
4	**PhI(OCOCF$_3$)$_2$**	**TFE**	**92**
5	PhI(OCOCF$_3$)$_2$	HFIP	88
6	PhI(OAc)$_2$	TFE	87
7	PhI(OPiv)$_2$	TFE	n.d.
8	PhI(OMe)$_2$	TFE	n.d.
9	PhIO	TFE	36
10	PhI(OH)(OTs)	TFE	50

[a] Reaction conditions: Substratre (0.20 mmol), iodine (III) (0.24 mmol), solvent (2.0 mL). [b] Determined by ^{1}H NMR spectroscopy.

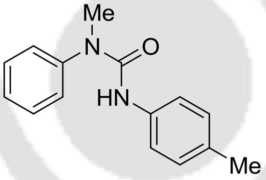
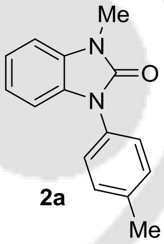
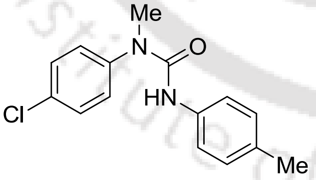
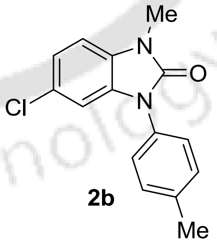
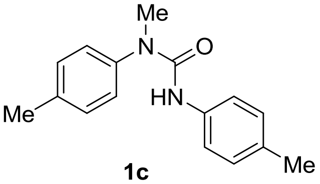
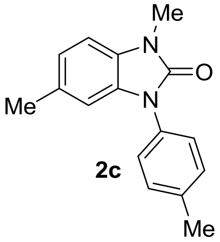
ture (Table 1). We were pleased to find that the reaction occurred efficiently to afford the desired 1-methyl-3-*p*-tolyl-1*H*-benzo[*d*]imidazol-2(3*H*)-one **2a** in 92% conversion when the substrate was stirred at room temperature using 1.2 equiv PhI(OCOCF$_3$)$_2$ in 1,1,1-trifluoroethanol (TFE). Solvents such as DCM, CH$_3$CN, DMF and HFIP afforded **2a** in <88% yield. In a set of screened hypervalent iodine reagents such as PhI(OCOCF$_3$)$_2$, PhI(OAc)$_2$, PhI(OPiv)$_2$, PhI(OMe)$_2$, PhIO and PhI(OH)(OTs), the former provided the best results.

Having the optimal conditions, we set out to explore the scope of the reactions of a series of substituted *N*,*N'*-diarylureas (Table 2). 1-Methyl-1-phenyl-3-*p*-tolyl-urea **1a** underwent

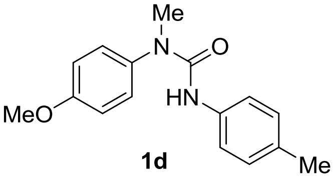
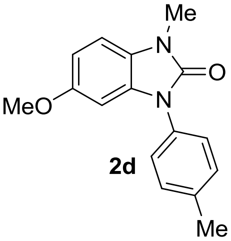
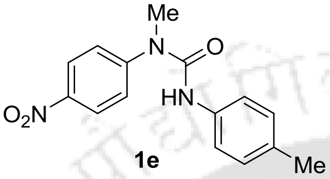
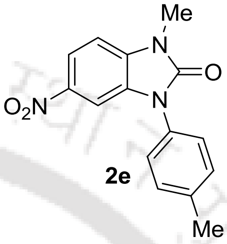
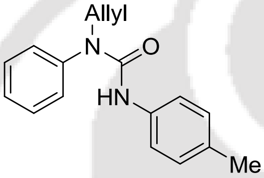
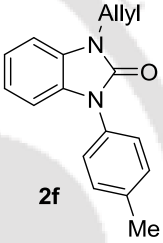
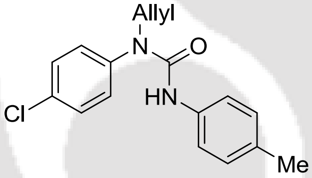
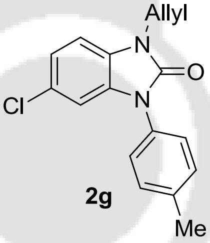
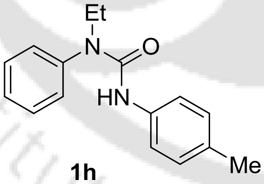
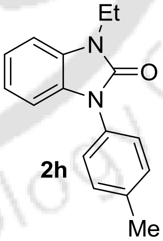
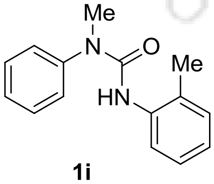
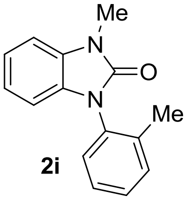
Table 2. [Bis(trifluoroacetoxy)iodo]benzene Mediated Synthesis of Benzimidazol-2-ones.[a]



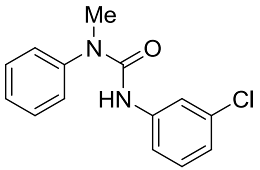
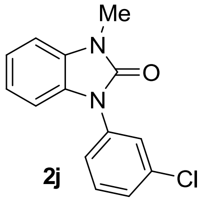
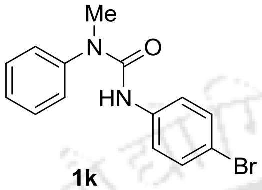
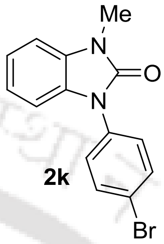
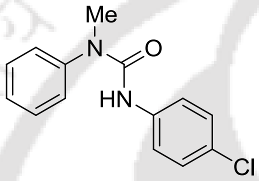
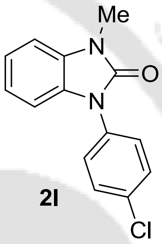
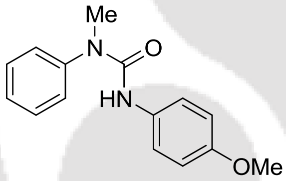
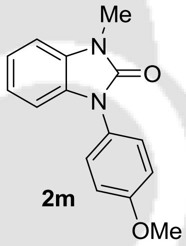
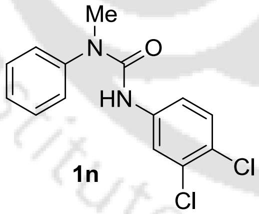
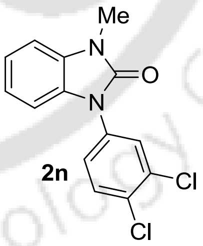
1a-n **2a-n**

entry	substrate	time (h)	product	yield (%)
1	 **1a**	1	 **2a**	86
2	 **1b**	1	 **2b**	87
3	 **1c**	1	 **2c**	59

Continued….

entry	substrate	time (h)	product	yield (%)
4	 **1d**	1	 **2d**	decomposed
5	 **1e**	6	 **2e**	n.d.
6	 **1f**	1	 **2f**	82
7	 **1g**	1	 **2g**	86
8	 **1h**	1	 **2h**	87
9	 **1i**	1	 **2i**	82

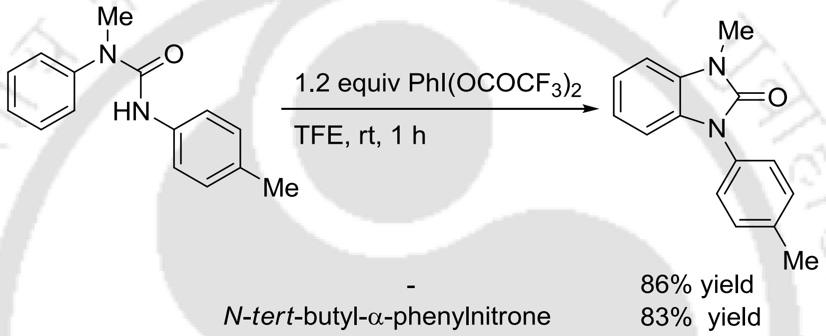
Continued….

entry	substrate	time (h)	product	yield (%)
10	 **1j**	1	 **2j**	84
11	 **1k**	1	 **2k**	79
12	 **1l**	1	 **2l**	88
13	 **1m**	2	 **2m**	68
14	 **1n**	1	 **2n**	77

[a] Reaction conditions: **1a-n** (0.20 mmol), PhI(OCOCF$_3$)$_2$ (1.2 equiv), TFE (2.0 mL), rt.

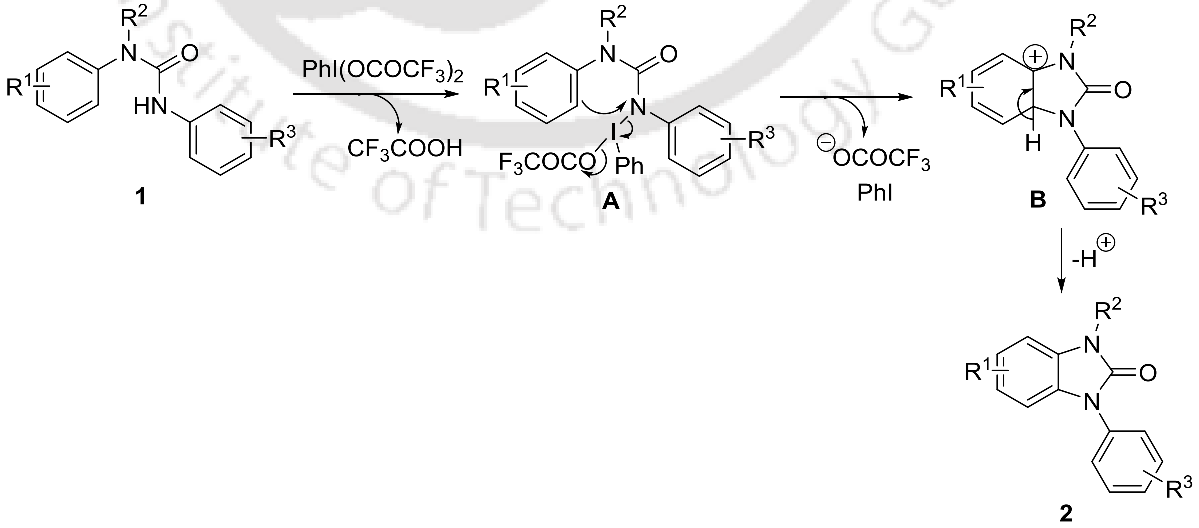
reaction to give 1-methyl-3-*p*-tolyl-1*H*-benzo[*d*]imidazol-2(3*H*)-one **2a** in 86% yield. The reactions of *N*,*N'*-diarylureas **1b** and **1c** with R^1 having 4-chloro and 4-methyl substituents produced **2b** and **2c** in 87 and 59% yields, respectively. The substrate **1d** with 4-methoxy group underwent decomposition, while **1e** substituted with 4-nitro group failed to react and the starting material was recovered intact. The reaction of the diarylureas **1f-h** with R^2 having allyl and ethyl groups gave the target heterocycles **2f-h** in 86-87% yields. Furthermore, ureas **1i-j** with R^2 = methyl and R^3 = 2-methyl, 3-chloro substituents underwent cyclization to provide the corresponding benzimidazol-2-ones **2i-j** in 82-84% yields. Similarly, the substrates **1k-n** having 4-bromo, 4-chloro, 4-methoxy and 3,4-dichloro substituents proceeded cyclization to provide the target heterocycles **2k-n** in 68-88% yields.

To have insight into the mechanism for the reaction, we have used radical scavenger for I^{III} species, *N*-*tert*-butyl-α-phenylnitrone[6] in the reaction and we observed it has no affect on the reaction and the target benzimidazol-2-ones was obtained in 83% yield (Scheme 9).



Scheme 9. Radical Scavenger Experiment with *N*-*tert*-Butyl-α-phenylnitrone

This result reveals that the radical might not be involved in the cyclization process. A putative reaction mechanism is shown in Scheme 10. The reaction of *N*,*N’*-diarylurea with



Scheme 10. Plausible Reaction Mechanism

$PhI(OCOCF_3)_2$ may generate an intermediate **A** by ligand exchange. Intramolecular cyclization of **A** can give the cationic intermediate **B** through a nitrenium ion intermediate. The intermediate **B** can furnish the target product **2** by aromatization.

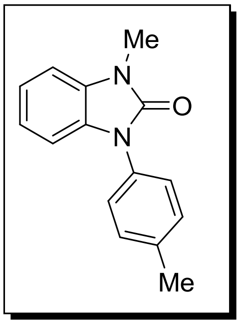
In conclusion, an efficient metal and base-free protocol for the synthesis of substituted benzimidazol-2-ones is described by oxidative cyclization of *N*,*N'*-diarylureas. This process is general and provides the target heterocycles in high yield.

5.3. Experimental Section

5.3.1. General Information: Anilines, phenyl isocyanates, $PhI(OPiv)_2$, HFIP and TFE were purchased from Aldrich and were used as received. ($PhI(OCOCF_3)_2$, PhIO, $PhI(OMe)_2$ and PhI(OH)(OTs) were prepared according to reported procedures.[7] Purification of the reaction products was carried out by column chromatography using Rankem silica gel (60-120 mesh). Analytical TLC was performed on Merck silica gel G/GF 254 plate. NMR spectra were recorded on DRX-400 Varian spectrometer and Bruker Avance III 600 spectrometer using $CDCl_3$ as solvent and Me_4Si as 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. FT-IR spectra were recorded using Perkin Elmer IR spectrometer. Mass spectra were recorded on a Waters Q-Tof Premier mass spectrometer.

5.3.2. General Procedure for Cyclization of Substituted Benzimidazol-2-ones 2a-n. To a stirred solution of $PhI(OCOCF_3)_2$ (0.24 mmol, 1.2 equiv) in TFE (1 mL) was added diarylurea (0.2 mmol, 1.0 equiv) dissolved in TFE (1 mL) at room temperature under air. The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. The reaction mixture was then treated with saturated $Na_2S_2O_3$ (1 mL) and $NaHCO_3$ (1 mL) solutions. The resultant mixture was extracted using ethyl acetate (3 x 10 mL) and washed with brine (2 x 5 mL) and water (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 to afford analytically pure substituted benzimidazol-2-ones.

5.4. Characterization Data of Substituted Benzimidazol-2-ones 2a-n



1-Methyl-3-*p*-tolyl-1*H*-benzo[*d*]imidazol-2(3*H*)-one 2a.[4b] Analytical TLC on silica gel, 3:7 ethyl acetate/hexane $R_f = 0.40$; yellow solid; 42 mg, yield 86%.

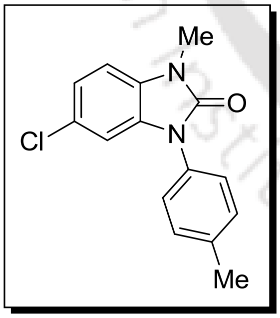
Mp: 102-103 °C (lit.[4b] mp 107 °C).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.17 (td, *J* = 6.8 Hz, 2.4 Hz, 1H), 7.08-7.03 (m, 3H), 3.49 (s, 3H), 2.42 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 153.9, 137.8, 132.3, 130.35, 130.3, 129.9, 126.1, 122.0, 121.6, 108.8, 107.7, 27.5, 21.4.

FT-IR (KBr) 2921, 2851, 1714, 1610, 1558, 1538, 1516, 1506, 1493, 1431, 1395, 1262, 1205, 1084, 1020, 812, 748 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{14}N_2OH$ 239.1184, found 239.1183.



5-Chloro-1-methyl-3-*p*-tolyl-1*H*-benzo[*d*]imidazol-2(3*H*)-one 2b. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane $R_f = 0.42$; orange solid; 47 mg, yield 87%.

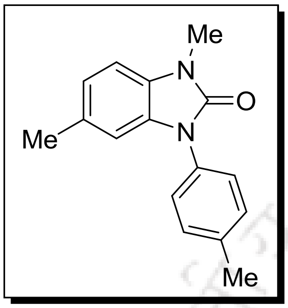
Mp: 148-149 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 (q, *J* = 8.4 Hz, 4H), 7.12 (d, *J* = 8.4 Hz, 1H), 7.01 (s, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 3.47 (s, 3H), 2.42 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 138.3, 131.7, 130.6, 130.5, 128.9, 127.2, 126.1, 121.9, 109.2, 108.4, 27.6, 21.4.

FT-IR (KBr) 3429, 2923, 1714, 1604, 1517, 1494, 1430, 1394, 1275, 1206, 1090, 798, 726 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{13}ClN_2OH$ 273.0795, found 273.0795.



1,5-Dimethyl-3-*p*-tolyl-1*H*-benzo[*d*]imidazol-2(3*H*)-one 2c. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane $R_f = 0.42$; brown solid; 30 mg, yield 59%.

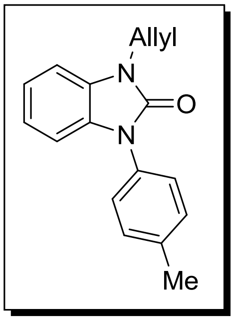
Mp: 73-74 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.39 (d, $J = 7.8$ Hz, 2H), 7.33 (d, $J = 7.8$ Hz, 2H), 6.95-6.91 (m, 2H), 6.85 (s, 1H), 3.46 (s, 3H), 2.42 (s, 3H), 2.35 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 137.7, 132.3, 131.4, 130.3, 129.9, 128.2, 126.2, 122.5, 109.4, 107.5, 27.5, 21.7, 21.4.

FT-IR (KBr) 3426, 2921, 1710, 1610, 1518, 1503, 1429, 1397, 1270, 1214, 1161, 1087, 822, 796 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{16}H_{16}N_2OH$ 253.1341, found 253.1340.



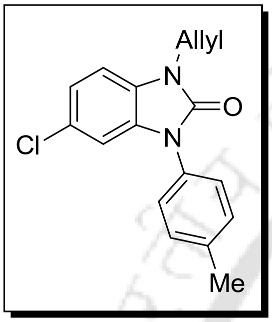
1-Allyl-3-*p*-tolyl-1*H*-benzo[*d*]imidazol-2(3*H*)-one 2f. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane $R_f = 0.45$; yellow liquid; 43 mg, yield 82%.

^{1}H NMR (600 MHz, CDCl$_3$) δ 7.42 (d, *J* = 7.2 Hz, 2H), 7.33 (d, *J* = 7.8 Hz, 2H), 7.11-7.04 (m, 4H), 5.99-5.93 (m, 1H), 5.32-5.27 (m, 2H), 4.59 (d, *J* = 4.8 Hz, 2H), 2.42 (s, 3H).

^{13}C NMR (150 MHz, CDCl$_3$) δ 153.4, 137.8, 132.2, 130.3, 129.9, 129.6, 126.1, 122.0, 121.6, 118.0, 108.9, 108.6, 58.6, 43.9, 21.4.

FT-IR (neat) 3416, 2921, 1713, 1609, 1517, 1489, 1433, 1398, 1227, 1174, 812, 750 cm^{-1}.

HRMS (ESI) m/z: [M+H]$^+$ calcd for $C_{17}H_{16}N_2OH$ 265.1341, found 265.1342.



1-Allyl-5-chloro-3-*p*-tolyl-1*H*-benzo[*d*]imidazol-2(3*H*)-one 2g. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane $R_f = 0.56$; white solid; 51 mg, yield 86%.

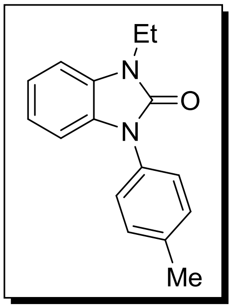
Mp: 55-56 °C.

^{1}H NMR (600 MHz, CDCl$_3$) δ 7.38 (d, *J* = 7.8 Hz, 2H), 7.34 (d, *J* = 7.8 Hz, 2H), 7.08 (d, *J* = 8.4 Hz, 1H), 7.03 (s, 1H), 6.95 (d, *J* = 8.4 Hz, 1H), 5.96-5.91 (m, 1H), 5.30-5.27 (m, 2H), 4.56 (d, *J* = 4.8 Hz, 2H), 2.43 (s, 3H).

^{13}C NMR (150 MHz, CDCl$_3$) δ 153.4, 138.3, 131.9, 131.7, 130.8, 130.4, 128.2, 127.3, 126.1, 121.9, 118.3, 109.3, 58.5, 44.0, 21.4.

FT-IR (KBr) 3426, 2922, 1715, 1604, 1518, 1490, 1397, 1299, 1227, 1178, 1067, 973, 841, 725 cm^{-1}.

HRMS (ESI) m/z: [M+H]$^+$ calcd for $C_{17}H_{15}ClN_2OH$ 299.0951, found 299.0951.



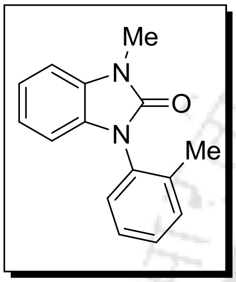
1-Ethyl-3-*p*-tolyl-1*H*-benzo[*d*]imidazol-2(3*H*)-one 2h. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane $R_f = 0.48$; yellow liquid; 44 mg, yield 87%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.16-7.12 (m, 1H), 7.08-7.05 (m, 3H), 4.05 (q, *J* = 7.2 Hz, 2H), 2.42 (s, 3H), 1.42 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ153.4, 137.7, 132.2, 130.3, 129.8, 129.4, 126.1, 121.9, 121.4, 108.9, 107.8, 36.2, 21.4, 13.8.

FT-IR (neat) 3471, 1715, 1610, 1538, 1489, 1402, 1239, 1195, 1092, 1023, 812, 749 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{16}H_{16}N_2OH$ 253.1341, found 253.1341.



1-Methyl-3-*o*-tolyl-1*H*-benzo[*d*]imidazol-2(3*H*)-one 2i.[4b] Analytical TLC on silica gel, 3:7 ethyl acetate/hexane $R_f = 0.46$; white solid; 39 mg, yield 82%.

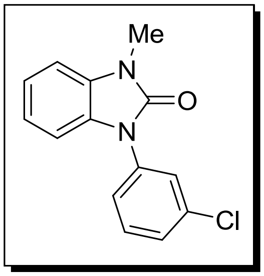
Mp: 88-89 °C (lit.[4b] mp 89 °C).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40-7.37 (m, 2H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.16 (t, *J* = 7.8 Hz, 1H), 7.06-7.02 (m, 2H), 6.70 (d, *J* = 7.8 Hz, 1H), 3.52 (s, 3H), 2.18 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 137.1, 133.3, 131.7, 130.4, 130.2, 129.3, 128.7, 127.3, 121.9, 121.6, 108.7, 107.7, 27.5, 18.1.

FT-IR (KBr) 3443, 2926, 1716, 1618, 1502, 1491, 1391, 1262, 1196, 1081, 1016, 749 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{14}N_2OH$ 239.1184, found 239.1182.



1-(3-Chlorophenyl)-3-methyl-1*H*-benzo[*d*]imidazol-2(3*H*)-one 2j.[4b] Analytical TLC on silica gel, 3:7 ethyl acetate/hexane $R_f = 0.43$; white solid; 43 mg, yield 84%.

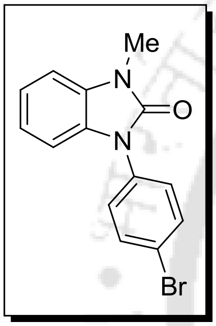
Mp: 141-142 °C (lit.[4b] mp 141 °C).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.46 (d, *J* = 4.8 Hz, 2H), 7.38-7.36 (m, 1H), 7.19 (td, *J* = 2.4 Hz, 8.4 Hz, 1H), 7.11-7.08 (m, 2H), 7.06 (d, *J* = 7.8 Hz, 1H), 3.49 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 136.1, 135.2, 130.6, 130.3, 129.0, 127.9, 126.2, 124.2, 122.5, 121.8, 108.8, 108.0, 27.5.

FT-IR (KBr) 3440, 1696, 1595, 1497, 1431, 1394, 1384, 1256, 1203, 1084, 1020, 743 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{11}ClN_2OH$ 259.0638, found 259.0637.



1-(4-Bromophenyl)-3-methyl-1*H*-benzo[*d*]imidazol-2(3*H*)-one 2k.[4b] Analytical TLC on silica gel, 3:7 ethyl acetate/hexane $R_f = 0.42$; orange solid; 48 mg, yield 79%.

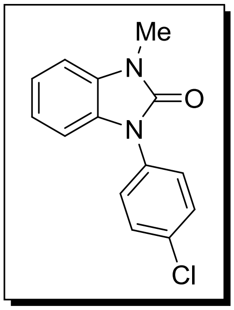
Mp: 158-159 °C (lit.[4b] mp 160 °C).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.18 (t, *J* = 7.2 Hz, 1H), 7.10-7.04 (m, 3H), 3.49 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 153.5, 134.1, 132.9, 130.4, 129.1, 127.6, 122.5, 121.8, 121.3, 108.7, 108.0, 27.5.

FT-IR (KBr) 3435, 2923, 1712, 1617, 1494, 1384, 1263, 1203, 1019, 811, 744 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{11}BrN_2OH$ 303.0133, found 303.0132.



1-(4-Chlorophenyl)-3-methyl-1*H*-benzo[*d*]imidazol-2(3*H*)-one 2l.[4b] Analytical TLC on silica gel, 3:7 ethyl acetate/hexane $R_f = 0.45$; white solid; 45 mg, yield 88%.

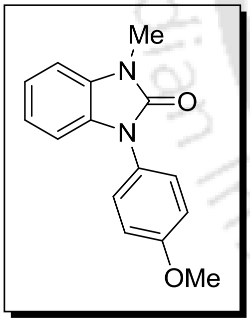
Mp: 157-158 °C (lit.[4b] mp 159 °C).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49 (s, 4H), 7.18 (t, J = 7.2 Hz, 1H), 7.10-7.04 (m, 3H), 3.49 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 153.5, 133.5, 133.3, 130.3, 129.9, 129.2, 127.3, 122.5, 121.8, 108.7, 108.0, 27.5.

FT-IR (KBr) 3414, 1712, 1618, 1497, 1488, 1384, 1263, 1203, 1089, 1011, 912, 813, 744 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{11}ClN_2OH$ 259.0638, found 259.0638.



1-(4-Methoxyphenyl)-3-methyl-1*H*-benzo[*d*]imidazol-2(3*H*)-one 2m. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane $R_f = 0.29$; white solid; 34 mg, yield 68%.

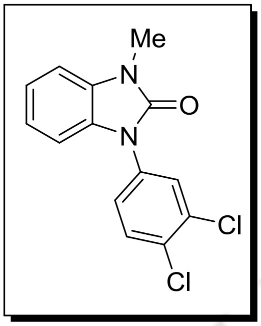
Mp: 116-117 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (d, J = 8.4 Hz, 2H), 7.15 (t, J = 7.8 Hz, 1H), 7.07-7.03 (m, 4H), 7.0 (d, J = 7.8 Hz, 1H), 3.86 (s, 3H), 3.49 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) δ 159.1, 154.1, 130.3, 130.1, 127.8, 127.6, 122.0, 121.6, 115.0, 108.7, 101.7, 55.8, 27.5.

FT-IR (KBr) 1713, 1699, 1559, 1517, 1494, 1459, 1398, 1295, 1253, 1206, 1138, 1084, 1026, 840, 754 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{15}H_{14}N_2O_2H$ 255.1134, found 255.1136.



1-(3,4-Dichlorophenyl)-3-methyl-1*H*-benzo[*d*]imidazol-2(3*H*)-one 2n. Analytical TLC on silica gel, 3:7 ethyl acetate/hexane R_f = 0.48; yellow solid; 45 mg, yield 77%.

Mp: 166-167 °C.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.20 (t, *J* = 7.2 Hz, 1H), 7.12-7.08 (m, 2H), 7.06 (d, *J* = 7.8 Hz, 1H), 3.49 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 134.4, 133.6, 131.7, 131.3, 130.3, 128.7, 127.8, 125.3, 122.8, 122.0, 108.7, 108.2, 27.6.

FT-IR (KBr) 3450, 2922, 1708, 1593, 1497, 1475, 1384, 1201, 1086, 1026, 814, 743 cm^{-1}.

HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{14}H_{10}Cl_2N_2OH$ 293.0248, found 293.0248.

5.5. References

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D.; Gulgeze, H. B.; Venables, B. L.; Wright, J. J. K.; Dalterio, R. A.; Zadjura, L.; Marino, A.; Dando, S.; D'Arienzo, C.; Kadow, K. F.; Cianci, C. W.; Li, Z.; Clarke, J.; Genovesi, E. V.; Medina, I.; Lamb, L.; Colonno, R. J.; Yang, Z.; Krystal, M.; Meanwell, N. A. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 895. (g) Meanwell, N. A.; Sit, S.-Y.; Gao, J.; Boissard, C. G.; Lum-Ragan, J.; Dworetzky, S. I.; Gribkoff, V. K. *Bioorg. Med. Chem. Lett*. **1996**, *6*, 1641.

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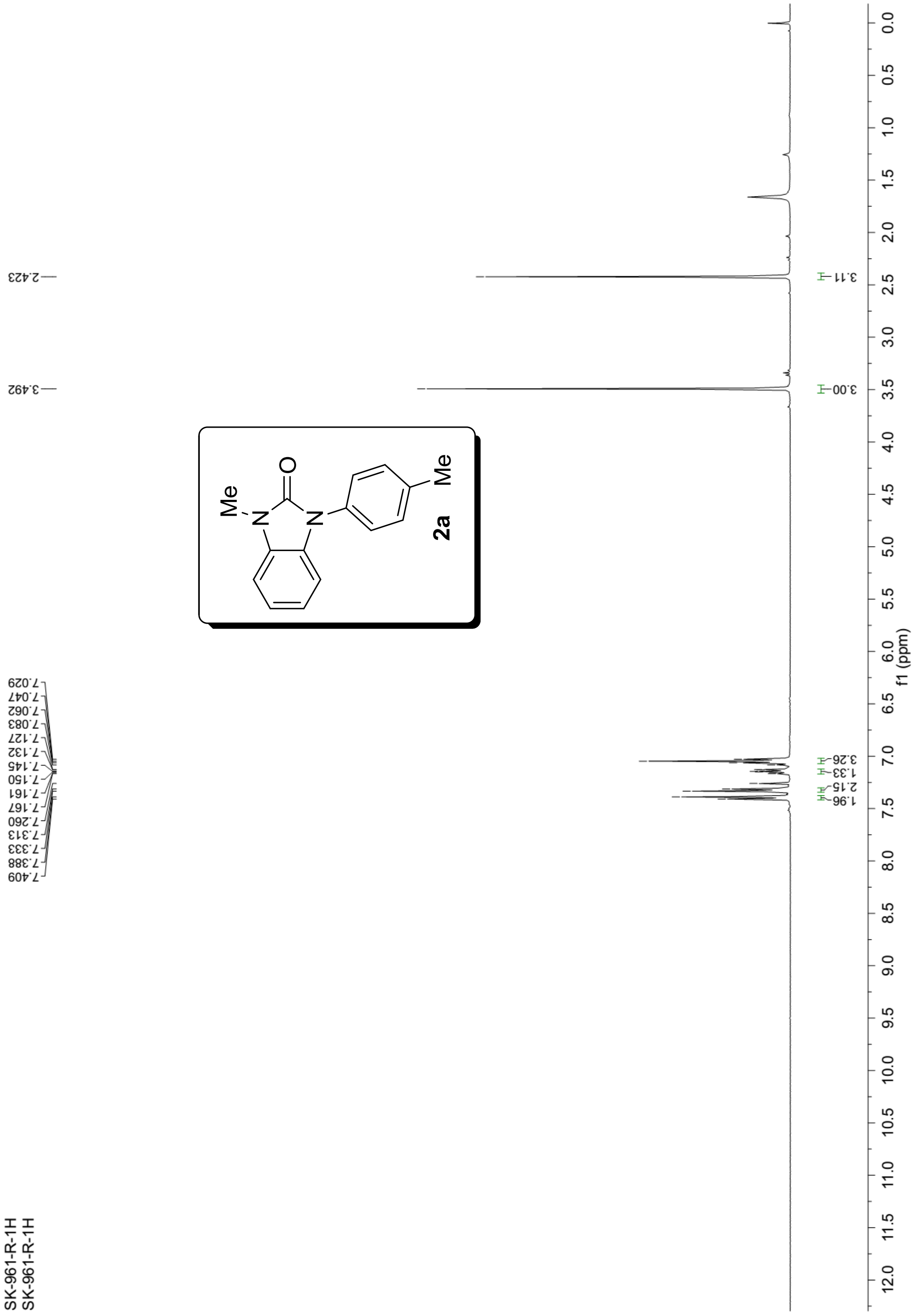
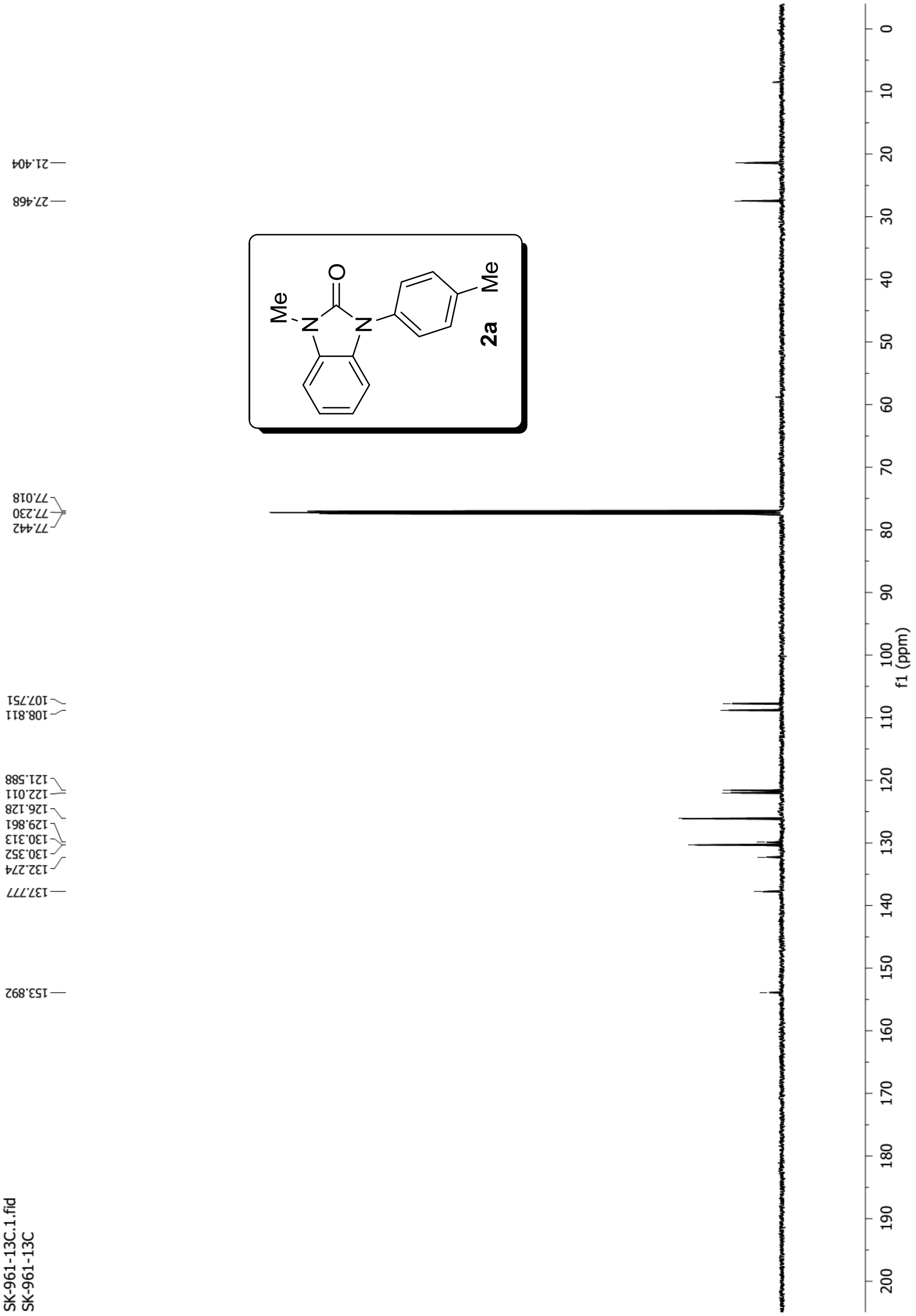
5.6. Selected Spectra

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N
Me
2a
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20
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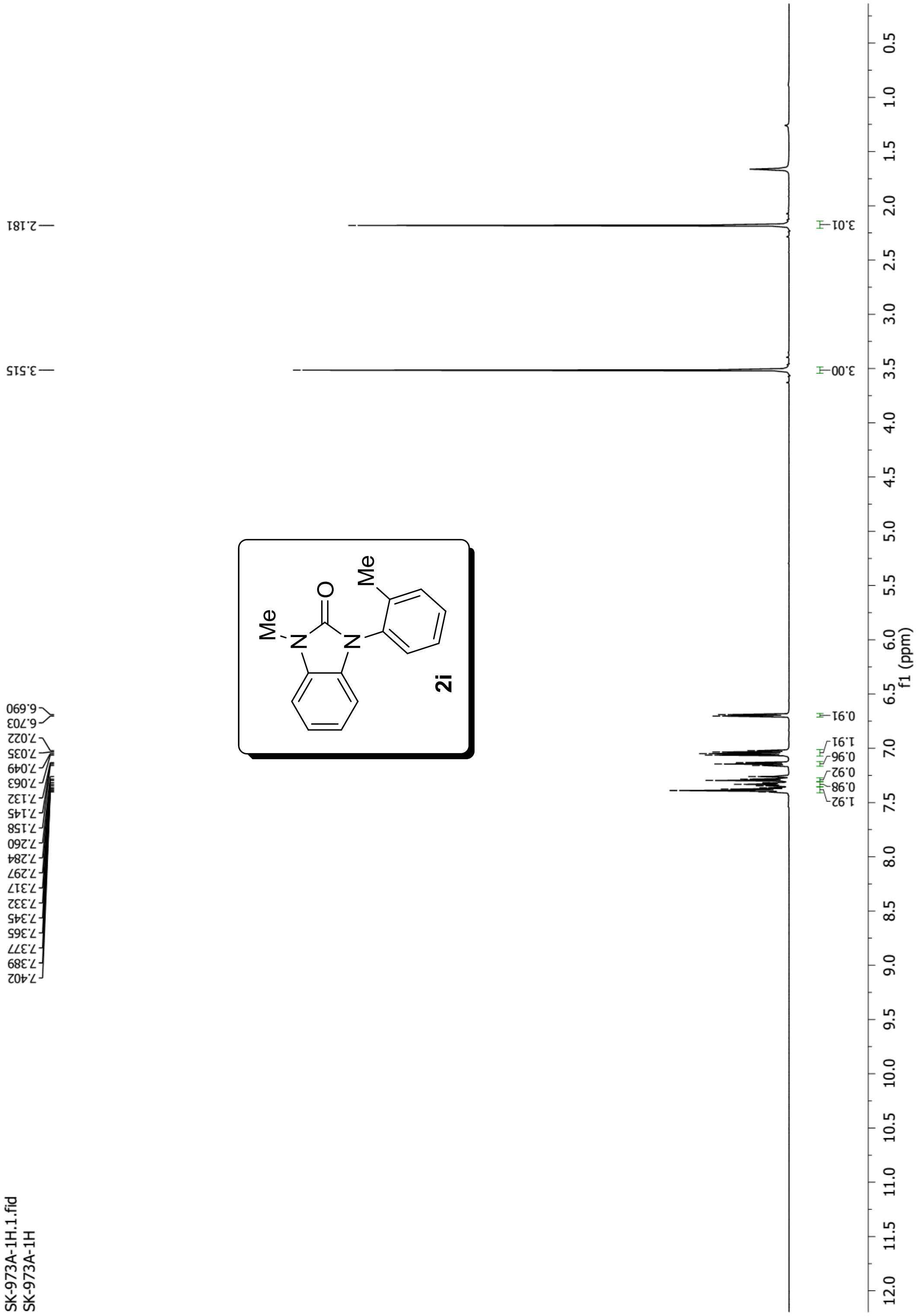
f1 (ppm)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7.389
7.402
3.01
3.00
0.91
1.91
0.96
0.92
0.98
1.92
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
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N
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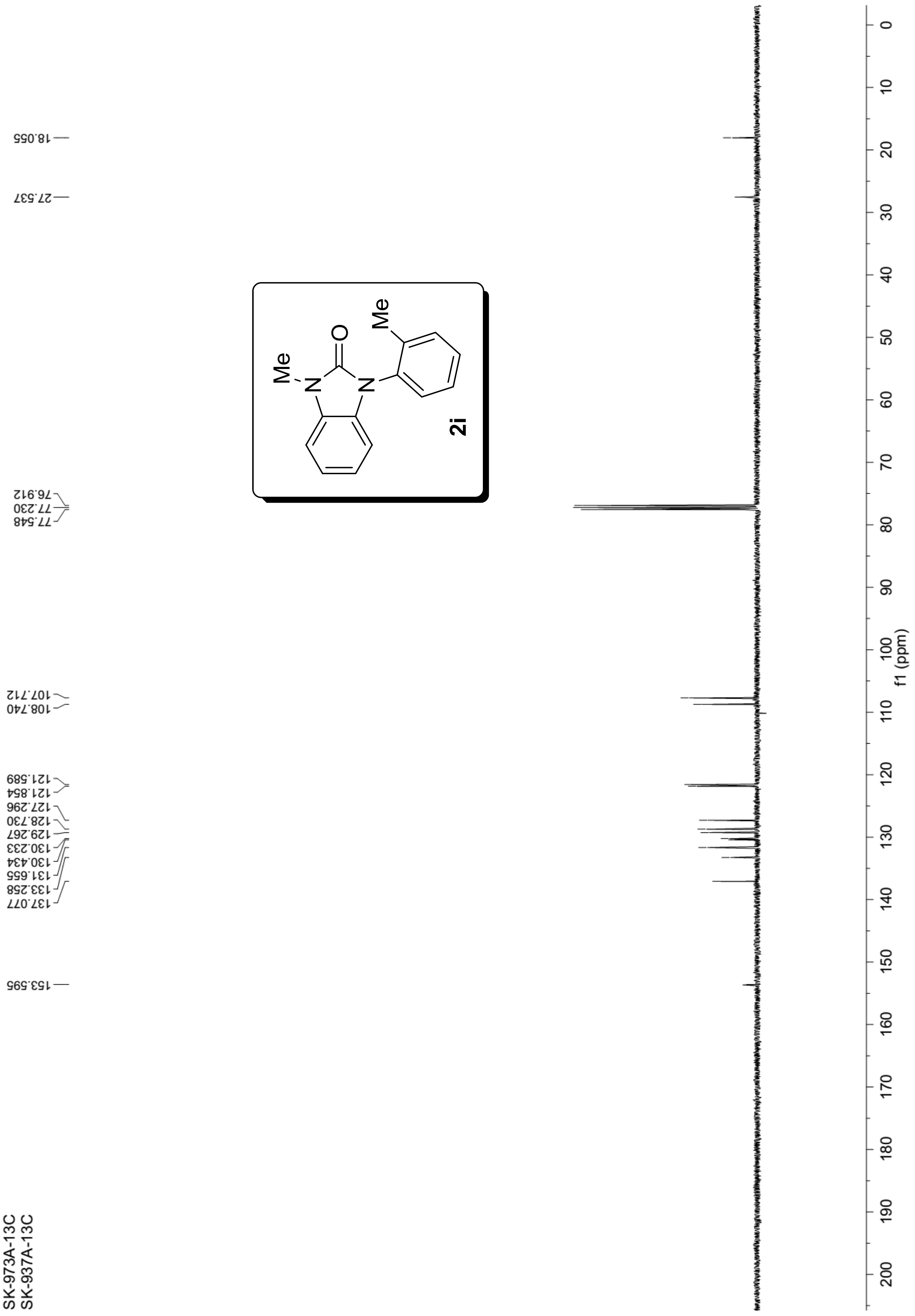
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O
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N
N
2i
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
f1 (ppm)

Conclusions

In conclusion, the chapter 1 focuses on the general aspects of hypervalent iodine compounds, including the definition, bonding, nomenclature and reactivity. The recent literature survey of the hypervalent iodine mediated/catalyzed carbon-carbon and carbon-heteroatom bond formation reactions are outlined. The hypervalent iodine reagents, owing to their mild, low toxic nature, have made considerable progress in the recent years.

In chapter 2, iodobenzene catalyzed synthesis of 2-substituted *N*-sulfonyl benzimidazoles and *N*-aryl benzimidazoles are described by the oxidative amination of *N''*-aryl-*N'*-tosyl/*N'*-methylsulfonylamidines and *N*,*N'*-bis(aryl)amidines in presence of *m*CPBA as a terminal oxidant at room temperature in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as a solvent. The reaction is based on the involvement of hypervalent iodine generated *in situ* from iodobenzene and *m*CPBA to afford the target products in moderate to good yields.

In chapter 3, a metal-free protocol for the synthesis of 2-alkyl/aryl benzoxazoles has been demonstrated from alkyl/arylanilides. The reaction is performed using 1-iodo-4-nitrobenzene as the catalyst and oxone as an inexpensive and environmentally benign terminal oxidant at room temperature. The scope of the reaction was carried out with different substituted anilides and the desired products have been obtained in moderate to high yields.

In chapter 4, the cyclization of alkyl/arylthioanilides to 2-alkyl/aryl benzothiazoles has been described. The reaction involves the same catalytic system employed in chapter 3 and a series of benzothiazoles have been synthesized.

In chapter 5, the synthesis of substituted benzimidazol-2-ones has been described under metal free condition using [bis(trifluoroacetoxy)iodo]benzene by oxidative cyclization of *N*, *N'*-diarylureas. The reaction is general and simple to provide the substituted benzimidazol-2-ones.

List of Publications

1. "Room-Temperature Cu(II)-Catalyzed Chemo- and Regioselective *Ortho*-Nitration of arenes *via* C-H Functionalization" Sadhu, P.; **Alla, S. K.**; Punniyamurthy. T. *J. Org. Chem*. **2015**, *80*, 8245.

2. "Organocatalytic Syntheses of Benzoxazoles and Benzothiazoles Using Aryl Iodide and Oxone *via* C-H Functionalization and *C-O/S* Bonds Formation" **Alla, S. K.**; Sadhu, P.; Punniyamurthy. T. *J. Org. Chem.* **2014**, *79*, 7502.

3. "Pd(II)-Catalyzed Aminotetrazole-Directed Ortho-Selective Halogenation of Arenes" Sadhu, P.; **Alla, S. K.**; Punniyamurthy. T. *J. Org. Chem.* **2013**, *78*, 6104.

4. "Iodobenzene Catalyzed C-H Amination of *N*-Substituted Amidines using *m*-Chloroperbenzoic Acid" **Alla, S. K.**; Kumar, R. K.; Sadhu, P.; Punniyamurthy. T. *Org. Lett.* **2013**, *15*, 1334.

Conferences

1. "Organocatalysis: Iodine(III) Catalyzed Syntheses of Heterocyclic Compounds via Oxidative C-H Functionalization/Carbon-Heteroatom Bond Formation" **Alla, S. K.**; Punniyamurthy, T. Chem Convene 2015, organized by IITG, Guwahati April, **2015**.

2. "Organocatalytic Syntheses of Benzoxazoles and Benzothiazoles Using Aryl Iodide and Oxone via C-H Functionalization and *C-O/S* Bonds Formation" **Alla, S. K.**; Sadhu, P.; Punniyamurthy. T. 3rd National Conference on Frontiers in Chemical Sciences organized by IITG, Guwahati December, **2014**.

3. "Iodobenzene Catalyzed C-H Functionalizaton of *N*-Substituted Amidines Using *m*-Chloroperbenzoic Acid" **Alla, S. K.**; Kumar, R. K.; Sadhu, P.; Punniyamurthy. T. 16th CRSI National Symposium in Chemistry organized by IITB, Mumbai February, **2014**.

4. “Iodobenzene Catalyzed C-H Amination of *N*-Substituted Amidines Using *m*-Chloroperbenzoic Acid” **Alla, S. K.**; Kumar, R. K.; Sadhu, P.; Punniyamurthy. T. 9th J-NOST Conference organized by IISER, Bhopal November, **2013**.