Study of Intramolecular *C-N*, *C-O* and *C-S* Cross-Coupling Reactions and Application of Self-Assembled Chiral Copper(II) Complexes for Asymmetric Acylation Reaction

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

DOCTOR OF PHILOSOPHY

by

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February 2011

Dedicated

To

My Family Members

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

STATEMENT

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

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

Guwahati — Prasenjit Saha

February 2011

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

CERTIFICATE

This is to certify that Mr. Prasenjit Saha has been working under my supervision since January 2007. I am forwarding his thesis entitled "*Study of Intramolecular C-N, C-O and C-S Cross-Coupling Reactions and Application of Self-Assembled Chiral Copper(II) Complexes for Asymmetric Acylation Reaction*" 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

February 2011

Prof. Tharmalingam Punniyamurthy

Supervisor

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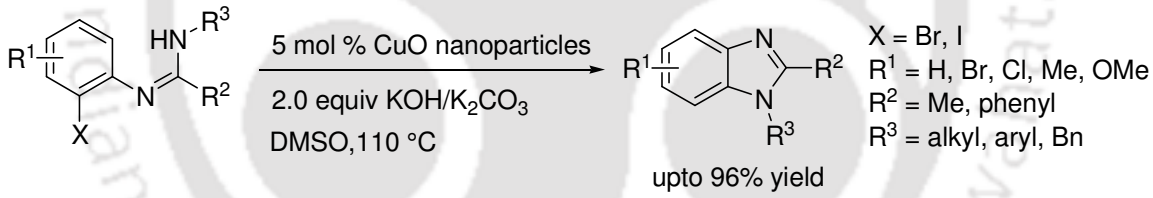
Prasenjit Saha

Abstract

The thesis contains four chapters. The first three chapters describe the synthesis of 2-substituted benzimidazoles, benzoxazoles and benzothiazoles by intramolecular *C-N*, *C-O* and *C-S* cross-coupling reactions using CuO nanoparticles as a recyclable catalyst. The fourth chapter describes the synthesis of self-assembled chiral copper(II) complexes and their application for the asymmetric acylation of secondary alcohols.

Chapter I. CuO Nanoparticles Catalyzed Intramolecular *C–N* Cross-Coupling Reaction: Synthesis of 2-Substituted Benzimidazoles

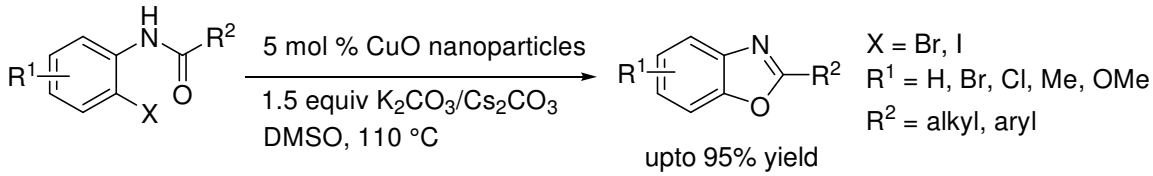
Benzimidazoles are privileged organic compounds due to their recognition in biological and therapeutic activities. This chapter describes CuO nanoparticles catalyzed synthesis of 2-substituted benzimidazoles from 2-bromoarylamidines and 2-bromoarylguanidines by intramolecular *C–N* cross-coupling reactions (Scheme 1). A variety of substrates undergo reactions to give the target products in high yield. The procedure is general and the catalyst is recyclable without loss of activity.



Scheme 1

Chapter II. CuO Nanoparticles Catalyzed Intramolecular *C–O* Cross-Coupling Reaction: Synthesis of 2-Alkyl and 2-Arylbenzoxazoles

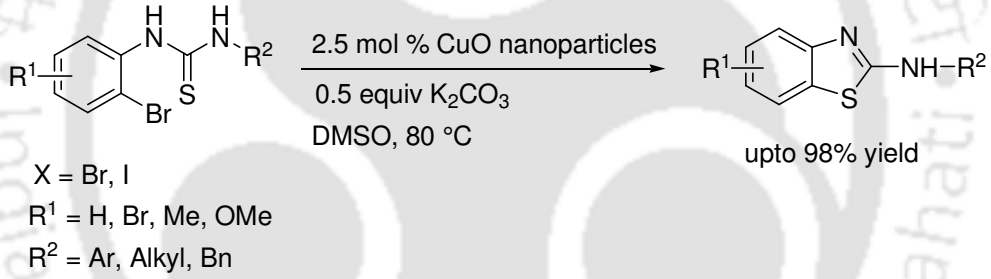
Benzoxazoles are an important structural motif found in wide range of natural products and therapeutically active agents. This chapter focuses on the synthesis of 2-substituted benzoxazoles from 2-haloarylamides using CuO nanoparticles (Scheme 2). The substrates undergo intramolecular *C–O* cross-coupling reaction in presence of 5 mol % CuO nanoparticles and 1.5 equiv of K_2CO_3 or Cs_2CO_3 at 110 °C to give the corresponding 2-aryl or alkylbenzoxazoles in high yield. The reactions are simple, general and the catalyst can be recovered and recycled without loss of activity and selectivity.



Scheme 2

Chapter III. CuO Nanoparticles Catalyzed Intramolecular *C–S* Cross-Coupling Reaction: Synthesis of 2-Aminobenzothiazoles

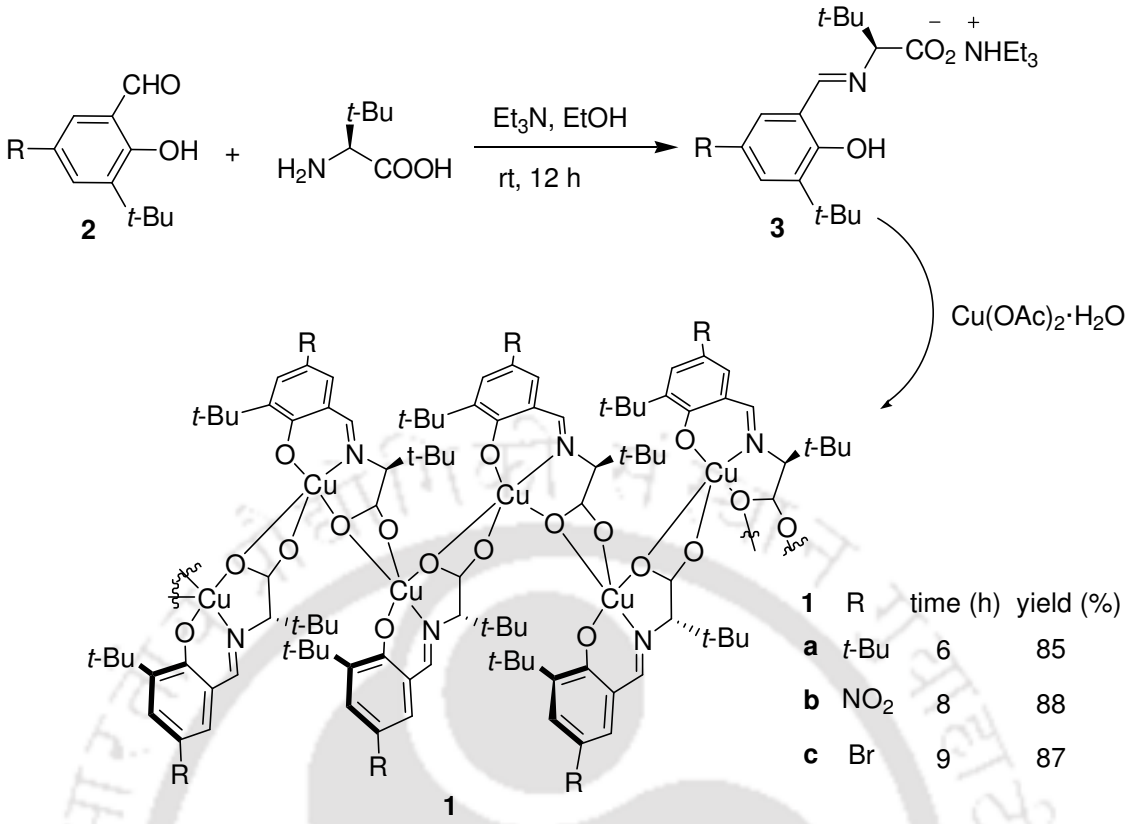
Substituted 2-aminobenzothiazoles are an important class of heterocyclic compounds due to their wide range of pharmaceutical and agrochemical properties. This chapter describes the synthesis of 2-aminobenzothiazoles using CuO nanoparticles from 2-haloarylthioureas. The substrates undergo intramolecular *C–S* cross coupling reaction to provide the target cross-coupled product with high yield (Scheme 3). The reactions are free from the addition of external ligands and work under milder reaction condition.



Scheme 3

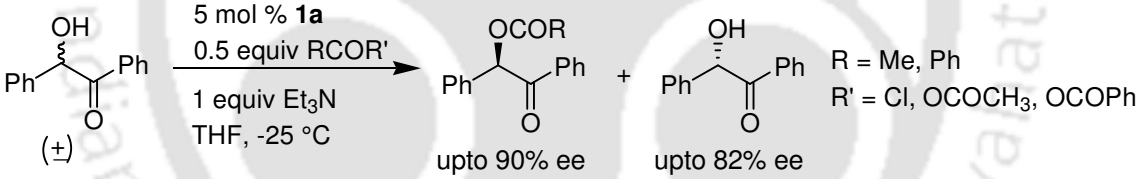
Chapter IV. Synthesis and Application of Self-Assembled Chiral Copper(II) Complexes for Asymmetric Acylation of Secondary Alcohols

The study of stereoregular chiral coordination polymers is a very active interdisciplinary research topic with potential applications in asymmetric catalysis, chiral sensor, nonlinear optical and chiral magnetic materials. This chapter describes the synthesis and application of self-assembled chiral copper(II) complexes **1a-c** for asymmetric acylation of secondary alcohols. Single-crystal X-ray analysis of **1a-c** showed that the polymers are stereoregular and the repeating units are connected to each other by perpendicular fashion through a carboxylate linker. The catalysts **1a-c** catalyze the kinetic resolution of secondary alcohols with acetic anhydride with up to 90% ee. The catalyst is recyclable without loss of activity (Scheme 4-5).



1	R	time (h)	yield (%)
a	*t*-Bu	6	85
b	NO_2	8	88
c	Br	9	87

Scheme 4



Scheme 5

Contents

Chapter I

CuO Nanoparticles Catalyzed Intramolecular *C–N* Cross-Coupling Reaction: Synthesis of 2-Substituted Benzimidazoles

Benzimidazoles are privileged organic compounds due to their recognition in biological and therapeutic activities.[1,2] Recent medicinal chemistry applications of these compounds include 5-lipoxygenase inhibitor,[3a] poly(ADP-ribose)polymerase (PARP) inhibitor,[3b] factor Xa(FXa) inhibitor,[3c] *N*-methyl-D-aspartate (NMDA) antagonist,[3d] neuropeptide YY1 receptor antagonist[3e] and nonpeptide thrombin inhibitor.[3f] Other applications of these compounds include their use as anti-inflammatory, antibacterial, antimicrobial and antiviral agents.[4] They also have been used as important synthetic intermediates for the preparation of dyes and high-temperature resistance polymers.[5] Development of general methods for the synthesis of these compounds is thus highly relevant to drug discovery and materials importance.

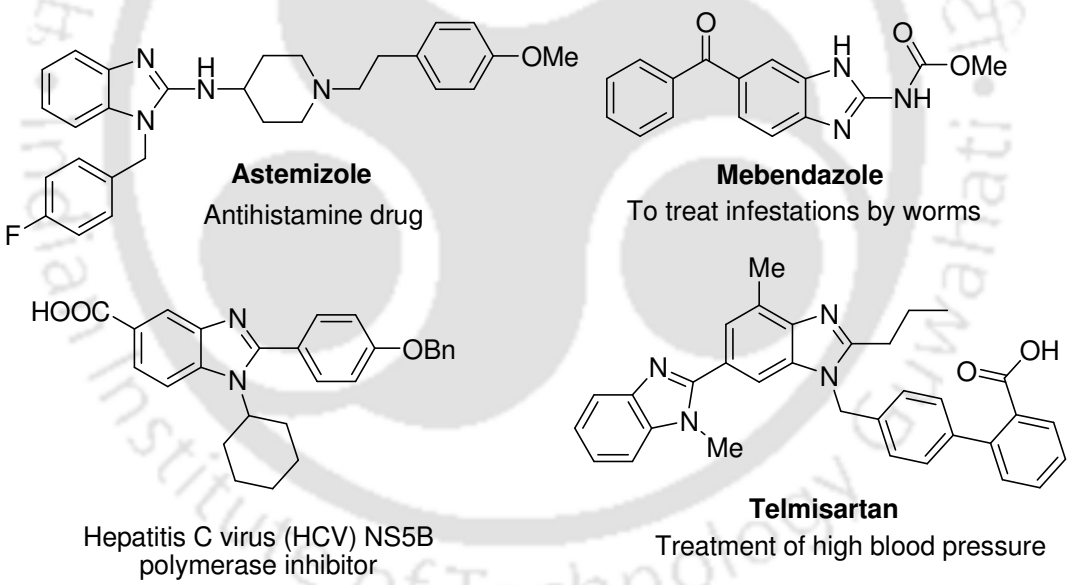


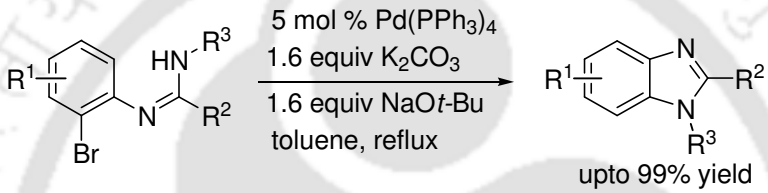
Figure 1. Examples of some biologically active compounds.

The classical methods used for the preparation of these compounds involve the condensation of 1,2-diaminoarenes with a carboxylic acid or its equivalents.[6] *o*-Nitroanilines can also be used in the place of the 1,2-diaminoarene derivatives under reducing conditions.[7] However, the drawbacks of these methods include the unavailability of suitably substituted 1,2-diaminoarenes or *o*-nitroanilines, harsh reaction conditions and lack of regioselectivity. Some of these drawbacks have been recently overcome by the

development of more sustainable cross-coupling reactions, using copper and palladium as a catalyst, which allow the efficient assembly of the target heterocycles under comparatively milder reaction conditions.[8,9]

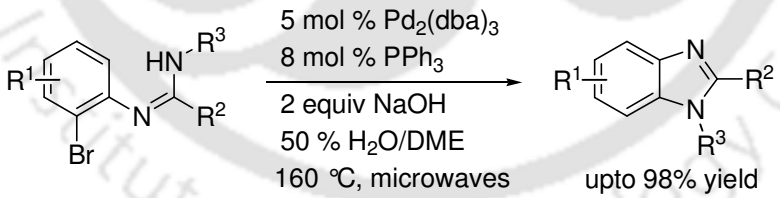
1.1 Palladium Catalysts

Palladium catalyzed intermolecular *C–N* cross-coupling reaction has been explored over the past few years. Recently, this methodology was applied in an intramolecular fashion to the synthesis of heterocyclic compounds. Brain and co-workers described the synthesis of substituted benzimidazoles from (*o*-bromophenyl)amidines in toluene under reflux condition by palladium catalyzed intramolecular *C–N* cross-coupling reaction. The reaction provides the cyclized product in high yield (Scheme 1).[10a]



Scheme 1

Later, they modified the reaction procedure for the synthesis of substituted benzimidazoles. They have used the combination of palladium and triphenylphosphine as a catalyst under microwave conditions in presence of NaOH in aqueous DME (Scheme 2).[10b]

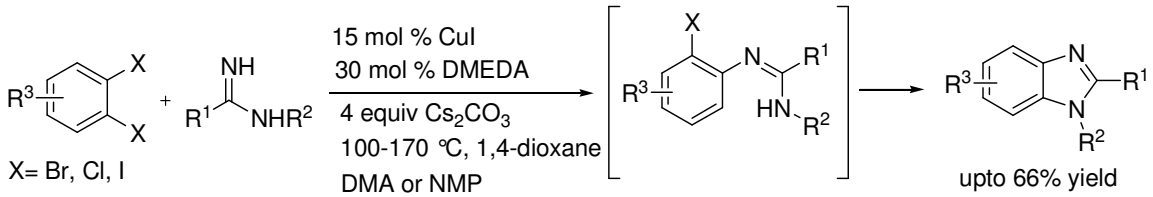


Scheme 2

1.2 Copper Catalysts

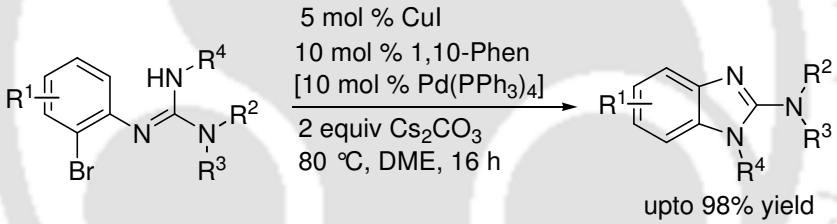
In the past decade, copper-mediated carbon-heteroatom bond formation reactions have drawn considerable attention due to their efficiency and low cost. Recently, copper-catalyzed strategies have been successfully applied for the assembly of various substituted benzimidazoles by *C–N* cross-coupling reaction. Deng and co-workers used CuI/*N*,*N*'-dimethylethylendiamine (DMEDA) for the tandem inter- and intramolecular

amination of 1,2-dihalobenzene with guanidine and equivalents to give the corresponding substituted benzimidazoles with good yield (Scheme 3).[11a]



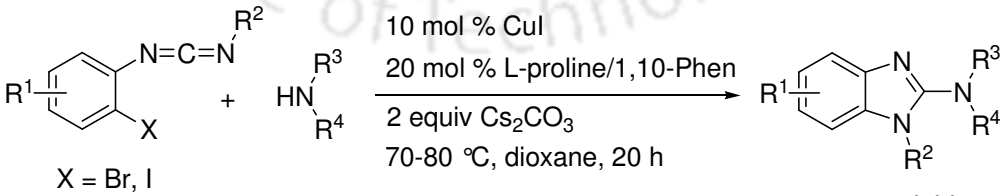
Scheme 3

Batey and co-workers reported an intramolecular aryl guadinylation to form 2-aminobenzimidazoles in the presence of palladium or copper catalysts. Inexpensive copper salts such as CuI are generally superior to palladium catalysts. The best results were observed with CuI/1,10-phenanthroline (1,10-Phen) in the presence of Cs_2CO_3 in DME whereas palladium catalysis results in the formation of regioisomeric products (Scheme 4).[11b]



Scheme 4

Recently, Bao and co-workers developed a method for the synthesis of *N*-substituted benzimidazoles by copper(I) catalyzed cascade intermolecular addition/intramolecular *C*–*N* coupling process from *o*-haloarylcarbodiimides and *N* or *O*-nucleophiles (Scheme 5).[11c]

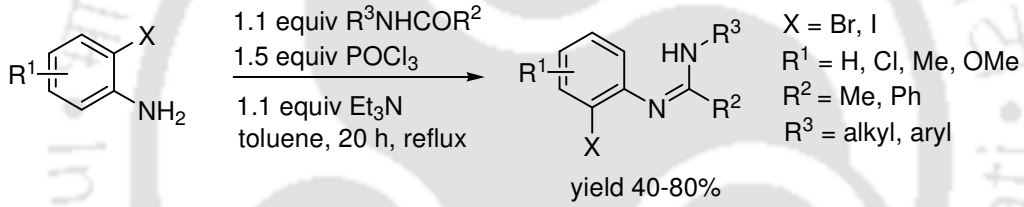


Scheme 5

1.3 Present Study

The use of CuO nanoparticles as efficient catalyst for cross-coupling reactions has attracted considerable interest in recent years. CuO nanoparticles have been used for cross-coupling reactions of aryl iodides with nitrogen, oxygen and sulfur nucleophiles under ligand-free conditions.[12] Since the CuO nanoparticles are readily accessible, air stable, recyclable and free from addition of external chelating ligands, we became further interested to investigate them for the synthesis of 2-substituted benzimidazoles. In this chapter, we describe a general method for the synthesis of substituted benzimidazoles and 2-aminobenzimidazoles by intramolecular *C–N* cross-coupling reaction in the presence of CuO nanoparticles. The procedure is experimentally simple and efficient to afford the target heterocyclic compounds in high yield.

2-Haloarylamidines were prepared by condensation of 2-haloanilines with amides in the presence of $POCl_3$ and Et_3N in toluene with good yield (Scheme 6).[10a]



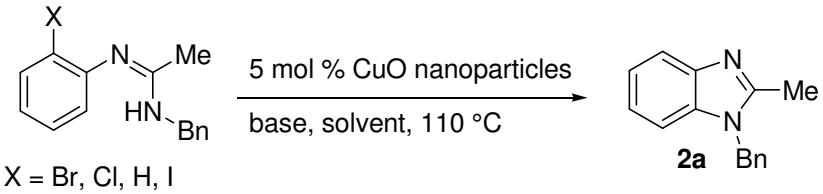
Scheme 6

The reaction conditions for the cyclization of 2-haloarylamidines were carried out with *N'*-(2-bromophenyl)-*N*-benzylmethylamidine **1a** as a model substrate using different bases and solvents (Table 1). Both *o*-iodo- and –bromoaryl derivatives readily underwent cyclization in presence of 5 mol % CuO nanoparticles and 2.0 equiv of KOH in DMSO at 110 ^oC to afford the 1-benzyl-2,6-dimethyl-1*H*-benzimidazole in high yield, whereas, bases such as K_2CO_3 and Cs_2CO_3 were ineffective providing the target product with 5% and 12% yield. In contrast, no reaction was observed with *o*-chloroaryl derivatives. Under these conditions, the cyclization *via C-H* activation did not occur. Control experiments of these reactions without CuO nanoparticles showed no reaction.

The scope of the reaction was next explored. The substrates **1a-i** having substituents such as Me, Cl, OMe group proceeded the cyclization to provide the corresponding *N*-alkylbenzimidazoles **2a-i** in 82-95% yield (Table 2). Both the substrates having electron donating and -withdrawing substituents underwent reaction with good yield. Likewise, the synthesis of *N*-arylbenzimidazoles could be accomplished replacing KOH with K_2CO_3

as a base (Table 3). The substrates **1j-p** underwent intramolecular *C–N* cross-coupling reaction to give the corresponding cyclized products **2j-p** with 80-96% yield.

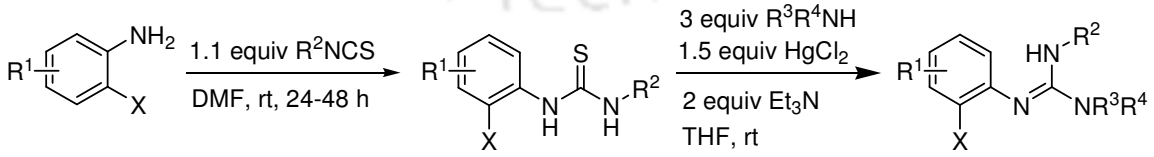
Table 1. Optimization of Reaction Conditions[a]



X = Br, Cl, H, I

entry	X	base	solvent	time (h)	conversion (%)[b]
1	Br	K_2CO_3	DMSO	24	5
2	Br	Cs_2CO_3	DMSO	24	12
3	Br	KOH	DMSO	14	99
4[c]	Br	KOH	DMSO	14	83
5[d]	Br	KOH	DMSO	24	nr
6	Br	KOH	DMF	24	6
7	I	KOH	DMSO	7	99
8	Cl	KOH	DMSO	24	nr
9	H	KOH	DMSO	24	nr

[a] Substrate (0.5 mmol), CuO nanoparticles (5 mol %) and base (1 mmol) were stirred at 110 °C in solvent (1 mL) under air. [b] Determined from 400 MHz ^{1}H NMR. [c] KOH (0.75 mmol) was used. [d] Reaction was carried out in absence of catalyst. nr = no reaction.



R^1 = H, Br, Me, OMe
R^2 = Ar, Bn, Alkyl
X = Br, Cl, I

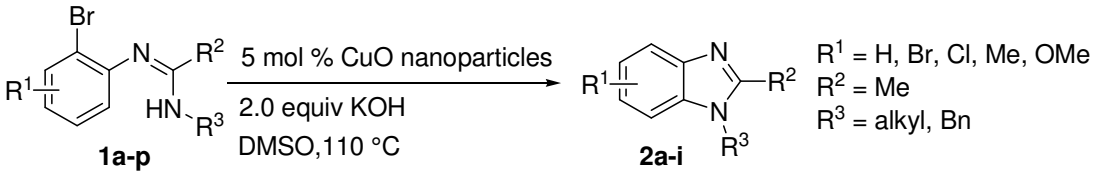
yield 88-93%

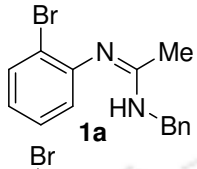
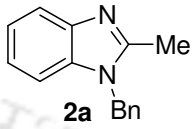
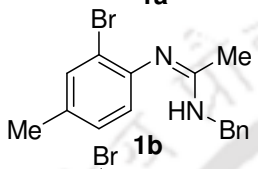
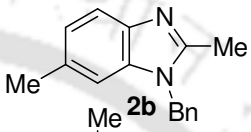
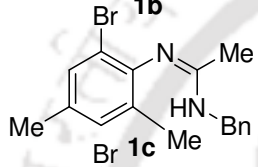
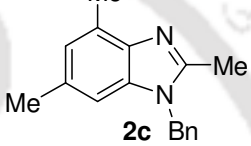
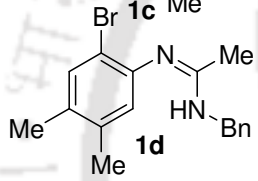
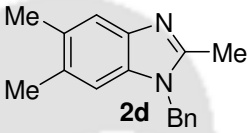
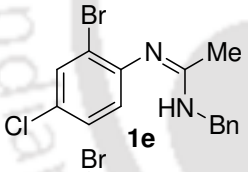
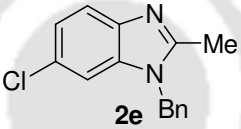
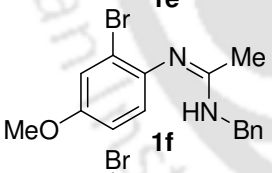
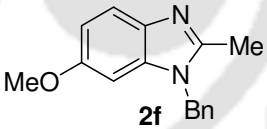
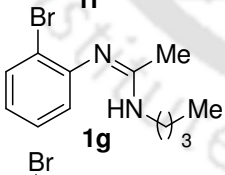
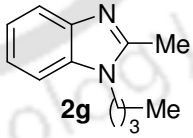
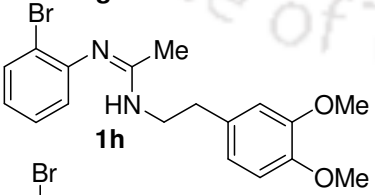
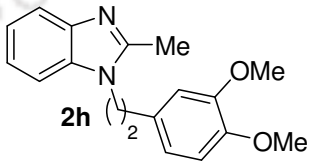
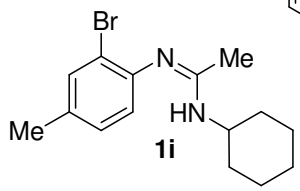
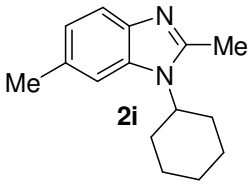
yield 75-95%

R^3R^4NH = pyrrolidine
morpholine
piperazine

Scheme 7

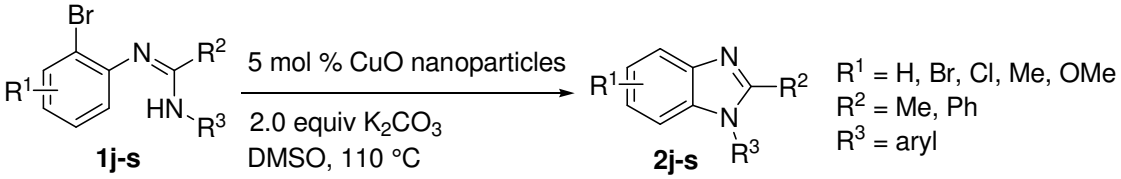
Table 2. CuO Nanoparticles Catalyzed Synthesis of Substituted *N*-Alkylbenzimidazoles[a]



entry	substrate	time (h)	product	yield (%)
1	 **1a**	12	 **2a**	95
2[b]	 **1b**	15	 **2b**	93
3[b]	 **1c**	15	 **2c**	88
4[b]	 **1d**	13	 **2d**	92
5	 **1e**	12	 **2e**	92
6	 **1f**	13	 **2f**	87
7	 **1g**	15	 **2g**	83
8	 **1h**	15	 **2h**	82
9[b]	 **1i**	16	 **2i**	91

[a] (*o*-Bromoaryl)amidine (0.5 mmol), CuO nanoparticles (5 mol %) and KOH (1 mmol) were stirred at 110 °C in DMSO (1 mL) under air. [b] KOH (1.5 mmol) was used.

Table 3. Synthesis of Substituted *N*-Arylbenzimidazoles[a]



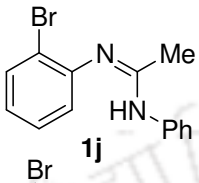
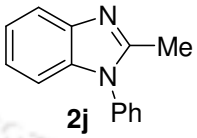
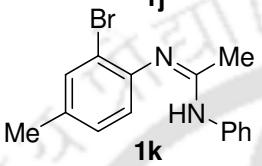
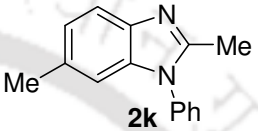
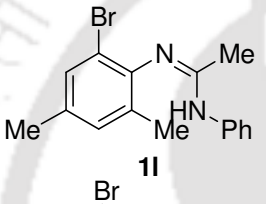
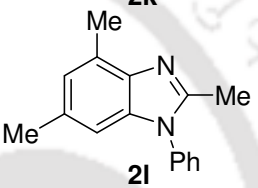
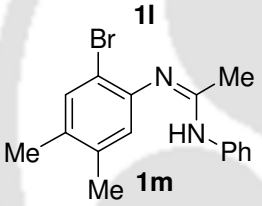
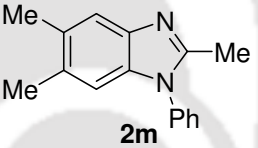
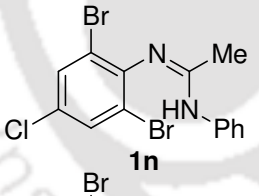
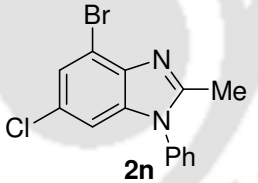
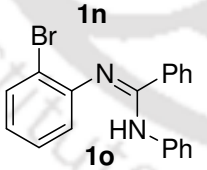
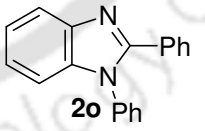
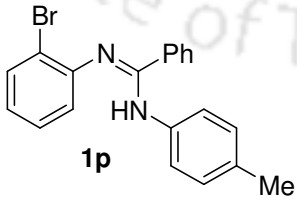
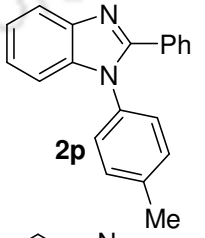
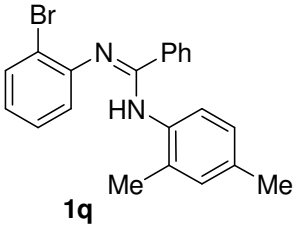
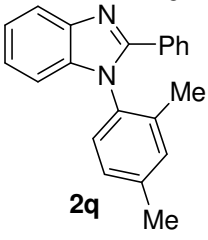
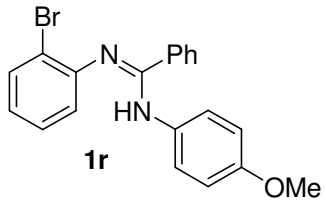
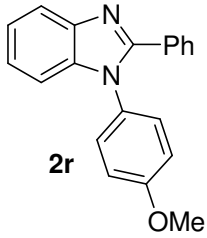
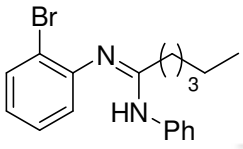
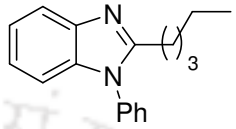
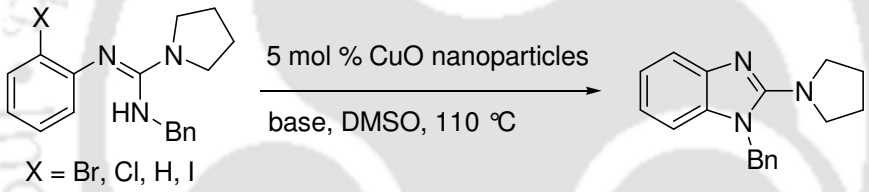
entry	substrate	time (h)	product	yield (%)
1	 **1j**	14	 **2j**	94
2	 **1k**	15	 **2k**	95
3	 **1l**	16	 **2l**	90
4	 **1m**	15	 **2m**	93
5	 **1n**	12	 **2n**	80
6	 **1o**	10	 **2o**	97
7	 **1p**	11	 **2p**	96
8	 **1q**	12	 **2q**	93

Table 3 continues…

9	 **1r**	9	 **2r**	89
10	 **1s**	15	 **2s**	90

[a] (*o*-Bromoaryl)amidine (0.5 mmol), CuO nanoparticles (5 mol %) and K_2CO_3 (1 mmol) were stirred at 110 °C in DMSO (1 mL) under air.

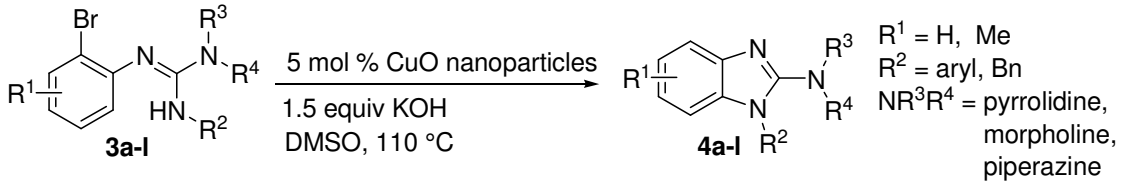
Table 4. Standardization of Reaction Condition for the Synthesis of Substituted 2-Aminobenzimidazoles[a]



entry	X	base	time (h)	conversion (%)[b]
1	Br	K_2CO_3	24	2
2	Br	Cs_2CO_3	24	4
3	Br	KOH	14	78
4[c]	Br	KOH	14	nr
5	I	KOH	7	98
6	Cl	KOH	24	nr
7	H	KOH	24	nr

[a] Substrate (0.5 mmol), CuO nanoparticles (5 mol %) and base (0.75 mmol) were stirred in DMSO (1 mL) at 110 °C under air. [b] Determined from 400 MHz ^{1}H NMR. [c] Reaction was carried out in absence of catalyst. nr = no reaction.

Table 5. Synthesis of Substituted 2-Aminobenzimidazoles[a]



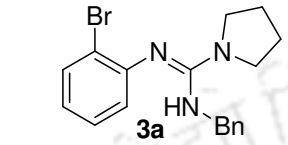
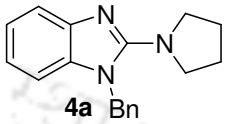
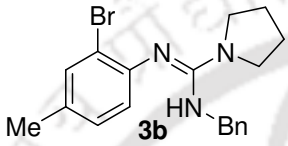
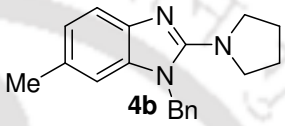
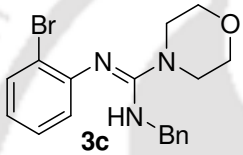
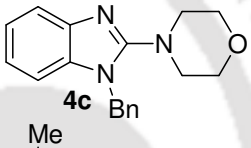
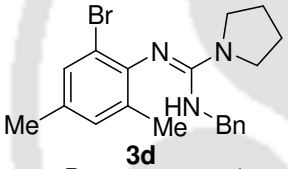
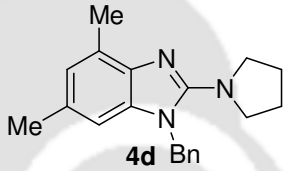
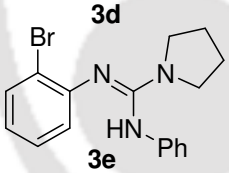
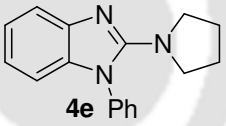
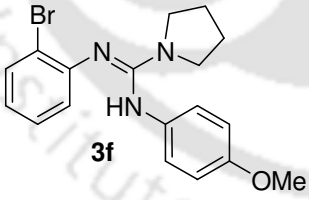
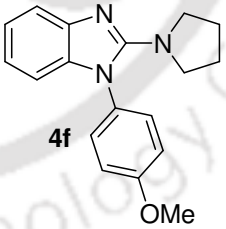
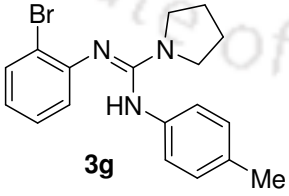
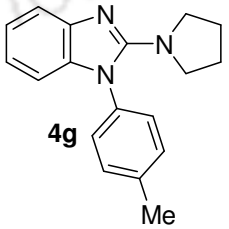
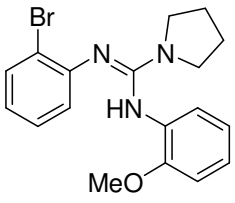
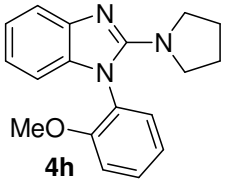
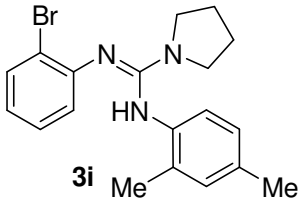
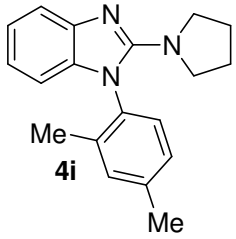
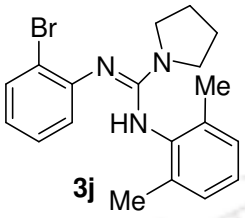
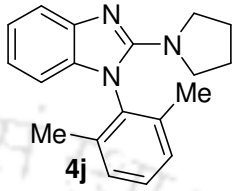
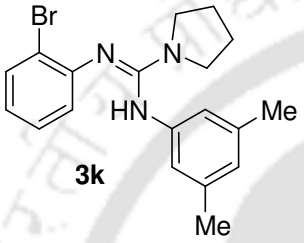
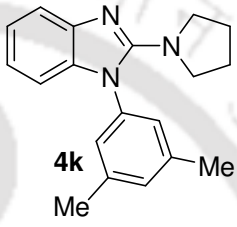
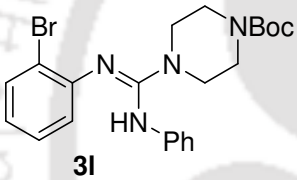
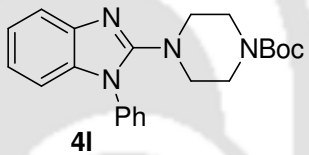
entry	substrate	time (h)	product	yield (%)
1	 **3a**	24	 **4a**	73
2	 **3b**	14	 **4b**	89
3	 **3c**	18	 **4c**	88
4	 **3d**	12	 **4d**	90
5	 **3e**	5	 **4e**	95
6	 **3f**	5	 **4f**	78
7	 **3g**	4	 **4g**	93
8	 **3h**	5	 **4h**	88

Table 5 continues..

9	 **3i**	5	 **4i**	83
10	 **3j**	5	 **4j**	80
11	 **3k**	4	 **4k**	95
12	 **3l**	4	 **4l**	90

[a] *o*-Bromoarylguanidine (0.5 mmol), CuO nanoparticles (5 mol %) and KOH (0.75 mmol) were stirred at 110 °C in DMSO (1 mL) under air.

Next, we have studied the synthesis of *N*-substituted 2-aminobenzimidazoles from *o*-haloarylguanidines. Reaction of *o*-haloanilines and isothiocyanate derivatives gave thioureas which on further reaction with amines in presence of $HgCl_2$ yielded *o*-haloarylguanidines (Scheme 7).[11b]

The reaction conditions for the synthesis of substituted 2-aminobenzimidazoles from *o*-haloarylguanidines were optimized (Table 4). The substrate *o*-bromoarylguanidine **3a** underwent cyclization in presence of 5 mol % CuO nanoparticles and 1.5 equiv of KOH to give the cyclized product **4a** with 78% yield. The bases such as K_2CO_3 and Cs_2CO_3 gave inferior results. *o*-Iodoaryl derivatives exhibited greater reactivity compared to *o*-bromoaryl derivatives, whereas *o*-chloroaryl derivatives showed no reaction. After optimisation of the reaction conditions, the scope of the procedure were further examined for other substrates. A series of *o*-bromoarylguanidines **3b-3l** underwent cyclization to provide the corresponding *C–N* cross-coupled 2-aminobenzimidazoles **4b-4l** in 73-95%

yield (Table 5). The substrates having R^2 = aryl substituents exhibited greater reactivity compared to that containing R^2 = alkyl substituents.

In conclusion, we have developed a general method for the synthesis of substituted benzimidazoles and 2-aminobenzimidazoles using CuO nanoparticles in high yield. The advantages of this procedure are simplicity of the reaction procedure, compatibility of the variety of substituent and recyclability of the catalyst.

Experimental Section

General Information

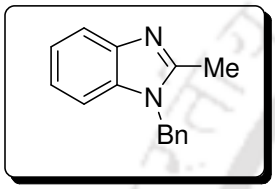
o-Haloanilines and CuO nanoparticles (particle size 33 nm and surface area 29 m^2/g) were purchased from Aldrich and used without further purification. Column chromatography was carried out with silica gel (60-120 mesh) using ethyl acetate and hexane as eluent. Analytical TLC was performed with silica gel 60 plates. NMR spectra (400 MHz for ^1H and 100 MHz for ^{13}C) were recorded using DRX-400 Varian spectrometer with $CDCl_3$ as solvent and Me_4Si as an internal standard. Melting points were determined using Buchi B-540 apparatus and uncorrected. Elemental analysis was carried out using CHNS analyzer. IR spectra were recorded using FT-IR spectrometer.

General Procedure for Synthesis of *o*-Bromoarylamidines

An oven dried 25 mL two necked round bottom flask was charged with 2-bromoaniline derivative (3.0 mmol), amide (3.3 mmol) and toluene (9 mL) under nitrogen atmosphere. The resultant mixture was stirred at room temperature for 2 minutes and treated with Et_3N (3.3 mmol) and $POCl_3$ (4.5 mmol). The reaction mixture was then refluxed for 15-20 h and the progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. After completion, the reaction mixture was cooled to room temperature and solvent was evaporated using rotary evaporater. The resultant residue was treated with water (15 mL) and ethyl acetate (25 mL) and the solution was neutralised with $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 10 mL). The combined organic solution was dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated using rotary evaporator. The residue was purified by silica gel column chromatography using ethyl acetate and hexane as eluent.

General Procedure for Synthesis of *N*-Alkyl and *N*-Arylbenzimidazoles

An oven dried 10 mL round bottom flask was charged with *o*-bromoarylamidine (0.5 mmol), CuO nanoparticles (5 mol %, 2 mg), KOH (1 mmol, 56 mg) or K_2CO_3 (1 mmol, 138 mg) and DMSO (1 mL). The mixture was stirred at 110 °C for the appropriate time (Table 2-3). The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. The reaction mixture was then cooled to room temperature and diluted with ethyl acetate (15 mL). The organic layer was washed successively with brine (1 x 4 mL) and water (2 x 4 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using ethyl acetate and hexane as eluent.



1-Benzyl-2-methyl-1*H*-benzo[*d*]imidazole (2a).[13a] Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.28; yellow solid; yield 95%.

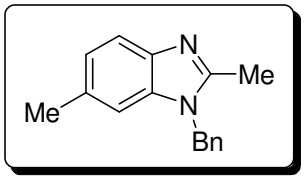
Mp: 67-68 °C (lit.[13b] 68-69 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.0 Hz, 1H), 7.32-7.19 (m, 6H), 7.05 (d, *J* = 8.0 Hz, 2H), 5.31 (s, 2H), 2.56 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.1, 142.8, 136.0, 135.6, 129.1, 128.0, 126.4, 122.4, 122.1, 119.2, 109.5, 47.2, 14.1.

FT-IR (KBr): 3060, 2929, 1655, 1618, 1518, 1454, 1404, 1355, 1330, 1286, 1251, 1143, 1029 cm^{-1}.

Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 81.14; H, 6.31; N, 12.55.



1-Benzyl-2,6-dimethyl-1*H*-benzo[*d*]imidazole (2b). Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.28; yellow solid; yield 93%.

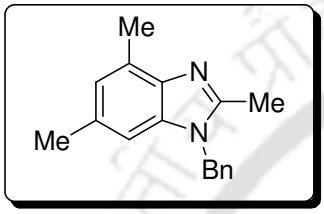
Mp: 141-142 °C (lit.[13c] 141 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 8.4 Hz, 1H), 7.31-7.26 (m, 3H), 7.07-7.01 (m, 4H), 5.26 (s, 2H), 2.52 (s, 3H), 2.43 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.4, 140.6, 136.0, 135.7, 132.3, 129.0, 127.9, 126.2, 123.6, 118.5, 109.3, 46.9, 21.8, 13.8.

FT-IR (KBr): 3029, 2922, 2854, 1660, 1624, 1518, 1465, 1451, 1399, 1360, 1328, 1277, 1253, 1074, 1030 cm^{-1}.

Anal. Calcd for $C_{16}H_{16}N_2$: C, 81.32; H, 6.82; N, 11.85. Found: C, 81.39; H, 6.81; N, 11.80.



1-Benzyl-2,4,6-trimethyl-1*H*-benzo[*d*]imidazole (2c). Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.28; yellow solid; yield 88%.

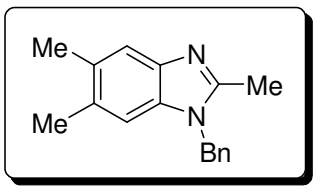
Mp: 62-63 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.24 (m, 3H), 7.04-7.02 (m, 2H), 6.87 (d, *J* = 10.8 Hz, 2H), 5.26 (s, 2H), 2.63 (s, 3H), 2.54 (s, 3H), 2.39 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.7, 139.9, 136.2, 135.5, 132.2, 129.1, 128.6, 127.9, 126.3, 124.3, 106.9, 47.1, 21.8, 16.8, 14.0.

FT-IR (KBr): 3021, 2925, 1671, 1621, 1604, 1520, 1496, 1453, 1421, 1376, 1347, 1333, 1312, 1274, 1231, 1066, 1033 cm^{-1}.

Anal. Calcd for $C_{17}H_{18}N_2$: C, 81.56; H, 7.25; N, 11.19. Found: C, 81.66; H, 7.23; N, 11.11.



1-Benzyl-2,5,6-trimethyl-1*H*-benzo[*d*]imidazole (2d). Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.37; yellow solid; yield 92%.

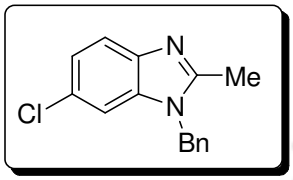
Mp: 139-140 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (s, 1H), 7.30-7.24 (m, 3H), 7.02-7.00 (m, 2H), 6.97 (s, 1H), 5.25 (s, 2H), 2.50 (s, 3H), 2.34 (s, 3H), 2.30 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.1, 141.3, 136.2, 134.1, 131.3, 130.7, 129.0, 127.8, 126.2, 119.3, 109.7, 47.0, 20.6, 20.3, 13.9.

FT-IR (KBr): 3018, 2968, 2919, 1626, 1520, 1451, 1402, 1362, 1251, 1318, 1267, 1020, 1002 cm^{-1}.

Anal. Calcd for $C_{17}H_{18}N_2$: C, 81.56; H, 7.25; N, 11.19. Found: C, 81.60; H, 7.24; N, 11.16.



1-Benzyl-6-chloro-2-methyl-1*H*-benzo[*d*]imidazole (2e). Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.29; yellow solid; yield 92%.

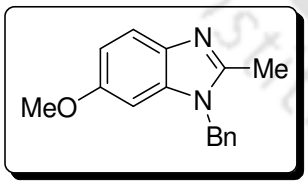
Mp: 124-125 °C (lit.[13d] 124 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, *J* = 8.4 Hz, 1H), 7.35-7.30 (m, 3H), 7.21-7.19 (m, 2H), 7.03 (d, *J* = 8.0 Hz, 2H), 5.28 (s, 2H), 2.56 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.0, 141.3, 136.2, 135.4, 129.2, 128.2, 126.3, 122.8, 120.0, 109.7, 47.3, 14.0.

FT-IR (KBr): 3027, 2922, 2857, 1613, 1583, 1519, 1495, 1437, 1402, 1355, 1322, 1267, 1229, 1054 cm^{-1}.

Anal. Calcd for $C_{15}H_{13}ClN_2$: C, 70.18; H, 5.10; N, 10.91. Found: C, 70.28; H, 5.07; N, 10.85.



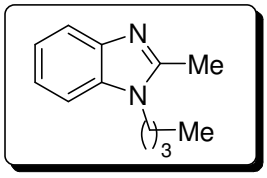
1-Benzyl-6-methoxy-2-methyl-1*H*-benzo[*d*]imidazole (2f). Analytical TLC on silica gel, 1:1 ethyl acetate/hexane R_f = 0.32; yellow liquid; yield 87%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, *J* = 7.2 Hz, 1H), 7.33-7.25 (m, 3H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.87 (d, *J* = 6.4 Hz, 1H), 6.70 (s, 1H), 5.26 (s, 2H), 3.79 (s, 3H), 2.51 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.5, 137.0, 135.8, 129.1, 128.0, 126.3, 119.6, 110.8, 93.8, 55.9, 47.2, 14.0.

FT-IR (neat): 3060, 2933, 2851, 1624, 1517, 1488, 1454, 1404, 1259, 1214, 1136, 1102, 1030 cm^{-1}.

Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.25; H, 6.38; N, 11.06.



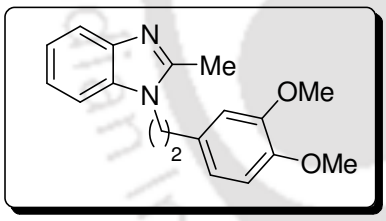
1-Butyl-2-methyl-1*H*-benzo[*d*]imidazole (2g). Analytical TLC on silica gel, 1:1 ethyl acetate/hexane R_f = 0.35; yellow liquid; yield 83%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69-7.67 (m, 1H), 7.30-7.21 (m, 3H), 4.10 (t, *J* = 7.2 Hz, 2H), 2.61 (s, 3H), 1.80-1.74 (m, 2H), 1.42-1.37 (m, 2H), 0.96 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.6, 142.6, 135.3, 122.1, 121.9, 119.1, 109.4, 43.8, 32.0, 20.3, 14.0, 13.9.

FT-IR (neat): 2959, 2873, 1655, 1514, 1458, 1406, 1330, 1286, 1136, 1010 cm^{-1}.

Anal. Calcd for $C_{12}H_{16}N_2$: C, 76.55; H, 8.57; N, 14.88. Found: C, 76.61; H, 8.56; N, 14.83.



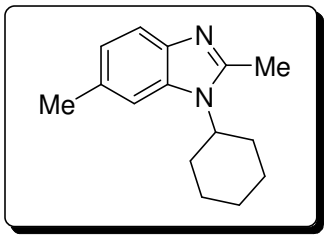
1-(3,4-Dimethoxyphenethyl)-2-methyl-1*H*-benzo[*d*]imidazole (2h). Analytical TLC on silica gel, 1:1 ethyl acetate/hexane R_f = 0.20; yellow liquid; yield 82%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70-7.68 (m, 1H), 7.29-7.22 (m, 3H), 6.74 (d, *J* = 8.4 Hz, 1H), 6.49 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.25 (s, 1H), 4.29 (t, *J* = 6.4 Hz, 2H), 3.83 (s, 3H), 3.66 (s, 3H), 3.01(t, *J* = 6.8 Hz, 2H), 2.17 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.0, 149.2, 148.3, 142.6, 134.7, 130.3, 122.1, 122.0, 120.9, 119.1, 112.2, 111.7, 56.0, 55.9, 45.7, 35.2, 13.5.

FT-IR (neat): 3065, 2934, 2851, 1647, 1613, 1516, 1458, 1405, 1355, 1262, 1238, 1157, 1027 cm^{-1}.

Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.99; H, 6.81; N, 9.39.



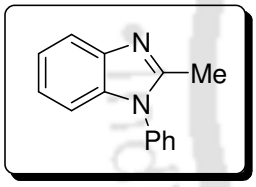
1-Cyclohexyl-2,6-dimethyl-1*H*-benzo[*d*]imidazole (2i). Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.27; yellow liquid; yield 91%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 8.0 Hz, 1H), 7.27 (s, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 4.16-4.09 (m, 1H), 2.59 (s, 3H), 2.48 (s, 3H), 2.25-2.00 (m, 4H), 1.97-1.52 (m, 4H), 1.51-1.32 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.7, 141.1, 134.3, 131.4, 123.0, 118.8, 111.5, 56.5, 31.4, 26.3, 25.5, 22.0, 15.2.

FT-IR (neat): 2933, 2858, 1633, 1524, 1444, 1401, 1286, 1095, 1005 cm^{-1}.

Anal. Calcd for $C_{15}H_{20}N_2$: C, 78.90; H, 8.83; N, 12.27. Found: C, 78.98; H, 8.80; N, 12.22.



2-Methyl-1-phenyl-1*H*-benzo[*d*]imidazole (2j).[13d] Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.40; colorless solid; yield 94%.

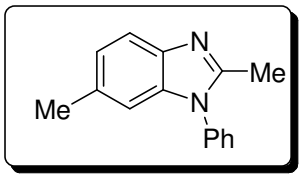
Mp: 68-69 °C (lit.[13d] mp 70-72 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, *J* = 8.4 Hz, 1H), 7.59-7.49 (m, 3H), 7.38-7.35 (m, 2H), 7.26 (t, *J* = 7.6 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), 2.51 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.7, 142.6, 136.6, 136.1, 130.0, 128.9, 127.2, 122.7, 122.5, 119.0, 110.0, 14.5.

FT-IR (KBr): 3060, 2967, 2917, 1613, 1597, 1519, 1500, 1457, 1395, 1326, 1287, 1247, 1188, 1074, 1016 cm^{-1}.

Anal. Calcd for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.81; H, 5.80; N, 13.39.



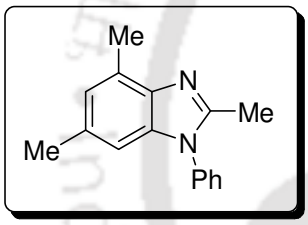
2,6-Dimethyl-1-phenyl-1*H*-benzo[*d*]imidazole (2k). Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.36; yellow liquid; yield 95%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60-7.49 (m, 4H), 7.35-7.32 (m, 2H), 7.05 (dd, *J* = 8.0, 0.8 Hz, 1H), 6.88 (s, 1H), 2.46 (s, 3H), 2.38 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.1, 140.7, 136.7, 136.3, 132.7, 130.0, 128.8, 127.2, 123.9, 118.5, 110.0, 21.8, 14.5.

FT-IR (neat): 3060, 2924, 2857, 1708, 1618, 1598, 1522, 1500, 1455, 1394, 1305, 1255, 1213, 1143, 1074, 1011 cm^{-1}.

Anal. Calcd for $C_{15}H_{14}N_2$: C, 81.05; H, 6.35; N, 12.60. Found: C, 81.15; H, 6.31; N, 12.54.



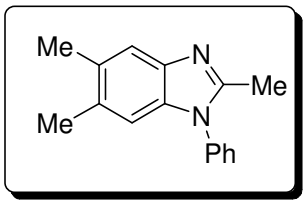
2,4,6-Trimethyl-1-phenyl-1*H*-benzo[*d*]imidazole (2l). Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.48; yellow liquid; yield 90%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57-7.48 (m, 3H), 7.34-7.31 (m, 2H), 6.88 (s, 1H), 6.72 (s, 1H), 2.63 (s, 3H), 2.48 (s, 3H), 2.35 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3, 139.8, 136.5, 136.4, 132.6, 130.0, 128.8, 128.4, 127.3, 124.6, 107.6, 21.7, 16.8, 14.4.

FT-IR (neat): 2925, 2851, 1637, 1596, 1500, 1456, 1392, 1327, 1253, 1231 cm^{-1}.

Anal. Calcd for $C_{16}H_{16}N_2$: C, 81.32; H, 6.82; N, 11.85. Found: C, 81.38; H, 6.80; N, 11.82.



2,5,6-Trimethyl-1-phenyl-1*H*-benzo[*d*]imidazole (2m). Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.36; yellow solid; yield 93%.

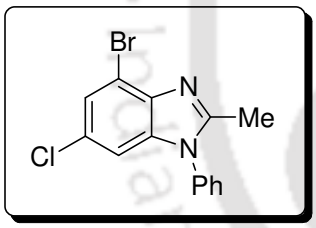
Mp: 146-147 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53-7.51 (m, 3H), 7.46 (s, 1H), 7.30-7.28 (m, 2H), 7.24 (s, 1H), 2.51 (s, 3H), 2.29 (s, 3H), 1.96 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2, 141.9, 137.9, 134.0, 132.2, 129.7, 129.6, 128.7, 123.1, 121.3, 117.9, 24.9, 18.1, 14.6.

FT-IR (KBr): 3043, 2966, 2915, 2858, 1704, 1597, 1523, 1498, 1439, 1407, 1377, 1361, 1325, 1296, 1260, 1161, 1089, 1034, 1013 cm^{-1}.

Anal. Calcd for $C_{16}H_{16}N_2$: C, 81.32; H, 6.82; N, 11.85. Found: C, 81.39; H, 6.80; N, 11.81.



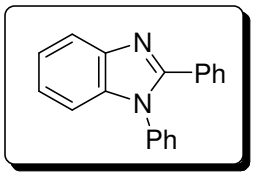
4-Bromo-6-chloro-2-methyl-1-phenyl-1*H*-benzo[*d*]imidazole (2n). Analytical TLC on silica gel, 1:1 ethyl acetate/hexane R_f = 0.56; yellow liquid; yield 80%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60-7.51 (m, 3H), 7.42 (d, *J* = 1.6 Hz, 1H), 7.32-7.28 (m, 2H), 7.01 (d, *J* = 1.6 Hz, 1H), 2.49 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.4, 140.3, 137.0, 135.2, 130.3, 129.6, 128.7, 127.0, 125.6, 112.6, 109.6, 14.5.

FT-IR (neat): 2956, 2929, 2857, 1614, 1517, 1500, 1454, 1421, 1385, 1324, 1256, 1173, 1072 cm^{-1}.

Anal. Calcd for $C_{14}H_{10}BrClN_2$: C, 52.29; H, 3.13; N, 8.71. Found: C, 52.38; H, 3.11; N, 8.63.



1,2-Diphenyl-1*H*-benzo[*d*]imidazole (2o).[13e] Analytical TLC on silica gel, 1:10 ethyl acetate/hexane R_f = 0.38; yellow solid; yield 97%.

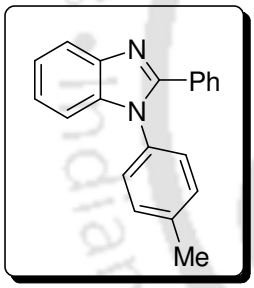
Mp: 109-110 °C (lit.[13f] 109-112 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, *J* = 8.0 Hz, 1H), 7.58-7.47 (m, 5H), 7.35-7.26 (m, 8H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.6, 143.2, 137.4, 137.2, 130.0, 129.6, 128.7, 128.5, 127.6, 123.5, 123.2, 120.0, 116.4, 110.6.

FT-IR (KBr): 3050, 3010, 2962, 1652, 1594, 1492, 1475, 1455, 1382, 1327, 1306, 1278, 1259, 1180, 1076, 1026 cm^{-1}.

Anal. Calcd for $C_{19}H_{14}N_2$: C, 84.42; H, 5.22; N, 10.36. Found: C, 84.49; H, 5.23; N, 10.28.



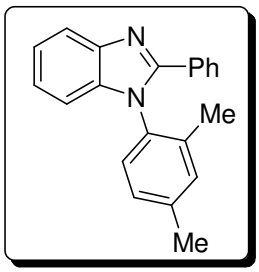
2-Phenyl-1-*p*-tolyl-1*H*-benzo[*d*]imidazole (2p).[13g] Analytical TLC on silica gel, 1:10 ethyl acetate/hexane R_f = 0.39; yellow liquid; yield 96%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89-7.86 (m, 1H), 7.59-7.57 (m, 2H), 7.35-7.18 (m, 10H), 2.44 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.5, 143.0, 138.6, 137.4, 134.4, 130.5, 130.1, 129.5, 128.3, 127.2, 123.3, 123.0, 119.8, 110.6, 21.3.

FT-IR (neat): 3061, 2924, 1610, 1515, 1473, 1455, 1384, 1324, 1262, 1180, 1109, 1020 cm^{-1}.

Anal. Calcd for $C_{20}H_{16}N_2$: C, 84.48; H, 5.67; N, 9.85. Found: C, 84.60; H, 5.64; N, 9.76.



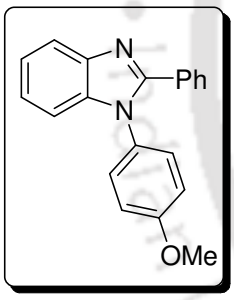
1-(2,4-Dimethylphenyl)-2-phenyl-1*H*-benzo[*d*]imidazole (2q). Analytical TLC on silica gel, 1:10 ethyl acetate/hexane R_f = 0.32; colorless liquid; yield 93%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, *J* = 8.0 Hz, 1H), 7.63-7.61 (m, 2H), 7.34-7.15 (m, 8H), 7.01-6.99 (d, *J* = 8.0 Hz, 1H), 2.43 (s, 3H), 1.86 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.4, 142.9, 139.4, 137.3, 135.6, 133.3, 132.3, 130.3, 129.5, 128.7, 128.4, 128.3, 128.2, 123.3, 122.8, 119.7, 110.6, 21.3, 17.5.

FT-IR (neat): 3061, 2959, 2922, 2858, 1613, 1505, 1472, 1455, 1441, 1380, 1322, 1308, 1277, 1263, 1239, 1206, 1192, 1155, 1136, 1074, 1029 cm^{-1}.

Anal. Calcd for $C_{21}H_{18}N_2$: C, 84.53; H, 6.08; N, 9.39. Found: C, 84.62; H, 6.07; N, 9.31.



1-(4-Methoxyphenyl)-2-phenyl-1*H*-benzo[*d*]imidazole (2r). Analytical TLC on silica gel, 1:10 ethyl acetate/hexane R_f = 0.29; colorless solid; yield 89%.

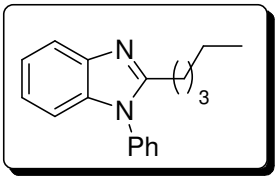
Mp: 119-120 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89-7.87 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.61-7.58 (m, 2H), 7.35-7.22 (m, 8H), 7.02-6.99 (m, 2H), 3.88 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.5, 152.6, 143.0, 137.7, 130.1, 129.7, 129.5, 128.6, 128.4, 123.3, 122.9, 119.8, 115.1, 110.6, 55.6.

FT-IR (KBr): 3062, 2957, 2839, 1606, 1514, 1472, 1458, 1442, 1325, 1311, 1294, 1276, 1250, 1212, 1192, 1104, 1077, 1030 cm^{-1}.

Anal. Calcd for $C_{20}H_{16}N_2O$: C, 79.98; H, 5.37; N, 9.33. Found: C, 80.11; H, 5.35; N, 9.24.



2-Pentyl-1-phenyl-1*H*-benzo[*d*]imidazole (2s). Analytical TLC on silica gel, 1:2 ethyl acetate/hexane R_f = 0.42; yellow liquid; yield 90%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, *J* = 8.0 Hz, 1H), 7.60-7.52 (m, 3H), 7.37-7.35 (d, *J* = 7.6 Hz, 2H), 7.28-7.25 (t, *J* = 8.0 Hz, 1H), 7.21-7.17 (t, *J* = 8.0 Hz, 1H), 7.10-7.08 (d, *J* = 7.6 Hz, 1H), 2.79-2.75 (t, *J* = 8.0 Hz, 2H), 1.79-1.74 (m, 2H), 1.35-1.24 (m, 4H), 0.83 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5, 142.7, 136.6, 136.2, 130.0, 129.0, 127.5, 122.6, 122.4, 119.2, 110.1, 31.6, 27.7, 27.8, 27.6, 22.4, 14.0.

FT-IR (neat): 3054, 2957, 2927, 2857, 1597, 1511, 1499, 1455, 1398, 1262, 1095, 1072, 1015 cm^{-1}.

Anal. Calcd for $C_{18}H_{20}N_2$: C, 81.78; H, 7.63; N, 10.60. Found: C, 81.89; H, 7.61; N, 10.50.

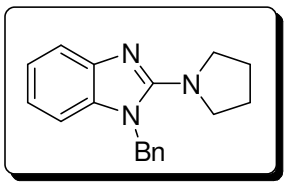
General Procedure for Synthesis of *o*-Bromoarylguanidines

To a stirred solution of 2-haloarylthiourea derivative (3.0 mmol), amine (6.0 mmol), Et_3N (6.0 mmol) and THF (9 mL) at room temperature, $HgCl_2$ (4.5 mol) was added and the stirring was further continued for 3-5 h. After completion, the reaction mixture was diluted with ethyl acetate (15 mL) and passed through celite. The solvent was evaporated and the residue was treated with ethyl acetate (25 mL). The solution was washed with aqueous ammonium chloride solution (10 mL) and water (10 mL). Drying (Na_2SO_4) and evaporation of the solvent afforded the titled compound which was sufficiently pure for the next step.

General Procedure for the Synthesis of Substituted 2-Aminobenzimidazoles

An oven dried 10 mL round bottom flask was charged with *o*-bromoarylguanidine (0.5 mmol), CuO nanoparticles (5 mol %, 2 mg), KOH (0.75 mmol, 42 mg) and DMSO (1 mL). The resultant mixture was stirred at 110 °C for the appropriate time (Table 5). The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. The reaction mixture was then cooled to room temperature and diluted with ethyl acetate (15 mL). The organic layer was washed successively with brine (1 x 4 mL) and water (2 x

4 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using ethyl acetate and hexane as eluent.



1-(Phenylmethyl)-2-(1-pyrrolidinyl)-1*H*-benzo[*d*]imidazole (4a). Analytical TLC on silica gel, 1:1 ethyl acetate/hexane R_f = 0.42; yellow solid; yield 73%.

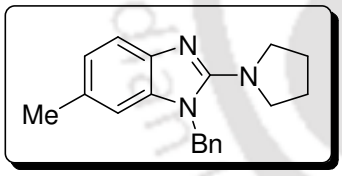
Mp: 132-133 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (d, *J* = 8.0 Hz, 1H), 7.32-7.27 (m, 3H), 7.16-7.12 (m, 2H), 7.02-6.95 (m, 3H), 5.27 (s, 2H), 3.54 (s, 4H), 1.91 (s, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.3, 142.5, 137.1, 136.3, 129.0, 127.6, 125.9, 121.9, 120.1, 116.7, 108.4, 50.6, 47.9, 25.8.

FT-IR (neat): 3027, 2958, 2924, 2868, 1606, 1594, 1552, 1484, 1455, 1406, 1361, 1349, 1285, 1008 cm^{-1}.

Anal. Calcd for $C_{18}H_{19}N_3$: C, 77.95; H, 6.90; N, 15.15. Found: C, 78.13, H, 6.87; N, 15.00.



1-(Phenylmethyl)-6-methyl-2-(1-pyrrolidinyl)-1*H*-benzo[*d*]imidazole (4b). Analytical TLC on silica gel, 1:1 ethyl acetate/hexane R_f = 0.46; yellow solid; yield 89%.

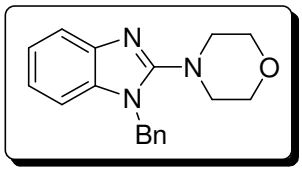
Mp: 125-126 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.0 Hz, 1H), 7.35-7.26 (m, 3H), 7.16 (d, *J* = 6.8 Hz, 2H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.77 (s, 1H), 5.25 (s, 2H), 3.50 (t, *J* = 6.8 Hz, 4H), 2.36 (s, 3H), 1.92-1.87 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.1, 140.3, 137.3, 136.5, 130.0, 129.0, 127.5, 125.9, 123.0, 116.4, 108.7, 50.7, 47.8, 25.7, 21.8.

FT-IR (KBr): 3021, 2924, 2856, 1623, 1596, 1549, 1489, 1449, 1411, 1352, 1280, 1257, 1026 cm^{-1}.

Anal. Calcd for $C_{19}H_{21}N_3$: C, 78.32; H, 7.26; N, 14.42. Found: C, 78.49; H, 7.20; N, 14.31.



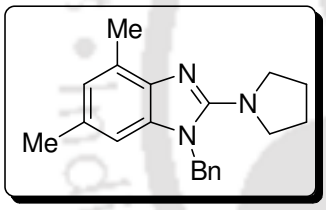
2-Morpholino-1-(phenylmethyl)-1*H*-benzo[*d*]imidazole (4c). Analytical TLC on silica gel, 2:3 ethyl acetate/hexane R_f = 0.34; thick liquid; yield 88%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J* = 8.0 Hz, 1H), 7.35-7.26 (m, 3H), 7.23-7.09 (m, 4H), 7.03 (d, *J* = 7.6 Hz, 1H), 5.25 (s, 2H), 3.81 (t, *J* = 4.4 Hz, 4H), 3.25 (t, *J* = 4.8 Hz, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.9, 141.6, 136.3, 135.6, 129.2, 127.9, 126.2, 122.3, 121.9, 118.4, 109.6, 66.7, 51.2, 47.8.

FT-IR (neat): 2950, 2923, 2851, 1613, 1536, 1517, 1412, 1382, 1283, 1252, 1234, 1116, 1026 cm^{-1}.

Anal. Calcd for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.32. Found: C, 73.83; H, 6.49; N, 14.20.



1-(Phenylmethyl)-4,6-dimethyl-2-(1-pyrrolidinyl)-1*H*-benzo[*d*]imidazole (4d). Analytical TLC on silica gel, 2:3 ethyl acetate/hexane R_f = 0.55; colorless solid; yield 90%.

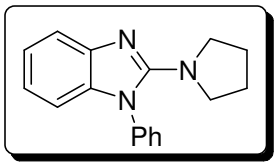
Mp: 116-117 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.25 (m, 3H), 7.15 (d, *J* = 8.0 Hz, 2H), 6.79 (s, 1H), 6.62 (s, 1H), 5.22 (s, 2H), 3.51-3.48 (m, 4H), 2.57 (s, 3H), 2.33 (s, 3H), 1.91-1.88 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.8, 139.3, 137.4, 136.1, 129.8, 128.9, 127.4, 126.2, 125.9, 123.9, 106.3, 50.8, 47.8, 25.7, 21.7, 16.8.

FT-IR (KBr): 2966, 2918, 2862, 1603, 1531, 1485, 1454, 1415, 1359, 1267, 1227, 997 cm^{-1}.

Anal. Calcd for $C_{20}H_{23}N_3$: C, 78.65; H, 7.59; N, 13.76. Found: C, 78.79; H, 7.53; N, 13.68.



1-Phenyl-2-(1-pyrrolidinyl)-1*H*-benzo[*d*]imidazole (4e). Analytical TLC on silica gel, 1:1 ethyl acetate/hexane R_f = 0.52; colorless solid; yield 95%.

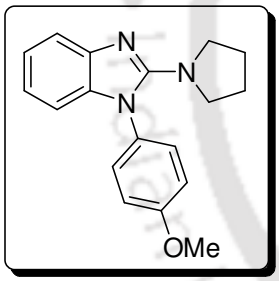
Mp: 109-110 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55-7.50 (m, 3H), 7.47-7.42 (m, 3H), 7.13 (dt, *J* = 7.2, 1.2 Hz, 1H), 6.95 (dt, *J* = 8.0, 1.2 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 3.32-3.28 (m, 4H), 1.85-1.82 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5, 142.4, 137.4, 137.0, 129.7, 128.4, 127.9, 122.1, 119.7, 116.1, 108.3, 49.9, 25.7.

FT-IR (KBr): 3026, 2952, 2924, 2852, 2875, 1613, 1599, 1557, 1482, 1461, 1411, 1289, 1267, 962 cm^{-1}.

Anal. Calcd for $C_{17}H_{17}N_3$: C, 77.54; H, 6.51; N, 15.96. Found: C, 77.72; H, 6.43; N, 15.85.



1-(4-Methoxyphenyl)-2-(1-pyrrolidinyl)-1*H*-benzo[*d*]imidazole (4f). Analytical TLC on silica gel, 2:3 ethyl acetate/hexane R_f = 0.28; yellow solid; yield 78%.

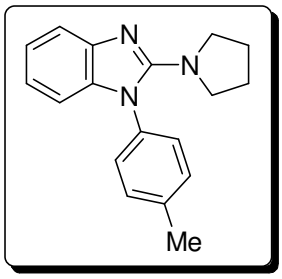
Mp: 228-229 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.12 (t, *J* = 7.6 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.95 (t, *J* = 8.0 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 3.88 (s, 3H), 3.30 (t, *J* = 6.4 Hz, 4H), 1.85-1.82 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.5, 155.6, 142.3, 137.5, 130.0, 129.3, 122.0, 119.6, 116.0, 114.8, 108.4, 55.7, 49.8, 25.7.

FT-IR (KBr): 3038, 2954, 2924, 2853, 1610, 1596, 1549, 1515, 1462, 1413, 1268, 1251, 1027 cm^{-1}.

Anal. Calcd for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.32. Found: C, 73.88; H, 6.50; N, 14.22.



1-(4-Methylphenyl)-2-(1-pyrrolidinyl)-1*H*-benzo[*d*]imidazole (4g). Analytical TLC on silica gel, 2:3 ethyl acetate/hexane R_f = 0.42; colorless solid; yield 93%.

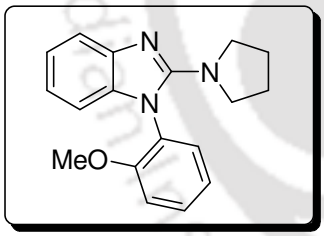
Mp: 169-170 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, *J* = 8.0 Hz, 1H), 7.30 (s, 4H), 7.12 (dt, *J* = 7.6, 1.2 Hz, 1H), 6.95 (dt, *J* = 8.0, 0.8 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 3.30 (t, *J* = 6.8 Hz, 4H), 2.45 (s, 3H), 1.85-1.82 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6, 142.5, 138.4, 137.2, 134.8, 130.3, 127.8, 122.0, 119.6, 116.1, 108.4, 49.9, 25.7, 21.4.

FT-IR (KBr): 3050, 3027, 2977, 2921, 2877, 2851, 1611, 1597, 1550, 1514, 1483, 1461, 1411, 1265, 1179, 1004, 962 cm^{-1}.

Anal. Calcd for $C_{18}H_{19}N_3$: C, 77.95; H, 6.90; N, 15.15. Found: C, 78.15; H, 6.85; N, 15.00.



1-(2-Methoxyphenyl)-2-(1-pyrrolidinyl)-1*H*-benzo[*d*]imidazole (4h). Analytical TLC on silica gel, 1:1 ethyl acetate/hexane R_f = 0.35; colorless solid; yield 88%.

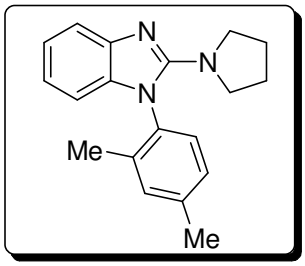
Mp: 175-176 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.43 (m, 2H), 7.34-7.32 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.12-7.04 (m, 3H), 6.91 (dt, *J* = 8.0, 1.2 Hz, 1H), 6.69-6.67 (m, 1H), 3.77 (s, 3H), 3.33-3.27 (m, 4H), 1.86-1.80 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.1, 155.5, 142.7, 137.1, 130.4, 130.2, 126.0, 121.7, 121.0, 119.2, 115.8, 112.1, 108.4, 55.9, 49.1, 25.7.

FT-IR (KBr): 3045, 3007, 2962, 2928, 2864, 1601, 1557, 1505, 1463, 1410, 1269, 1269, 1171, 1022 cm^{-1}.

Anal. Calcd for $C_{18}H_{19}N_3O$: C, 73.69; H, 6.53; N, 14.32. Found: C, 73.82; H, 6.49; N, 14.20.



1-(2,4-Dimethylphenyl)-2-(1-pyrrolidinyl)-1*H*-benzo[*d*]imidazole (4i). Analytical TLC on silica gel, 1:1 ethyl acetate/hexane $R_f = 0.50$; colorless solid; yield 83%.

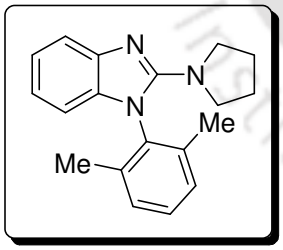
Mp: 115-116 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, *J* = 8.0 Hz, 1H), 7.21-7.09 (m, 4H), 6.93 (t, *J* = 8.0 Hz, 1H), 6.65 (d, *J* = 7.6 Hz, 1H), 3.34-3.22 (m, 4H), 2.41 (s, 3H), 2.04 (s, 3H), 1.85-1.81 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.2, 142.6, 139.1, 136.7, 133.6, 131.8, 129.0, 127.8, 121.8, 119.5, 116.0, 108.4, 49.2, 25.7, 21.3, 17.6.

FT-IR (KBr): 3036, 2964, 2925, 2878, 2852, 1610, 1596, 1539, 1484, 1458, 1410, 1264, 1181, 1147, 1003, 961 cm^{-1}.

Anal. Calcd for $C_{19}H_{21}N_3$: C, 78.32; H, 7.26; N, 14.42. Found: C, 78.53; H, 7.20; N, 14.27.



1-(2,6-Dimethylphenyl)-2-(1-pyrrolidinyl)-1*H*-benzo[*d*]imidazole (4j). Analytical TLC on silica gel, 1:1 ethyl acetate/hexane $R_f = 0.47$; colorless solid; yield 80%.

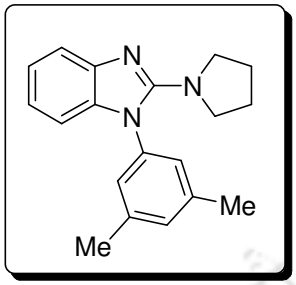
Mp: 138-139 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, *J* = 8.4 Hz, 1H), 7.28 (t, *J* = 8.0 Hz, 1H), 7.17 (d, *J* = 7.6 Hz, 2H), 7.12 (dt, *J* = 7.6, 1.2 Hz, 1H), 6.92 (dt, *J* = 7.6, 1.2 Hz, 1H), 6.57 (dd, *J* = 8.0, 0.4 Hz, 1H), 3.28-3.24 (m, 4H), 2.05 (s, 6H), 1.85-1.82 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 154.5, 143.0, 137.5, 135.3, 135.1, 129.1, 128.5, 121.8, 119.4, 116.0, 108.1, 48.7, 25.7, 17.9.

FT-IR (KBr): 3004, 2974, 2950, 2863, 1613, 1600, 1556, 1455, 1398, 1286, 1267, 1173, 1144, 959 cm^{-1}.

Anal. Calcd for $C_{19}H_{21}N_3$: C, 78.32; H, 7.26; N, 14.42. Found: C, 78.60; H, 7.19; N, 14.21.



1-(3,5-Dimethylphenyl)-2-(1-pyrrolidinyl)-1*H*-benzo[*d*]imidazole (4k). Analytical TLC on silica gel, 1:1 ethyl acetate/hexane $R_f = 0.51$; colorless solid; yield 95%.

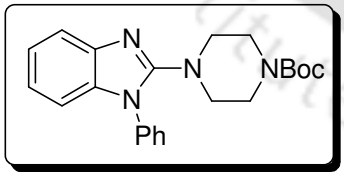
Mp: 187-188 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, *J* = 7.2 Hz, 1H), 7.12 (dt, *J* = 7.2, 1.2 Hz, 1H), 7.07 (s, 1H), 7.03 (s, 2H), 6.95 (dt, *J* = 7.6, 0.8 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 3.34-3.30 (m, 4H), 2.38 (s, 6H), 1.86-1.83 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5, 142.4, 139.5, 137.3, 137.2, 130.1, 125.6, 122.0, 119.6, 116.0, 108.5, 50.0, 25.8, 21.5.

FT-IR (KBr): 3016, 2962, 2923, 2873, 1610, 1602, 1560, 1460, 1406, 1273, 1179, 1151, 1049 cm^{-1}.

Anal. Calcd for $C_{19}H_{21}N_3$: C, 78.32; H, 7.26; N, 14.42. Found: C, 78.45; H, 7.22; N, 14.37.



***tert*-Butyl-4-(1-phenyl-1*H*-benzo[*d*]imidazol-2-yl)piperazine-1-carboxylate (4l).** Analytical TLC on silica gel, 2:3 ethyl acetate/hexane $R_f = 0.51$; thick liquid; yield 90%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62-7.43 (m, 6H), 7.27-7.18 (m, 1H), 7.12-7.08 (m, 2H), 3.40-3.38 (m, 4H), 3.21-3.18 (m, 4H), 1.44 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.2, 154.8, 141.4, 136.9, 135.9, 130.05, 128.3, 126.1, 122.4, 121.4, 117.6, 108.9, 80.1, 48.8, 28.4.

FT-IR (neat): 3049, 2976, 2929, 2858, 1695, 1597, 1530, 1416, 1247, 1169, 1127, 999 cm^{-1}.

Anal. Calcd for $C_{22}H_{26}N_4O_2$: C, 69.82; H, 6.92; N, 14.80. Found: C, 69.99; H, 6.86; N, 14.68.

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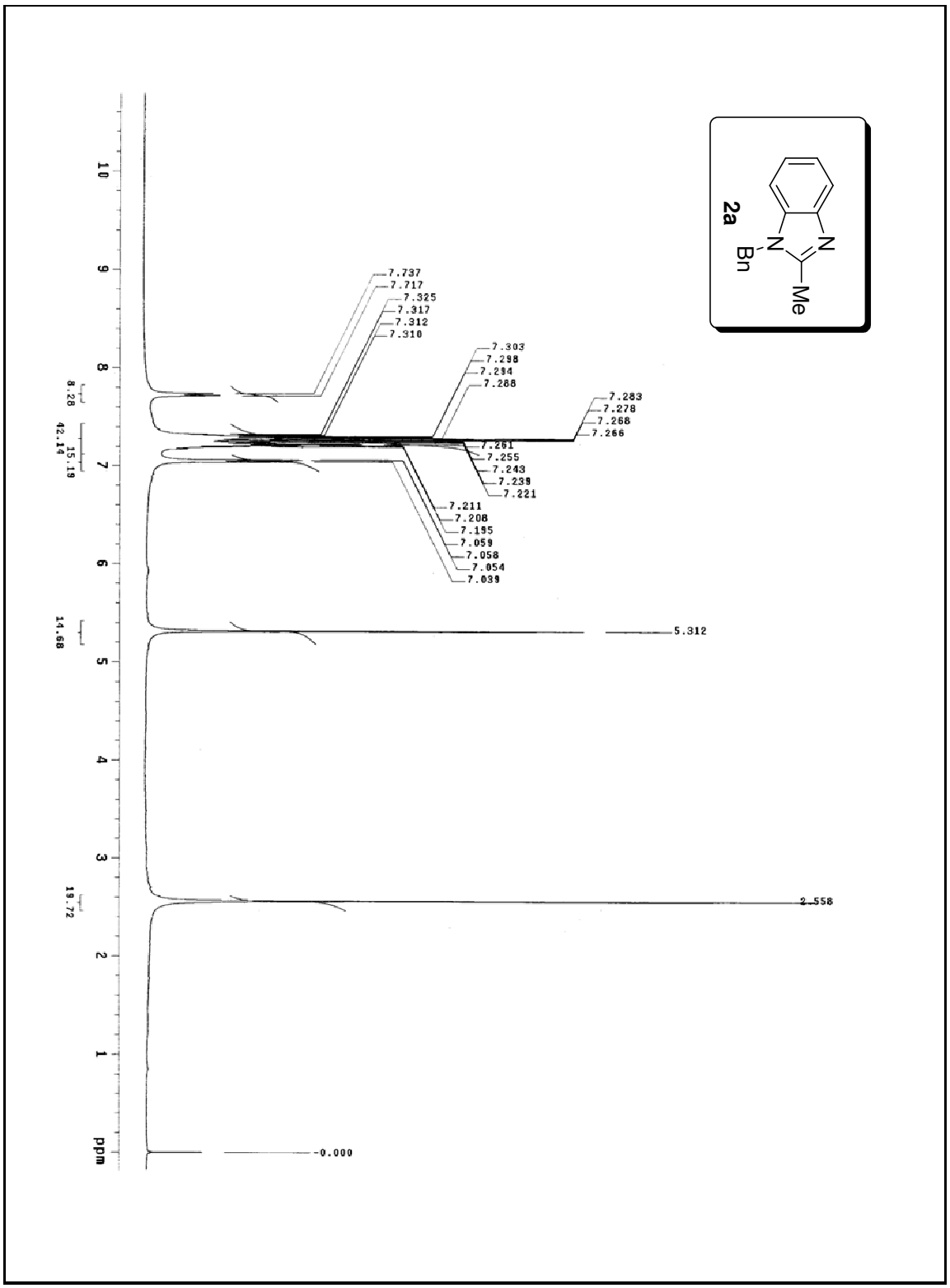
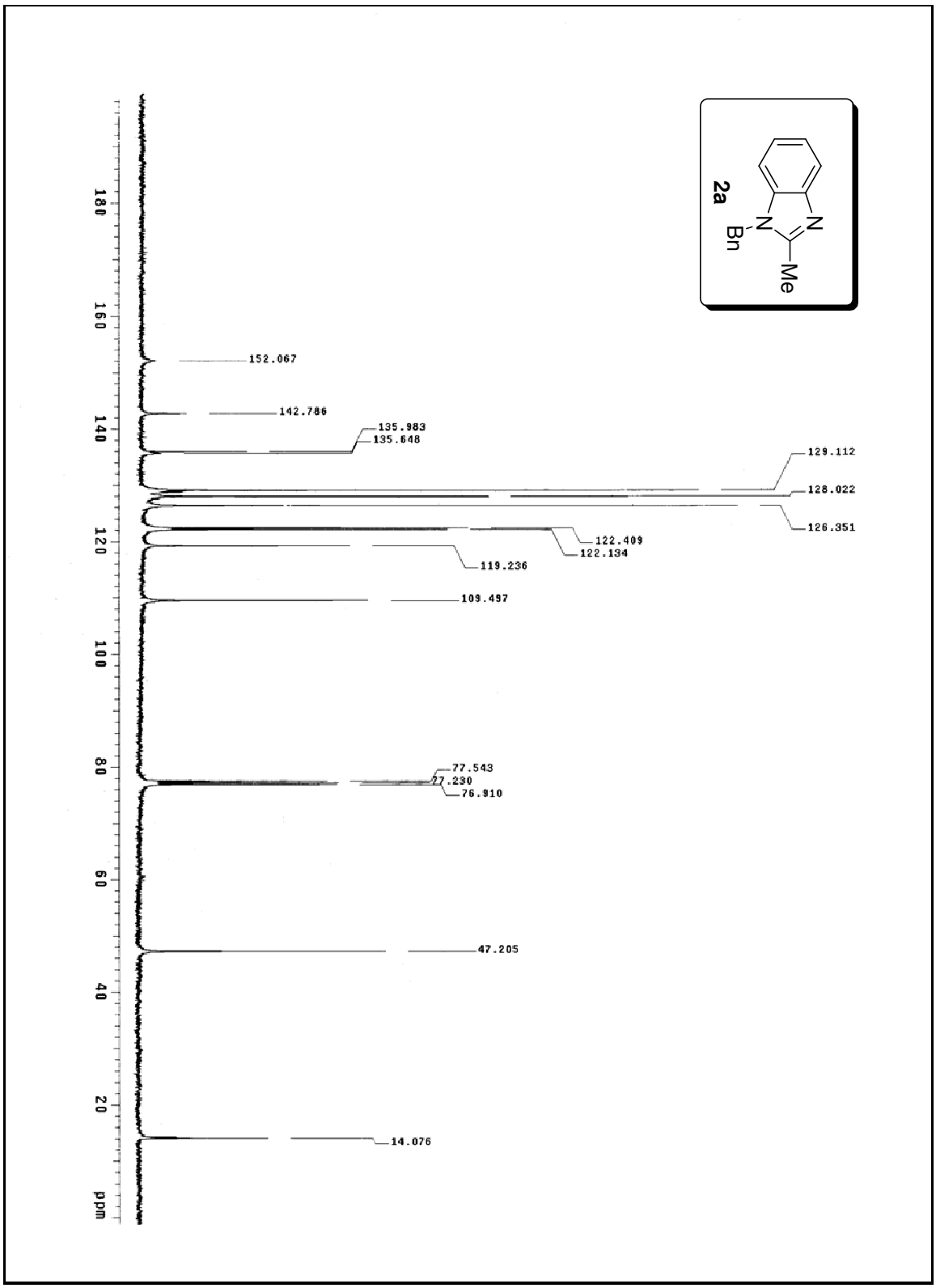
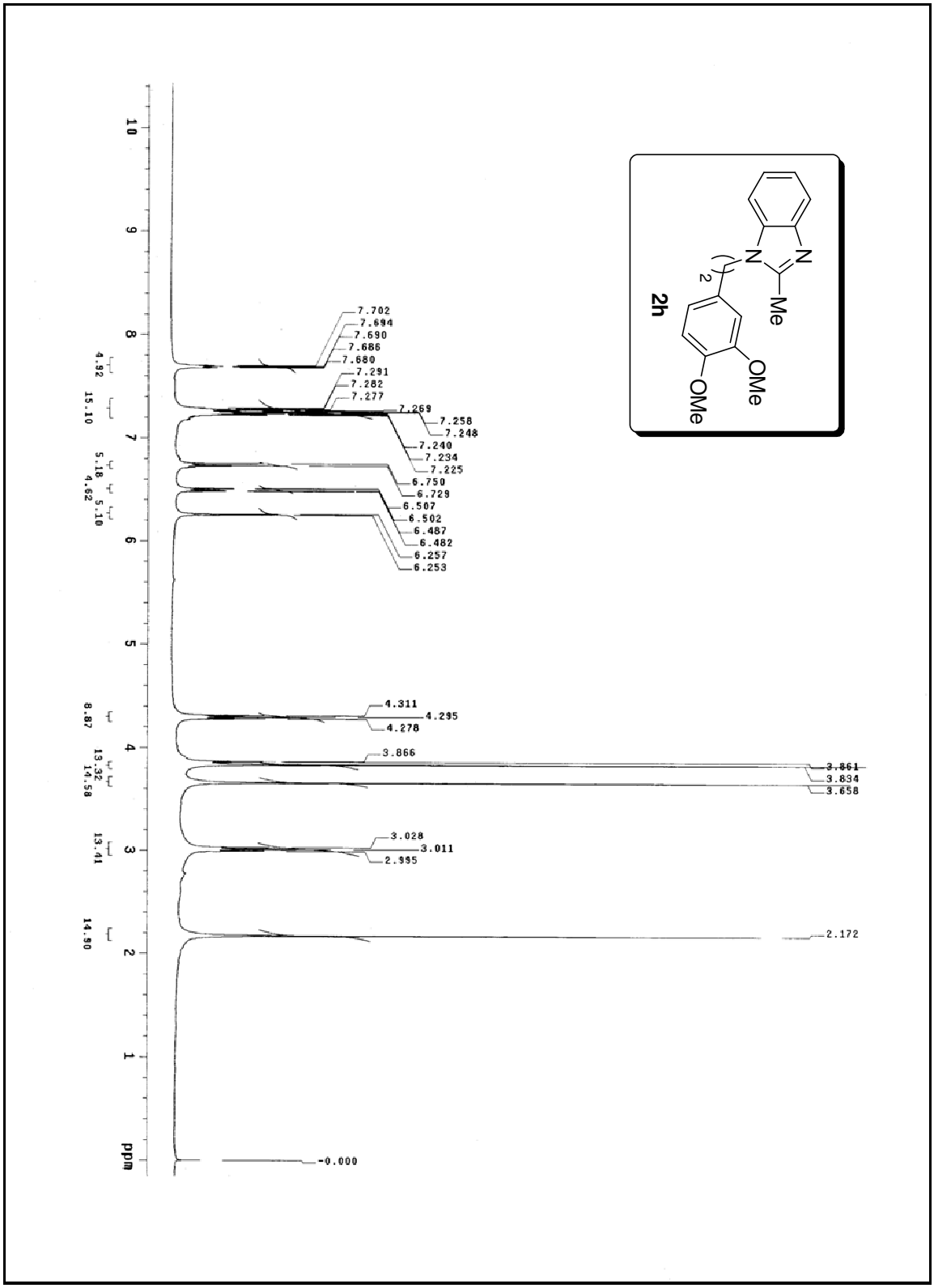
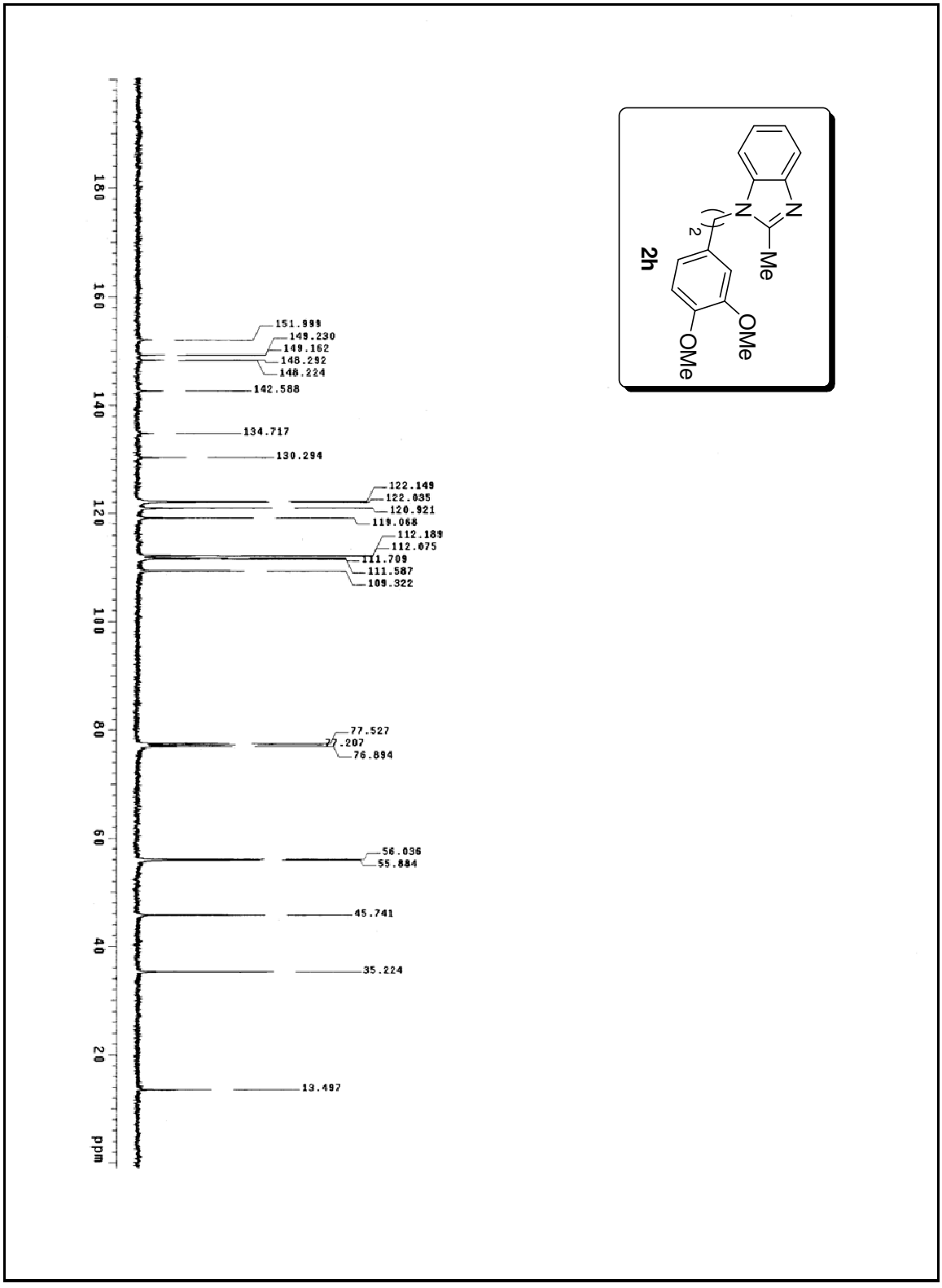
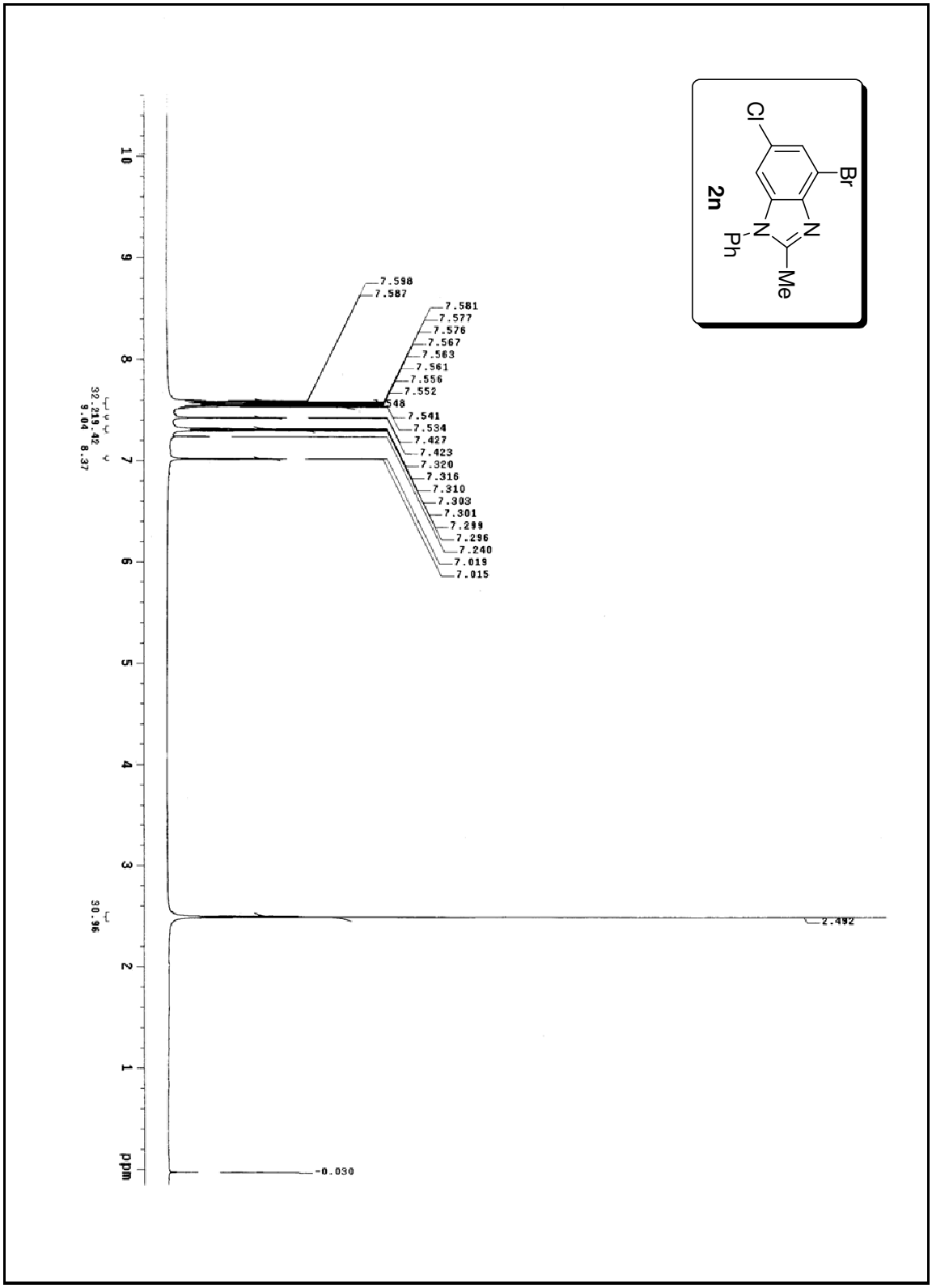
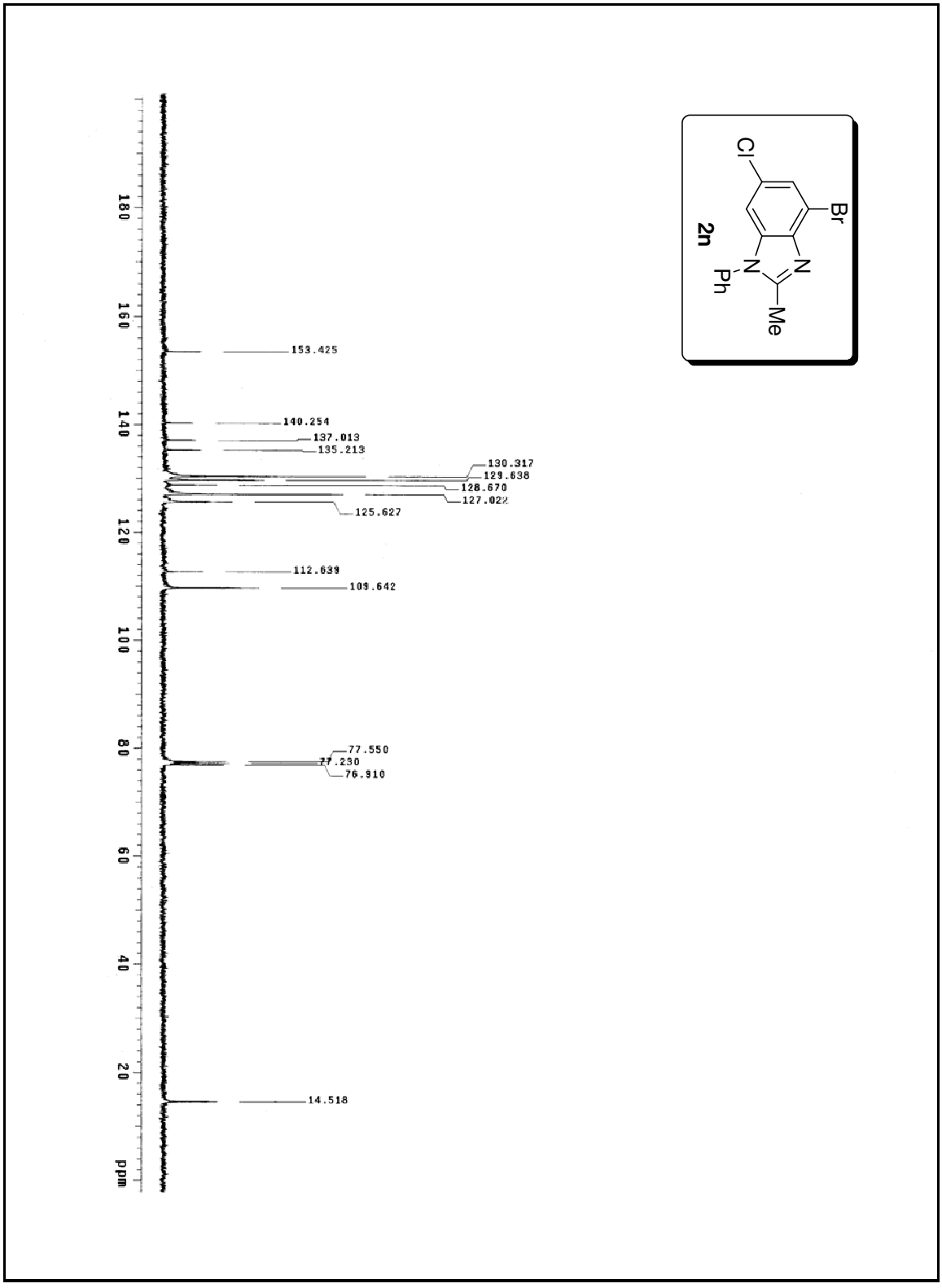


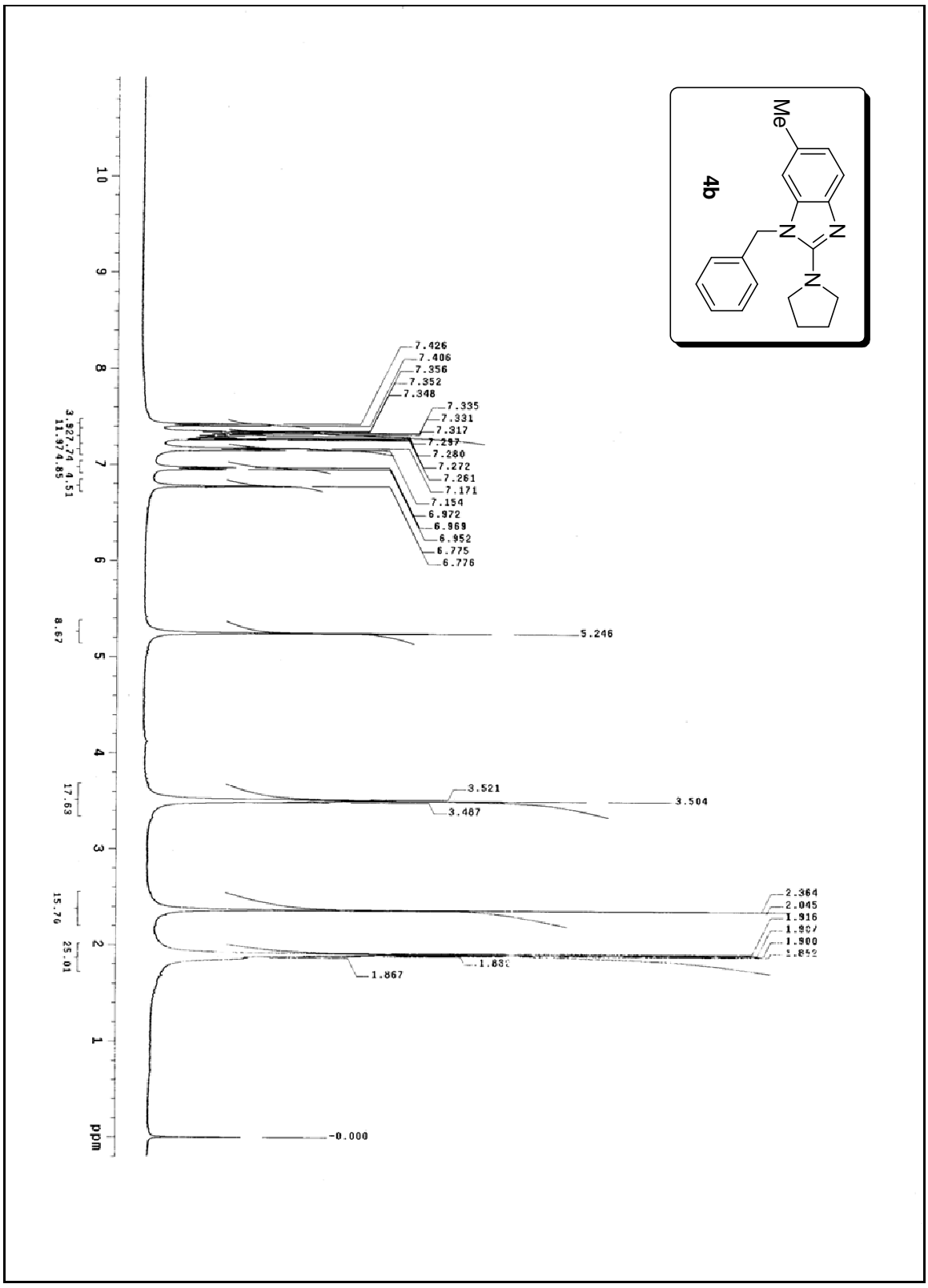


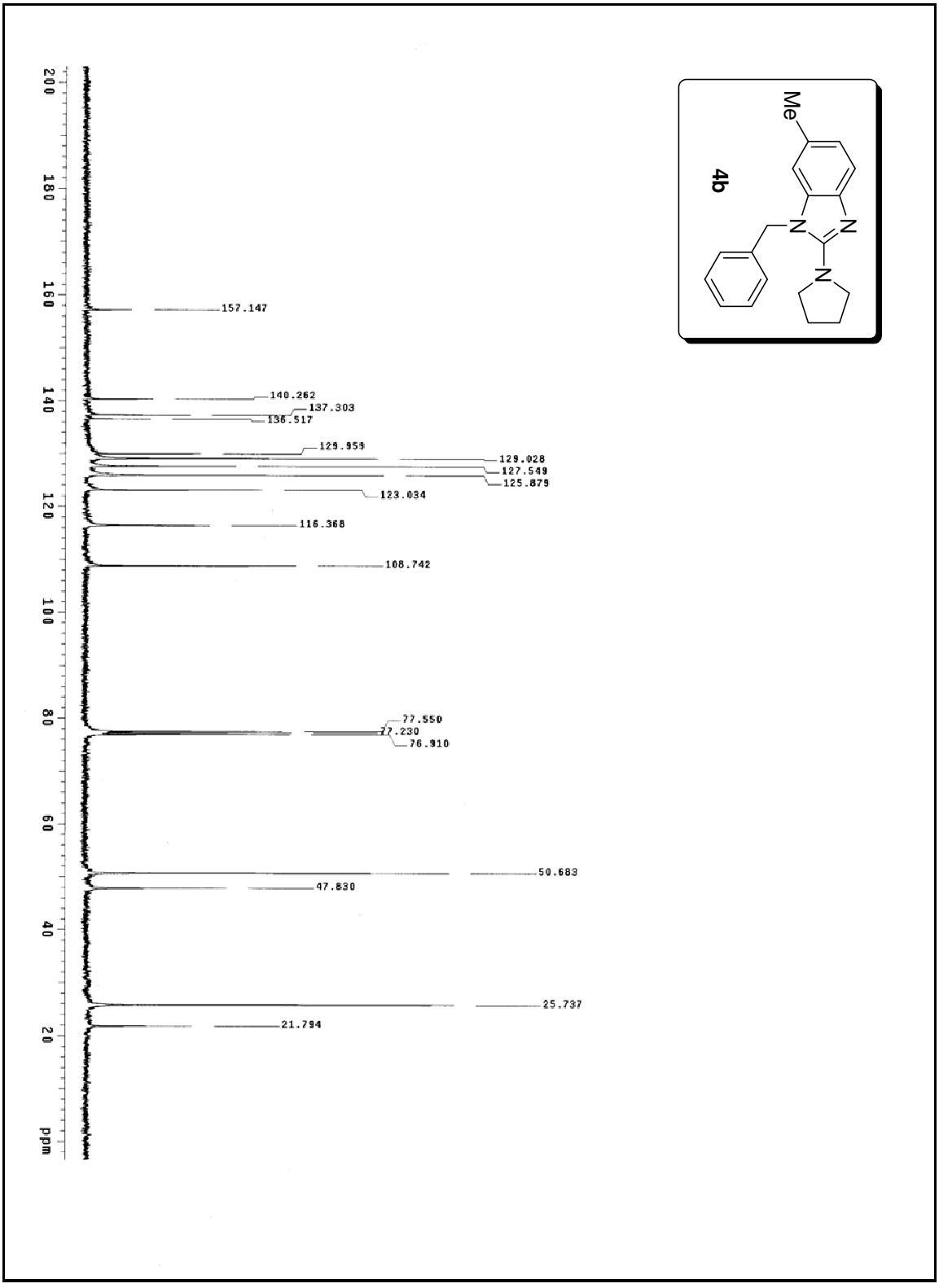


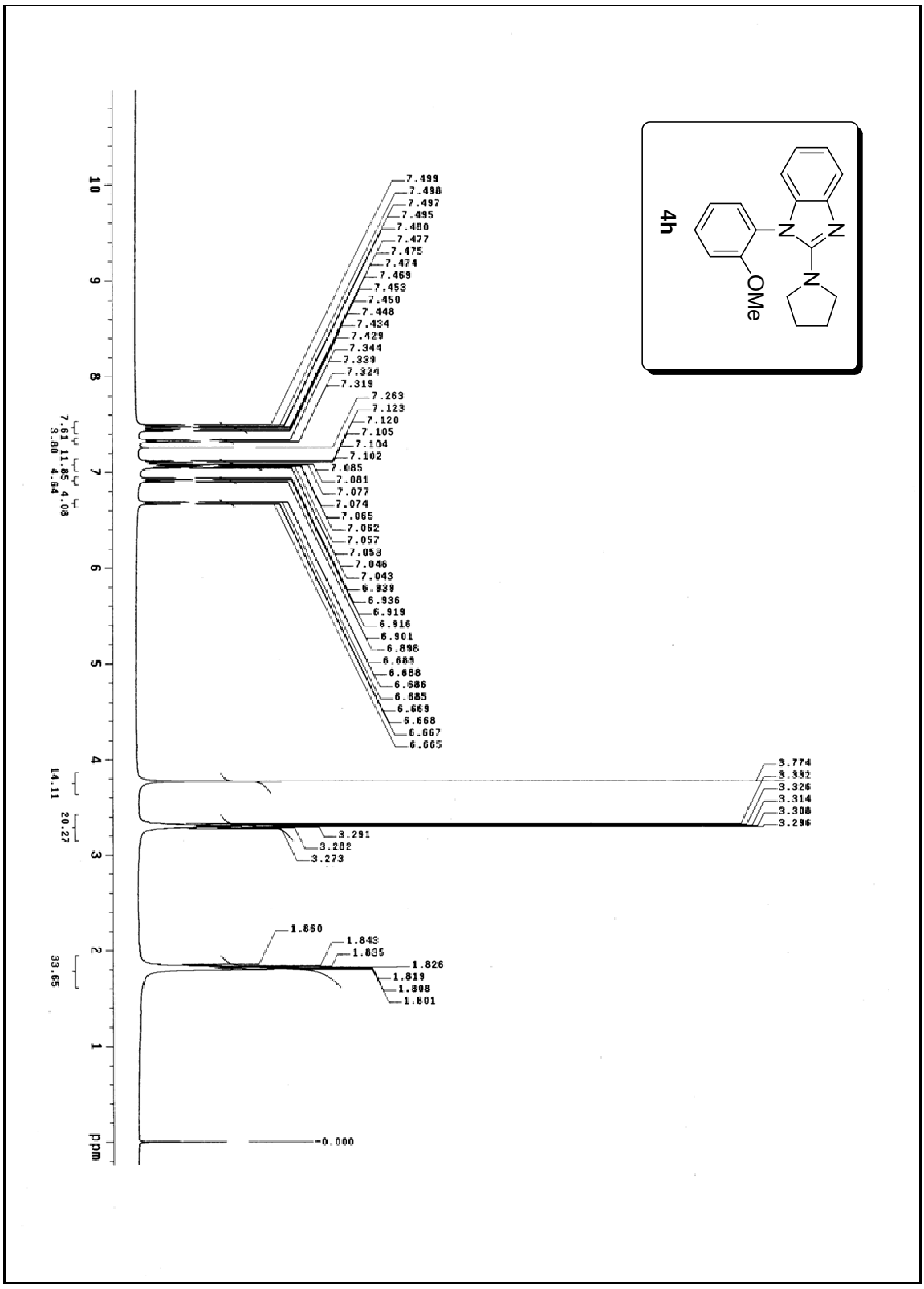


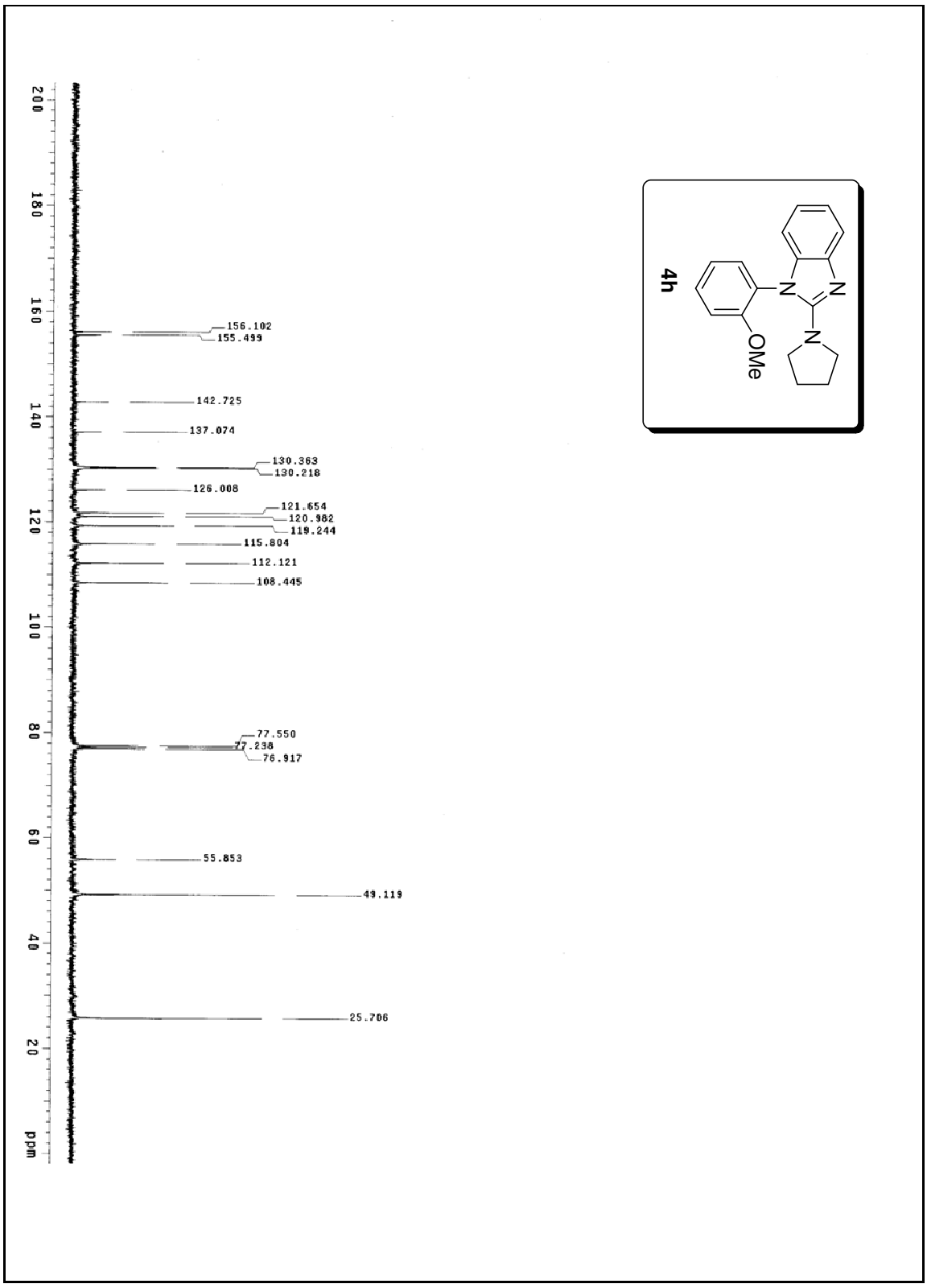












Chapter II

CuO Nanoparticles Catalyzed Intramolecular *C–O* Cross-Coupling Reaction: Synthesis of 2-Alkyl and 2-Arylbenzoxazoles

Benzoxazoles are an important structural motif found in wide range of natural products and biologically active compounds (Figure 1).[1] For examples, benzoxazole moiety has been found in variety of cytotoxic natural products such as antimycobacterial pseudopteroxazole,[2a-b] salvianen,[2c] UK-1[2d] and AJI9561.[2e] They also have been used in medicinal chemistry due to their biological activities such as 5-HT3 receptor agonist,[3a] HIV reverse transcriptase inhibitor L-697,661,[3b] estrogen receptor-β agonist ERB-041,[3c] selective peroxisome proliferator-activated receptor γ antagonist JTP-426467,[3d] anticancer agent NSC-693638[1a] and orexin-1 receptor antagonist SB-334867.[3e] In addition, they also have been used as herbicides, such as fenoxaprop and as fluorescent whitening agent dyes such as bisbenzoxazolyl ethylenes and arenes.[4]

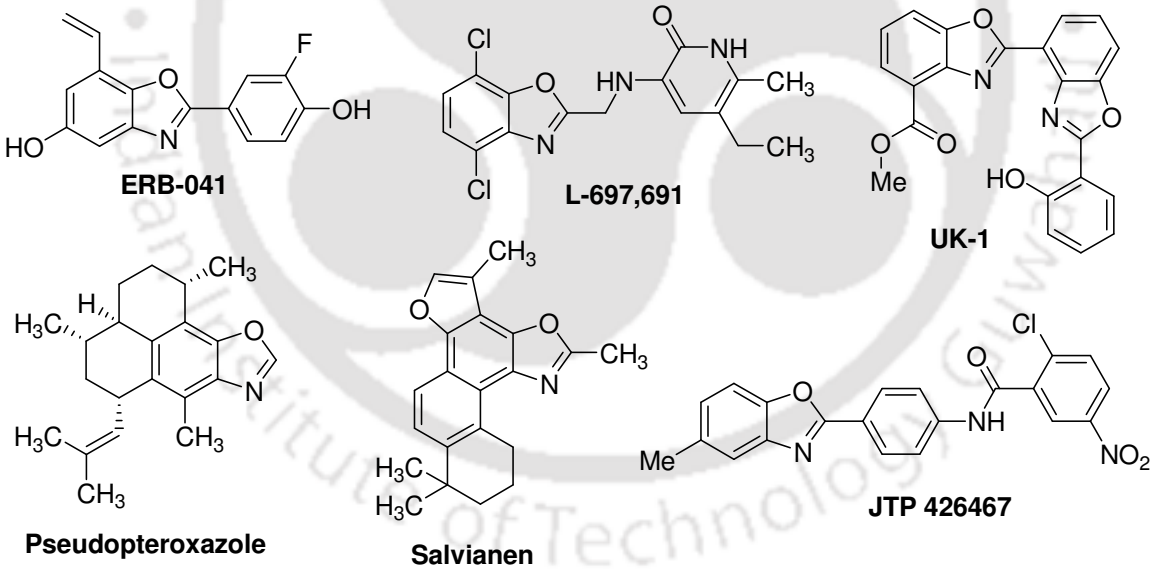


Figure 1. Examples of some biologically active compounds and natural products.

The common methods used for the preparation of benzoxazoles involve the condensation of *o*-aminophenol with either carboxylic acid under strong acidic condition[5] or an aldehyde followed by oxidative cyclization using oxidant such as 2,3-dichloro-5,6-dicyano-l,4-benzoquinone (DDQ),[6a] $PhI(OAc)_2$,[6b] $ThClO_4$,[6c] $Ba(MnO_4)_2$,[6d] $Mn(OAc)_2$,[6e] NiO_2,[6f] $Pb(OAc)_4$[6g] and pyridiniumchlorochromate (PCC)[6h] (Figure 2). However, the

classical methods are often limited with non-availability of the suitably substituted substrates and requirement of harsh reaction conditions. To overcome these drawbacks, much attention has been recently paid to the development of efficient method for the synthesis of benzoxazoles under relatively milder conditions.

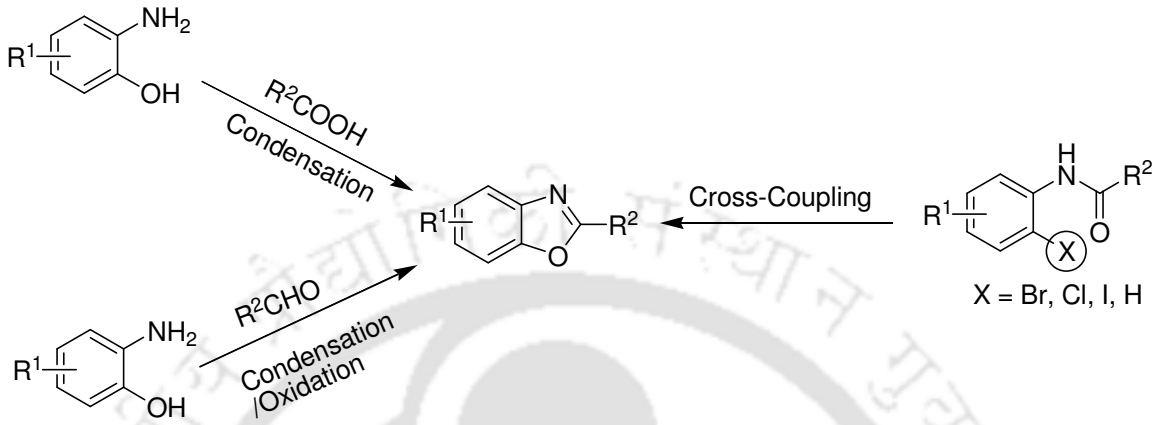
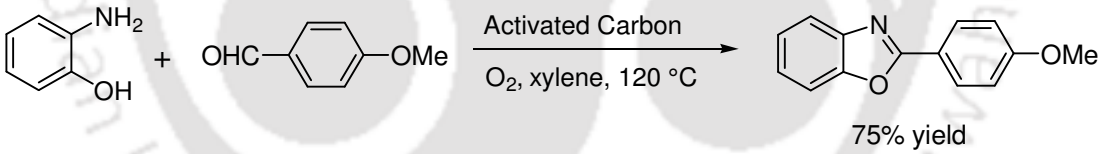


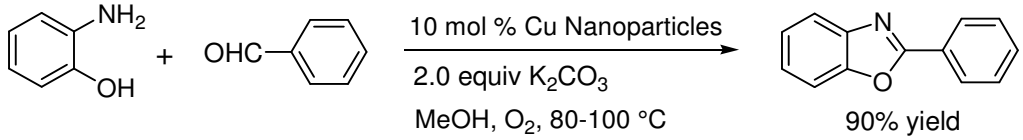
Figure 2. Different approaches for the synthesis of 2-substituted benzoxazoles.

Hayashi and co-workers developed a method for the synthesis of 2-arylbenzoxazoles from substituted 2-aminophenols and aldehydes in the presence of activated carbon (Dacro KB) in xylene under an oxygen atmoshphere (Scheme 1).[6i]



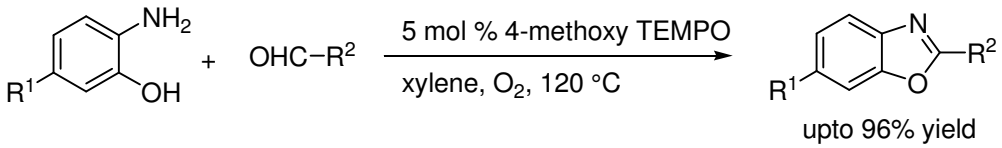
Scheme 1

Kidwai and co-workers reported the synthesis of 2-arylbenzoxazoles by the coupling of aromatic or heteroaromatic aldehydes with substituted 2-aminophenols through the oxidative cyclization of the Schiff bases using 10 mol % of the Cu nanoparticles in the presence of K_2CO_3 in MeOH (Scheme 2).[6j] This method involves molecular oxygen as oxidant and the products can be obtained in good yield.



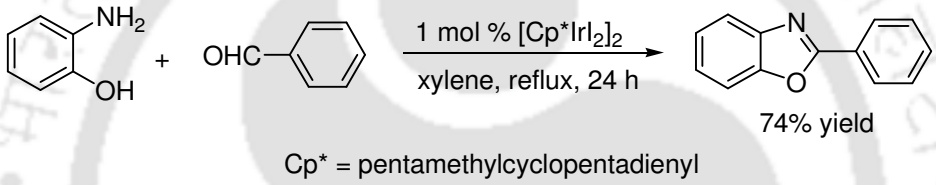
Scheme 2

Han and co-workers demonstrated the aerobic catalytic oxidative synthesis of 2-substituted benzoxazoles from 2-benzylideneaminophenols (Scheme 3).[6k] 2-Substituted benzoxazoles can be prepared by the reaction of aldehydes and 2-aminophenols in presence of 4-methoxy-TEMPO as the catalyst.



Scheme 3

Blacker and co-workers developed a procedure for the synthesis of 2-arylbenzoxazoles from benzaldehyde and 2-aminophenol using 1 mol % of $[Cp^*IrI_2]_2$ as a catlyst in xylene under reflux condition with good yield.[6l]

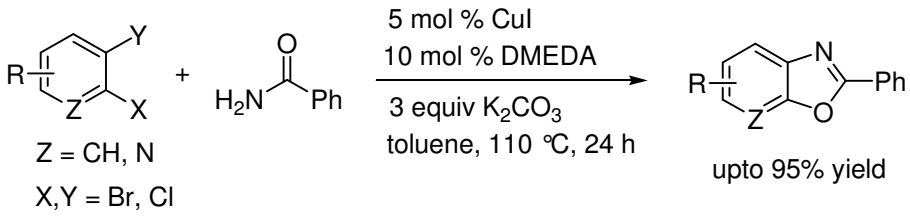


Scheme 4

However, these routes are limited by the non-availability of the suitably substituted *o*-aminophenols. Thus, much attention has been focused recently to develop alternative routes for benzoxazole preparation.

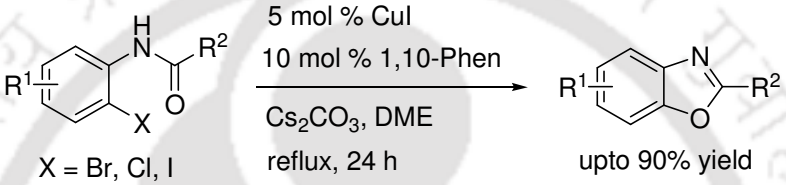
2.1 Copper Catalysts

Copper catalyzed intermolecular *C–O* cross-coupling reactions have been explored in the past few years.[7] Recently, synthesis of benzoxazoles has been achieved by copper mediated intramolecular *C–O* cross coupling reactions. Altenhoff and Glorius reported the synthesis of benzoxazoles using domino *C–N* and *C–O* cross-coupling reactions of *o*-dihalobenzene with primary amides (Scheme 5).[8a] They have used the combination of CuI and *N,N'*-dimethylethylenediamine (DMEDA) as a catalyst for these reactions. The reaction provides the target benzoxazoles with good yield.



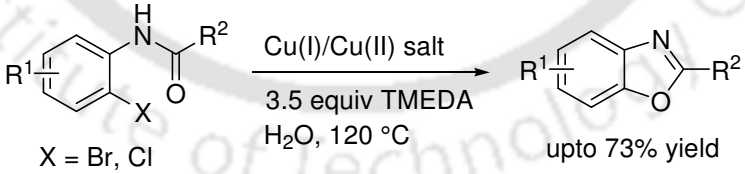
Scheme 5

Evindar and Batey reported the synthesis of benzoxazoles by intramolecular *C–O* cross-coupling of the *o*-halobenzanilides using CuI/1,10-phenanthroline in presence of Cs_2CO_3 in DME under reflux conditions (Scheme 6).[8b-c] Under these conditions, *o*-halobenzanilides undergo cyclization to give benzoxazoles with high yield.



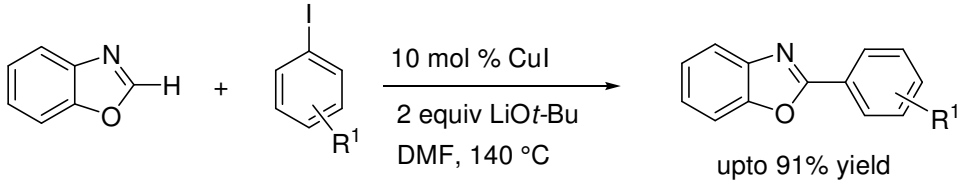
Scheme 6

Dominguez and co-workers showed the synthesis of benzoxazoles through an intramolecular *O*-arylation of *o*-halobenzanilides (Scheme 7).[8d] The reaction consists of the use of catalytic amount of copper salt and tetramethylethylenediamine (TMEDA) in the presence of base in water. Under these conditions, *o*-bromo- and *o*-chlorobenzanilides undergo cyclization to give benzoxazole with moderate yield, whereas *o*-iodobenzanilides give the cyclized product with poor yield.



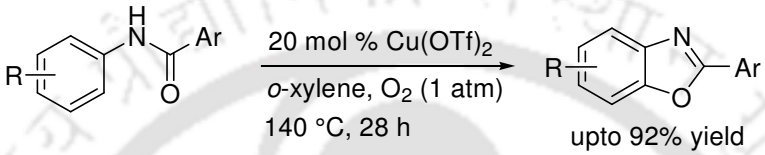
Scheme 7

Do and Dougulis developed a method for the synthesis of 2-arylbenzoxazoles by copper catalyzed arylation of hetrocyclic *C–H* bonds with aryl iodides (Scheme 8).[8e] The best results are obtained by reaction with aryl iodides with lithium *tert*-butoxide as a base.



Scheme 8

Ueda and Nagasawa reported the synthesis of 2-arylbenzoxazoles using $Cu(OTf)_2$ as a catalyst by intramolecular oxidative aromatic *C–O* coupling of benzanilides with high yield (Scheme 9).[8f]



Scheme 9

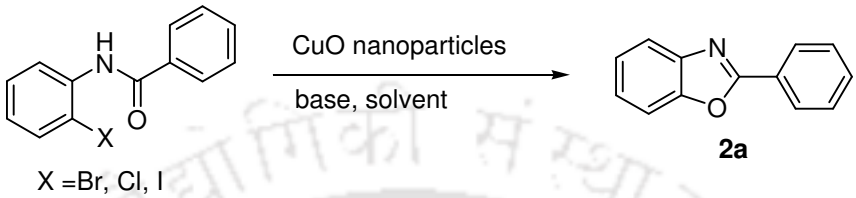
2.2 Present Study

Following the success of CuO nanoparticles catalyzed synthesis of 2-substituted benzimidazoles, we have studied the synthesis of benzoxazoles from *o*-halobenzanilides. *o*-Halobenzanilides were prepared from the readily available *o*-haloanilines and acid chlorides. Optimization of the reaction conditions was carried out using *N*-(2-bromophenyl)benzamide **1a** as a standard substrate (Table 1). We were pleased to observe that the substrate underwent intramolecular *C–N* cross-coupling reaction to give the desired 2-phenylbenzoxazole **2a** with 99% conversion when the substrate was stirred in presence of 5 mol % of CuO nanoparticles and 1.5 equiv of K_2CO_3 in DMSO at 110 °C. The bases such as Cs_2CO_3 and KOH showed similar reactivity. Among the solvents studied, 2-propanol, toluene and acetonitrile were ineffective, whereas DMF and 1,4-dioxane gave moderate yield. When the quantitity of the catalyst (2.5 mol %) or temperature (90 °C) was reduced, the yield of the target molecule was dropped. *o*-Iodophenylbenzamides are more reactive compared to *o*-bromophenylbenzamides, whereas no reaction was observed with *o*-chlorophenylbenzamide. Control experiment without CuO nanoparticles showed no reaction.

The scope of the procedure was next investigated for other substrates (Table 2). *N*-(*o*-Bromophenyl)arylamides **1b-e** having Br, NO_2 and 4-Me substituents underwent intramolecular *C-N* cross-coupling reaction to give the corresponding 2-arylbenzoxazoles

2b-e with 60-92% yield. Likewise, *N*-(*o*-bromoaryl)benzamides **1f-j** substituted with Br, Cl, OMe and Me groups could be cyclized with 61-91% yields. The subsrtates having electron withdrawing group shows moderate reactivity compared to that containing electron donating group.

Table 1. Optimization of Reaction Conditions[a]



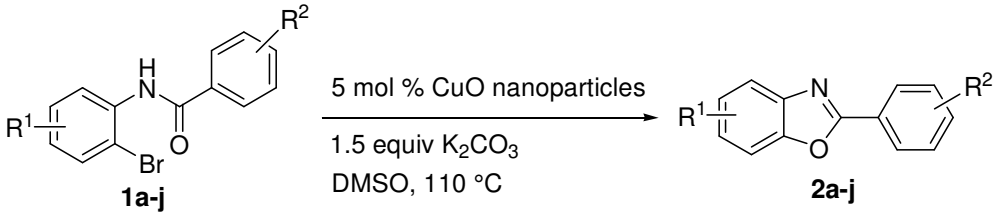
X =Br, Cl, I

2a

entry	X	base	solvent	temp (℃)	time (h)	conversion (%)[b]
1	Br	Cs_2CO_3	DMSO	110	15	99
2	Br	K_2CO_3	DMSO	110	16	99 (95)
3	Br	KOH	DMSO	110	16	99
4	Br	K_2CO_3	DMF	110	16	81
5	Br	K_2CO_3	toluene	110	16	10
6	Br	K_2CO_3	1,4-dioxane	110	16	66
7	Br	K_2CO_3	CH_3CN	110	16	25
8	Br	K_2CO_3	*i*-PrOH	110	16	25
9	I	K_2CO_3	DMSO	110	10	99
10	Cl	K_2CO_3	DMSO	110	24	nr
11	Br	K_2CO_3	DMSO	90	24	26
12	I	K_2CO_3	DMSO	90	24	73
13[c]	Br	K_2CO_3	DMSO	110	24	80
14[d]	Br	K_2CO_3	DMSO	110	24	62
15[e]	Br	K_2CO_3	DMSO	110	24	nr

[a] *o*-Halophenylbenzamide (0.5 mmol), CuO nanoparticles (5 mol %) and base (0.75 mmol) were stirred at appropriate temperature in solvent (1 mL) under air. [b] Determined from 400 MHz ^{1}H NMR. [c] 2.5 mol % CuO was used. [d] K_2CO_3 (0.5 mmol) was used. [e] Reaction was carried out in absence of CuO nanoparticles. nr = No reaction. Isolated yield in parenthesis.

Table 2. CuO Nanoparticles Catalyzed Synthesis of 2-Arylbenzoxazoles[a]



1a-j **2a-j**

R^1 = H, Br, Cl, Me, OMe

R^2 = H, Br, Me, NO_2

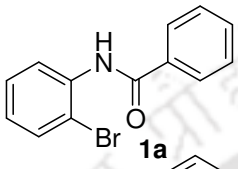
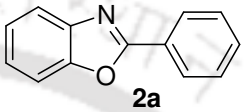
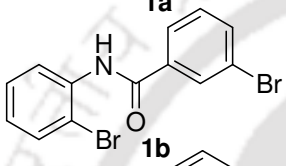
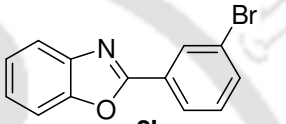
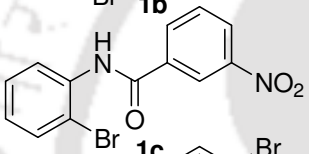
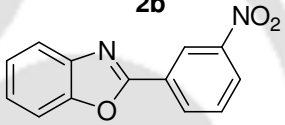
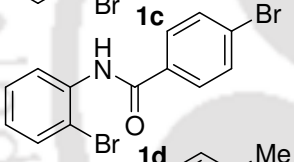
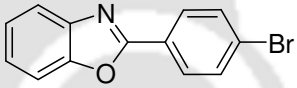
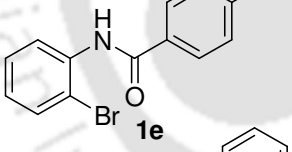
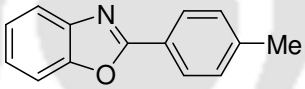
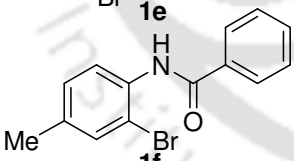
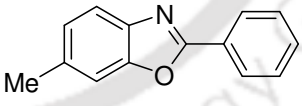
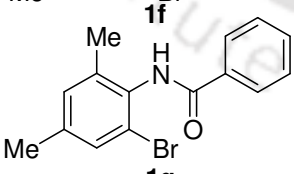
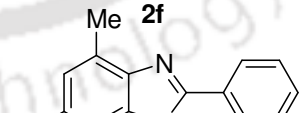
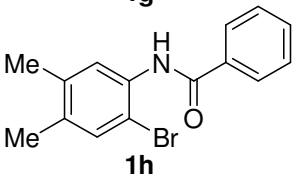
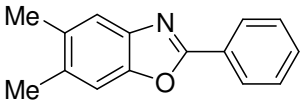
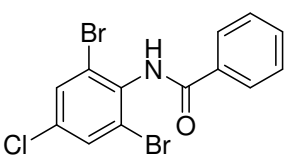
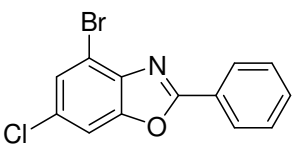
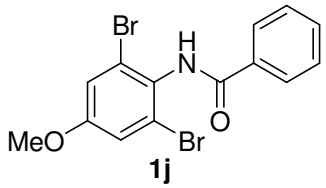
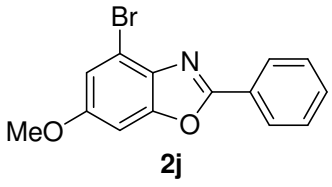
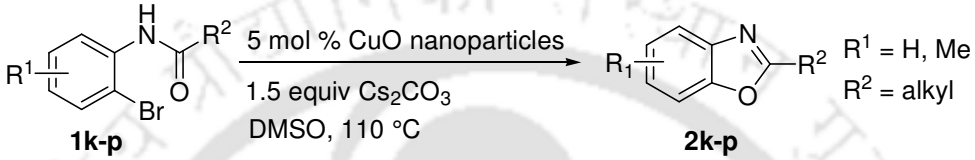
entry	substrate	time (h)	product	yield (%)
1	 **1a**	16	 **2a**	95
2	 **1b**	24	 **2b**	79
3	 **1c**	26	 **2c**	60
4	 **1d**	27	 **2d**	71
5	 **1e**	16	 **2e**	92
6	 **1f**	30	 **2f**	61
7[b]	 **1g**	30	 **2g**	81
8[b]	 **1h**	25	 **2h**	86
9	 **1i**	12	 **2i**	91

Table 2 continues…

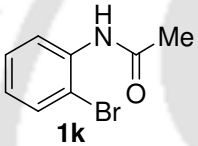
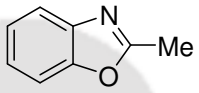
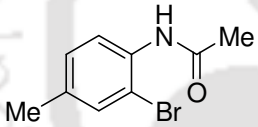
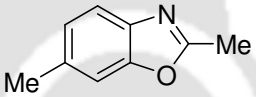
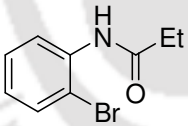
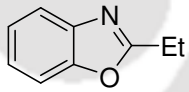
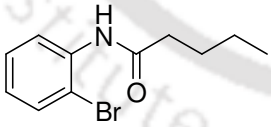
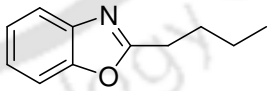
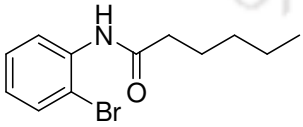
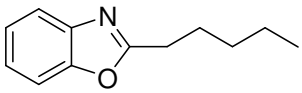
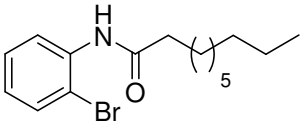
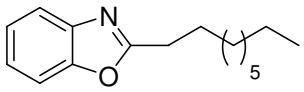
10	 **1j**		16	 **2j**	89

[a] *o*-Bromoanilide (0.5 mmol), CuO nanoparticles (5 mol %) and K_2CO_3 (0.75 mmol) were stirred at 110 °C in DMSO (1 mL) under air. [b] 2.0 equiv K_2CO_3 was used.

Table 3. CuO Nanoparticles Catalyzed Synthesis of 2-Alkylbenzoxazoles[a]

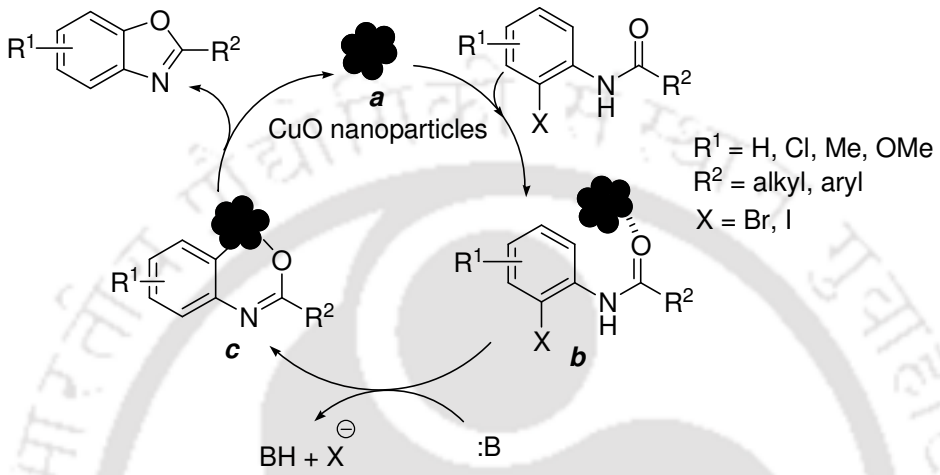


1k-p **2k-p**

entry	substrate	time (h)	product	yield (%)
1	 **1k**	15	 **2k**	79
2	 **1l**	21	 **2l**	67
3	 **1m**	15	 **2m**	82
4	 **1n**	16	 **2n**	81
5	 **1o**	16	 **2o**	80
6	 **1p**	16	 **2p**	84

[a] *o*-Bromoanilide (0.5 mmol), CuO nanoparticles (5 mol %), and Cs_2CO_3 (0.75 mmol) were stirred at 110 °C in DMSO (2 mL) under air.

Next, we studied the synthesis of 2-alkylbenzoxazoles from *N*-(*o*-bromophenyl)-alkylamides (Table 3). The substrates *N*-(*o*-bromophenyl)alkylamides **1k-p** underwent reaction in presence of 5 mol % CuO nanoparticles and 1.5 equiv of Cs_2CO_3 in DMSO at 110 °C to afford the corresponding 2-alkylbenzoxazoles **2k-p** in 67-84% yield. These results clearly reveal that the present method is general and can be used for the synthesis of substituted 2-alkyl and 2-arylbenzoxazoles in high yield.

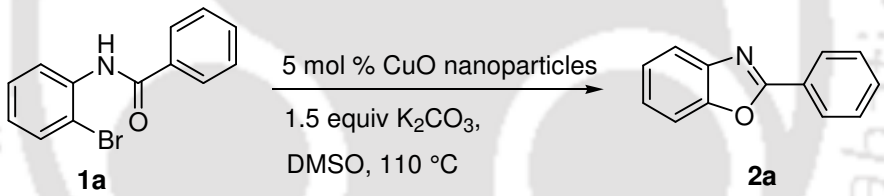


Scheme 10. Proposed Catalytic Cycle

The proposed catalytic cycle is shown in Scheme 10. CuO nanoparticles ***a*** may undergo reaction with the substrate on their surface to generate intermediate ***b*** and the positive charge developed could be shared among the CuO nanoparticles present on the surface of the cluster. The intermediate ***b*** can transform to intermediate ***c*** in the presence of base which could complete the catalytic cycle by the reductive elimination of the product. To reveal the leaching of the catalyst, the CuO nanoparticles were stirred at reaction temperature (110 °C) for 16 h in the presence of K_2CO_3 in DMSO. The solution was then cooled to room temperature and subjected to centrifugation. The particles were recovered and the clear solution was investigated for the cyclization of *N*-(*o*-bromophenyl)benzamide in the presence of fresh K_2CO_3. No reaction was, however, obtained and the starting material *N*-(*o*- bromophenyl)benzamide was recovered intact. Furthermore, the atomic absorption spectroscopy (AAS) showed the amount of copper species present in the clear solution was below the detection limit (<0.25%). These studies suggest that the reaction involves heterogeneous process and the leaching of CuO nanoparticles has not occurred under this condition.

Recyclability Experiment. CuO nanoparticles are recyclable without loss of activity (Table 4). After completion of the cyclization of *o*-bromophenylbenzamide **1a**, the reaction mixture was treated with ethyl acetate and water. The aqueous solution having the CuO nanoparticles was centrifuged and the catalyst was collected. After washing with water and acetone, the catalyst was dried under vacuum and reused for the cyclization of fresh *o*-bromophenylbenzamide. This process was repeated for five runs and the reactions occurred efficiently to afford the product with >97% conversion and 98% catalyst recoverability. These studies further reveal that the CuO nanoparticles do not leach under this condition. In addition, the TEM images of the fresh CuO nanoparticles and the catalyst recovered after the fifth cycle reveal that the particle size and shape of the CuO nanoparticles remain same during the cyclization process (Figure 3). Furthermore, the powder X-ray diffraction analysis of the fresh and recovered catalyst after fifth cycle exhibited peaks correspond to CuO nanoparticles (Figure 4).[9] Thus, the catalyst does not undergo leaching under these conditions and they can be recycled without loss of activity.

Table 4. Recyclability of CuO Nanoparticles[a]



run	catalyst recoverability (%)	product conversion (%)[b]
1	99	99
2	99	99
3	99	98
4	98	98
5	98	97

[a] *N*-(2-Bromophenyl)benzamide (2.5 mmol), CuO nanoparticles (5 mol %) and K_2CO_3 (3.75 mmol) were stirred at 110 °C in DMSO (5 mL) under air. [b] Determined from 400 MHz ^{1}H-NMR.

In conclusion, the synthesis of 2-aryl and 2-alkylbenzoxazoles are described using CuO nanoparticles under ligand-free conditions. The reactions are simple, general, efficient and the catalyst can be recovered and recycled without loss of activity and selectivity. It is a clean technological process and a wide range of substrates can undergo reactions in high yield.

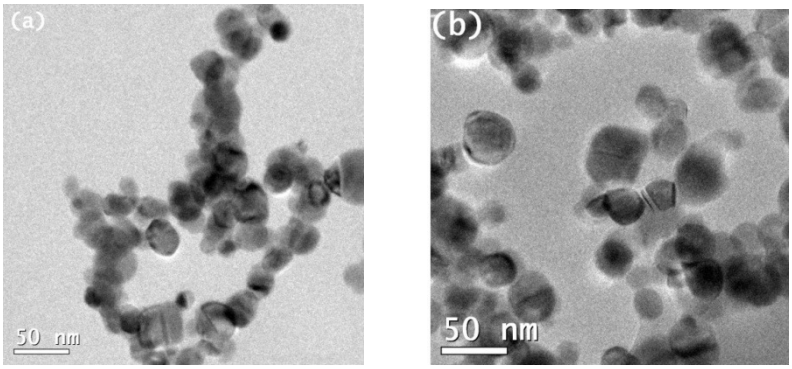


Figure 3. TEM images of fresh (a) and recovered (b) catalysts.

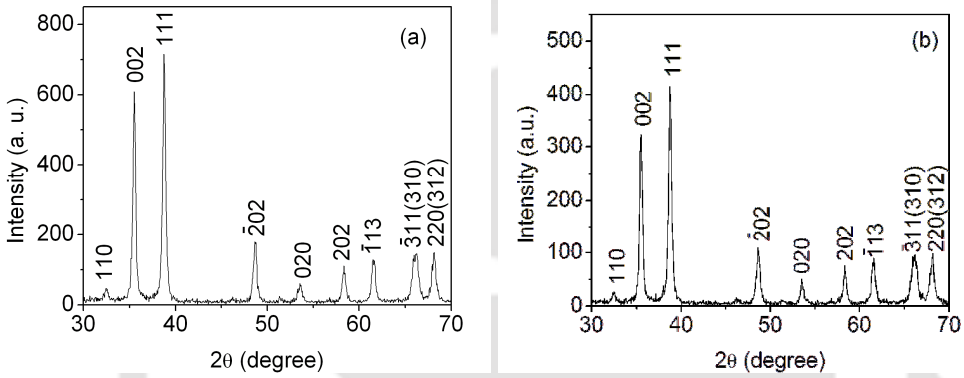


Figure 4. Powder XRD of fresh (a) and recovered (b) catalyst.

Experimental Section

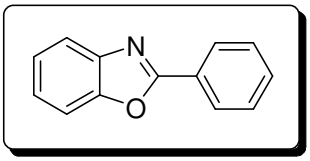
General Information

o-Haloanilines were purchased from Aldrich and used without further purification. Column chromatography was carried out with silica gel (60-120 mesh) using ethyl acetate and hexane as eluent. Analytical TLC was performed with silica gel 60 plates. NMR spectra (400 MHz for ^{1}H and 100 MHz for ^{13}C) were recorded using DRX-400 Varian spectrometer with $CDCl_3$ as solvent and Me_4Si as internal standard. Melting points were determined using melting point apparatus and uncorrected. Elemental analysis was carried out using CHNS analyzer. IR spectra were recorded using FT-IR spectrometer.

General Procedure for Synthesis of 2-Arylbenzoxazoles

An oven-dried 10 mL round bottom flask was charged with *o*-haloanilide (0.5 mmol), CuO nanoparticles (5 mol %, 2 mg) and K_2CO_3 (0.75 mmol, 103.5 mg) in DMSO (1 mL). The mixture was stirred at 110 °C for the appropriate time (Table 2). Progress of the

reaction was monitored by TLC using ethyl acetate and hexane as eluent. The reaction mixture was then cooled to room temperature and diluted with ethyl acetate (15 mL). The organic layer was washed with brine (1 x 5 mL) and water (2 x 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on silica gel column chromatography using ethyl acetate and hexane as eluent.



2-Phenylbenzoxazole (**2a**).[8b] Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.47; colorless solid; yield 95%.

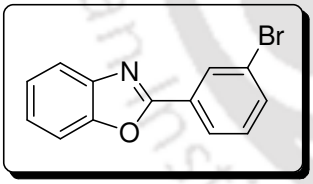
Mp: 100-101 ºC (lit.[8b] mp 101-102 ºC).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26-8.24 (m, 2H), 7.77-7.75 (m, 1H), 7.58-7.56 (m, 1H), 7.53-7.49 (m, 3H), 7.35-7.33 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.2, 150.9, 142.2, 131.7, 129.1, 127.8, 127.3, 125.3, 124.7, 120.2, 110.8.

FT-IR (KBr): 3060, 2961, 1616, 1552, 1472, 1447, 1344, 1318, 1241, 1196, 1052, 1022 cm^{-1}.

Anal. Calcd for $C_{13}H_9NO$: C, 79.98; H, 4.65; N, 7.17. Found: C, 80.12; H, 4.59; N, 7.08.



2-(3-Bromophenyl)benzoxazole (2b).[10a] Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.65; colorless solid; yield 79%.

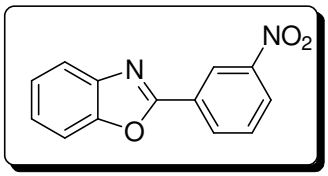
Mp: 128-129 ºC (lit.[10a] mp 128-130 ºC).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41-8.40 (t, J = 1.6 Hz, 1H), 8.18-8.16 (dd, J = 8.0, 1.2 Hz, 1H), 7.78-7.76 (m, 1H), 7.66-7.63 (m, 1H), 7.59-7.57 (m, 1H), 7.41-7.35 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.6, 150.9, 142.0, 134.6, 130.63, 129.2, 126.2, 125.7, 124.9, 123.27, 120.5, 110.9.

FT-IR (KBr): 2925, 2854, 1614, 1570, 1547, 1451, 1429, 1292, 1239, 1195, 1071, 1051 cm^{-1}.

Anal. Calcd for $C_{13}H_8BrNO$: C, 56.96; H, 2.94; N, 5.11. Found: C, 57.13; H, 2.89; N, 5.02.



2-(3-Nitrophenyl)benzoxazole (2c).[10b] Analytical TLC on silica gel, 1:9 ethyl acetate/hexane R_f = 0.38; yellow solid; yield 60%.

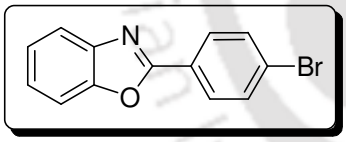
Mp: 210-211 ºC (lit.[10c] mp 210-211 ºC).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.08-9.07 (t, *J* = 1.6 Hz, 1H), 8.58-8.56 (dd, *J* = 7.6, 1.2 Hz, 1H), 8.38-8.36 (m, 1H), 7.81-7.79 (m, 1H), 7.74-7.70 (t, *J* = 8.0 Hz, 1H), 7.63-7.61 (m, 1H), 7.44-7.37 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8, 151.1, 148.9, 141.9, 133.2, 130.3, 129.1, 126.3, 125.9, 125.3, 122.7, 120.7, 111.1.

FT-IR (KBr): 3096, 2963, 1625, 1583, 1556, 1528, 1473, 1452, 1351, 1297, 1261, 1240, 1187, 1114, 1097, 1049 cm^{-1}.

Anal. Calcd for $C_{13}H_8N_2O_3$: C, 65.00; H, 3.36; N, 11.66. Found: C, 65.21; H, 3.30; N, 11.52.



2-(4-Bromophenyl)benzoxazole (2d).[10b] Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.75; colorless solid; yield 71%.

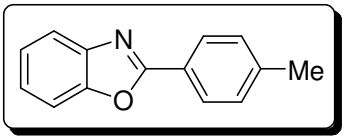
Mp: 156 ºC (lit.[10b] mp 157-158 ºC).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12-8.09 (m, 2H), 7.77-7.74 (m, 1H), 7.67-7.63 (m, 2H), 7.58-7.55 (m, 1H), 7.36-7.33 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.3, 150.9, 142.1, 132.4, 129.1, 126.4, 126.2, 125.6, 124.9, 120.3, 110.8.

FT-IR (KBr): 3057, 2924, 1615, 1592, 1547, 1484, 1452, 1400, 1342, 1294, 1261, 1244, 1176, 1107, 1069, 1052, 1009 cm^{-1}.

Anal. Calcd for $C_{13}H_8BrNO$: C, 56.96; H, 2.94; N, 5.11. Found: C, 57.11; H, 2.91; N, 5.02.



2-(4-Methylphenyl)benzoxazole (2e).[10b] Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.61; white solid; yield 92%.

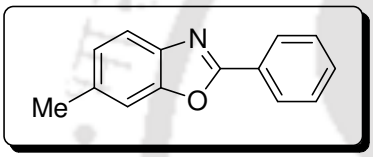
Mp: 116-117 ºC (lit.[10b] mp 116 ºC).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14-8.12 (d, *J* = 8.4 Hz, 2H), 7.75-7.73 (m, 1H), 7.57-7.54 (m, 1H), 7.34-7.31 (m, 4H), 2.42 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5, 150.8, 142.3, 132.4, 129.8, 127.8, 127.3, 125.1, 124.7, 120.0, 110.7, 21.8.

FT-IR (KBr): 3281, 2964, 2920, 2855, 1651, 1622, 1581, 1530, 1502, 1451, 1435, 1411, 1346, 1262, 1244, 1172, 1019 cm^{-1}.

Anal. Calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.60; H, 5.26; N, 6.59.



6-Methyl-2-phenylbenzoxazole (2f).[8b] Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.48; colorless solid; yield 61%.

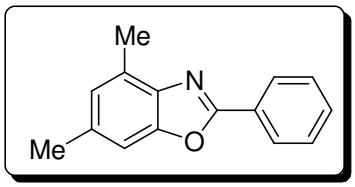
Mp: 92-93 ºC (lit.[8b] mp 93 ºC).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25-8.21 (m, 2H), 7.63-7.61 (d, *J* = 8.0 Hz, 1H), 7.51-7.48 (m, 3H), 7.37 (t, *J* = 0.8 Hz, 1H), 7.16-7.14 (dd, *J* = 8.4, 0.8 Hz, 1H), 2.49 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.7, 151.2, 140.06, 135.7, 131.4, 129.0, 127.6, 127.5, 126.0, 119.5, 110.9, 22.0.

FT-IR (KBr): 3054, 2920, 2856, 1615, 1554, 1481, 1448, 1337, 1289, 1274, 1247, 1172, 1125, 1099, 1073, 1021 cm^{-1}.

Anal. Calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.65; H, 5.27; N, 6.60.



4,6-Dimethyl-2-phenylbenzoxazole (2g). Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.40; colorless solid; yield 81%.

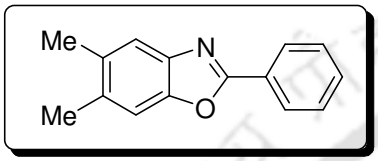
Mp: 166-167 ºC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22-8.19 (m, 2H), 7.50-7.48 (m, 4H), 7.34 (s, 1H), 2.37 (s, 3H), 2.35 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.5, 149.6, 140.4, 134.5, 133.4, 131.3, 129.0, 127.6, 120.2, 111.0, 20.7, 20.4.

FT-IR (KBr): 3056, 2923, 2863, 1552, 1488, 1463, 1445, 1333, 1290, 1270, 1151, 1049, 1020, 998 cm^{-1}.

Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.81; H, 5.86; N, 6.18.



5,6-Dimethyl-2-phenylbenzoxazole (2h). Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.46; colorless solid; yield 86%.

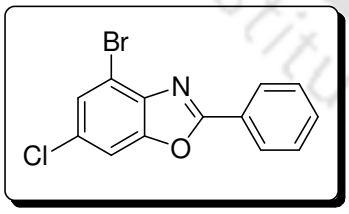
Mp: 132-133 ºC.

^{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, 151.0, 139.4, 135.3, 131.2, 130.0, 128.9, 127.8, 127.6, 126.6, 108.2, 21.9, 16.7.

FT-IR (KBr) 3058, 2922, 2855, 1614, 1596, 1554, 1477, 1447, 1405, 1374, 1338, 1292, 1264, 1225, 1167, 1069, 1049, 1019 cm^{-1}.

Anal. Calcd for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.79; H, 5.85; N, 6.21.



4-Bromo-6-chloro-2-phenylbenzoxazole (2i). Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.57; colorless solid; yield 91%.

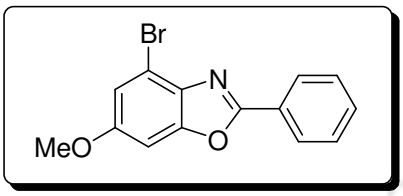
Mp: 135-136 ºC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26-8.24 (m, 2H), 7.56-7.49 (m, 5H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 150.8, 140.8, 132.4, 131.2, 129.1, 128.3, 128.2, 126.3, 113.0, 110.7.

FT-IR (KBr): 3010, 2925, 2853, 1610, 1594, 1482, 1451, 1408, 1337, 1325, 1307, 1261, 1231, 1200, 1073, 1124, 1051, 1033, 1019 cm^{-1}.

Anal. Calcd for $C_{13}H_7BrClNO$: C, 50.60; H, 2.29; N, 4.54. Found: C, 50.46; H, 2.33; N, 4.49.



4-Bromo-6-methoxy-2-phenylbenzoxazole (2j). Analytical TLC on silica gel, 1:19 ethyl acetate/hexane R_f = 0.55; colorless solid; yield 89%.

Mp: 105-106 ºC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23-8.21 (m, 2H), 7.51-7.48 (m, 3H), 7.13 (d, *J* = 2.0 Hz, 1H), 7.04 (d, *J* = 2.4 Hz, 1H), 3.85 (s, 3H).

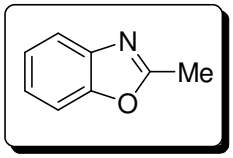
^{13}C NMR (100 MHz, $CDCl_3$): δ 162.8, 158.6, 151.6, 135.8, 131.7, 129.0, 127.8, 126.9, 116.0, 112.7, 95.3, 56.4.

FT-IR (KBr): 2925, 1613, 1591, 1551, 1490, 1450, 1396, 1325, 1280, 1244, 1182, 1070, 1046, 1020 cm^{-1}.

Anal. Calcd for $C_{14}H_{10}BrNO_2$: C, 55.29; H, 3.31; N, 4.61. Found: C, 55.15; H, 3.43; N, 4.42.

General Procedure for Synthesis of 2-Alkylbenzoxazoles

An oven-dried 10 mL round bottom flask was charged with the *o*-haloanilide (0.5 mmol), CuO nanoparticles (5 mol %, 2 mg) and Cs_2CO_3 (0.75 mmol, 244.5 mg) in DMSO (1 mL). The mixture was stirred at 110 °C for the appropriate time (Table 3). Progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. The reaction mixture was then cooled to room temperature and diluted with ethyl acetate (15 mL). The organic layer was washed with brine (1 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 ethyl acetate and hexane as eluent.



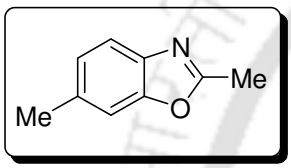
2-Methylbenzoxazole (2k).[10d] Analytical TLC on silica gel, 1:10 ethyl acetate/hexane R_f = 0.51; yellow oil; yield 79%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65-7.62 (m, 1H), 7.46-7.44 (m, 1H), 7.29-7.26 (m, 2H), 2.63 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 151.1, 141.5, 124.7, 124.3, 119.5, 110.4, 14.7.

FT-IR (neat): 2962, 2928, 2851, 1613, 1519, 1462, 1382, 1344, 1257, 1033 cm^{-1}.

Anal. Calcd for C_8H_7NO: C, 72.16; H, 5.30; N, 10.52. Found: C, 72.34; H, 5.29; N, 10.46.



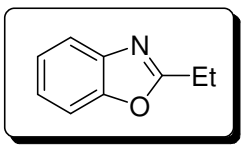
2,6-Dimethylbenzoxazole (2l). Analytical TLC on silica gel, 1:10 ethyl acetate/hexane R_f = 0.49; colorless oil; yield 67%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50-7.48 (d, *J* = 8.0 Hz, 1H), 7.25 (s, 1H), 7.10-7.07 (m, 1H), 2.59 (s, 3H) 2.45 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 1.63.4, 151.5, 139.5, 134.9, 125.42, 118.9, 110.6, 21.85, 14.7.

FT-IR (neat): 2925, 2950, 2846, 1634, 1516, 1456, 1440, 1380, 1278, 1254, 1226, 1176, 1033 cm^{-1}.

Anal. Calcd for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.67; H, 6.10; N, 9.41.



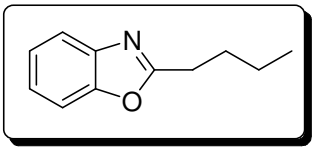
2-Ethylbenzoxazole (2m).[8b] Analytical TLC on silica gel, 1:10 ethyl acetate/hexane R_f = 0.55; colorless oil; yield 82%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61-7.59 (m, 1H), 7.41-7.39 (m, 1H), 7.23-7.19 (m, 2H), 2.92-2.86 (q, *J* = 7.2 Hz, 2H) 1.40-1.18 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 150.9, 141.5, 124.6, 124.2, 119.7, 110.4, 22.4, 11.1.

FT-IR (neat): 2950, 2925, 2851, 1662, 1602, 1539, 1517, 1459, 1382, 1292, 1253, 1229, 1033 cm^{-1}.

Anal. Calcd for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.65; H, 6.15; N, 9.41.



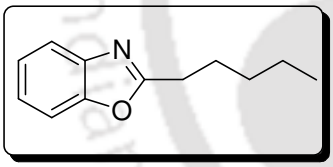
2-Butylbenzoxazole (2n).[10e] Analytical TLC on silica gel, 1:10 ethyl acetate/hexane R_f = 0.59; yellow oil; yield 81%.

^1H NMR (400 MHz, $CDCl_3$): δ 7.66-7.63 (m, 1H), 7.47-7.44 (m, 1H), 7.29-7.24 (m, 2H), 2.93-2.89 (t, *J* = 7.6 Hz, 2H) 1.89-1.81 (m, 2H), 1.46-1.40 (m, 2H), 0.97-0.93 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 150.9, 141.6, 124.6, 124.2, 119.7, 110.5, 29.0, 28.6, 22.5, 13.9.

FT-IR (KBr): 3060, 2960, 2928, 2873, 1615, 1573, 1517, 1456, 1377, 1242, 1153, 1104, 1028 cm^{-1}.

Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.26; H, 7.46; N, 7.90.



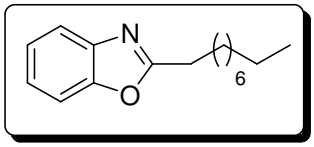
2-Pentylbenzoxazole (2o).[10f] Analytical TLC on silica gel, 1:10 ethyl acetate/hexane R_f = 0.65; yellow oil; yield 80%.

^1H NMR (400 MHz, $CDCl_3$): δ 7.68-7.66 (m, 1H), 7.48-7.46 (m, 1H), 7.31-7.26 (m, 2H), 2.94-2.90 (t, *J* = 7.6 Hz, 2H), 1.92-1.85 (m, 2H), 1.43-1.34 (m, 4H), 0.93-0.89 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 150.9, 141.5, 124.6, 124.2, 119.7, 110.4, 31.5, 28.8, 26.6, 22.5, 14.1.

FT-IR (neat): 2956, 2927, 2851, 1634, 1544, 1517, 1456, 1440, 1380, 1283, 1253, 1229, 1179, 1032 cm^{-1}.

Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.29; H 7.97; N, 7.28.



2-Nonylbenzoxazole (2p). Analytical TLC on silica gel, 1:10 ethyl acetate/hexane R_f = 0.69; yellow oil; yield 84%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66-7.63 (m, 1H), 7.46-7.44 (m, 1H), 7.29-7.24 (m, 2H), 2.92-2.88 (t, *J* = 7.6 Hz, 2H), 1.90-1.82 (m, 2H), 1.43-1.24 (m, 12H), 0.87-0.83 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.6, 150.9, 141.6, 124.5, 124.2, 119.7, 110.4, 32.04, 29.6, 29.4, 29.4, 29.4, 28.8, 26.9, 22.9, 14.3.

FT-IR (neat): 3054, 2925, 2855, 1615, 1573, 1517, 1481, 1455, 1378, 1243, 1145, 1104, 1031, 1006 cm^{-1}.

Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.52; H 9.40; N, 5.63.

2.3 References

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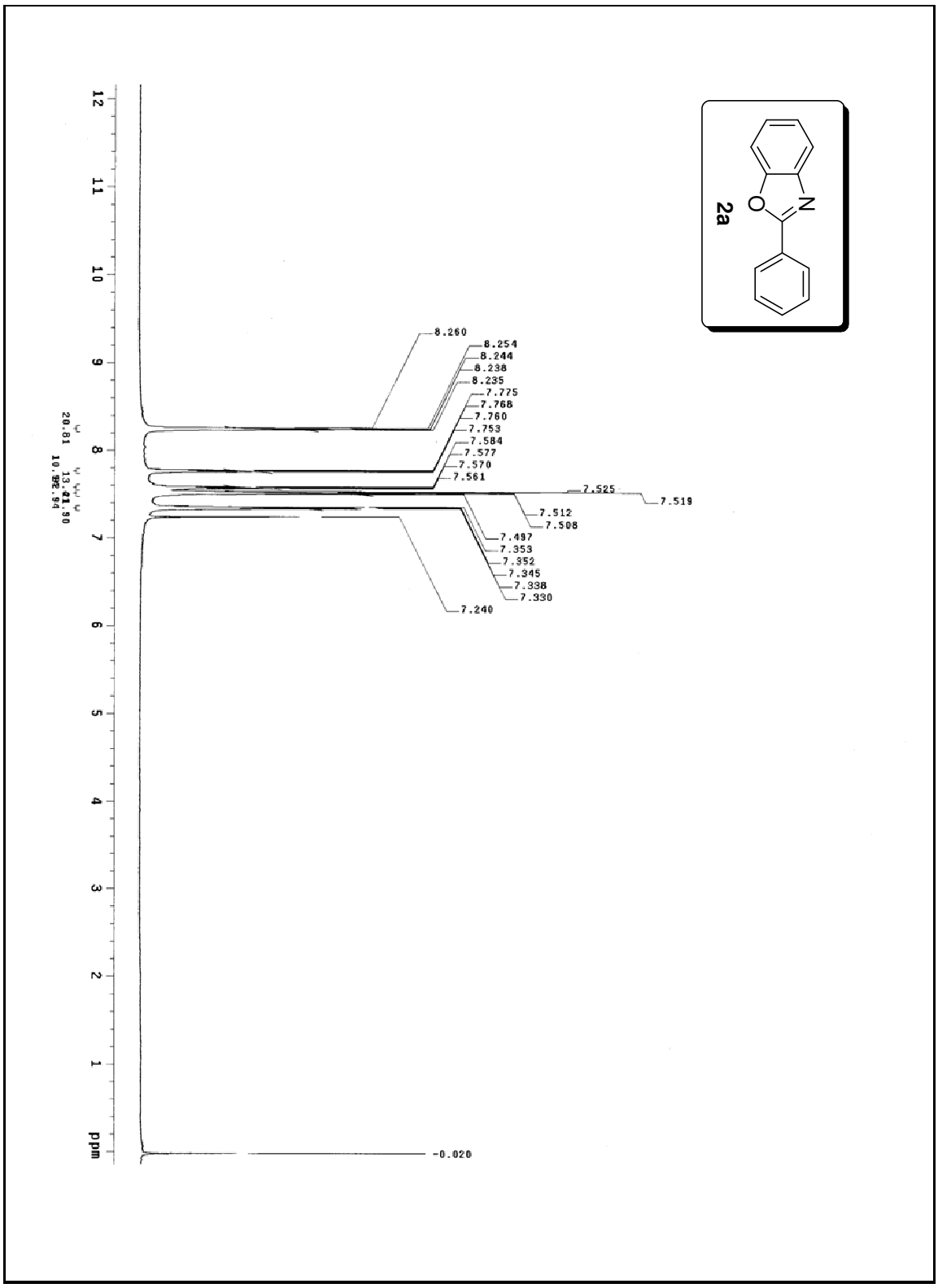
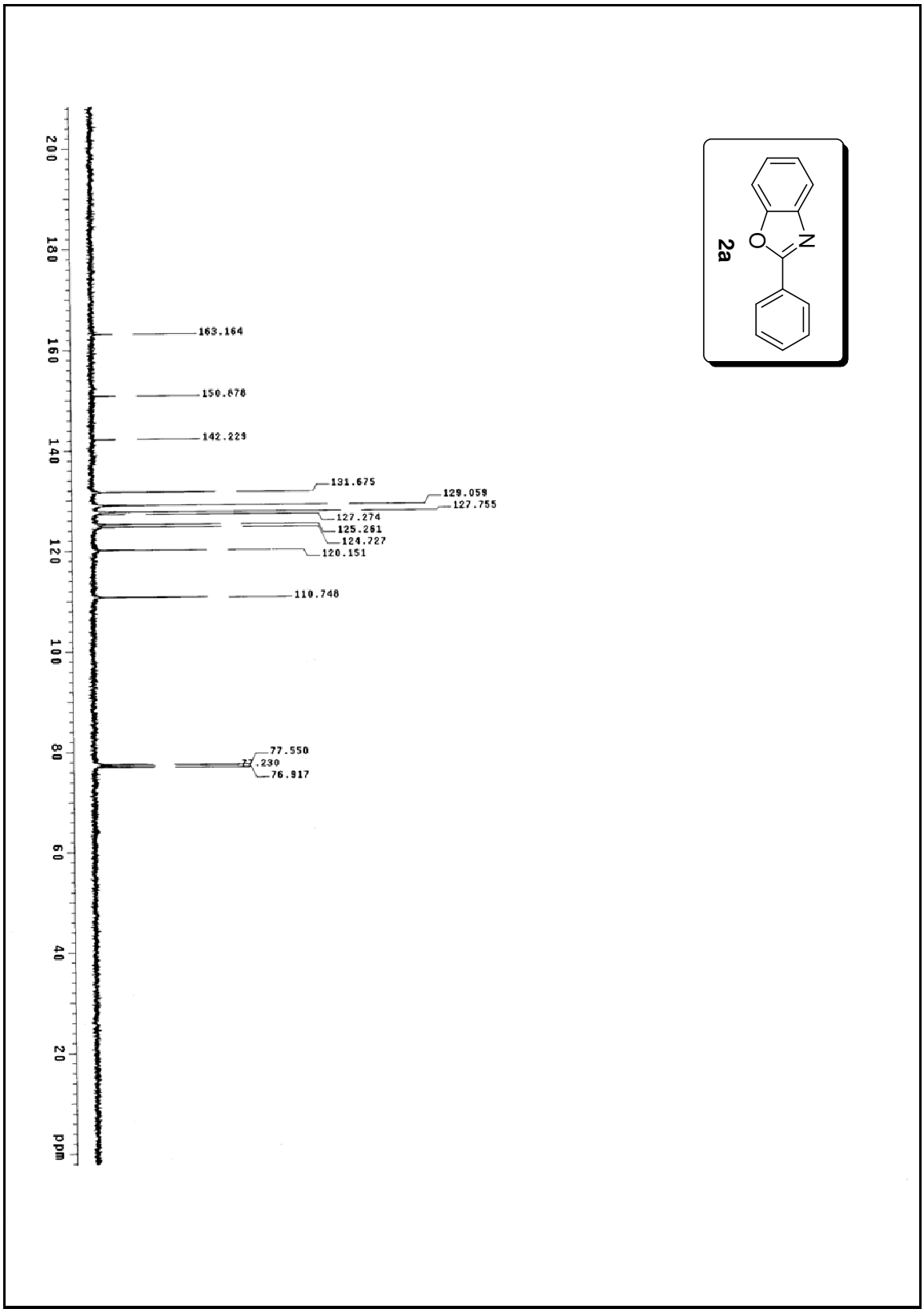
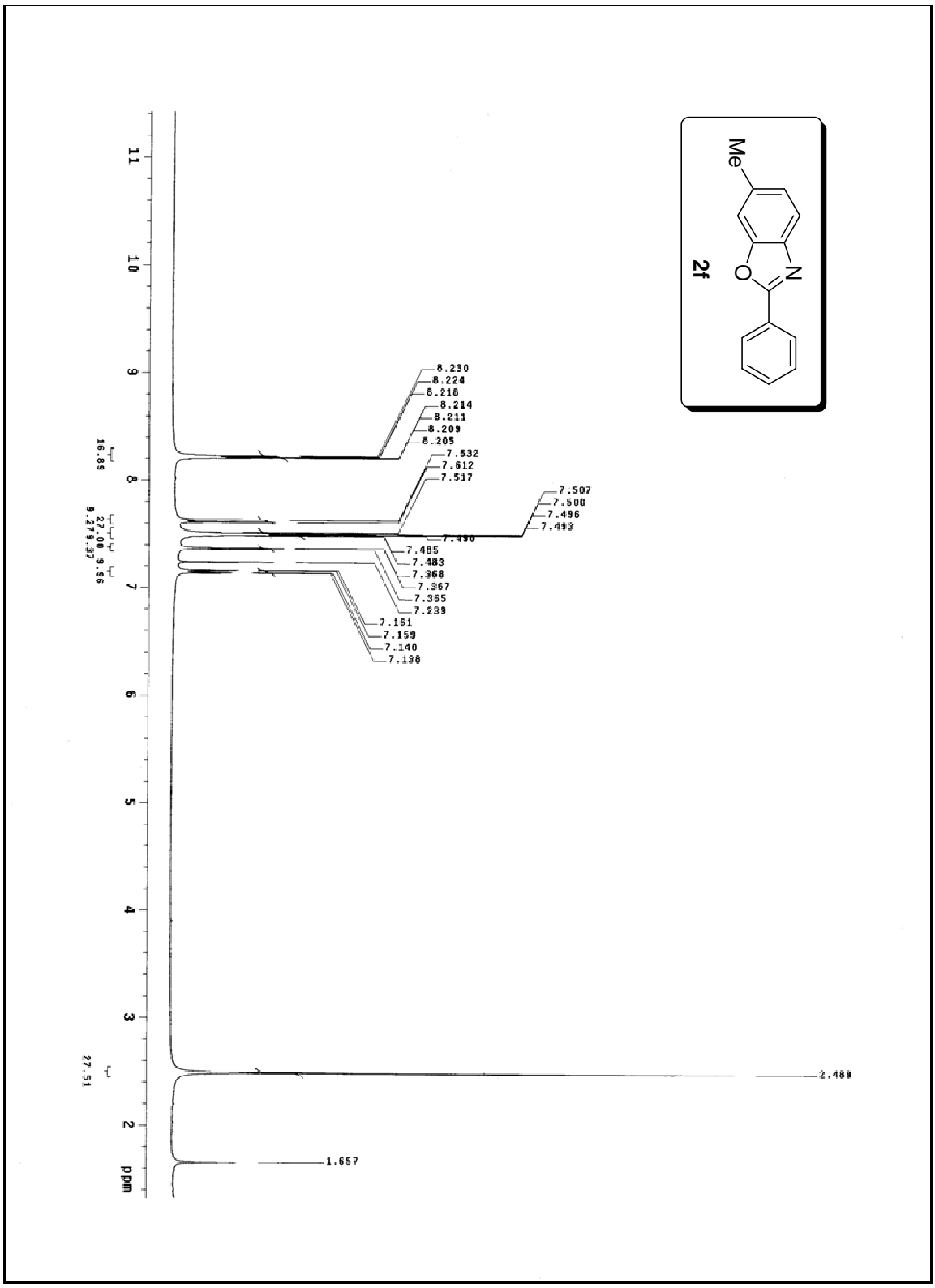
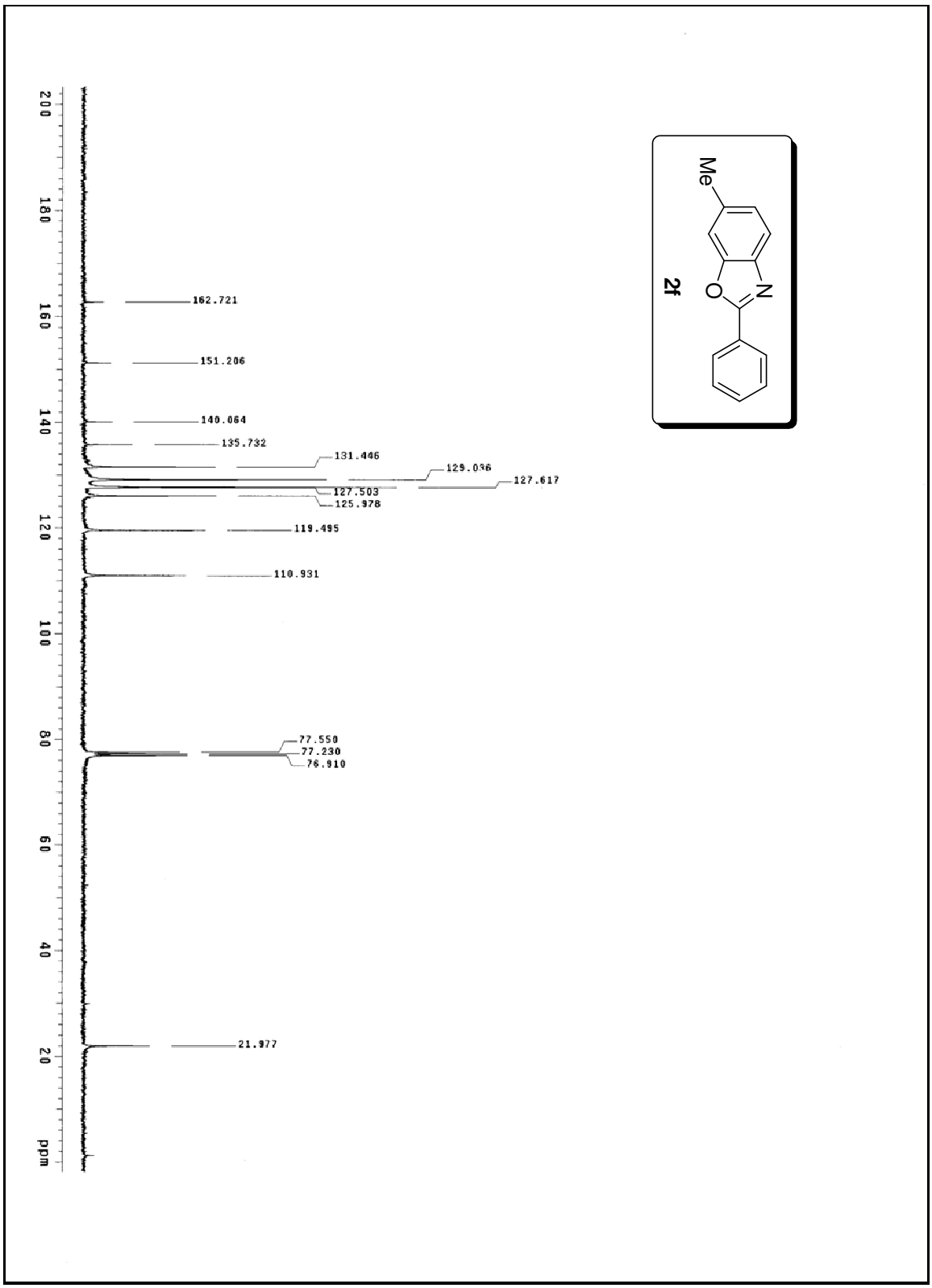
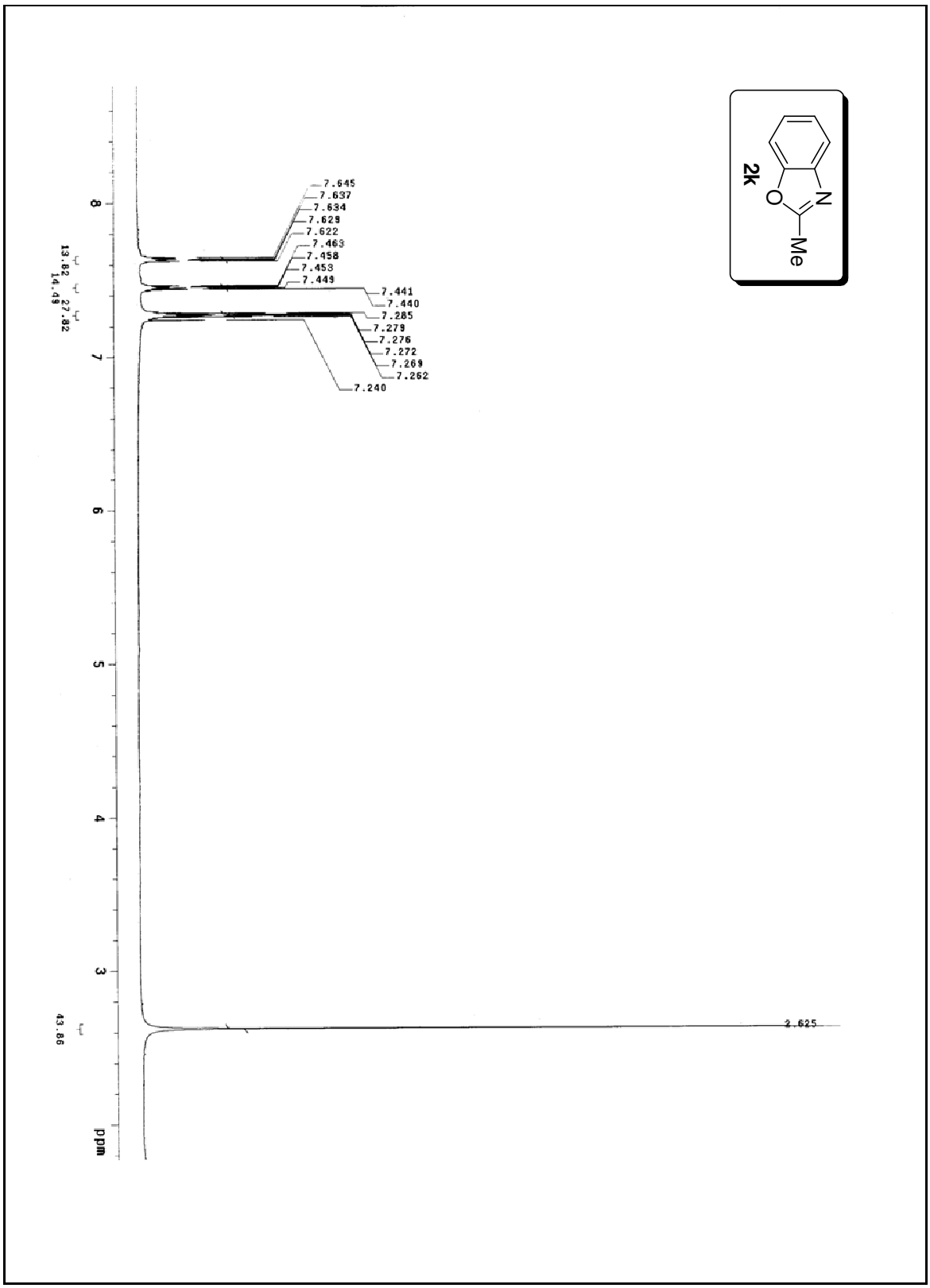
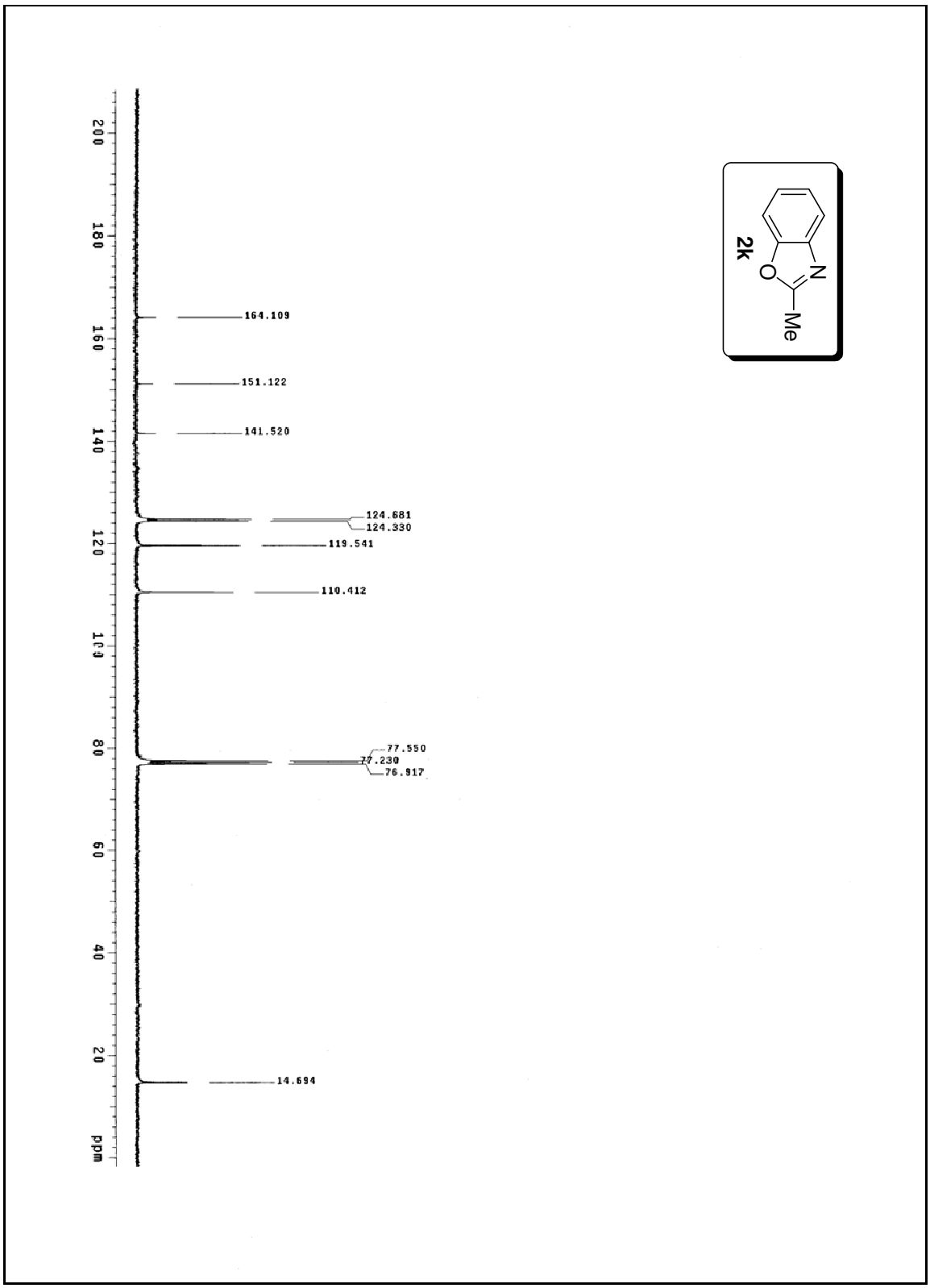












Chapter III

CuO Nanoparticles Catalyzed Intramolecular *C–S* Cross-Coupling Reaction: Synthesis of 2-Aminobenzothiazoles

2-Aminobenzothiazoles are an important class of heterocyclic compounds due to their wide range of pharmaceutical and agrochemical properties.[1] For examples, it has been used for the treatment of diabetes,[1e] epilepsy,[2a-b] inflammation,[2c] amyotrophic lateral sclerosis,[2d] analgesia,[2e] tuberculosis[2f] and viral infections.[1b] Riluzole has been found to interfere with glutamate neurotransmission in biochemical and electrophysiological experiments.[3]

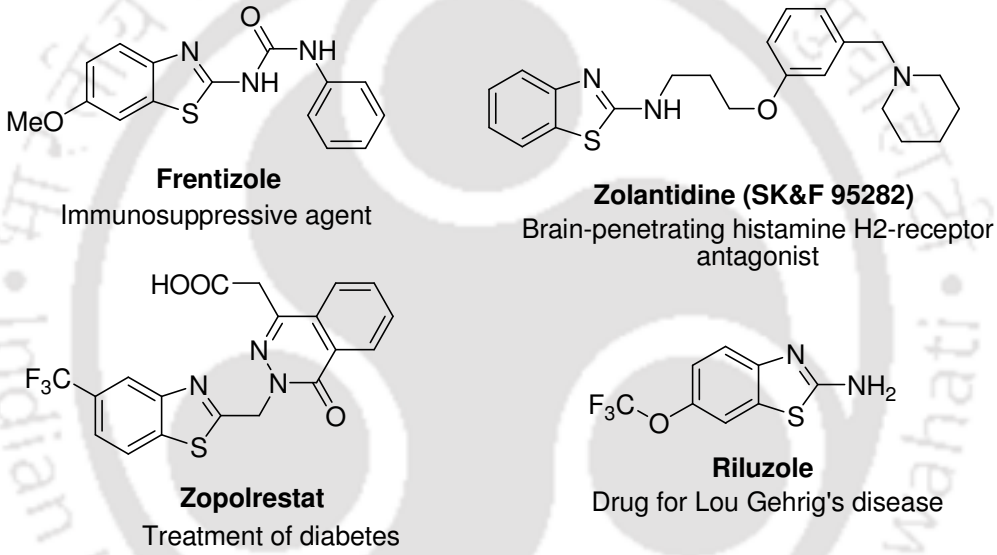
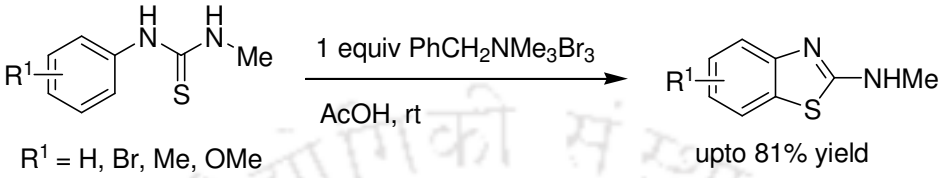


Figure 1. Examples of some biologically active compounds.

Synthesis of this privileged class of compounds has recently attracted much attention due to their wide range of biological activities. In 1887, Hoffmann first reported the cyclization of 2-aminothiophenol to 2-aminobenzothiazole.[4] Hofmann also observed the formation of 2-anilinobenzothiazole from the reaction of 2-aminothiophenol and phenyl isothiocyanate. In 1900, Hugerschoff found that an arylthiourea can be cyclized with liquid bromine in chloroform to form a 2-aminobenzothiazole. The reaction of molecular bromine with arylthiourea is known as Hugerschoff Reaction.[5] Jordan and co-workers used benzyltrimethylammonium tribromide ($PhCH_2NMe_3Br_3$), a stable electrophilic bromine source, for the conversion of substituted arylthiourea to 2-aminobenzothiazole under mild conditions (Scheme 1).[6] In addition, this reagent is also used for one-pot synthesis of 2-aminobenzothiazoles from isothiocyanates and amines or a substituted

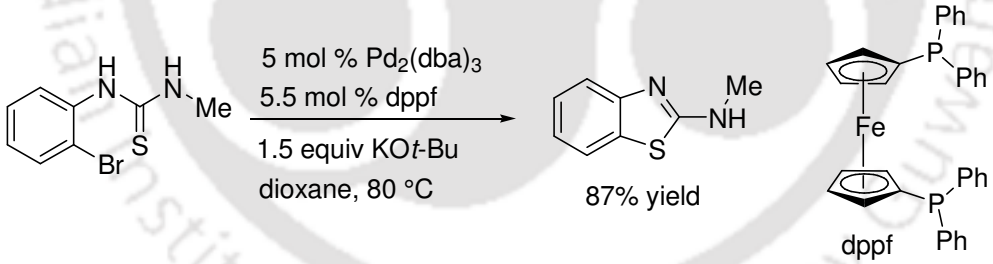
aniline and tetrabutylammonium thiocyanates. The advantages of this reagent compared to molecular bromine are ease of addition and handling, which minimizes the risk of forming brominated side products. However, these approaches are limited due to the lack of regioselectivity and functional group tolerance. Recently, some of these limitations have been overcome by transition metal-catalyzed cross-coupling reaction.



Scheme 1

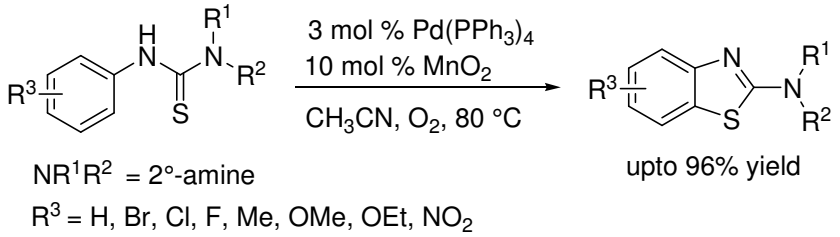
3.1 Palladium Catalysts

Palladium-catalyzed *C–S* cross-coupling reactions are highly useful for the synthesis of arylthioethers and have found numerous applications in organic synthesis.[7] Castillon and co-workers showed the palladium catalyzed synthesis of 2-aminobenzothiazoles by intramolecular *C–S* cross coupling of 2-bromophenylthioureas with good yield (Scheme 2).[8a]



Scheme 2

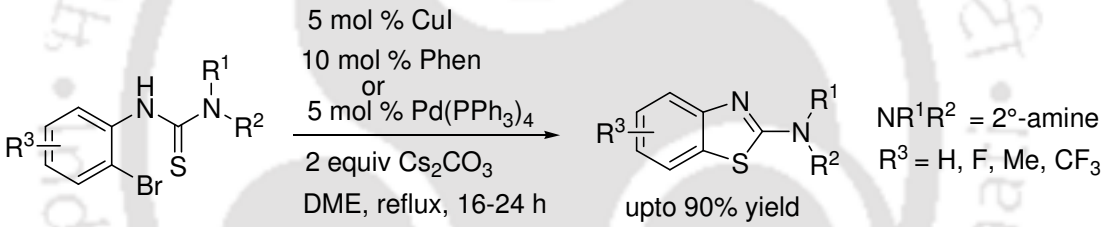
Batey and co-workers reported the synthesis of 2-aminobenzothiazoles from *N*-arylthiourea *via C–S* bond formation/*C–H* bond functionalization using $Pd(PPh_3)_4$ and MnO_2 under oxygen atmosphere (Scheme 3). The target products are obtained with high yield.[8b]



Scheme 3

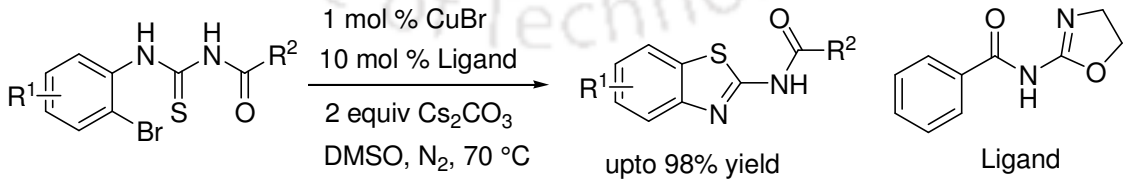
3.2 Copper Catalysts

Recently, copper catalysis has shown to be efficient in the synthesis of arylthioethers.[9] Palladium has disadvantages over copper such as high cost, requirement of bulky phosphine ligand, etc. The intramolecular cyclization of *o*-haloarylthioureas has been carried out using copper and palladium based catalysts to afford substituted 2-aminobenzothiazoles. The best results are observed using CuI/1,10-phenanthroline in the presence of Cs_2CO_3 in DME under reflux condition (Scheme 4).[10a]



Scheme 4

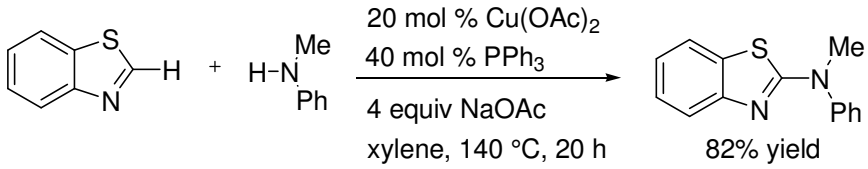
Pan and co-workers demonstrated an efficient intramolecular *C–S* cross-coupling reaction of substituted 1-arylacyl-3-(2-bromophenyl)thiourea using CuI/N-(4,5-dihydrooxazol-2-yl)benzamide (Scheme 5). The desired products, *N*-benzothiazol-2-yl-amides are synthesized with high yield.[10b]



Scheme 5

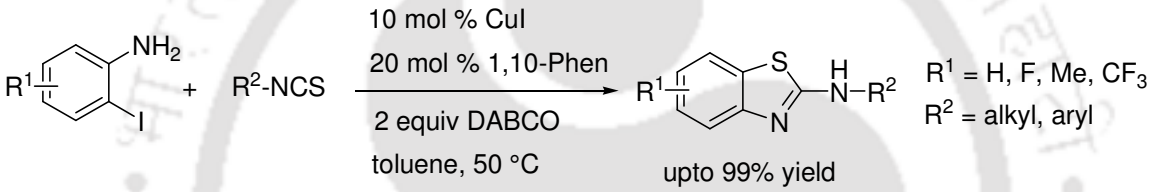
Mori and co-workers developed a method for the formation of 2-aminobenzothiazoles by intermolecular cross-coupling of benzothiazole with amines in the presence of copper

salt in xylene under reflux condition (Scheme 6). The reactions occurred efficiently to afford the target compounds with up to 82% yield.[10c]



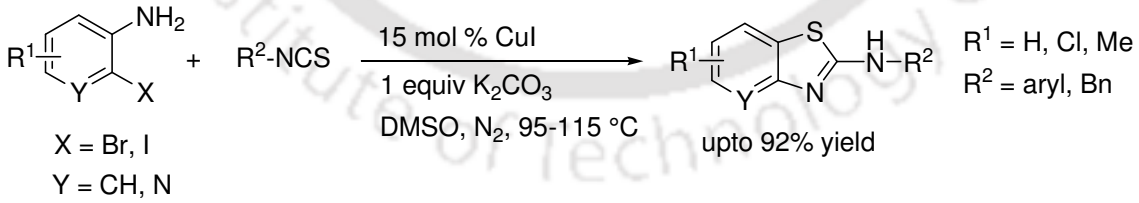
Scheme 6

Ding and co-workers described copper(I) catalyzed tandem reaction of 2-iodoanilines with isothiocyanates for the synthesis of 2-aminobenzothiazoles (Scheme 7). They have used the combination of CuI and 1,10-phenanthroline and the reaction proceeds to give the products with good yield.[10d]



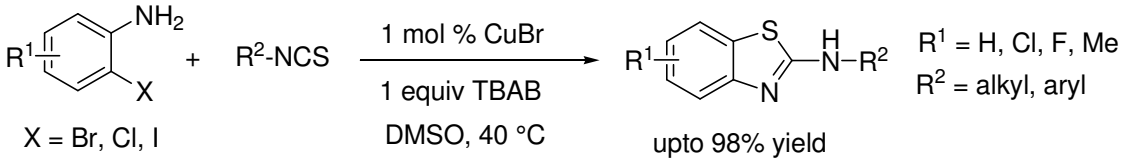
Scheme 7

Bao and co-workers reported a cascade/cyclization reaction for the synthesis of 2-aminobenzothiazoles using CuI under ligand free condition (Scheme 8). A variety of 2-haloanilines underwent reaction with isothiocyanates to give the corresponding *N*-substituted 2-aminobenzothiazoles with high yield.[10e]



Scheme 8

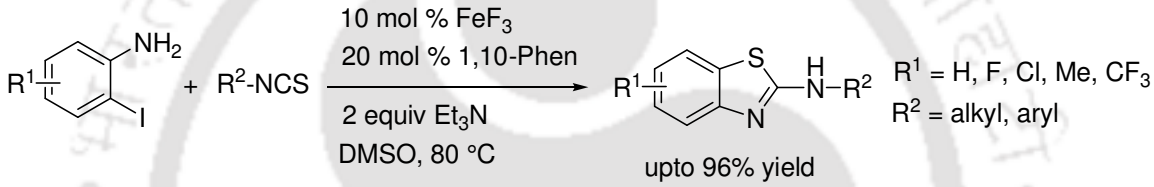
Li and co-workers developed a tandem method for the synthesis of 2-aminobenzothiazoles. In the presence of CuBr and TBAB (*tetra*-n-butylammonium bromide), a variety of 2-haloanilines underwent reaction with isothiocyanates to provide the corresponding 2-aminobenzothiazoles in moderate to excellent yield (Scheme 9). The advantages of this method are the reaction is free from the addition of base and ligands.[10f]



Scheme 9

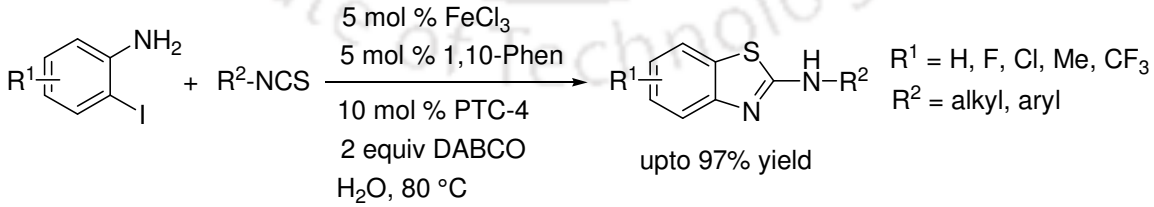
3.3 Iron Catalysts

In recent years, iron catalysts have attracted considerable interest in cross-coupling reactions because it is cheap, environmentally benign and non toxic. Li and co-workers established an iron-catalyzed tandem reaction for the synthesis of 2-aminobenzothiazoles (Scheme 10). 2-Haloanilines and aryl or alkyl isothiocyanates underwent tandem reactions in presence of FeF_3 and 1,10-phenanthroline to provide the corresponding 2-aminobenzothiazoles in moderate to excellent yield.[11a]



Scheme 10

A highly efficient synthesis of 2-aminobenzothiazoles has been developed by Ding and co-workers in water. The tandem reactions of 2-iodoanilines with isothiocyanates in presence of $FeCl_3$ and octadecyltrimethylammonium chloride as a phase-transfer catalyst gave the corresponding product 2-aminobenzothiazoles with high yield (Scheme 11). In addition, the reaction media can be recovered and reused for the fresh reaction without loss of efficiency.[11b]

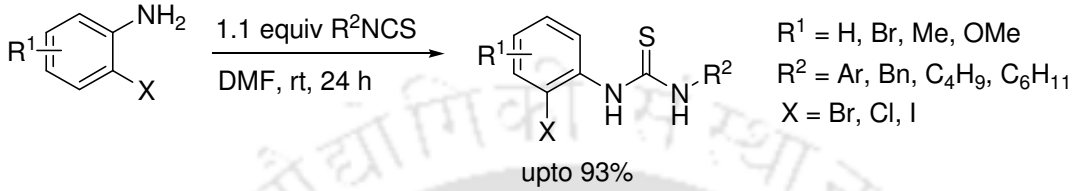


PTC-4 = octadecyltrimethylammonium chloride

Scheme 11

3.4 Present Study

Following the synthesis of substituted benzimidazoles and benzoxazoles using CuO nanoparticles, we have studied the synthesis of *N*-substituted 2-aminobenzothiazoles. The cyclization precursor, *o*-bromoarylthiourea, has been prepared from 2-bromoaniline and isothiocyanate in high yield (Scheme 12).[10a]



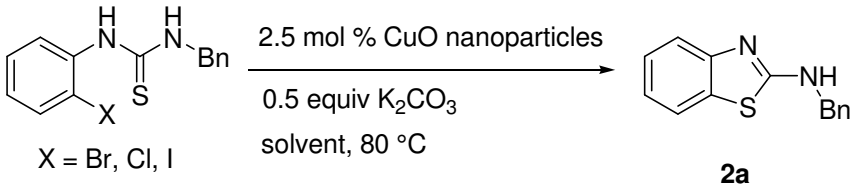
Scheme 12. Synthesis of *o*-Haloarylthiourea

After the synthesis of starting materials, we have optimized the reaction condition for the intramolecular *C–S* cross-coupling reaction. 1-Benzyl-3-(2-bromophenyl)thiourea **1a** was chosen as a model substrate for the reaction (Table 1). When the substrate was stirred with 2.5 mol % CuO nanoparticles in presence of 0.5 equiv of K_2CO_3 in DMSO at 80 °C, it underwent intramolecular cyclization to give the product *N*-benzylbenzothiazol-2-amine **2a** with 98% yield. Among the solvents studied, DMSO and DMF were more effective compared to 1,4-dioxane, toluene and acetonitrile. 2-Iodo derivatives are more reactive in comparison to 2-bromo and 2-chloro derivatives. Under these reaction conditions, 1-benzyl-3-(2-chlorophenyl)thiourea gave the target product with 28% yield. Control experiment without CuO nanoparticles showed no reaction.

Next, the substrate scope was evaluated for the reaction. The substrates **1b-g** having alkyl groups (R^2) such as benzyl, cyclohexyl and n-butyl have proceeded reactions to give the cyclized products **2b-g** in 82-98% yield. In contrast, the substrates **1h-j** containing aryl groups (R^2) afforded the desired cyclized products **2h-j** in 27-37% yield.[12]

These reaction conditions have been further examined for the cyclization of *o*-bromophenylbenzothioamide (Scheme 13). However, both the blank reaction as well as the reaction with CuO nanoparticles exhibit the cyclization affording the 2-phenylbenzothiazole in 73% and 99% yield, respectively.

Table 1. Optimization of Reaction Conditions[a]



X = Br, Cl, I

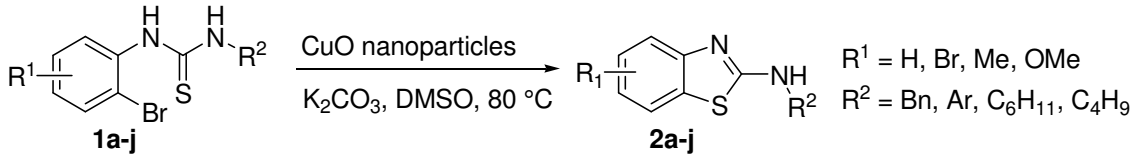
2a

entry	X	solvent	time (h)	conversion (%)[b]
1	Br	DMSO	10	99
2	Br	1,4-dioxane	10	28
3	Br	DMF	10	99
4	Br	toluene	10	45
5	Br	CH_3CN	10	50
6[c]	Br	DMSO	10	99
7[d]	Br	DMSO	10	99
8[e]	Br	DMSO	10	99
9	I	DMSO	3	99
10	Cl	DMSO	24	28
11[f]	Br	DMSO	24	0

[a] 1-Benzyl-3-(2-halophenyl)thiourea (0.5 mmol), CuO nanoparticles (5 mol %) and K_2CO_3 (1.5 mmol) were stirred at 80 °C in DMSO (1 mL) under air. [b] Determined from 400 MHz ^{1}H NMR. [c] K_2CO_3 (0.5 mmol) was used. [d] K_2CO_3 (0.25 mmmol) was used. [e] 2.5 mol % CuO nanoparticles was used. [f] The reaction was carried out in absence of CuO nanoparticles.

In conclusions, the syntheses of 2-aminobenzothiazoles are demonstrated using CuO nanoparticles. A wide variety of substrates undergo cyclization to give the products with high yield. The reactions are free from addition of external ligands and works under milder reaction condition.

Table 2. CuO Nanoparticles Catalyzed Synthesis of 2-Aminobenzothiazoles[a]



1a-j 2a-j

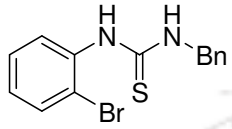
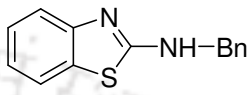
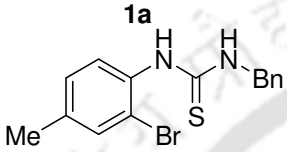
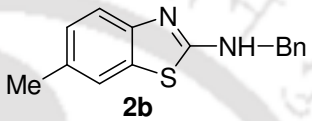
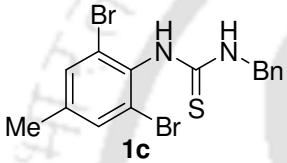
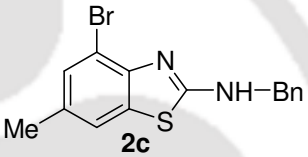
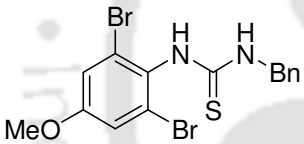
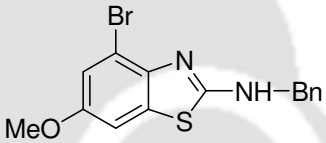
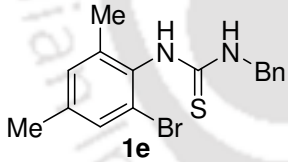
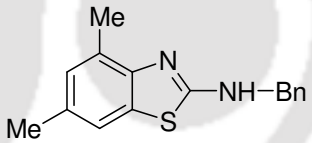
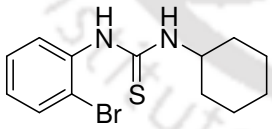
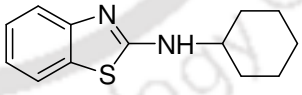
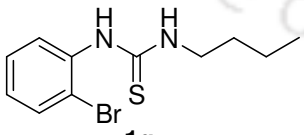
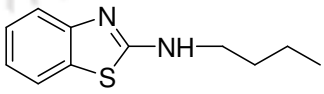
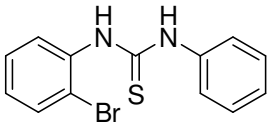
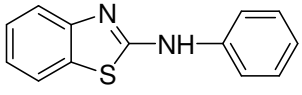
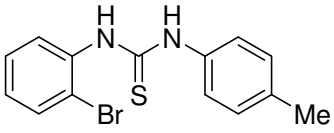
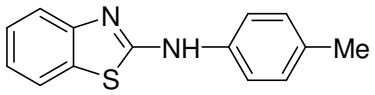
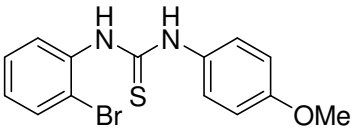
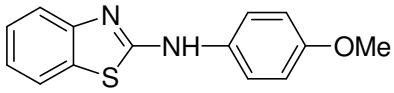
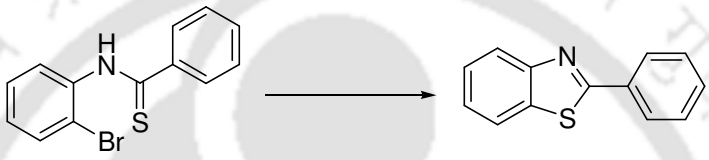
entry	substrate	time (h)	product	yield (%)
1	 **1a**	10	 **2a**	98
2	 **1b**	10	 **2b**	98
3	 **1c**	14	 **2c**	85
4	 **1d**	14	 **2d**	80
5	 **1e**	10	 **2e**	82
6	 **1f**	10	 **2f**	90
7	 **1g**	10	 **2g**	97
8	 **1h**	8	 **2h**	37

Table 2 continues…

9	 **1i**	8	 **2i**	34
10	 **1j**	8	 **2j**	27

[a] *o*-Bromoarylthiourea (0.5 mmol), CuO nanoparticles (2.5 mol %) and K_2CO_3 (0.25 mmol) were stirred at 80 °C in DMSO (1 mL) under air.



Reaction Conditions	yield
1.5 equiv K_2CO_3, 80 °C, 5 h	73%
2.5 mol % CuO nanoparticles, 1.5 equiv K_2CO_3, 80 °C, 5 h	99%

Scheme 13. Cyclization Reaction of *N*-(2-Bromophenyl)benzothioamide

Experimental Section

General Information

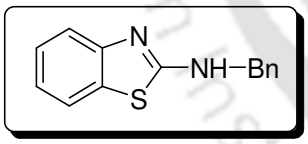
o-Haloanilines were purchased from Aldrich and used without further purification. Alkyl and aryl isothiocyanates were prepared according to literature.[13] Column chromatography was carried out with Rankem silica gel (60-120 mesh) using ethyl acetate and hexane as eluent. Analytical TLC was performed with silica gel 60 plates. NMR spectra (400 MHz for ^{1}H and 100 MHz for ^{13}C) were recorded using DRX-400 Varian spectrometer with $CDCl_3$ and DMSO-d_6 as solvent and Me_4Si as an internal standard. Melting points were determined using Buchi B-540 apparatus and uncorrected. Elemental analysis was carried out using CHNS analyzer. IR spectra were recorded using Perkin Elmer FT-IR spectrometer.

General Procedure for Synthesis of *o*-Haloarylthioureas

An oven dried round bottom flask was charged with 2-haloaniline (2 mmol) and DMF (3 mL). To the flask alkyl or aryl isothiocyanate (2 mmol) was added and stirred at room temperature for 24-48 h. After the completion of reaction, ethyl acetate (25 mL) was added to the reaction mixture and successively washed with water (2 x 5 mL) and brine (1 x 5 mL). The organic layers was separated, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to afford a residue. The residue was purified by column chromatography using ethyl acetate and hexane as eluent to give analytically pure target molecule.

General Procedure for the Synthesis of 2-Aminobenzothiazoles

An oven dried 10 mL round bottom flask was charged with the *N*-(2-bromoaryl)thiourea (0.5 mmol), CuO nanoparticles (2.5 mol %, 1.0 mg), K_2CO_3 (0.25 mmol, 34.5 mg) and DMSO (1 mL) and the mixture was stirred at 80 °C for appropriate time (Table 1). The progress of the reaction was monitored by TLC using ethyl acetate and hexane as eluent. The reaction mixture was then cooled to room temperature and diluted with ethyl acetate (15 mL). The organic layer was successively washed with brine (1 x 4 mL) and water (2 x 4 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue which was purified on silica gel column chromatography using ethyl acetate and hexane as eluent.



***N*-Benzylbenzo[*d*]thiazol-2-amine (2a).**[14a] Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.48; colorless solid; yield 98%.

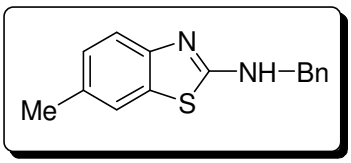
Mp: 156-157 ºC (lit.[14a] mp 155-157 ºC).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.41-7.26 (m, 6H), 7.08 (t, *J* = 7.2 Hz, 1H), 6.15 (s, 1H), 4.64 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9, 152.3, 137.6, 129.0, 128.0, 127.8, 126.2, 127.0, 121.8, 121.0, 119.0, 49.6.

FT-IR (KBr): 3184, 2898, 2853, 1619, 1574, 1447, 1355, 1265, 1107 cm^{-1}.

Anal. Calcd for $C_{14}H_{12}N_2S$: C, 69.97; H, 5.03; N, 11.66; S, 13.34. Found: C, 70.24; H, 5.05; N, 11.59; S, 13.12.



***N*-Benzyl-6-methylbenzo[*d*]thiazol-2-amine (2b).** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.49; colorless solid; yield 98%.

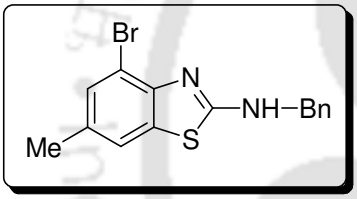
Mp: 177-178 ºC (lit.[14a] mp 176-178 ºC).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.28 (m, 7H), 7.09-7.06 (m, 1H), 5.66 (s, 1H), 4.61 (s, 2H), 2.37 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.6, 150.1, 138.1, 130.9, 130.5, 128.5, 127.6, 127.4, 126.7, 120.6, 118.2, 48.6, 21.0.

FT-IR (KBr): 3089, 2981, 2899, 2854, 1621, 1590, 1468, 1356, 1309, 1269, 973 cm^{-1}.

Anal. Calcd for $C_{15}H_{14}N_2S$: C, 70.83; H, 5.55; N, 11.01; S, 12.61. Found: C, 70.96; H, 5.50; N, 10.96; S, 12.58.



***N*-Benzyl-4-bromo-6-methylbenzo[*d*]thiazol-2-amine (2c).** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.50; colorless solid; yield 85%.

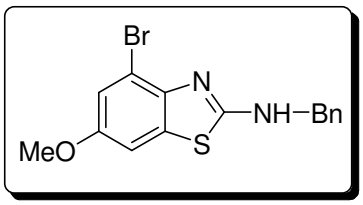
Mp: 159-160 ºC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.30 (m, 7H), 6.08 (s, 1H), 4.57 (s, 2H), 2.36 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7, 148.6, 137.3, 132.6, 131.1, 130.4, 129.0, 128.0, 127.7, 120.4, 111.6, 50.0, 21.0.

FT-IR (KBr): 3210, 3008, 2918, 2850, 1558, 1533, 1513, 1462, 1347, 1220, 1193 cm^{-1}.

Anal. Calcd for $C_{15}H_{13}BrN_2S$: C, 54.06; H, 3.93; N, 8.41; S, 9.62. Found: C, 54.30; H, 3.88; N, 8.31; S, 9.53.



***N*-Benzyl-4-bromo-6-methoxybenzo[*d*]thiazol-2-amine (2d).** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f = 0.51$; colorless solid; yield 80%.

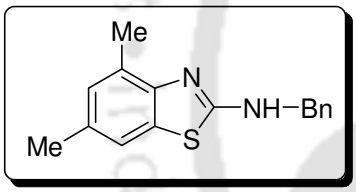
Mp: 164-165 ºC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.31 (m, 5H), 7.11 (d, *J* = 2.4 Hz, 1H), 7.07 (d, *J* = 2.4 Hz, 1H), 5.89 (s, 1H), 4.57 (s, 2H), 3.79 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4, 155.3, 145.2, 137.4, 131.8, 129.0, 128.1, 127.8, 116.9, 112.0, 105.5, 56.3, 49.9.

FT-IR (KBr): 3210, 3009, 2850, 1557, 15147, 1463, 1347, 1220, 1194 cm^{-1}.

Anal. Calcd for $C_{15}H_{13}BrN_2OS$: C, 51.59; H, 3.75; N, 8.02; S, 9.18. Found: C, 51.76; H, 3.68; N, 7.96; S, 9.10.



***N*-Benzyl-4,6-dimethylbenzo[*d*]thiazol-2-amine (2e).** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane $R_f = 0.52$; colorless solid; yield 82%.

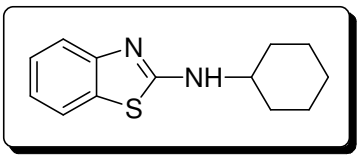
Mp: 120-121 ºC.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39-7.26 (m, 5H), 7.21 (s, 1H), 6.92 (s, 1H), 5.49 (s, 1H), 4.57 (s, 2H), 2.51 (s, 3H), 2.33 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4, 149.3, 137.9, 131.3, 130.5, 128.9, 128.4, 128.3, 127.9, 127.8, 118.5, 49.7, 21.3, 18.5.

FT-IR (KBr): 3216, 2863, 1595, 1423, 1355, 1321, 1215 cm^{-1}.

Anal. Calcd for $C_{16}H_{16}N_2S$: C, 71.61; H, 6.01; N, 10.44; S, 11.95. Found: C, 71.83; H, 5.99; N, 10.32; S, 11.80.



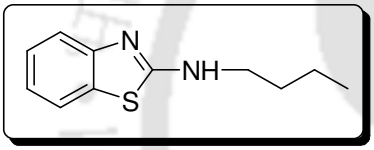
***N*-Cyclohexylbenzo[*d*]thiazol-2-amine (2f).**[10d] Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.43; yellow liquid; yield 90%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.25 (dt, *J* = 7.2, 1.2 Hz, 1H), 7.04 (dt, *J* = 7.6, 1.2 Hz, 1H), 5.39 (s, 1H), 3.54 (s, 1H), 2.11 (d, *J* = 3.2 Hz, 2H), 1.80-1.61 (m, 4H), 1.45-1.13 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 152.5, 130.3, 126.0, 121.3, 120.9, 118.6, 54.8, 33.4, 25.6, 24.9.

FT-IR (neat): 2927, 2851, 1596, 1544, 1440, 1251, 1033 cm^{-1}.

Anal. Calcd for $C_{13}H_{16}N_2S$: C, 67.20; H, 6.94; N, 12.06; S, 13.80. Found: C, 67.30; H, 6.91; N, 12.09; S, 13.70.



***N*-Butylbenzo[*d*]thiazol-2-amine (2g).** Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.46; colorless solid; yield 97%.

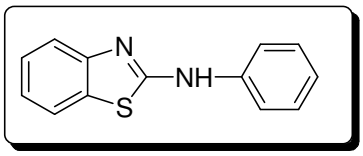
Mp: 67-68 ºC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (td, *J* = 8.0, 0.6 Hz, 1H), 7.49 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.28-7.24 (m, 1H), 7.04 (dt, *J* = 8.0, 1.2 Hz, 1H), 5.67 (s, 1H), 3.38 (t, *J* = 7.2 Hz, 2H), 1.67-1.61 (m, 2H), 1.46-1.37 (m, 2H), 0.97-0.88 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 152.6, 130.4, 126.1, 121.4, 120.9, 118.7, 45.6, 31.8, 20.2, 13.9.

FT-IR (KBr): 3219, 2949, 2920, 2864, 1616, 1573, 1557, 1446, 1372, 1340, 1301, 1278, 1238, 1090 cm^{-1}.

Anal. Calcd for $C_{11}H_{14}N_2S$: C, 64.04; H, 6.84; N, 13.58; S, 15.54. Found: C, 64.26; H, 6.81; N, 13.50; S, 15.43.



***N*-Phenylbenzo[*d*]thiazol-2-amine (2h).**[14b] Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.52; colorless solid; yield 37%.

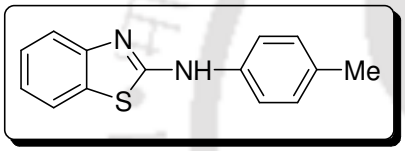
Mp: 158-159 ºC (lit.[14b] mp 158 ºC).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (s, 1H), 7.63-7.58 (m, 2H), 7.50-7.47 (m, 2H), 7.41-7.36 (m, 2H), 7.32 (dt, *J* = 7.2, 1.6 Hz, 1H), 7.14 (dt, *J* = 8.0, 1.2 Hz, 2H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 152.1, 140.5, 130.2, 129.1 125.8, 122.9, 122.2, 120.6, 119.5, 118.9;

FT-IR (KBr): 3185, 2832, 1622, 1575, 1513, 1449, 1240, 1010 cm^{-1}.

Anal. Calcd for $C_{13}H_{10}N_2S$: C, 69.00; H, 4.45; N, 12.38; S, 14.17. Found: C, 69.23; H, 4.39; N, 12.23; S, 14.15.



***N*-*p*-Tolylbenzo[*d*]thiazol-2-amine (2i).**[14c] Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.51; colorless solid; yield 34%.

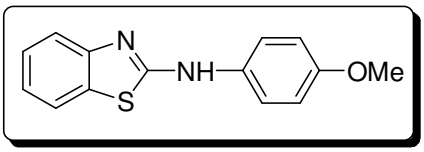
Mp: 176-177 ºC (lit.[14c] mp 177-179 ºC).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (s, 1H), 7.60-7.54 (q, *J* = 8.0 Hz, 2H), 7.36-7.28 (m, 3H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.12 (dt, *J* = 7.6, 1.2 Hz, 1H), 2.34 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$:DMSO): δ 164.0, 152.1, 137.9, 132.9, 129.7, 125.8, 122.0, 120.6, 119.7, 119.2, 115.2, 20.8.

FT-IR (KBr): 3184, 3029, 2914, 1622, 1573, 1514, 146, 1248, 1224, 1020 cm^{-1}.

Anal. Calcd for $C_{14}H_{12}N_2S$: C, 69.97; H, 5.03; N, 11.66; S, 13.34. Found: C, 70.15; H, 4.98; N; 11.55, S, 13.32.



***N*-(4-Methoxyphenyl)benzo[*d*]thiazol-2-amine (2j).**[10d] Analytical TLC on silica gel, 1:4 ethyl acetate/hexane R_f = 0.46; colorless solid; yield 27%.

Mp: 156-157 ºC (lit.[13b] mp 154-155 ºC).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.45-7.37 (m, 3H), 7.26 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.08 (dt, *J* = 7.2, 1.2 Hz, 1H), 6.94 (dd, *J* = 6.8, 2.0 Hz, 2H), 3.83 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$:DMSO-d_6): δ 164.4, 155.8, 152.1, 133.6, 129.9, 125.6, 121.6, 120.4, 118.8, 114.2, 55.3.

FT-IR (KBr): 3183, 3066, 2836, 1621, 1573, 1513, 1454, 1231, 1037 cm^{-1}.

Anal. Calcd for $C_{14}H_{12}N_2OS$: C, 65.60; H, 4.72; N, 10.93; S, 12.51. Found: C, 65.82; H, 4.66; N; 10.86, S, 12.40.

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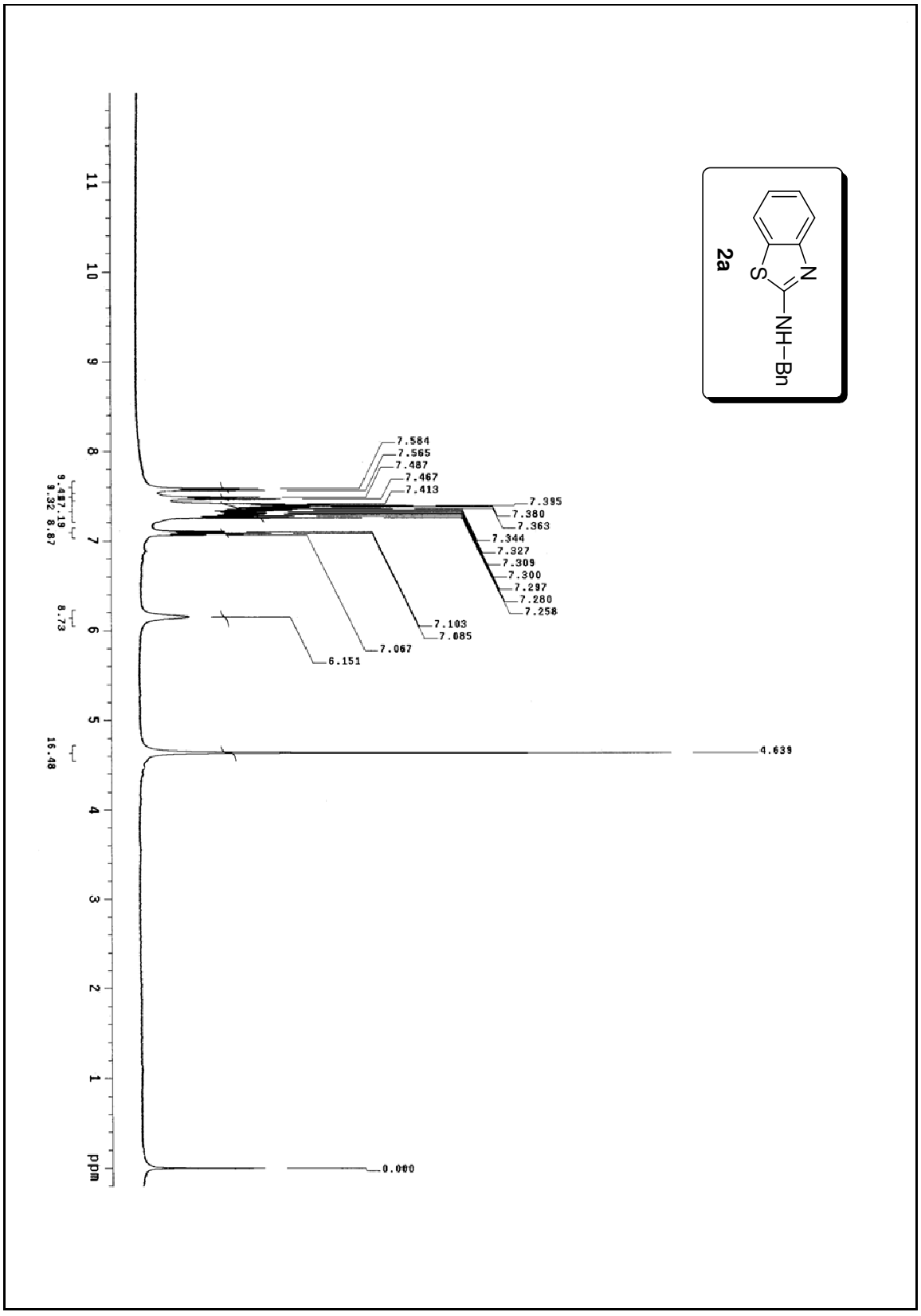
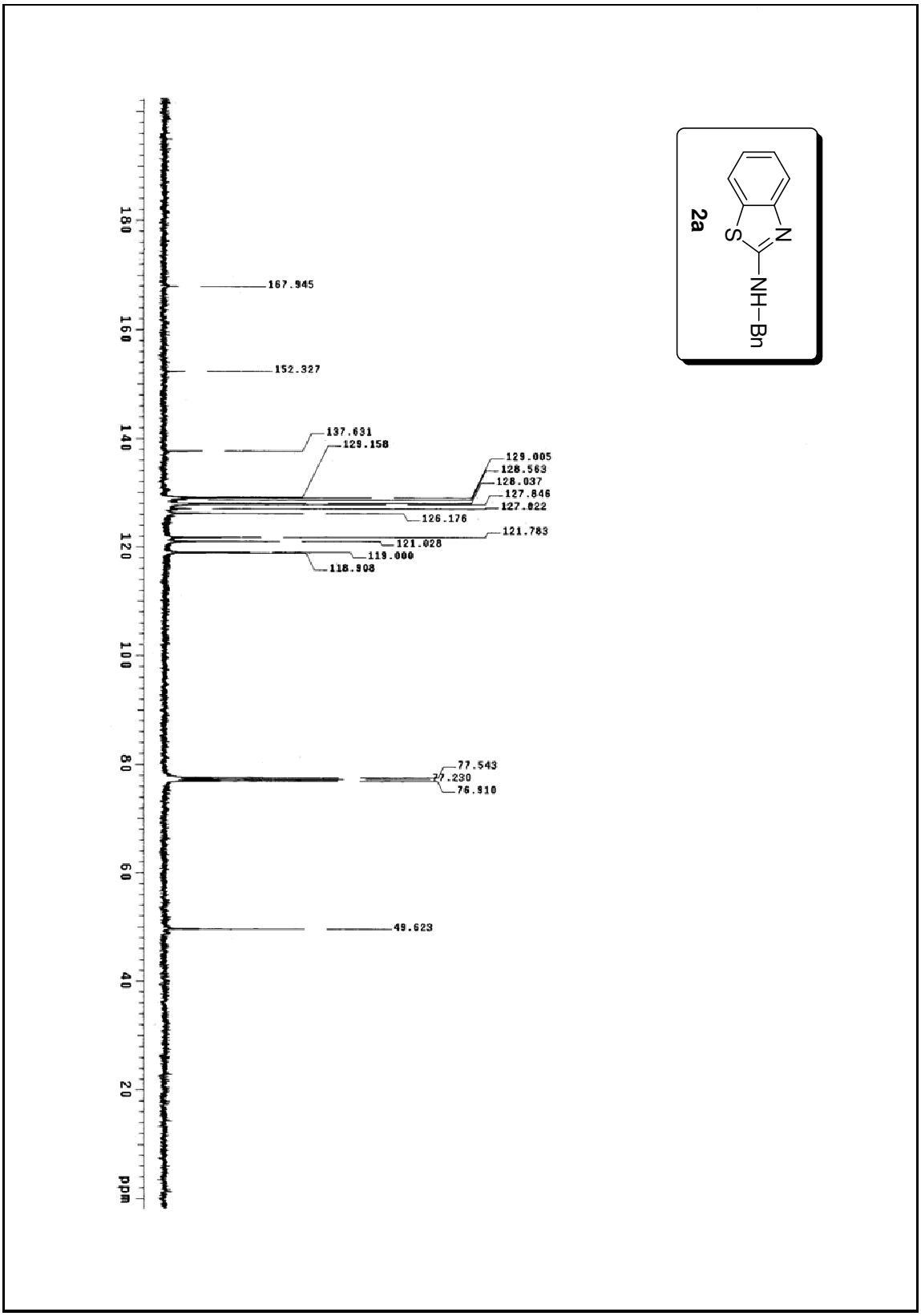
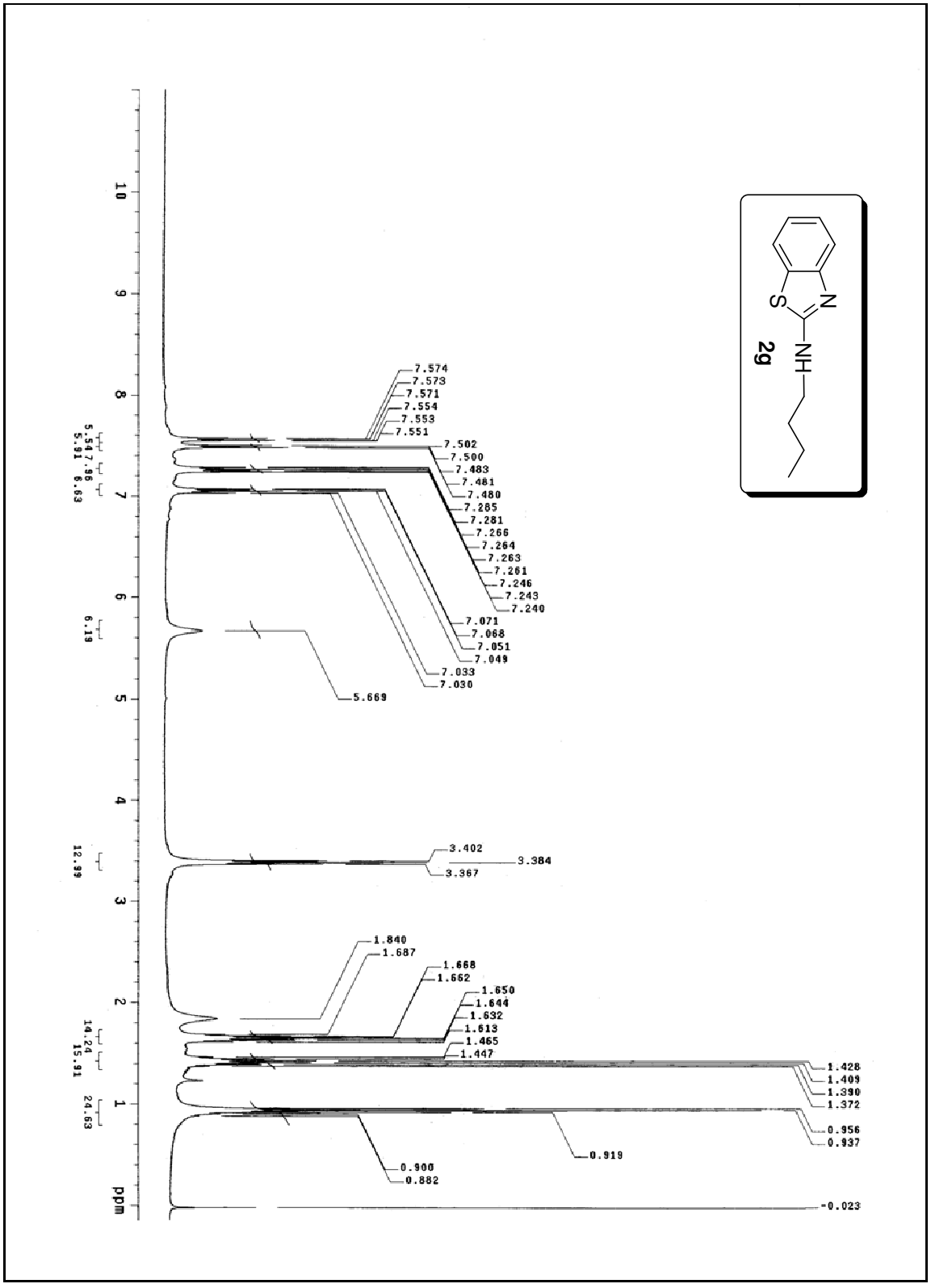
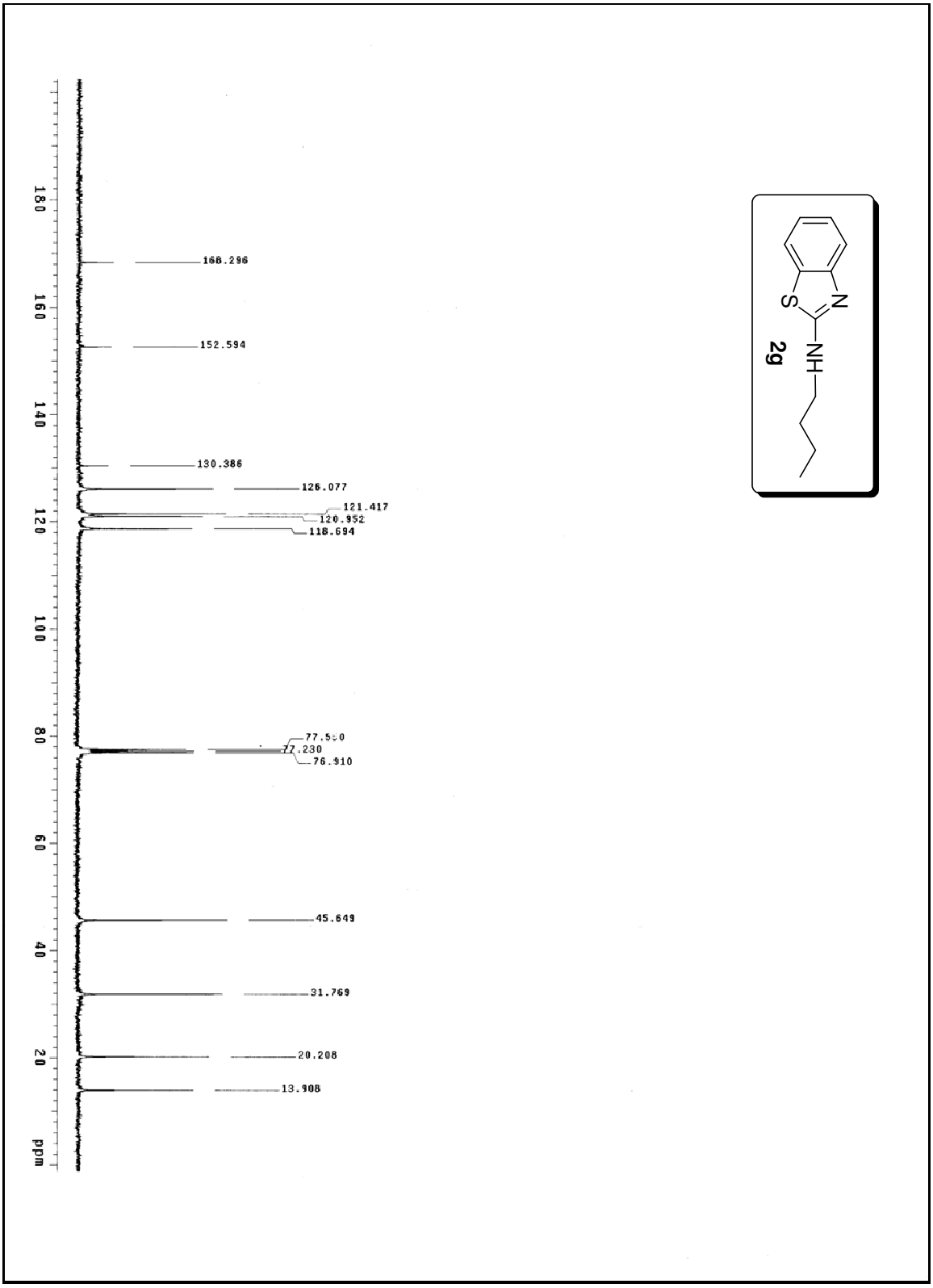
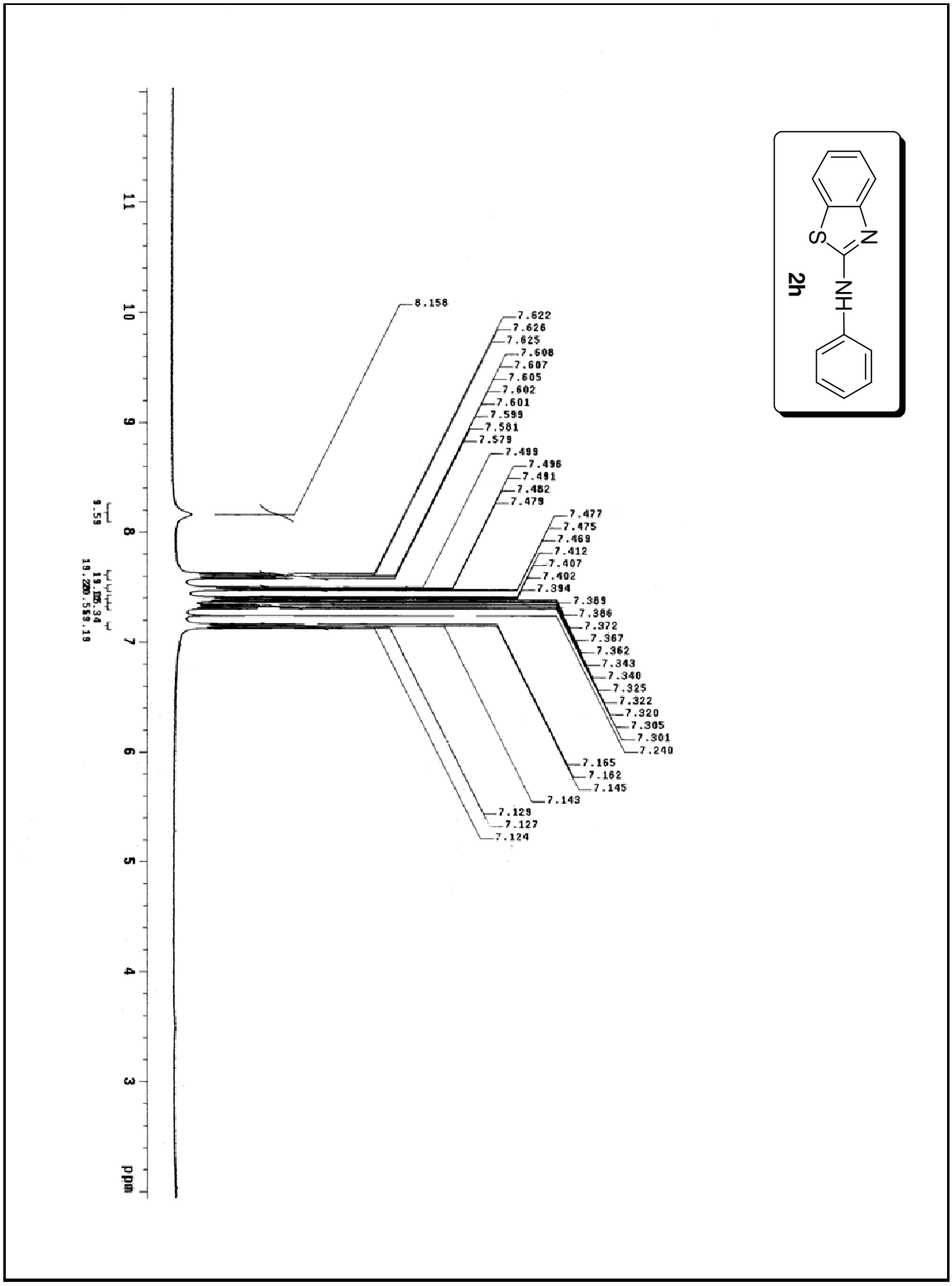
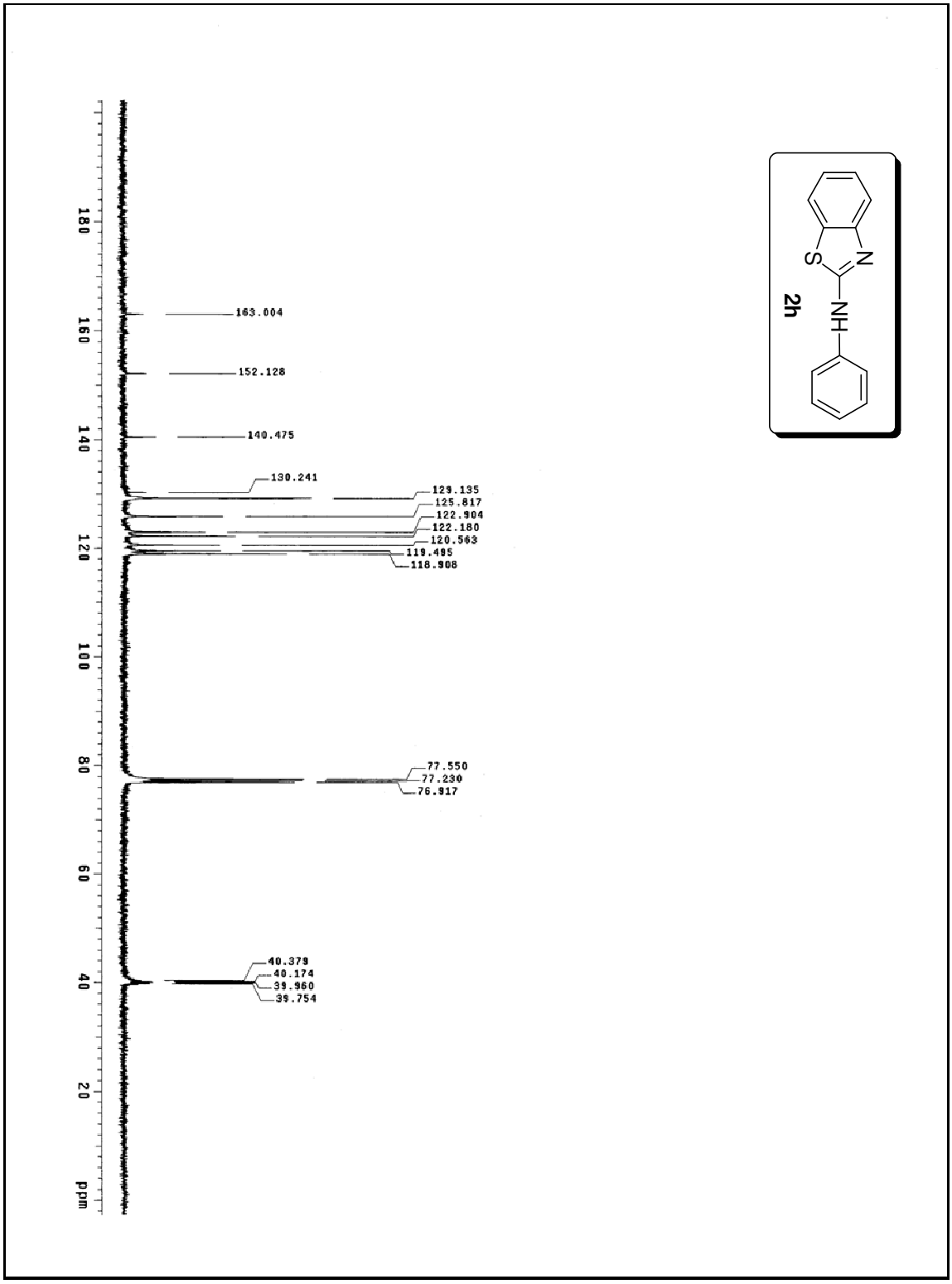










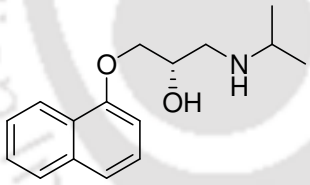


Chapter IV

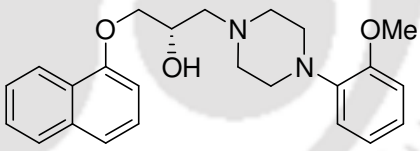
Synthesis and Application of Self-Assembled Chiral Copper(II) Complexes for Asymmetric Acylation of Secondary Alcohols

The study of stereoregular chiral coordination polymers is a very active interdisciplinary research topic with potential applications in asymmetric catalysis, chiral sensor, nonlinear optical and chiral magnetic materials.[1,2] The building blocks approach include the possibility of introducing chiral centers in either metal complexes or ligands to obtain chiral network.[3] Transition metal complexes of chiral Schiff base ligands having multifunctional coordination groups (carbonyl and carboxylate oxygen) could be good candidates to be used as metalloligands for constructing extended multi-dimensional chiral supramolecular coordination polymers.

Optically active alcohols and their derivatives are versatile intermediates for the synthesis of natural products, biologically active compounds and chiral ligands.[4] For examples, (*S*)-propranolol and (*S*)-naftopidil are β-blocking agents whose biological activity is associated with only (*S*)-enantiomer that is (*S*)-isomer is 100 times more potent than the (*R*)-isomer. Kinetic resolution of alcohols is a fundamental and one of the effective methods to avail optically active alcohols.



***S*-Propranolol**
β-Adrenergic blocking agents



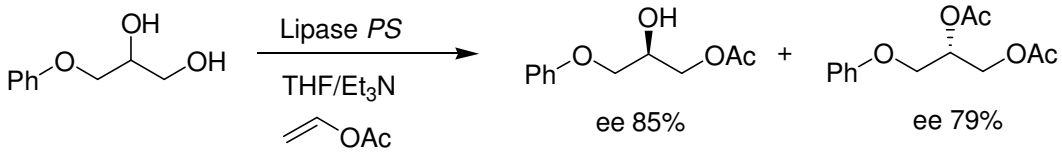
***S*-Naftopidil**
antihypersensitive drug

Figure 1. Examples of biologically active compounds.

4.1 Enzyme-Catalyzed Kinetic Resolution of Alcohols

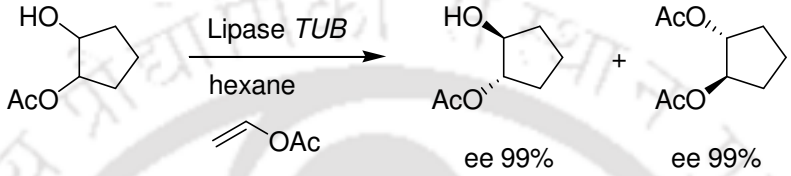
Enantioselective acyl transfer provides a convenient method for kinetic resolution of racemic alcohols. Enzyme catalyzed asymmetric acylation reactions are powerful tools for the kinetic resolution of alcohols.

Theil and co-workers investigated the kinetic resolution of racemic 1,2-diols using lipase *Amano PS* as a catalyst (Scheme 1). The enantioselectivity of the reaction depends on the substitution pattern of the aryl ring.[5a]



Scheme 1

Bodai and co-workers reported lipase catalyzed acylation of *trans*-2-acetoxycycloalkan-1-ols using vinyl acetate as acylating agent (Scheme 2).[5b] The products are obtained with good enantioselectivity.



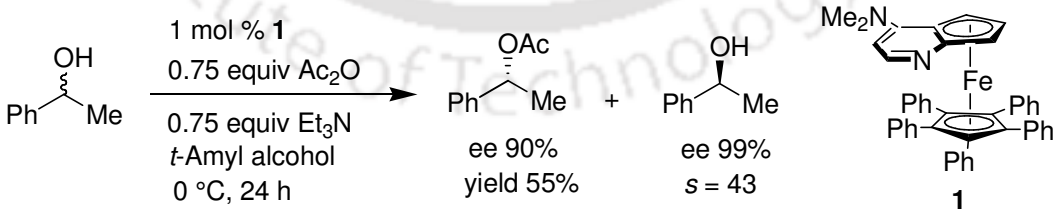
Scheme 2

4.2 Metal-Catalyzed Kinetic Resolution of Alcohols

In recent years, a number of non-enzymatic chiral catalysts have been developed for the kinetic resolution of alcohols by asymmetric acylation which, in some cases, exhibit practically useful levels of enantioselectivity.

4.2.1 Iron Catalyst

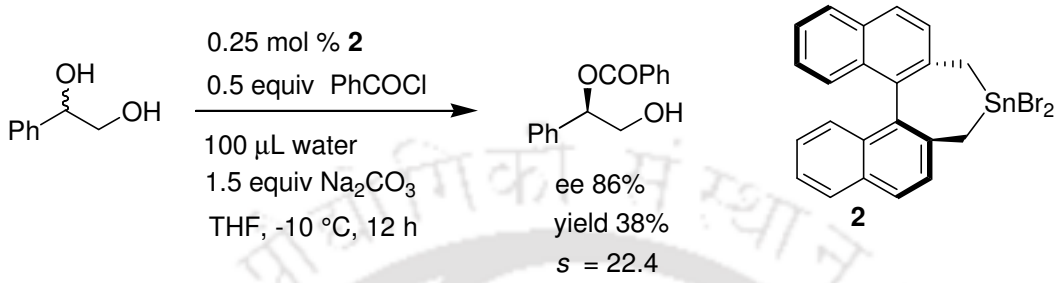
Fu and co-workers employed planar chiral DMAP derivatives **1** as nucleophilic catalyst for the kinetic resolution of secondary alcohols with high enantioselectivity (Scheme 3).[6a,b]



Scheme 3

4.2.2 Tin Catalyst

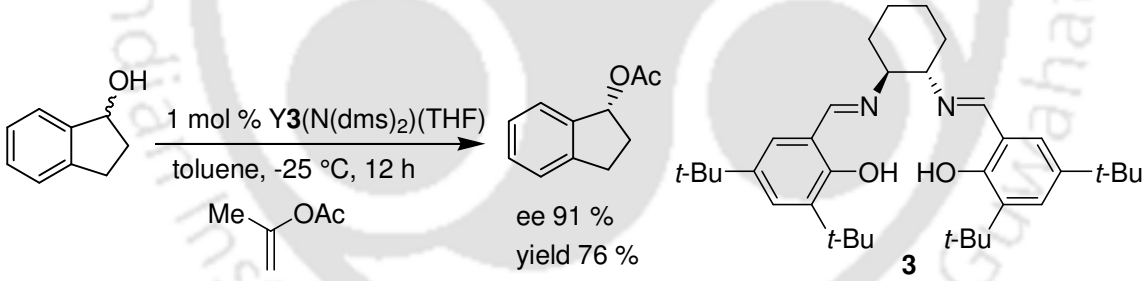
Matsumura and co-workers used chiral tin complex **2** for monobenzoylation of cyclic and acyclic diols (Scheme 4).[6c] The reactions occurred to afford the benzoylated product with up to 86% ee.



Scheme 4

4.2.3 Yttrium Catalyst

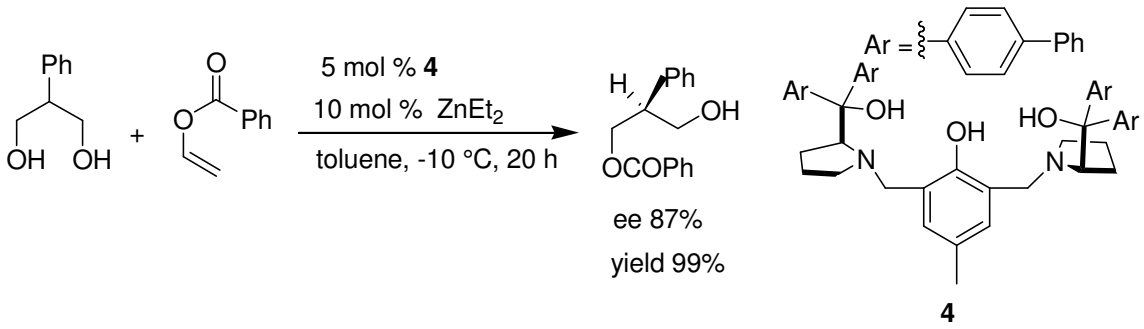
Rajanbabu and co-workers reported yttrium-salen complex for the kinetic resolution of secondary alcohols with isopropenyl acetate as the acylating agent. Under these reaction conditions, indanol is resolved with 91% ee (Scheme 5).[6d]



Scheme 5

4.2.4 Zinc Catalyst

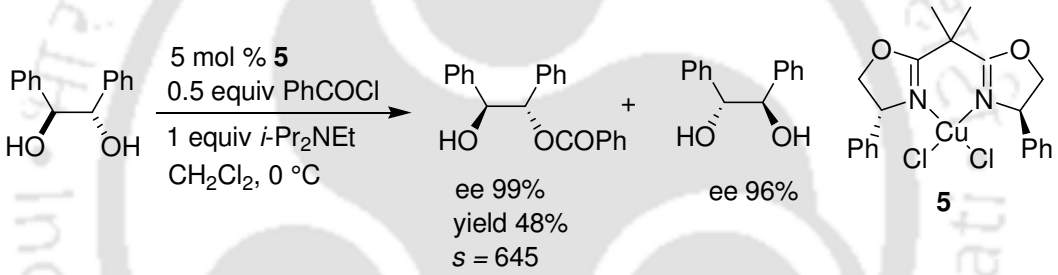
Trost and Mino employed binuclear zinc catalyst derived from $ZnEt_2$ and ligand **4** for the resolution of 1,3-diols and 1,4-diols with high enantioselectivity (Scheme 6).[6e] On increasing the size of the chiral pocket, the yield and enantioselectivity of the reaction were increased. The reaction is suitable with electron donating phenyl rings and hetero aromatic rings.



Scheme 6

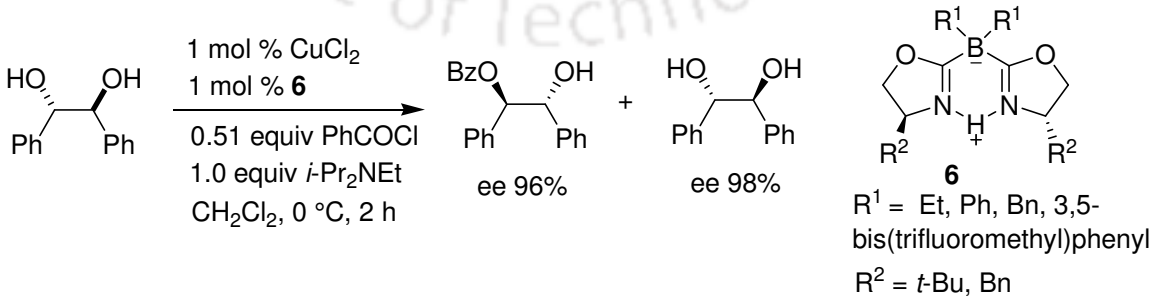
4.2.5 Copper Catalysts

Matsumura and co-workers described a stereoselective monobenzoylation of *trans*-1,2-diols using copper(II) bisoxazoline based catalysts with high enantioselectivity (Scheme 7). The selectivity of the reaction strongly depends on the bulkiness of the acylating agents.[6f]



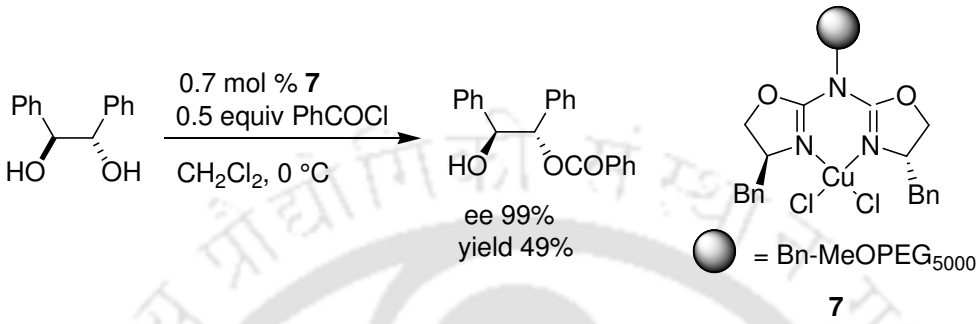
Scheme 7

Pfaltz and co-workers used the combination of $CuCl_2$ and boron bridged bisoxazoline ligands for the kinetic resolution of *trans*-1,2-diols and pyridyl alcohols (Scheme 8). High enantioselectivities are observed when a large substituent is adjacent to the hydroxy group.[6g,h]



Scheme 8

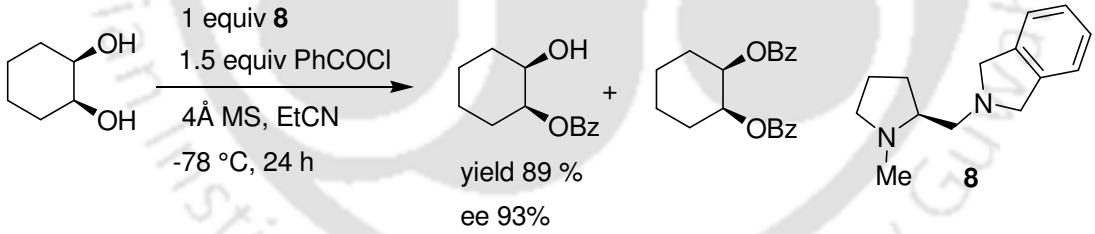
Reiser and co-workers demonstrated the asymmetric benzoylation of racemic 1,2-diols and α-hydroxyl carbonyl compounds in presence of copper(II)-aza(bisoxazoline) catalysts. The reaction gave the monobenzoylated product with high enantioselectivity. The catalyst can be recovered and reused after being immobilized on a poly(ethyleneglycol) support.[6i]



Scheme 9

4.3. Organo-Catalyzed Kinetic Resolution of Diols

Oriyama and co-workers reported the asymmetric acylation of *meso*-diols with benzoyl chloride in presence of chiral diamine derived from (*S*)-proline (Scheme 10). The desired monobenzoylated products are obtained with high yield and enantioselectivity.[7a]

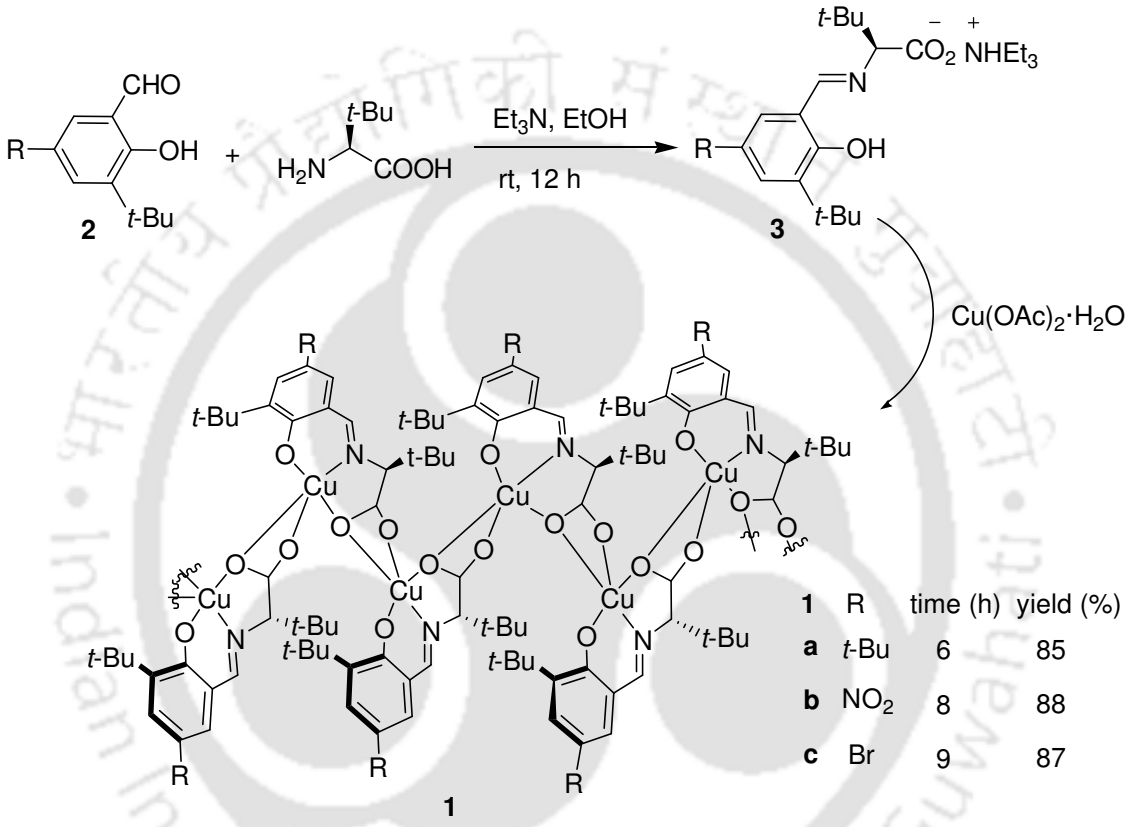


Scheme 10

4.4 Present Study

This chapter reports the synthesis and application of self-assembled chiral copper(II) complexes **1a-c** for asymmetric acylation of secondary alcohols. The synthesis of the self-assembled structures **1a-c** is shown in Scheme 11. Reaction of the salicylaldehyde derivatives **2a-c** with L-*tert*-leucine[8] in the presence of Et_3N provided Schiff bases **3a-c** which were reacted *in situ* with $Cu(OAc)_2 \cdot H_2O$ to afford the polymers **1a-c** as green colored crystals in 85-88% yield.[9] Recrystallization of the polymers **1a-c** in a mixture of MeOH and CH_2Cl_2 gave single crystals which were analyzed by X-ray analysis. ORTEP

diagram of the coordination polymers are shown in figure 2-4. Polymers **1a-c** are stereoregular and the repeating units having *O–H* interaction are connected to each other by perpendicular fashion. The copper(II) atoms are pentacoordinated with distorted square pyramidal geometry for **1a-b** and square planar geometry for **1c**.[9] The UV-Vis spectra of the polymers **1a-c** in methanol show a charge transfer absorption band at 384, 365 and 380 nm, respectively (Figure 5). The EPR analysis showed that the oxidation state of copper is +2.



Scheme 11. Synthesis of Coordination Polymers **1a-c**

Since the polymers **1a-c** are stereoregular, we were interested to study catalytic activities for asymmetric catalysis. First, we examined the kinetic resolution of secondary alcohols by acylation. The reaction of benzoin was studied as a model substrate with different acylating agents (Table 1). We were pleased to find that the reaction occurred to afford the desired acylated product with up to 62% ee when the substrate was stirred at 0 °C in the presence of 0.5 equiv of acylating agent, 1 equiv of base and 5 mol % of copper(II) polymer **1a-c** (with respect to monomeric unit). When the reaction temperature was further lowered to 25 °C, the enantioselectivity of the acylated product was enhanced up to 90% ee (*s* = 50). Of the acylating agents studied, benzoyl chloride, benzoic

anhydride, acetic anhydride and acetyl chloride, the later was less effective affording the acylated product with 15% ee. The reactions with benzoyl chloride and benzoic anhydride

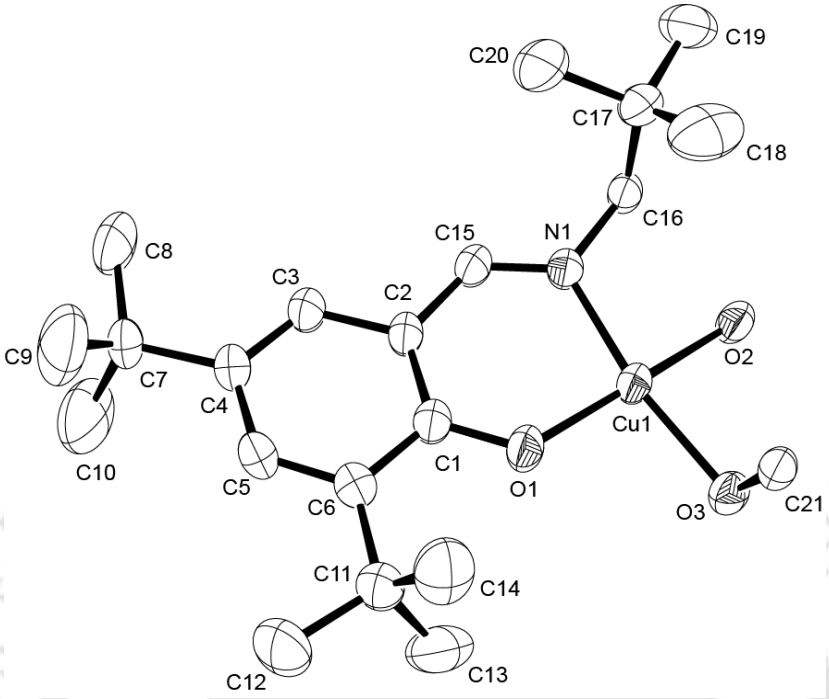


Figure 2. ORTEP diagram of a repeating unit of **1a** with thermal ellipsoid set to 50% probability. H-Atoms are omitted for clarity.

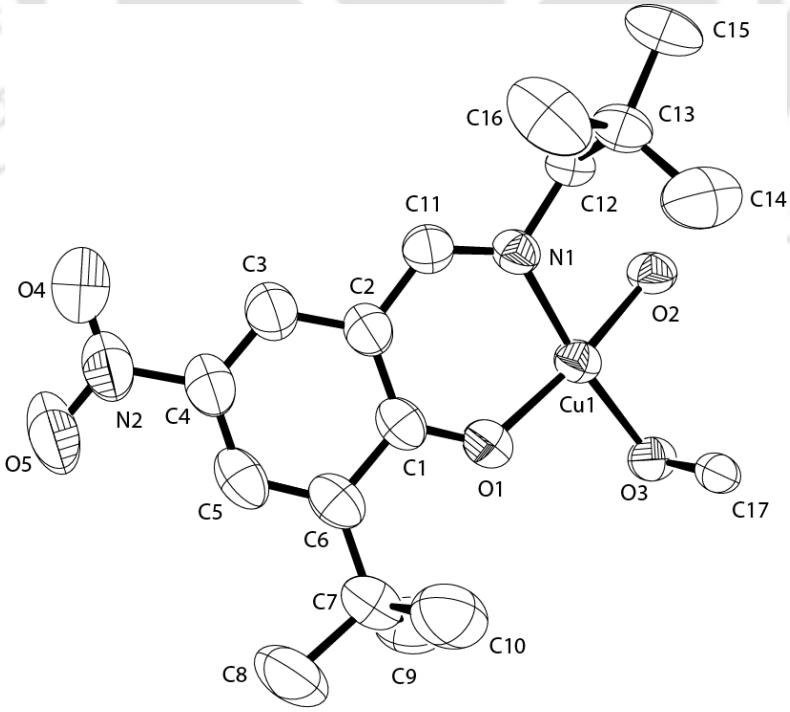
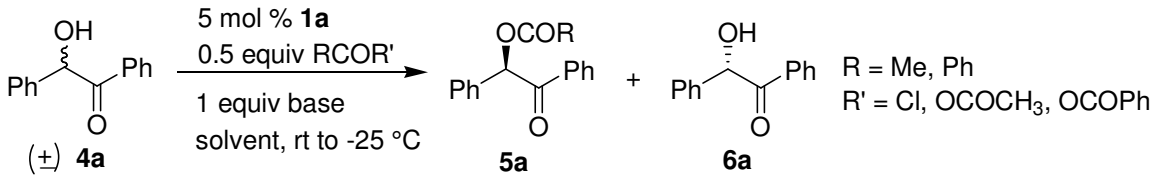


Figure 3. ORTEP diagram of a repeating unit of **1b** with thermal ellipsoid set to 50% probability. H-Atoms are omitted for clarity.

Table 1. Kinetic Resolution of (±)-Benzoin: Optimization of Reaction Conditions[a]



entry	catal-yst	solvent	RCOR'	base	T (°C)	time (h)	**5a** ee (%)[b]	**6a** ee (%)[c]	conv. (%)	s[d]
1	**1a**	CH_2Cl_2	PhCOCl	Et_3N	0	4.5	42	35	45	3.4
2	**1a**	acetone	PhCOCl	Et_3N	0	4.5	60	56	48	6.9
3	**1a**	toluene	PhCOCl	Et_3N	0	4.5	41	38	48	3.4
4	**1a**	THF	PhCOCl	Et_3N	0	4.5	62	53	46	9.9
5	**1a**	THF	PhCOCl	Et_3N	-10	6.5	65	58	47	8.3
6	**1a**	THF	PhCOCl	Et_3N	-25	8	78	75	49	18
7	**1a**	THF	$(PhCO)_2O$	Et_3N	-25	10	75	64	46	13.3
8	**1a**	THF	CH_3COCl	Et_3N	-25	6	15	9	37	1.5
9	**1a**	THF	Ac_2O	Et_3N	-25	15	68	55	44	8.9
10	**1a**	Et_2O	Ac_2O	Et_3N	-25	15	90	82	48	50
11	**1b**	Et_2O	Ac_2O	Et_3N	-25	15	50	42	46	4.5
12	**1c**	Et_2O	Ac_2O	Et_3N	-25	15	41	34	45	3.8
13	**1a**	THF	PhCOCl	*i*-$PrNH_2$	-25	22	43	35	45	3.5
14	**1a**	THF	PhCOCl	2,6-lutidine	-25	25	35	25	41	2.6
15	**1a**	THF	PhCOCl	pyridine	-25	25	0	0	-	-

[a] Substrate (1 mmol), catalyst **1a-c** (5 mol % with respect to repeating unit), acylating agent (0.5 mmol) and base (1 mmol) were stirred in solvent (2 mL). [b] Determined by HPLC using chiralcel OD-H column with hexane and isopropanol (95:5). [c] Determined by HPLC using chiralcel OD column with hexane and isopropanol (95:5). [d] Determined according to ref 6h.

showed similar results providing the benzoylated product with up to 78% ee. While the reaction with acetic anhydride exhibited up to 90% ee. Among the bases screened, Et_3N,

i-Pr_2NH, pyridine and 2,6-lutidine, the former provided the best result. Of the solvents examined, THF, Et_2O, CH_2Cl_2, acetone and toluene, THF provided the highest *ee* for

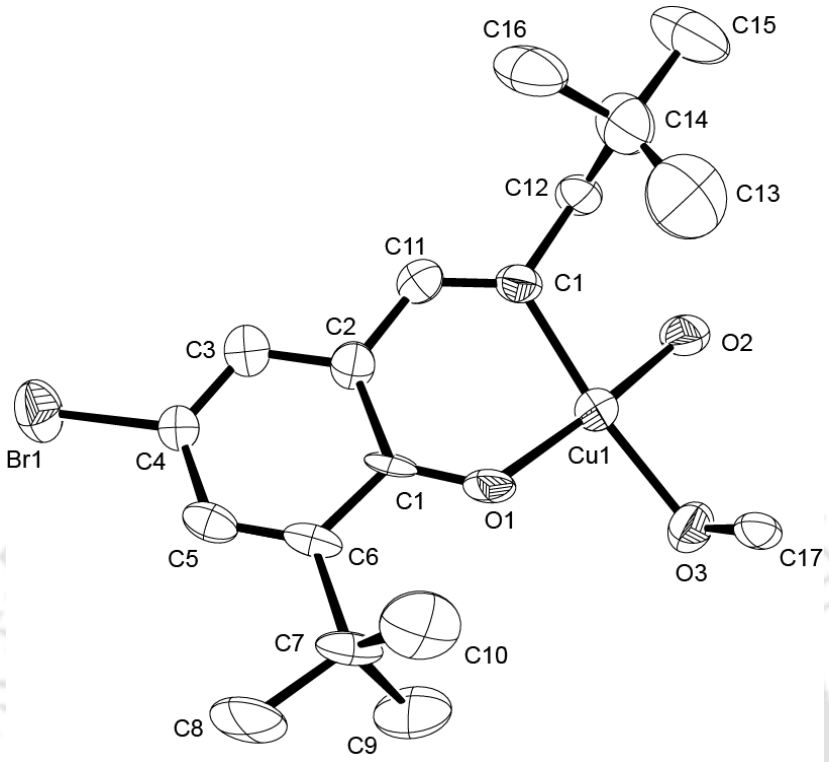


Figure 4. ORTEP diagram of a repeating unit of **1c** with thermal ellipsoid set to 50% probability. H-Atoms are omitted for clarity.

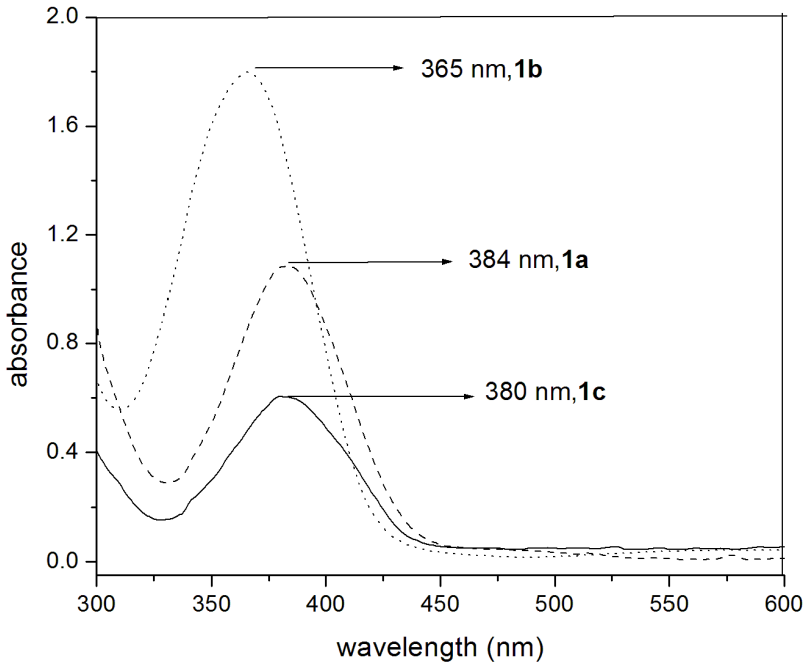
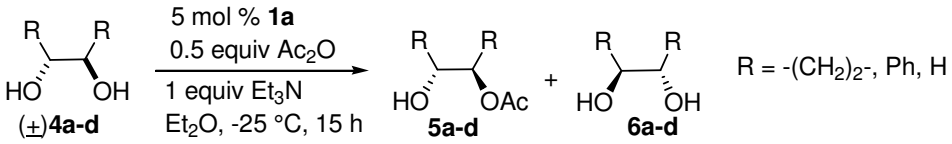
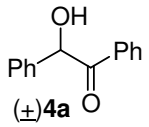
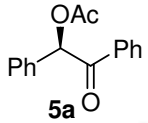
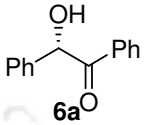
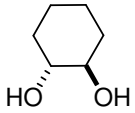
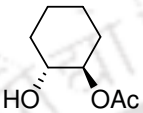
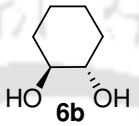
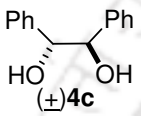
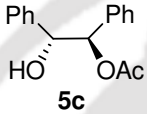
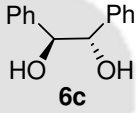
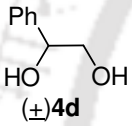
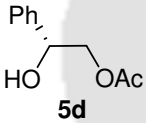
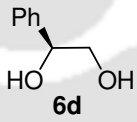


Figure 5. UV-Vis spectra of the polymers **1a-c** in MeOH solution at C = 0.0066 gm/mL.

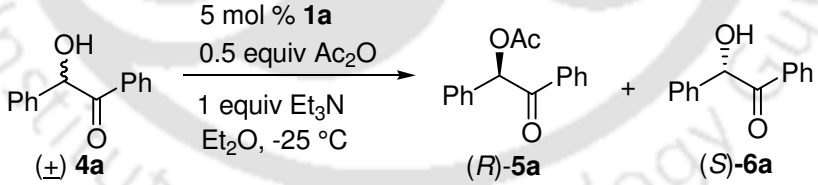
Table 2. Kinetic Resolution of (±)-Benzoin and (±)-*trans*-1,2-Diols by Acylation[a]



entry	(±)4a-d	5a-d	ee (%)[b]	6a-d	ee (%)[b]	conv. (%)[c]	s[c]	5a-d (confign)
1	 (±)4a	 5a	90	 6a	82	48	50	*R*
2	 (±)4b	 5b	72	 6b	68	48	12.3	*1R,2R*
3	 (±)4c	 5c	64	 6c	55	46	7.8	*1R,2R*
4	 (±)4d	 5d	22	 6d	18	45	1.9	*R*

[a] Substrate (1 mmol), catalyst **1a** (5 mol % with respect to repeating unit), Ac_2O (0.5 mmol) and Et_3N (1 mmol) were stirred in Et_2O (2 mL). [b] Determined by HPLC with hexane and isopropanol. [c] Determined according to ref 6h.

Table 3. Recyclability of Catalyst[a]



run	recoverability (%)	**5a** ee (%)	**6a** ee (%)	conversion (%)
1	90	90	82	48
2[b]	87	89	80	47
3[b]	82	89	81	48

[a] Benzoin (1 mmol), catalyst **1a** (5 mol %, with respect to monomeric unit), Ac_2O (0.5 mmol) and Et_3N (1 mmol) were stirred at -25 °C for 15 h in Et_2O (2 mL). [b] Recovered catalyst used.

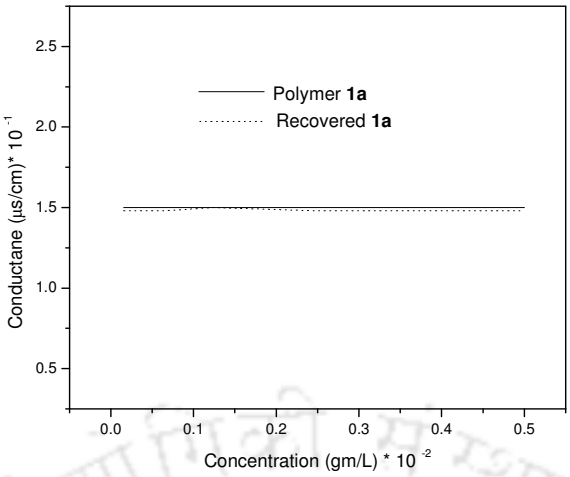


Figure 6. Conductivity of polymer **1a** and recovered catalyst at different concentrations.

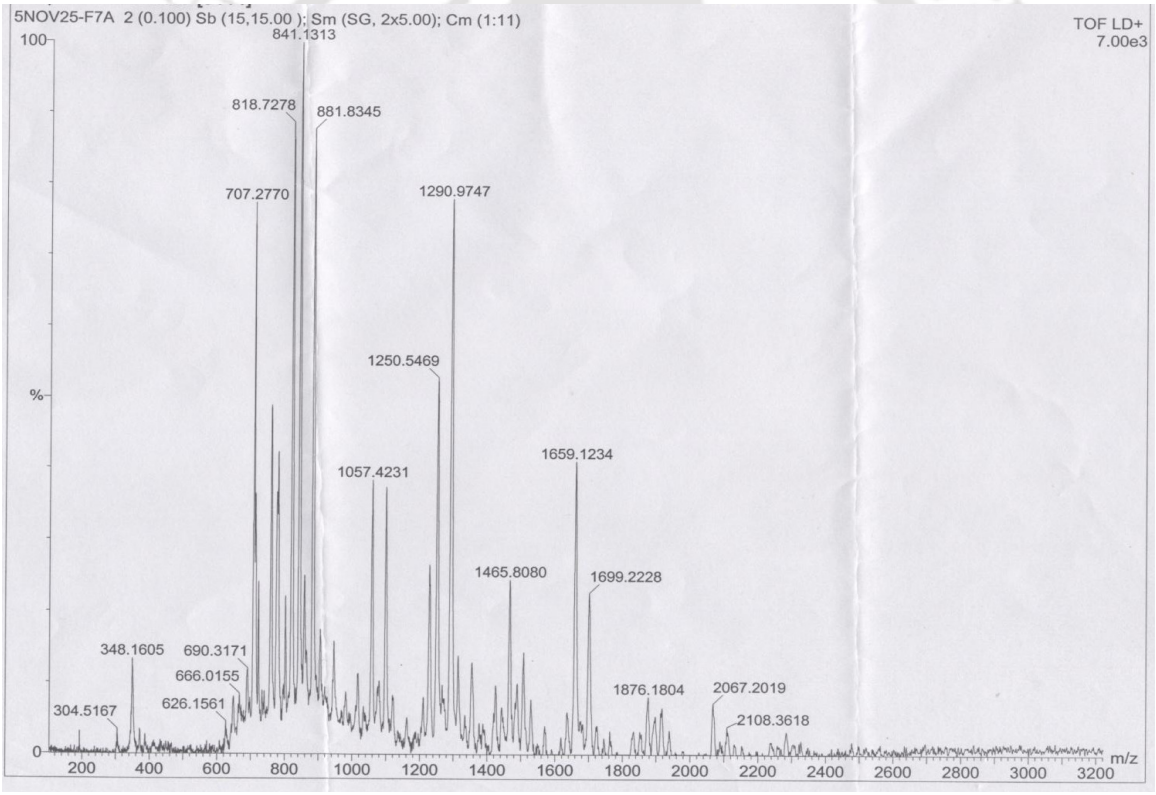
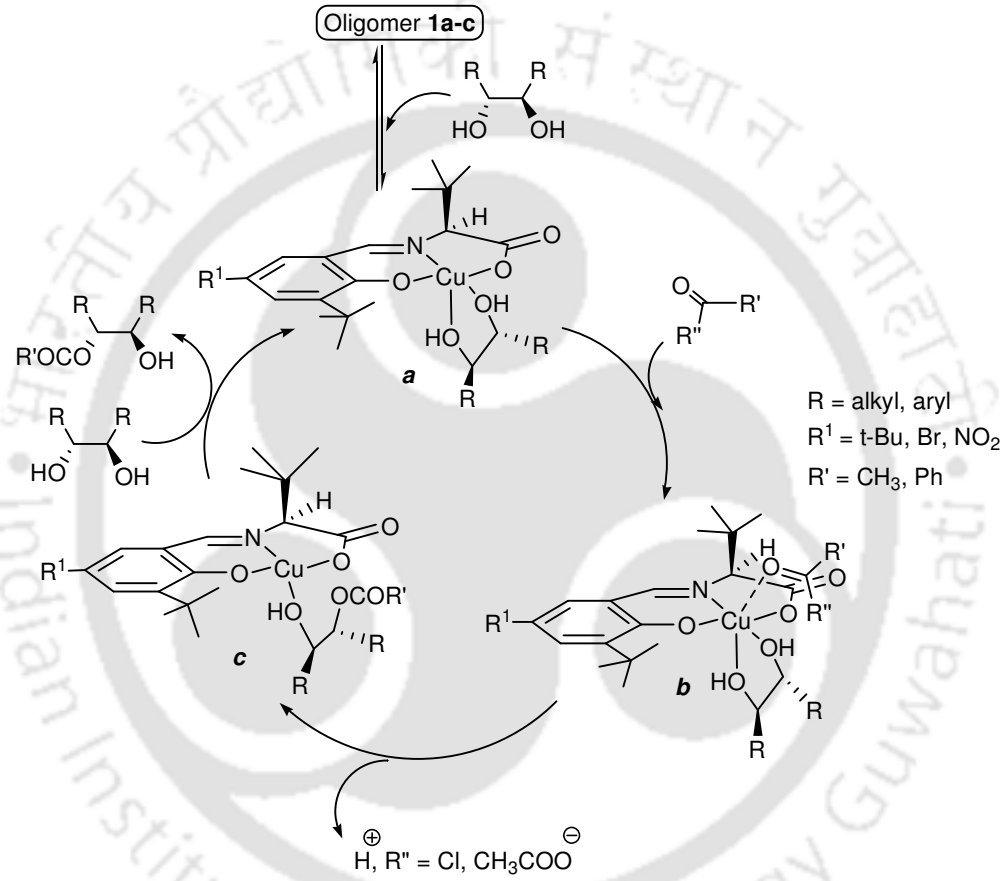


Figure 7. MALDI TOF MS of the polymer **1a** in $CHCl_3$.

benzoylation, while Et_2O was found to be the choice for acetylation. In catalysts, **1a** was found to superior to **1b**-**c** exhibiting the highest *ee*. These results suggest that the success of the reactions depends on the combination of solvent, acylating agent and the catalyst.

Next, to study the scope of the procedure, the polymer **1a** was investigated for the monoacylation of (±)-*trans*-1,2-diols using acetic anhydride as acylating agents (Table 2). (±)-*trans*-1,2-Cyclohexanediol **4b** and (±)-*trans*-1,2-diphenylethane-1,2-diol **4c** underwent reaction to give the monoacylated products **5b** and **5c** in 72% and 64% ee, respectively. Under these conditions, (±)-1-phenyl-1,2-ethanediol **4d** was selectively acylated with primary hydroxy group without affecting secondary OH group in 22% ee. The reactions were selective and no diacetylated product was obtained.



Scheme 11. Proposed Catalytic Cycle

The catalyst was recyclable without loss of activity (Table 3). After completion of the acetylation of benzoin with polymer **1a**, the reaction mixture was successively washed with saturated $NaHCO_3$ solution and water. Drying (Na_2SO_4) and evaporation of the solvent provided a residue which was treated with CH_3CN (0.5 mL for 0.05 mmol of catalyst). The insoluble green colored copper(II) catalyst was filtered and reused for the fresh reaction of acetylation of benzoin. This process was repeated up to three runs and the reactions occurred to afford the desired **5a** and **6a** without loss of activity and

selectivity. The recovered catalyst was further examined by optical rotation, UV-Vis spectrscopy and conductivity experiments. The specific rotation, $[\alpha]_D^{25}$ = +219 (c = 0.02, MeOH), UV-vis absorption and conductance data were identical to that of the polymer **1a** (before the reaction) (Figure 6). These studies reveal that the recovered catalyst and polymer **1a** are same.

To reveal the nature of these polymers in solution, MALDI TOF MS of **1a** in $CHCl_3$ was studied. Peaks corresponding to dimer, trimer, tetramer and pentamer were observed suggesting that the polymer undergoes dissociation into oligomers in solution (Figure 7). Thus, these oligomers may be dissociated into monomers during the reaction process and catalyze the reaction. Reaction of the oligomers with 1,2-diol may give the monomeric complex ***a*** that could react with the acylating agent to give intermediate ***b***. The latter ***b*** could be transformed to intermediate ***c*** by intramolecular acylation of the OH group with acylating agent. The intermediate ***c*** can complete the catalytic cycle by replacing the acylated product with fresh 1,2-diol (Scheme 11).

In conclusion, self-assembled chiral copper(II) complexes **1a-c** have been prepared in one-pot with high yield. Single-crystal X-ray analysis showed that the polymers are stereoregular and the repeating units are connected to each other by perpendicular fashion through a carboxylate linker. The polymers **1a-c** catalyze efficiently the kinetic resolution of secondary alcohols with up to 90% ee. The catalysts can be recyclabled without loss of activity.

Experimental Section

General. All experiments were carried out under nitrogen atmosphere. L-*tert*-Leucine (99%) and 2,4-di-*tert*-butylphenol (96%) were obtained from Aldrich. $Cu(OAc)_2 \cdot H_2O$ (99%) was purchased from Merck. 3,5-Di-*tert*-butyl salicylaldehyde,[10a] 3-*tert*-butyl-5-bromo-salicylaldehyde[10b] and 3-*tert*-butyl-5-nitrosalicylaldehyde[10c] were prepared according to literature. FT-IR spectra were recorded using Perkin Elmer FT-IR spectrometer. Optical rotation was measured using Perkin Elmer-343 polarimeter. Elemental analysis was obtained from Perkin Elmer-2400 CHNS analyzer. Column chromatography was preformed using 230-400 mesh silica gel. UV-vis spectra were recorded using Perkin Elmer Lambda-25 spectrometer. EPR spectrum was recorded using JES-FA-200 spectrometer. HPLC analysis was carried out on Waters-2478 with chiral stationary phase columns (chiralcel OJ, OD, OD-H and OB-H). NMR spectra (400 MHz for ^1H and 100 MHz for ^{13}C) were recorded using DRX-400 Varian spectrometer with

Me_4Si as an internal standard. Melting points were recorded using Buchi B-540 apparatus and uncorrected. 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 Gottington, Germany.

General Procedure for the Preparation of Polymers 1a-c

Aldehyde **2a-c** (3 mmol), L-*tert*-leucine (3 mmol, 393.5 mg) and Et_3N (3 mmol, 139 µL) were stirred in EtOH (10 mL) for 12 h at room temperature. The resultant yellow solution having **3a-c** was treated with $Cu(OAc)_2 \cdot H_2O$ (3 mmol, 598 mg) and the stirring was continued for an additional 6-9 h. The solvent was evaporated under reduced pressure and the residue was purified on silica gel flash column chromatography using CH_2Cl_2 and methanol (19:1) as eluent to afford **1a-c** as green colored crystals.

Polymer 1a: Green color solid; yield 85%.

$[\alpha]_D^{25}$ = +220 (c = 0.02, MeOH).

UV/vis (MeOH): λ_{max} (ε) = 384 (52076 $mol^{-1}dm^3cm^{-1}$).

EPR (X-band, MeOH, liquid N_2) $g_\perp$ = 2.040, $g_\parallel$ = 2.291, $A_\parallel$ = 283.11 G.

IR (KBr): 2960, 1619, 1585, 1466, 1439, 1379, 1205, 1168, 1096, 1035, 840, 789, 595, 549, 415 cm^{-1}.

Anal. Calcd for $(C_{21}H_{31}CuNO_3)_n$: C, 72.05; H, 8.92; N, 4.32. Found: C, 72.20; H, 8.78; N, 4.35.

Polymer 1b: Green color solid; yield 88%.

$[\alpha]_D^{25}$ = +578 (c = 0.02, MeOH).

UV/vis (MeOH): λ_{max} (ε) = 365 nm (104945 $mol^{-1}dm^3cm^{-1}$).

EPR (X-band, MeOH, liquid N_2): $g_\perp$ = 2.0, $g_\parallel$ = 2.25, $A_\parallel$ = 286.7 G.

IR (KBr): 3838, 3567, 2963, 1638, 1593, 1496, 1468, 1423, 1382, 1222, 1199, 1176, 1114, 1084, 1030, 991, 910, 820, 777, 750, 731, 576, 518 cm^{-1}.

Anal. Calcd for $(C_{17}H_{22}CuN_2O_5)_n$: C, 51.4; H, 5.67; N, 7.0. Found: C, 50.8; H, 5.67; N, 6.69.

Polymer 1c: Green color solid; yield 87%.

$[\alpha]_D^{25}$ = +121 (c = 0.02, MeOH).

UV/vis (MeOH): λ_{max} (ε) = 380 nm (39190 mol^{-1} dm^3cm^{-1}).

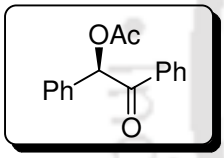
EPR (X-band, MeOH, liquid N_2): $g_\perp$ = 2.0, $g_\parallel$ = 2.26, $A_\parallel$ = 285.7 G.

IR (KBr): 3854, 3748, 3650, 2953, 2366, 1615, 1569, 1433, 1407, 1371, 1273, 1162, 1086, 866, 775, 723, 575 cm^{-1}.

Anal. Calcd for $(C_{17}H_{22}BrCuNO_3)_n$: C, 47.2; H, 5.1; N, 3.2. Found: C, 47.13; H, 5.8; N, 3.15.

General Procedure for Acylation Reaction

To a stirred solution of the substrates **4** (1 mmol), catalysts **1a-c** (5 mol %, with respect to repeating unit), base (1 mmol) and solvent (2 mL), acylating agent (0.5 mmol) was added, and the stirring was further continued for the appropriate time (Table 1-2). Progress of the reaction was monitored by thin layer chromatography (TLC). After completion, the solvent was evaporated under reduced pressure and the residue was dissolved in CH_2Cl_2 (25 mL), and successively washed with saturated $NaHCO_3$ solution (2 x 5 mL) and water (1 x 5 mL). Drying (Na_2SO_4) and evaporation of the solvent afforded a residue that was purified on silica gel flash column chromatography using ethyl acetate and hexane as eluent.



(*R*)-2-Acetyloxy-1,2-diphenylethanone (5a).[11a] Colorless solid; yield 48%.

Mp: 82-83 °C.

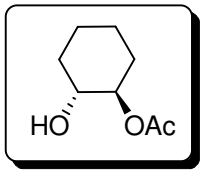
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94-7.92 (m, 2H), 7.53-7.34 (m, 8H), 6.86 (s, 1H), 2.21 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.9, 170.7, 134.7, 133.7, 129.6, 129.4, 129.0, 128.9, 128.9, 77.9, 21.0.

IR (KBr): 3472, 3034, 1721, 1453, 1273, 1113, 704 cm^{-1}.

$[\alpha]^{20}_D$ = -217.9 (c = 1.0, benzene).

HPLC: Chiralcel OD-H column, *n*-hexane : isopropanol (95:5), wavelength: 254 nm, flow rate: 0.7 mL/min, 90% ee.



(*R*,*R*)-2-Acetoxycyclohexan-1-ol (5b).[5b] Colorless solid; yield 48%.

Mp: 57-59 °C.

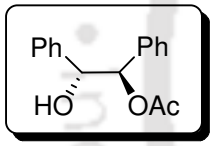
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.57 (m, 1H), 3.55 (m, 1H), 2.09 (s, 3H), 2.07-2.02 (m, 2H) 1.69 (m, 2H) 1.39-1.25 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 78.3, 72.8, 33.2, 30.1, 24.0, 23.9, 21.5.

IR (KBr): 3432, 2936, 2896, 1732, 1384, 1232,1080, 1040 cm^{-1}.

$[\alpha]^{25}_{D}$ = -30.9 (c = 1.0, $CHCl_3$).

HPLC: The product **5b** was hydrolysed using aqueous K_2CO_3 followed by monobenzoylation with benzoyl chloride, Et_3N and $Cu(OAc)_2 \cdot H_2O$ (5 mol %) in THF. HPLC analysis of the monobenzoylated product: Chiralcel OJ column, *n*-hexane : isopropanol (97:3), wavelength: 254 nm, flow rate: 1.0 mL/min, 72% ee.



(*R*,*R*)-1-Acetoxy-2-hydroxy-1,2-diphenylethane (5c).[11c] Colorless liquid; yield 46%.

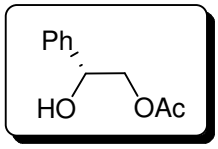
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23-7.18 (m, 6H), 7.12-7.07 (m, 4H), 5.81 (d, *J* =7.2 Hz, 1H), 4.89 (d, *J* =7.6 Hz, 1H), 2.60 (s, OH), 2.09 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 139.2, 137.0, 128.4, 128.3, 127.5, 127.2, 80.3, 21.4.

$[\alpha]^{20}_{D}$ = +15.0 (c = 0.1, MeOH).

IR (KBr): 3472, 3034, 1721, 1453, 1273, 1113, 704 cm^{-1}.

HPLC: Chiralcel OD-H column, *n*-hexane : isopropanol (95:5), wavelength: 254 nm, flow rate: 0.7 mL/min, 64% ee.



(*R*)-2-hydroxy-2-phenylethyl acetate (5d).[11d] Colorless liquid; yield 45%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.22 (m, 5H), 4.88-4.85 (dd, *J* = 8.4, 3.2 Hz, 1H), 4.21-4.17 (dd, *J* = 7.6, 3.2 Hz, 1H), 4.10-4.05 (dd, *J* = 11.6, 4.4 Hz, 1H), 2.70 (s, OH) 2.02 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 139.9, 128.8, 128.4, 126.3, 72.5, 69.5, 21.1.

IR (KBr): 3472, 3034, 1721, 1453, 1273, 1113, 704 cm^{-1}.

$[\alpha]^{20}_{D}$ = -8.0 (c = 1.1, $CHCl_3$).

HPLC: OD-H column, *n*-hexane : isopropanol (95:5), wavelength: 254 nm, flow rate: 0.7 mL/min, 22% ee.

Recyclability Experiment

To a stirred solution of benzoin (1 mmol, 212 mg), catalyst **1a** (5 mol %, 20 mg) and Et_3N (1 mmol, 101 mg) in Et_2O (2 mL), acetic anhydride (0.5 mmol, 51 mg) was added, and the stirring was continued for an additional 15 h (Table 3). The reaction mixture was then treated with Et_2O (25 mL) and successively washed with saturated $NaHCO_3$ solution (2 x 5 mL) and water (1 x 5 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was treated with CH_3CN. The insoluble catalyst was filtered and recycled for the fresh reaction of benzoin with acetic anhydride in the presence of Et_3N. This process was repeated up to three runs and no loss of activity was observed.

Single Crystal X-Ray Analysis

Crystallization of **1a-c** in MeOH and CH_2Cl_2 mixture provided air stable needle shaped green crystals whose X-ray analysis data are given below:

Crystal Data and Structure Refinement 1a

Identification code	tp02_0m	
Empirical formula	$(C_{21}H_{31}CuNO_3)_n$	
Formula weight	409.06	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	*P2 $_1$2$_1$2$_1$*	
	Loop xyz 'x, y, z' '-x+1/2, -y, z+1/2' '-x, y+1/2, -z+1/2' 'x+1/2, -y+1/2, -z'	
Unit cell dimensions	*a* = 6.2168(7) Å	α= 90°
	b = 16.4734(18) Å	β= 90°

	c = 21.668(2) Å	γ = 90°
Volume	2219.0(4) Å^3	
Z	2	
Density (calculated)	1.202 Mg/m^3	
Absorption coefficient	1.012 mm^{-1}	
F(000)	814	
Crystal size	0.50x 0.16 x 0.10 mm^3	
Theta range for data collection	6.26 to 28.32 °	
Index ranges	-8<=h<=8, -21<=k<=-7,-28<=l<=25	
Reflections collected	5416	
Independent reflections	4428 [R (int) = 0.0606]	
Completeness to theta = 28.38°	78.9 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5416 / 1.016 /245	
Goodness-of-fit on F^2	1.016	
Final R indices [I>2sigma (I)]	$R1$ = 0.0489, $wR2$ = 0.0848	
R indices (all data)	$R1$ = 0.0360, $wR2$ = 0.0785	
Absolute structure parameter	0.014(13)	
Extinction coefficient	0.0000(19)	

Crystal Data and Structure Refinement 1b

Identification code	Lp-01	
Empirical formula	$(C_{17}H_{22}CuN_2O_5)_n$	
Formula weight	397.91	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
	Loop xyz, x, y, z, -x, y+1/2,-z	
Unit cell dimensions	a = 10.9225(3) Å	α= 90°
	b = 6.47180(10)Å	β= 100.0060(10)°
	c = 13.8434(3) Å	γ = 90°
Volume	963.68 Å^3	
Z	2	
Density (calculated)	1.371 Mg/m^3	
Absorption coefficient	1.160 mm^{-1}	
F(000)	414	

Crystal size	0.45x 0.20 x 0.8 mm^3
Theta range for data collection	2.99 to 23.47 °
Index ranges	-14<=h<=14, -8<=k<=-8,-18<=l<=-17
Reflections collected	4939
Independent reflections	2681 [R (int) = 0.0606]
Completeness to theta = 28.38°	87 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5416 / 1.001 /245
Goodness-of-fit on F^2	1.001
Final R indices [I>2sigma (I)]	*R1* = 0.0509, *wR2* = 0.0663
R indices (all data)	*R1* = 0.0336, *wR2* = 0.0733
Absolute structure parameter	0.014(13)
Extinction coefficient	0.0000(19)

Crystal Data and Structure Refinement 1c

Identification code	Lp-01-Br	
Empirical formula	$(C_{17}H_{22}BrCuNO_3)_n$	
Formula weight	431.81	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	*P*2(1)	
	Loop xyz, x, y, z, -x, y+1/2,-z	
Unit cell dimensions	*a* = 11.6599(8) Å	α= 90°
	b = 7.2927(6) Å	β= 113.928(4)°
	c = 12.0335(9) Å	γ = 90°
Volume	935.29(13) $Å^3$	
Z	2	
Density (calculated)	1.533 Mg/m^3	
Absorption coefficient	3.316 mm^{-1}	
F(000)	394	
Crystal size	0.50x 0.16 x 0.10 mm^3	
Theta range for data collection	0.95 to 28.85 °	
Index ranges	-15<=h<=15, 8<=k<=-9,-18<=l<=16	
Reflections collected	4899	
Independent reflections	2635 [R (int) = 0.0606]	

Completeness to theta = 28.38°	84 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4139 / 1 /208
Goodness-of-fit on F^2	1.603
Final R indices [I>2sigma (I)]	*R1* = 0.1455, *wR2* = 0.3769
R indices (all data)	*R1* = 0.1330, *wR2* = 0.3824
Absolute structure parameter	0.014(13)
Extinction coefficient	0.0000(11)

4.5 References

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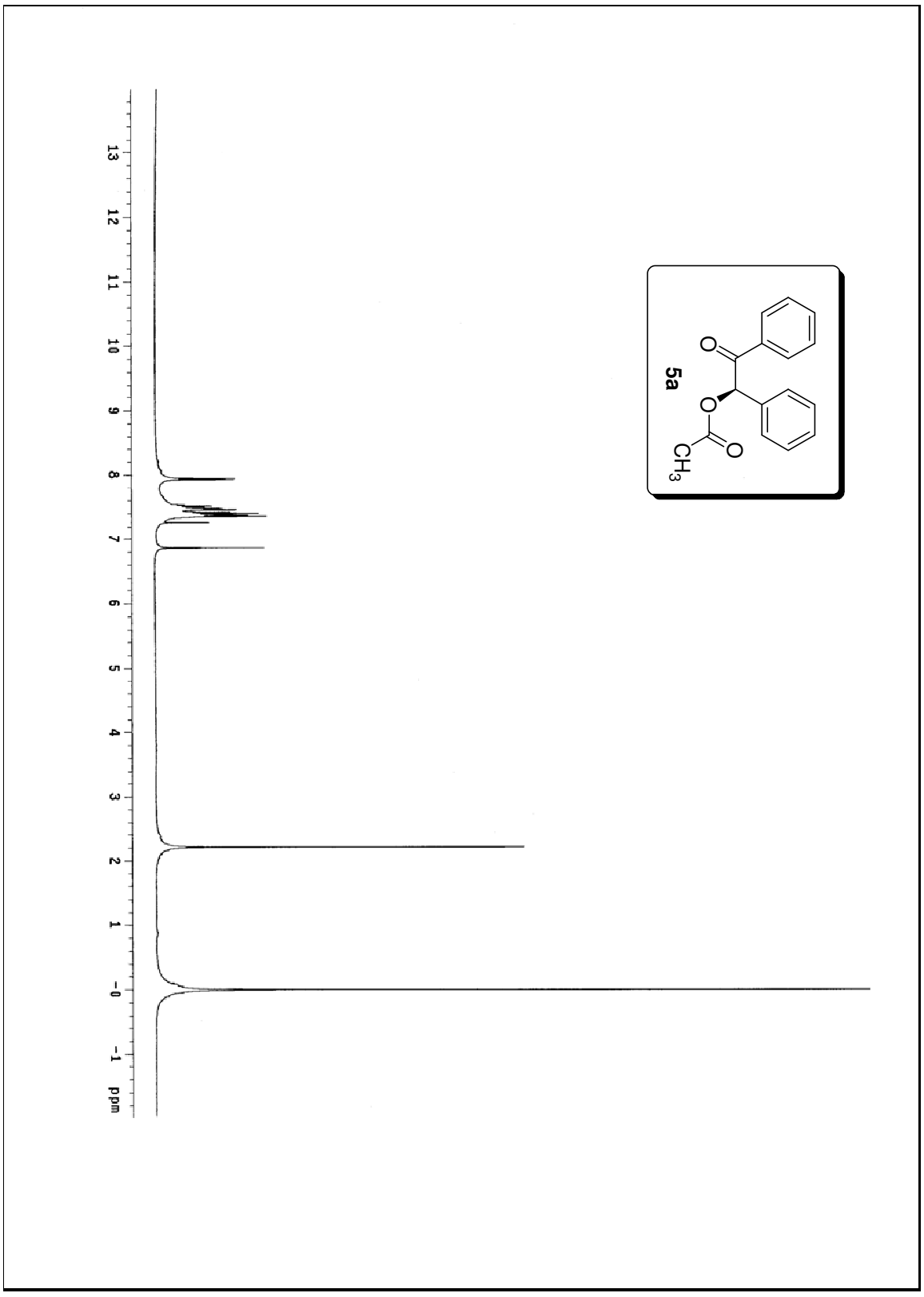

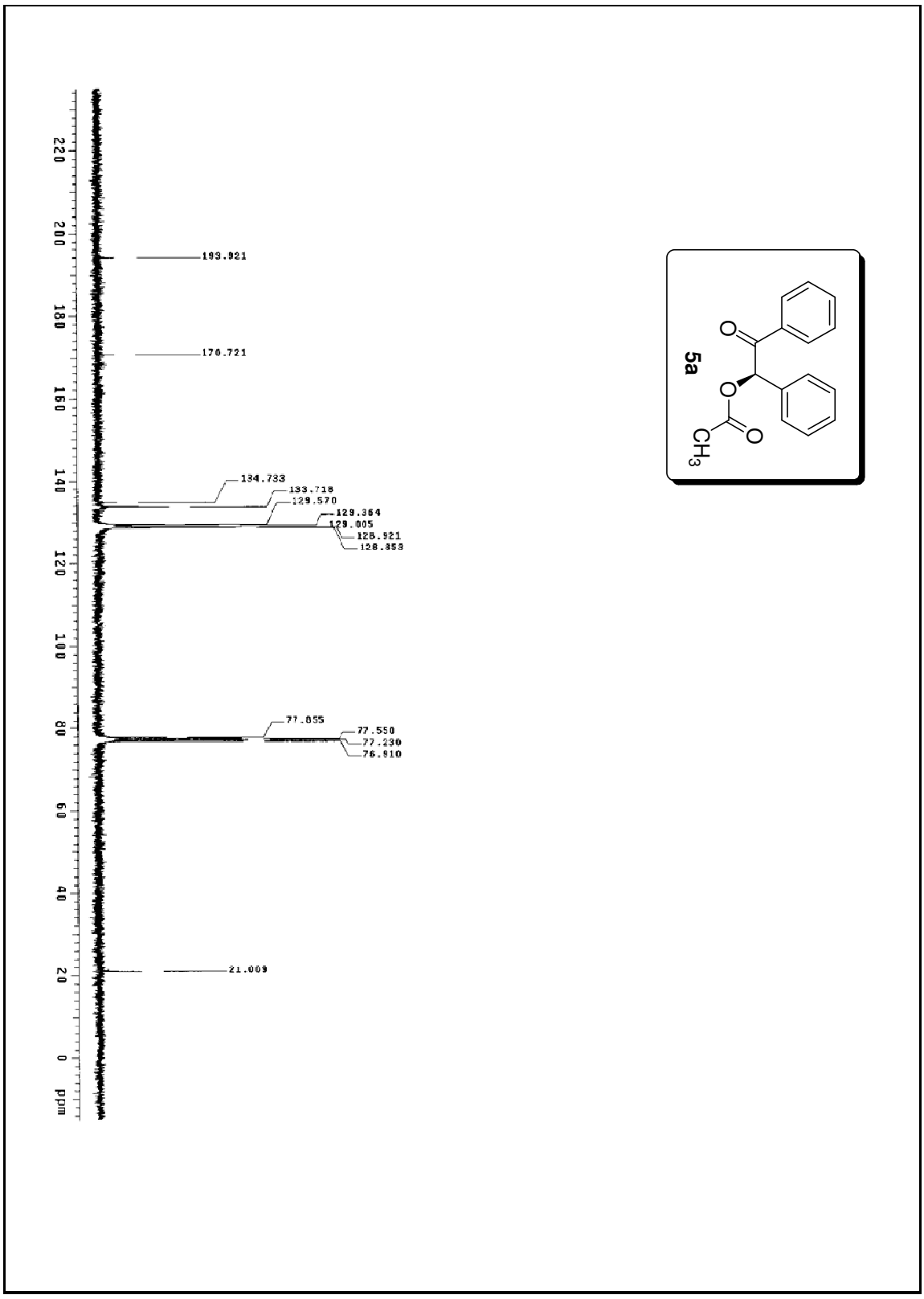

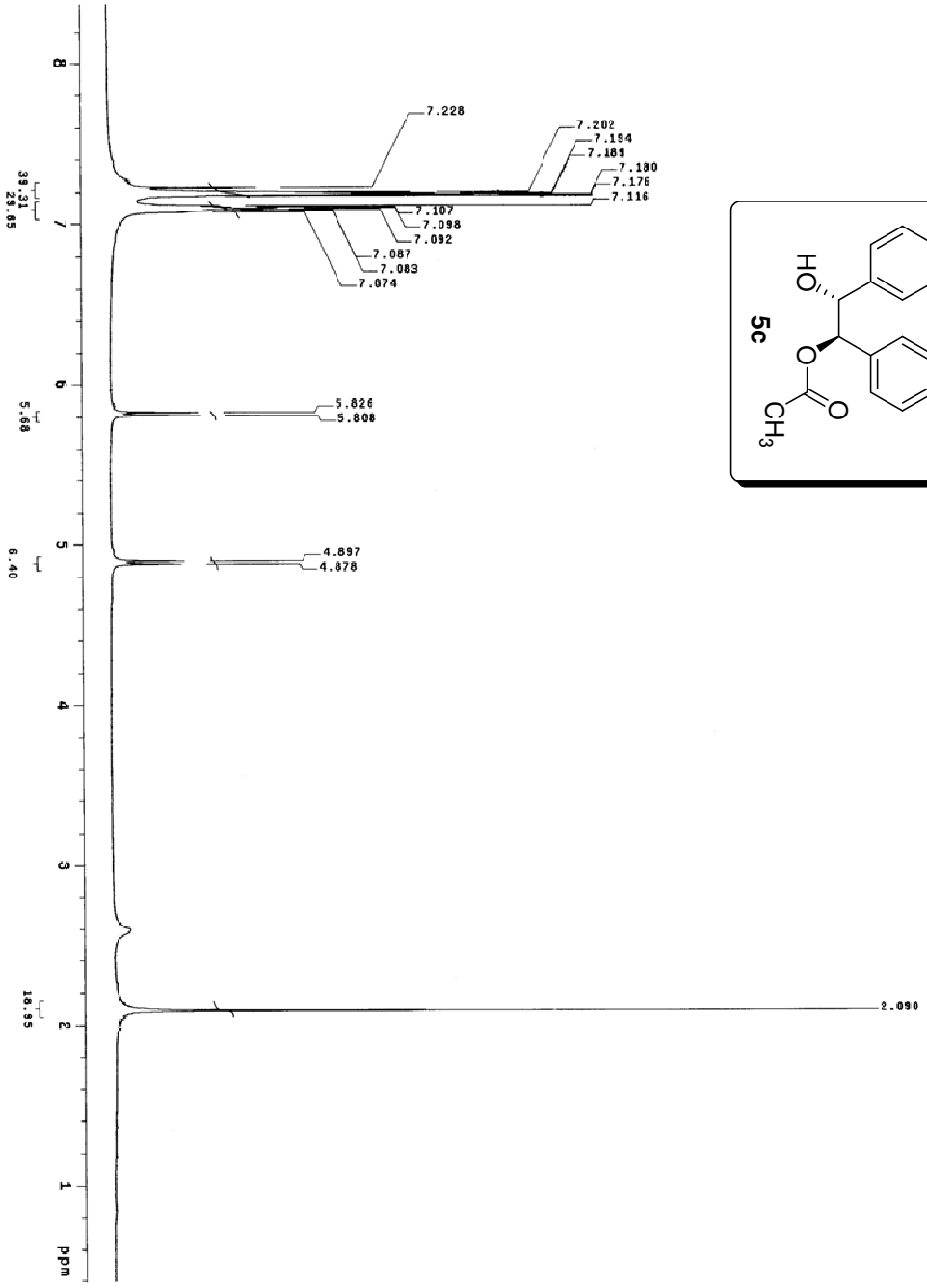

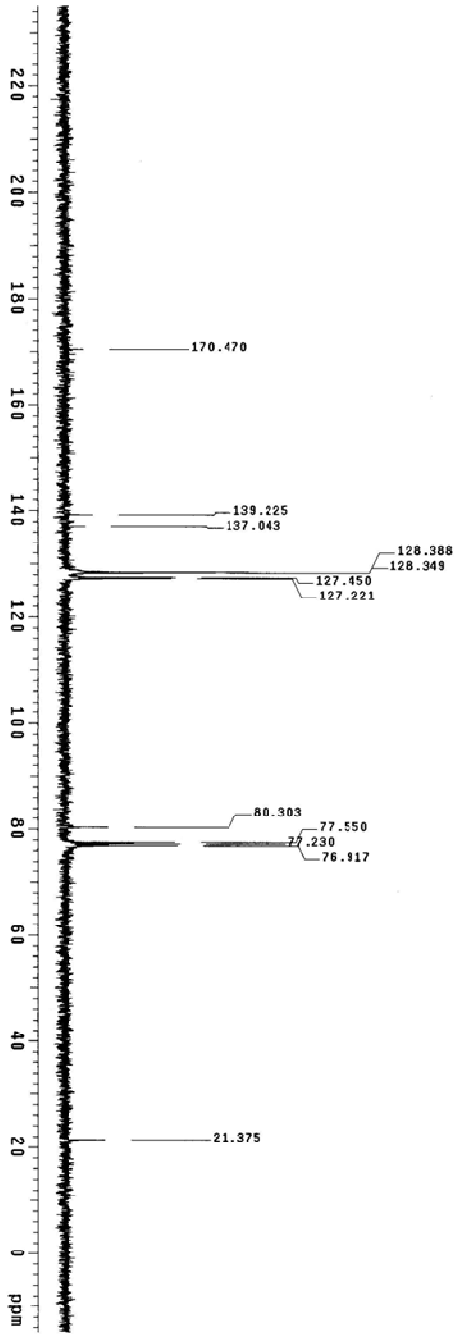

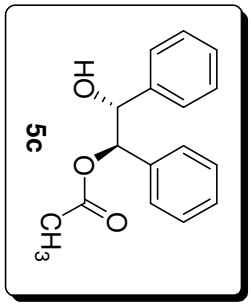

List of Publications

1. Cobalt-Catalyzed Intramolecular *C-N* and *C-O* Cross-Coupling Reactions: Synthesis of Benzimidazoles and Benzoxazoles.
   Saha, P.; Ali, M. A.; Ghosh, P.; Punniyamurthy, T. *Org. Biomol. Chem.* **2010,** *8*, 5692**.**

2. Efficient Copper Catalyzed *N*-Arylation of Amides and Imidazoles with Aryl Iodides.
   Ali, M. A.; Saha, P.; Punniyamurthy, T. *Synthesis* **2010**, 908.

3. Copper-Catalyzed Domino Intra and Intermolecular *C-S* Cross-Coupling Reactions: Synthesis of 2-(Arylthio)arylcyanamides.
   Ramana, T.; Saha, P.; Das, M.; Punniyamurhty, T. *Org. Lett.* **2010***, 12,* 84.

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

5. Ligand-Free Copper-Catalyzed Synthesis of Substituted Benzimidazoles, 2-Aminobenzimidazoles, 2-Aminobenzothiazoles, and Benzoxazoles.
   Saha, P.; Ramana, T.; Purkait, N.; Ali, M. A.; Paul R.; Punniyamurthy, T. *J. Org. Chem.* **2009**, *74*, 8719.

6. CuO Nanoparticles Catalyzed *C-N*, *C-O*, and *C-S* Cross-Coupling Reactions: Scope and Mechanism.
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7. Chiral Binuclear Copper(II) Catalysed Nitroaldol Reaction: Scope and Mechanism.
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8. Synthesis, Crystal Structure and Application of Chiral Copper(II) Polymers for Asymmetric Acylation.
   Jammi, S.; Rout, L.; Saha, P.; Akkilagunta, V. K.; Sanyasi, S.; Punniyamurthy, T. *Inorg. Chem.* **2008**, *47*, 5093.

9. Efficient Ligand-Free Nickel Catalyzed *C-S* Cross Coupling of Thiols with Aryl Halides.
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10. Cadmium Catalyzed *C-N* Cross Coupling of Amines with Aryl Iodides.
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11. Efficient Copper(I) Catalyzed *C-S* Cross-Coupling of Thiols with Aryl Halides in Water.
    Rout, L.; Saha, P.; Jammi, S.; Punniyamurthy, T. *Eur. J. Org. Chem.* **2008**, *4,* 640.

Conferences

1. Ligand-Free Copper-Catalyzed Synthesis of Substituted Benzimidazoles, 2-Aminobenzimidazoles, 2-Aminobenzothiazoles, and Benzoxazoles.
   Saha, P.; Ramana, T.; Purkait, N.; Ali, M. A.; Paul R.; Punniyamurthy, T. *Frontiers in Chemical Sciences (FICS-2010)*, Indian Institute of Technology Guwahati, December 3-4, **2010**.