Copper Catalyzed *C-C*, *C-N* and *C-S* Bond Formations and Synthesis of Chiral 1,2-Diamine Based Main Chain Polymers

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

DOCTOR OF PHILOSOPHY

by

Suribabu Jammi

Department of Chemistry
Indian Institute of Technology Guwahati
Guwahati-781039, INDIA
August 2009

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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
August 2009

Suribabu Jammi

INDIAN INSTITUTE OF TECHNOLOGY GUWAHATI

Department of Chemistry

CERTIFICATE

This is to certify that Mr. Suribabu Jammi has been working under my supervision since July 2005. I am forwarding his thesis entitled "*Copper Catalyzed C-C, C-N and C-S Bond Formations and Synthesis of Chiral 1,2-Diamine Based Main Chain Polymers*" 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
August 2009

Prof. Tharmalingam Punniyamurthy
Supervisor

INDIAN INSTITUTE OF TECHNOLOGYGUWAHATI

Department of Chemistry

COURSE CERTIFICATE

This is to certify that Mr. Suribabu Jammi has satisfactorily completed all the courses required for the Ph.D. degree programme. These courses include:

CHM 611	Bioinorganic Chemistry
CHM 605	Applied Crystallography
CHM 621	New Reagents for Organic Synthesis
CHM 630	A Fundamental Approach to Physical Chemistry

Mr. Suribabu Jammi has successfully completed his Ph.D. qualifying examination in May 2006.

Prof. A. Chattopadhyay	Prof. T. Punniyamurthy
Head	Secretary
Department of Chemistry	Departmental Post Graduate Committee
I.I.T. Guwahati	Department of Chemistry
	I.I.T. Guwahati

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I owe my sincere thanks to my group mates Dr. S. Velusamy, Dr. L. Rout, Sridhar, Prasenjit, Sakthivel, Rajesh, Ashif and Ramana for their pleasant company during my research period. I am also thankful to my all friends for their support and encouragement.

I would like to thank my Doctoral committee members Prof. J. B. Barua, Dr. A. K. Saikia and Dr. Arun Goyal for their valuable suggestions.

I thank all faculty members, research scholars, supporting staff of the Department of Chemistry and CIF for their kind cooperation in all respects.

I acknowledge the Indian Institute of Technology, Guwahati for providing institute fellowship for the entire period of the Ph.D. programme.

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

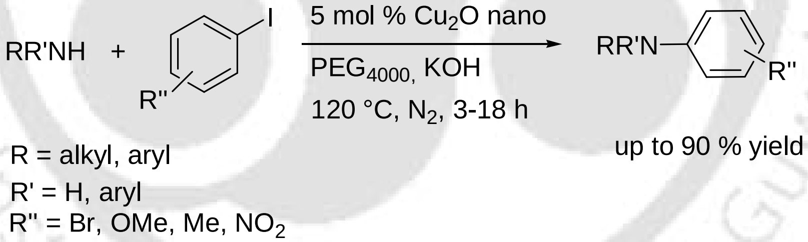
Suribabu Jammi

Abstract

The thesis contains five chapters. The first two chapters describe the *N*-arylation of amides and imidazoles and *S*-arylation of thiols using Cu_2O nanoparticles as a recyclable catalytic system. The third and fourth chapters focus on the synthesis, structure and application of copper complexes for nitroalodol reaction in asymmetric and non-asymmetric versions. The fifth chapter is devoted to the synthesis and application of chiral main chain polymers with optically active (1*R*,2*R*)-1,2-diamines for the asymmetric synthesis.

1. Copper(I) Oxide Nanoparticles Catalyzed *N*-Arylation of Amides and Imidazoles

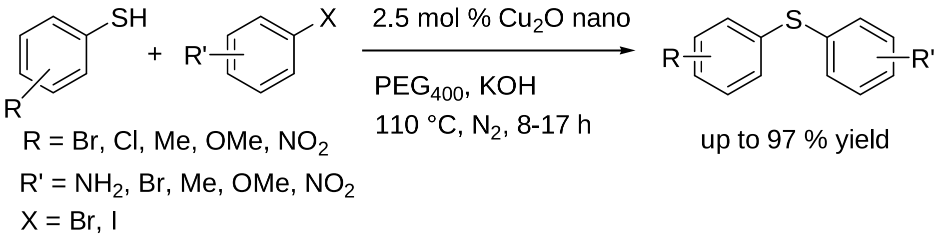
Transition metal catalyzed *C-N* bond formation via cross-coupling reaction of nitrogen nucleophiles with aryl halides affords powerful tool for the synthesis of vital compounds utilized in biological, material and pharmaceutical sciences. This chapter describes a simple and efficient procedure for the one pot synthesis and catalysis of Cu_2O nanoparticles in PEG_{4000} for the *C-N* cross-coupling reactions of amides and azoles with aryl iodides under ligand-free conditions (Scheme 1).



Scheme 1

2. Copper(I) Oxide Nanoparticles Catalyzed *S*-Arylation of Thiols

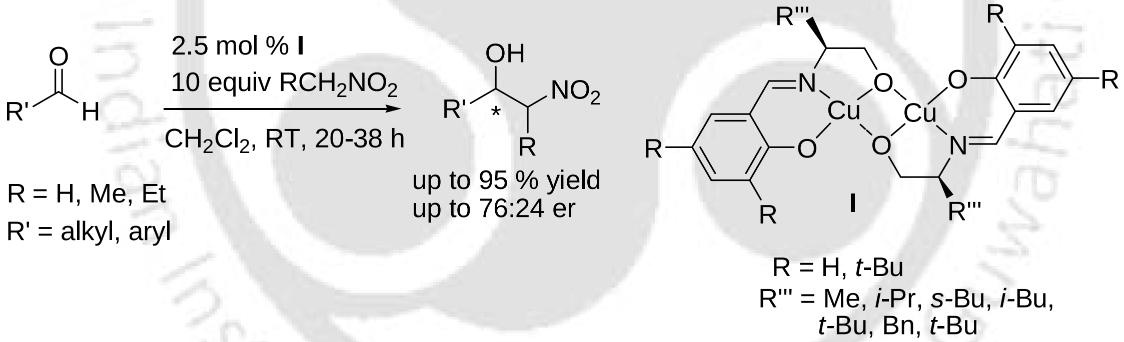
Methods for the formation of *C-S* bonds are indispensable tools in synthetic chemistry. Their importance stems from the prevalence of *C-S* bonds in many molecules that are of biological, pharmaceutical and material interest. This chapter focuses on the *C-S* cross-coupling of aryl halides with thiols using CuI/PEG_{400} system with KOH at 110 ºC (Scheme 2). Under these conditions a variety of substituted thiols and substituted iodobenzenes underwent reaction to afford the *C-S* cross coupled products in high yields.



Scheme 2

3. Chiral Binuclear Copper(II) Catalyzed Asymmetric Nitroaldol Reaction

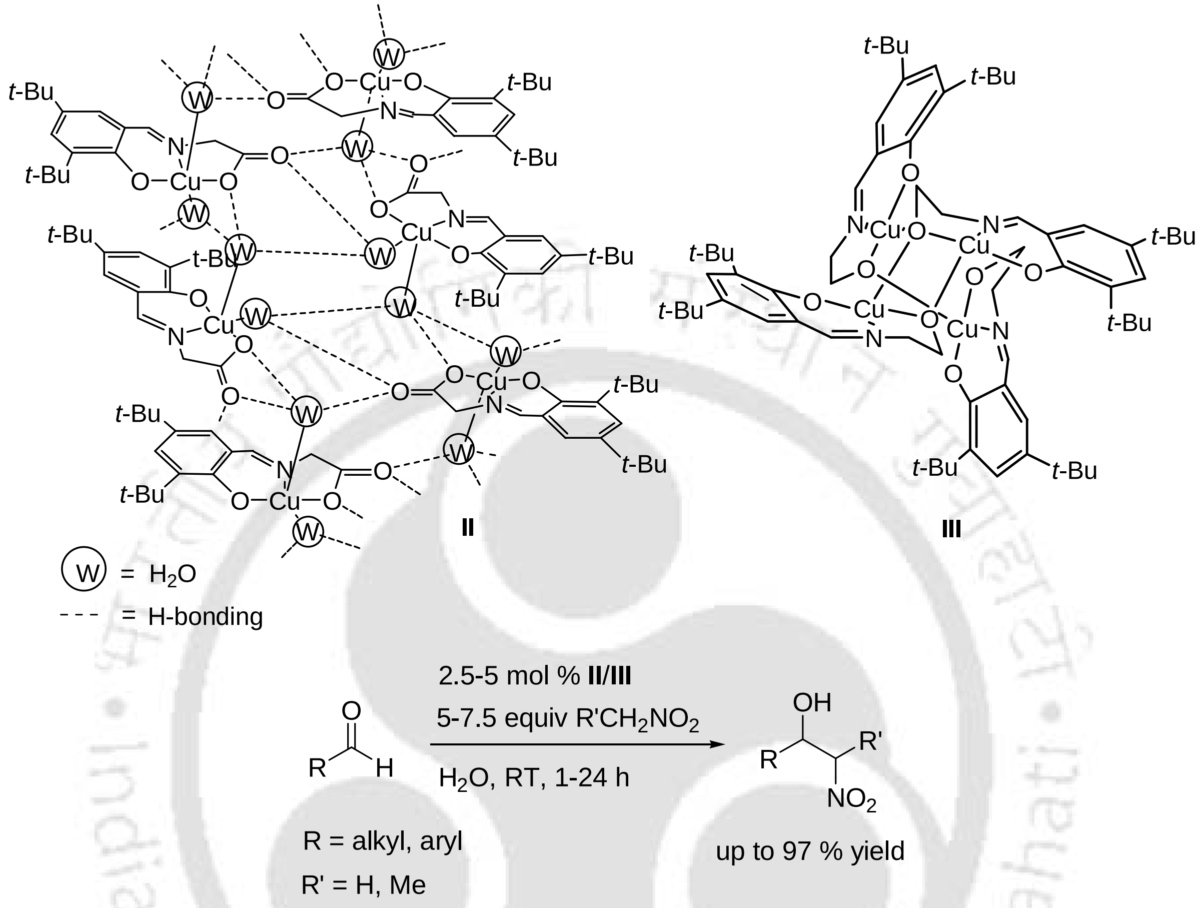
The addition of nitroalkanes to carbonyl compounds, known as nitroaldol (or Henry) reaction, is a fundamental synthetic tool for the formation of carbon-carbon bonds. The diversity of the transformation of the adducts opens numerous applications for this reaction in organic chemistry for the synthesis of natural products and pharmaceuticals. This chapter describes the synthesis, crystal structure and application of chiral binuclear copper(II) schiff base complexes for the addition of nitroalkanes to aldehydes at ambient conditions with 76:24 er (Scheme 3).



Scheme 3

4. Self-Assembly and Application of Copper(II) Complexes for Acceleration of Nitroaldol Reaction "On Water"

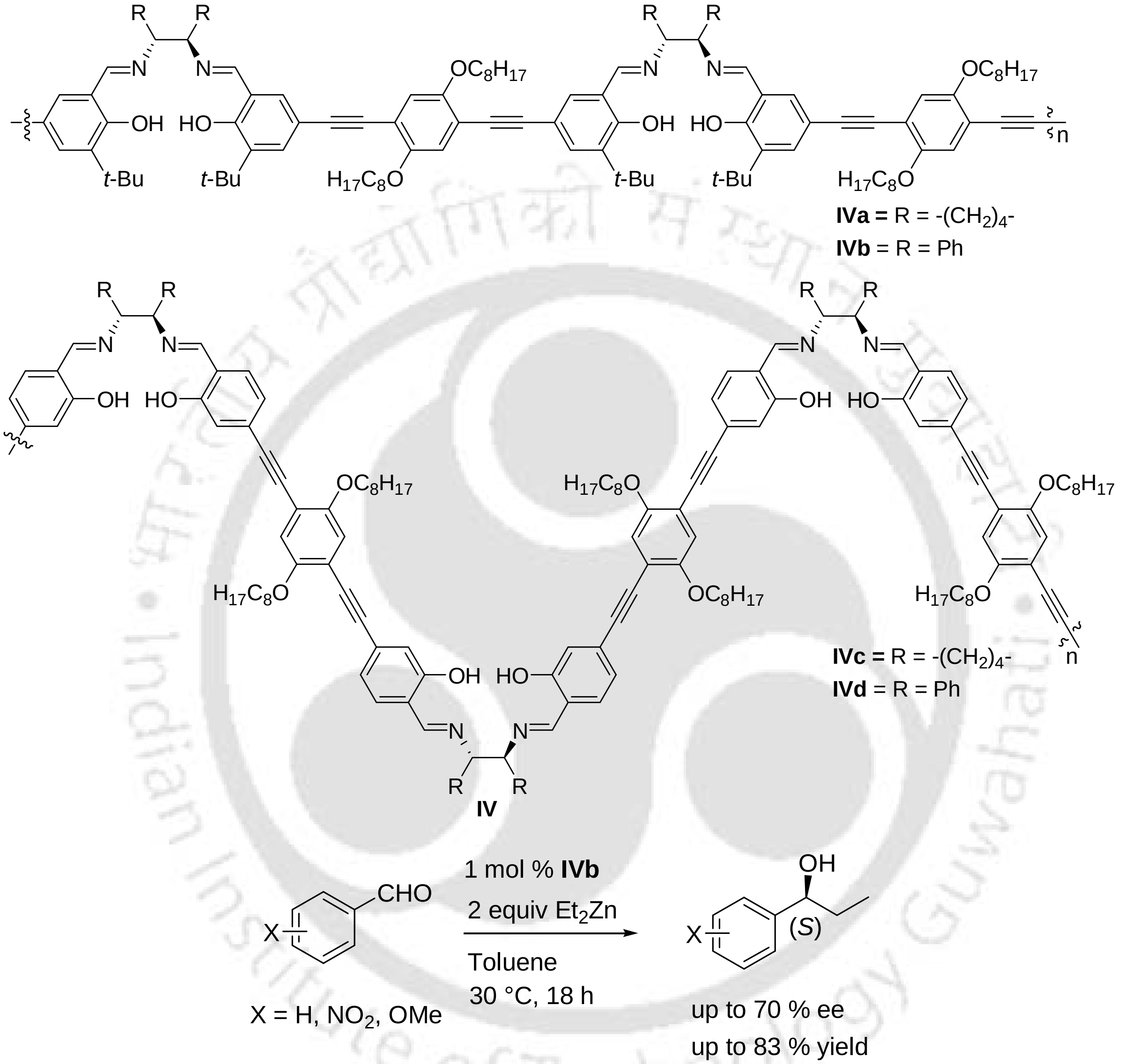
In recent years, there has been increasing recognition that water is an attractive medium for many organic reactions. The aqueous medium with respect to organic solvent is less expensive and environmentally-benign. This chapter describes the synthesis, crystal structure and application of self-assembled copper(II) complexes **II** and **III** for nitro alodol reaction "on water" (Scheme 4). The reactions exhibit enhanced reactivity on water in comparison to that in organic solvents.



Scheme 4

5. Synthesis of New Chiral Main Chain Polymers with (1*R*,2*R*)-1,2-Diamines

The application of optically active 1,2-diamine derivatives for asymmetric synthesis has attracted very extensive attention in recent time, because these molecules have demonstrated excellent chiral induction in a number of organic transformations when used either as chiral auxiliary or chiral ligand. Thus, the development of chiral polymer catalysts with optically active 1,2-diamines will be valuable for asymmetric synthesis because using polymers allow the easy recovery and reuse of the often quite expensive chiral ligands. This chapter focuses on the synthesis of chiral 1,2-diamine based polymers **IV** using palladium catalyzed Sonogashira cross-coupling and schiff's base formation for asymmetric catalysis. These polymers are soluble in common organic solvents such as CH_2Cl_2, $CHCl_3$, toluene and THF, and catalyze the Et_2Zn addition to aldehydes with up to 70 % ee (Scheme 5).



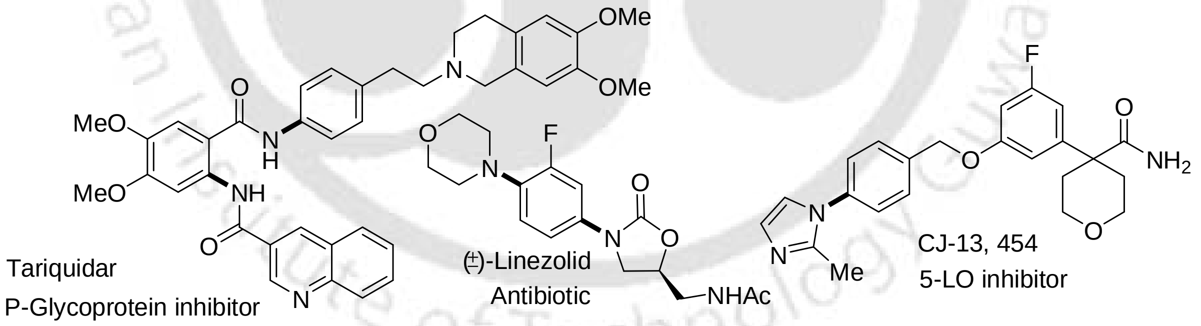
Scheme 5

Contents

Chapter I

Copper(I) Oxide Nanoparticles Catalyzed *N*-Arylation of Amides and Imidazoles

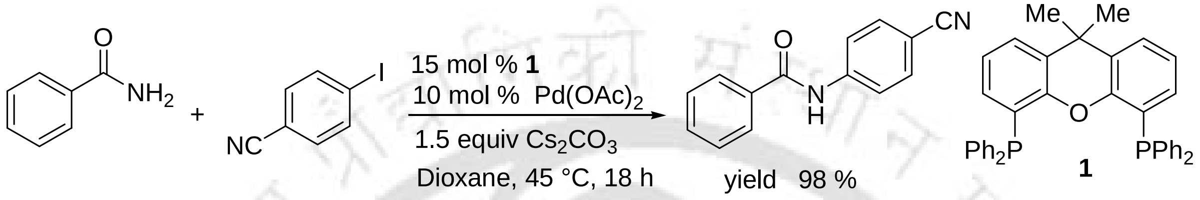
The aryl-heteroatom bond formation by cross-coupling reaction constitutes a powerful strategy for the synthesis of numerous important compounds in biological, material and pharmaceutical sciences.[1] Among them, the *N*-arylation of amides and imidazoles are of particular interest as their products contain structural motifs of numerous natural products and biologically active molecules (Figure 1).[2] The most common synthetic methods used for their preparation are the well known classical Ullmann and Goldberg-type coupling reactions. However, these reactions often require harsh conditions such as exposure of the substrates at high temperature (>200 °C), use of polar solvents such as DMF, collidine, pyridine etc, and stoichiometric or greater amount of copper reagents which on scale-up leads to the problem of waste disposal.[3] To overcome these drawbacks, palladium[4] with sterically hindered phosphines such as xantphos,[4a,4e,4h] biarylmonophosphine,[4b,4g] ferrocenyl phosphine,[4i,4j] and $P(t\text{-}Bu)_3$,[4f] and copper[5,6] with electron rich bidentate ligands such as 1,2-diamine,[5b,5c,5j,5k,6i] amino acids,[5d,6a] 1,3-diketone,[5o] 1,10-phenanthroline,[6i] salicylaldoxime[5e] and 8-hydroxyquinoline[6o] have been studied for the cross-coupling of amides and imidazoles with aryl halides. These are homogeneous processes and the ligands chelated with the metals play a crucial role in the catalysis. Despite this significant progress, the development of simple, general, and efficient catalytic methods are still in demand for large scale productions.



Scheme 1

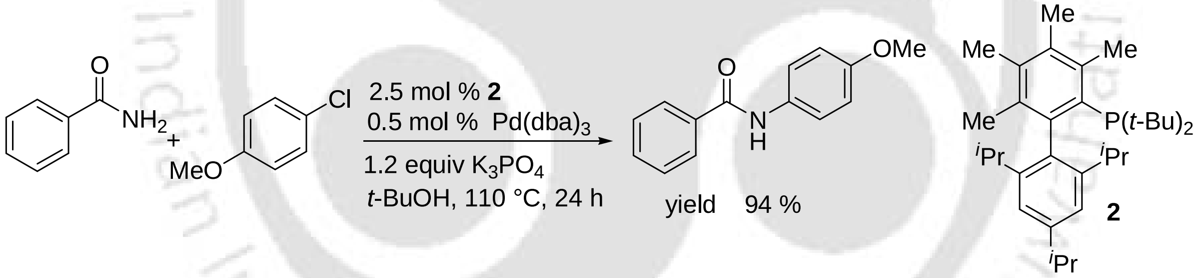
1.1 Palladium Catalysts

Palladium based catalysts are considerably studied for amidation reactions.[4] In 2000, Buchwald and Yin have reported the first general intermolecular cross-coupling of amides with aryl halides using $Pd(OAc)_2$ and xantphos **1** in the presence of Cs_2CO_3 in THF/1,4-dioxane (Scheme 2).[4e] Aryl iodide, -bromide and -triflates are compatible with this catalytic system affording the cross-coupled products in high yield.



Scheme 2

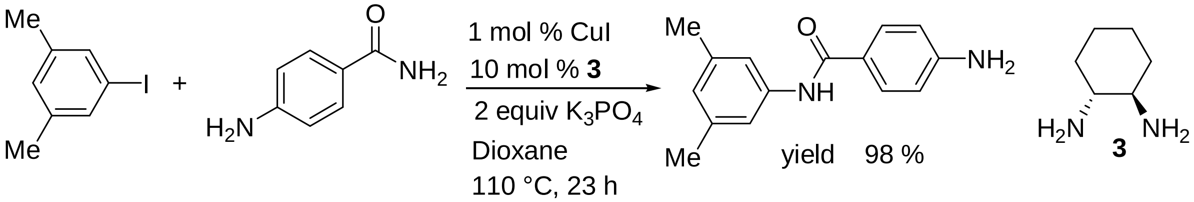
More recently, they have employed $Pd_2(dba)_3$ for the amidation of aryl chlorides using monodentate biaryl phosphine ligand **2** with high yield. The reaction functions in presence of K_3PO_4 in *t*-BuOH (Scheme 3).[4d]



Scheme 3

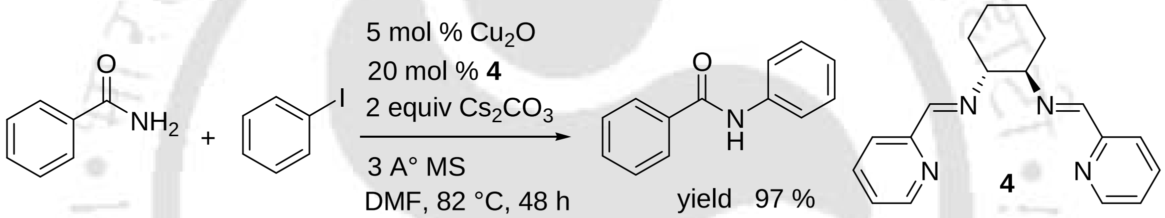
1.2 Copper Catalysts

Copper complexes bearing electron rich ligands are extensively studied for the arylation of amides and *N*-heterocycles with aryl halides.[5,6] These catalytic systems are more attractive compared to the palladium based systems. Buchwald and co-workers have extensively studied the amidation of aryl halides and the *N*-arylation of nitrogen heterocycles. They have developed an experimentally simple and inexpensive catalytic system based on the use of CuI, 1,2-diamine ligands and K_3PO_4, Cs_2CO_3 or K_2CO_3 as base. Under these conditions a variety of functional groups are tolerated in the reaction, including many that are not compatible with the palladium catalysis (Scheme 4).[5b]



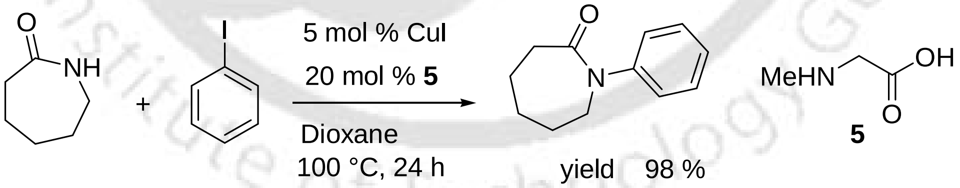
Scheme 4

Crestau and Taillefer have shown the use of Cu_2O in combination with ligand **4** for the amidation of aryl halides. This reaction functions in DMF in presence of Cs_2CO_3 at 82 °C with up to 97 % yield (Scheme 5).[6d] These conditions are also suitable for *N*-arylation of imidazoles.



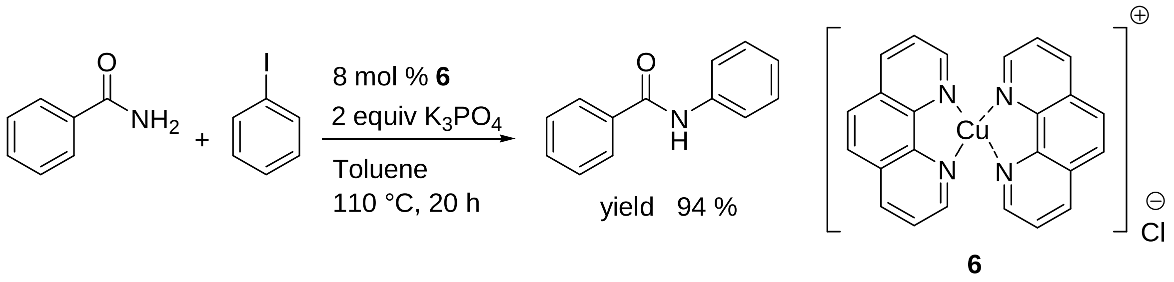
Scheme 5

Liu and co-workers have demonstrated the use of CuI/*N*-methyl glycine system for *N*-arylation of amides. The reaction has occurred efficiently to provide the cross-coupled products at 100 °C in presence of K_3PO_4 in dioxane (Scheme 6).[6a]



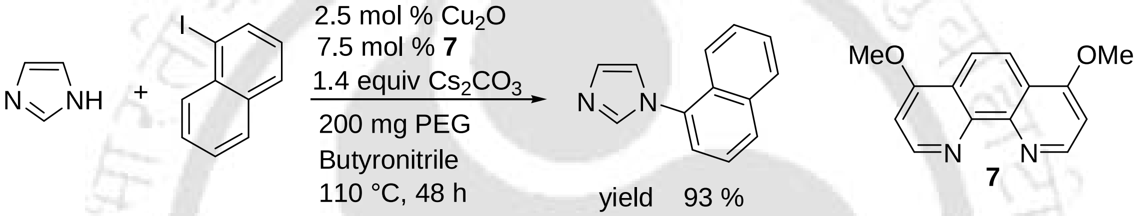
Scheme 6

Moriwaki and co-workers have reported amidation of aryl iodides using copper(I)–phenanthroline complex **6** at 110 °C in presence of K_3PO_4 (Scheme 7).[6g] Using this procedure the coupling of benzamide with iodobenzene is accomplished in 94 % yield.



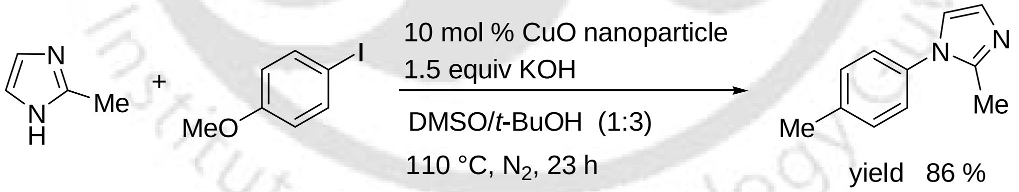
Scheme 7

Buchwald and co-workers have demonstrated the utility of 4,7-dimethoxy-1,10–phenanthroline **7** for the copper-catalyzed arylation of imidazoles and benzimidazoles with aryl and heteroaryl iodides and bromides in combination with PEG and Cs_2CO_3 (Scheme 8).[6i]



Scheme 8

Recently, we have reported CuO nanoparticles catalyzed *N*-arylation of amides and imdazoles with aryl iodides at 110 °C in presence of KOH (Scheme 9).[7b-c] The procedure is simple, general, ligand-free and efficient to give the cross-coupled products in high yield.



Scheme 9

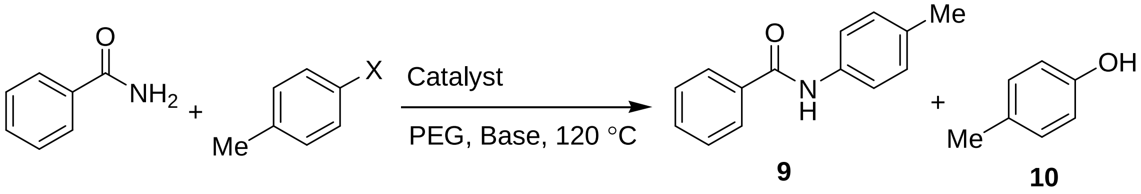
1.3 Present Study

The use of copper oxide nanoparticles as efficient catalysts for cross-coupling reactions has attracted considerable interest in recent years. CuO nanoparticles have been used for *C-N*, *C-O* and *C-S* cross-coupling reactions under ligand-free conditions in DMSO.[7a-c] In addition, Stille and Sonogashira reactions were investigated using Cu_2O nanoparticles in the presence of $P(Ar)_3$ in tetrabutylammonium bromide.[7d-e] These are heterogeneous processes providing the advantages of high atom efficiency, simplified product isolation and easy recovery and recyclability of the catalysts. Furthermore, the catalysts are readily accessible, cheap and air stable. These salient aspects let us to explore copper oxide based nanoparticles for experimentally simple, general and efficient cross-coupling reactions. In this chapter, we describe a one pot synthesis and application of spherical Cu_2O nanoparticles in poly(ethylene glycol) (PEG) for the cross-coupling of amides and imidazoles with aryl iodides. This protocol is a clean technological process, free from the additional chelating ligands and the catalyst can be recovered and recycled without loss of activity.

First, the *C-N* cross-coupling of benzamide with 1-iodo-4-methylbenzene was investigated as model substrate (Table 1-2). A series of reactions were performed in PEG of different molecular weights 200, 400, 1500, 4000 and 6000 using different bases and copper sources at varied temperature. It was found that the reaction proceeds well at 120 ^{o}C giving the best yield using 10 mol % CuI in PEG_{4000}. PEG such as PEG_{200}, PEG_{400}, PEG_{1500} and PEG_{6000} were inferior to PEG_{4000} by either providing 4-methylphenol as by-product or exhibiting decreased reactivity. Among the bases studied, KOH was superior to NaOH, K_2CO_3, Cs_2CO_3 and K_3PO_4. The reaction with CuI provided the best results in comparison to Cu_2O (< 5 micron), CuO nanoparticles (~33 nm),[7a-c] $CuSO_4{\cdot}5H_2O$ and $CuCl_2{\cdot}2H_2O$. Controlled experiment without the copper source showed no reaction. Under these conditions, bromobenzene and chlorobenzene did not undergo reaction and the starting materials were recovered intact.

To study the scope of the protocol, the reactions of other substrates were next investigated (Table 3). Benzamide proceeded reaction with a series of aryl iodides to produce the corresponding *N*-arylamides in 70-80 % yield (Table 3, entries 1-7). With both electron donating and -withdrawing substituents on the aromatic ring of aryl iodides the reaction occurred without any difficulty (Table 3, entries 2-6). In addition, aliphatic amides, acetamide, hexanoamide and 2-oxazolidinone underwent reaction with iodobenzene to afford the corresponding *N*-arylamides in 70-75 % yield. The reactions of aliphatic amides were faster compared to that of aryl amides.

Table 1. *N*-Arylation of Benzamide with aryl halide: Effect of PEG and Base[a]

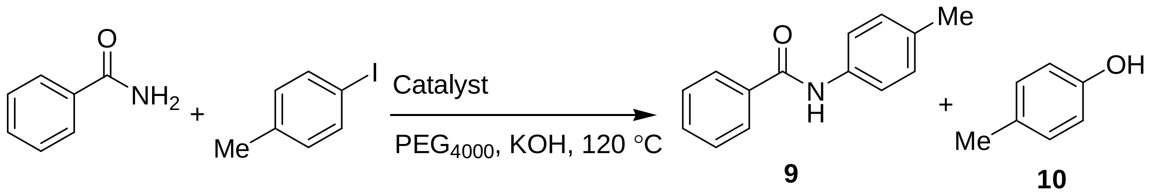


						Product (%)[b]	
Entry	X	PEG	Base	Catalyst	Time (h)	**9**	**10**
1	I	PEG_{200}	KOH	CuI	12	56	24
2	I	PEG_{400}	KOH	CuI	12	62	10
3	I	PEG_{1500}	KOH	CuI	12	68	7
4	I	PEG_{4000}	KOH	CuI	12	79	nd
5	I	PEG_{6000}	KOH	CuI	20	72	nd
6	I	PEG_{4000}	NaOH	CuI	12	60	nd
7	I	PEG_{4000}	$CsCO_3$	CuI	12	30	nd
8	I	PEG_{4000}	K_2CO_3	CuI	12	36	nd
9	I	PEG_{4000}	K_3PO_4	CuI	12	46	nd
10	Br	PEG_{4000}	KOH	CuI	12	nr	-
11	Cl	PEG_{4000}	KOH	CuI	12	nr	-
12	I	PEG_{4000}	KOH	-	12	nr	-

[a] Benzamide (1.2 mmol), aryl halide (1 mmol), catalyst (10 mol %) and base (1.5 mmol) were stirred at 120 °C in PEG (1 g) under nitrogen atmosphere.

[b] Determined from 400 MHz ^{1}H NMR. nr = no reaction. nd = not detected.

Table 2. *N*-Arylation of Benzamide with 1-Iodo-4-methylbenzene: Effect of Copper Source[a]



Entry	Catalyst	Time (h)	Product (%)[b]	
			9	**10**
1	CuI	12	79	nd
2	CuI	12	67[c]	nd
3	Cu_2O	12	69[d]	nd
4	CuO nano	12	53	nd
5	$CuCl_2{\cdot}2H_2O$	12	32	nd
6	$CuSO_4{\cdot}5H_2O$	12	37	nd

[a] Benzamide (1.2 mmol), 1-iodo-4-methylbenzene (1 mmol), catalyst (10 mol %) and KOH (1.5 mmol) were stirred at 120 °C in PEG (1 g) under nitrogen atmosphere.

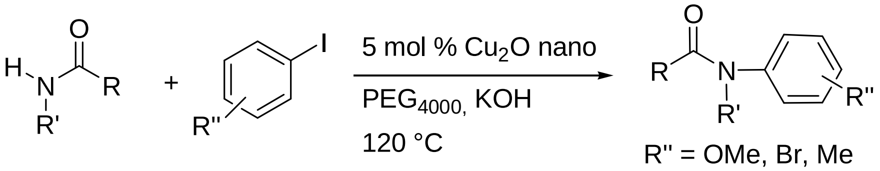
[b] Determined from 400 MHz ^{1}H NMR.

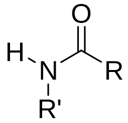
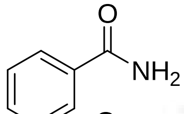
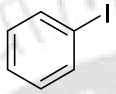
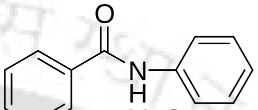
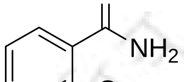
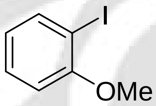
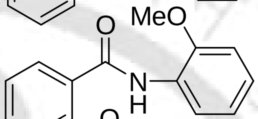
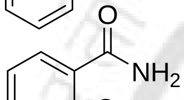
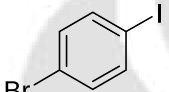
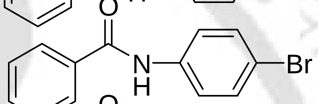
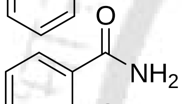
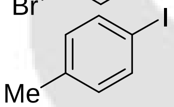
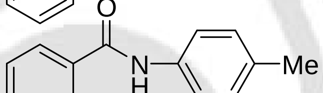
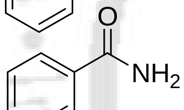
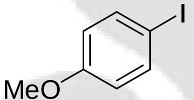
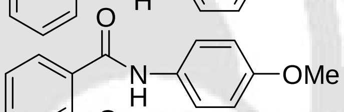
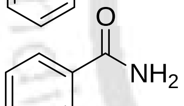
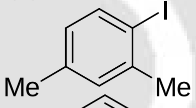
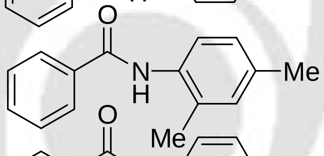
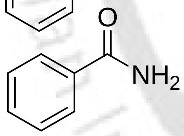
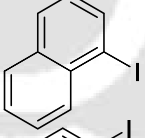
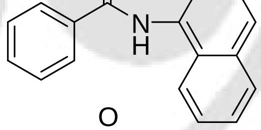
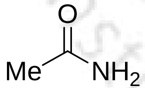
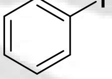
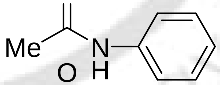
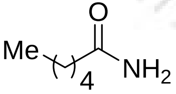
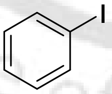
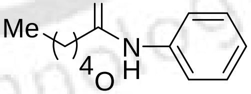
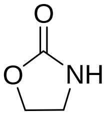
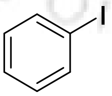
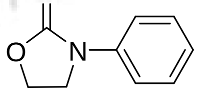
[c] 5 mol % CuI used.

[d] 5 mol % Cu_2O used. nd = not detected.

These reaction conditions were also suitable for *C-N* cross-coupling of imidazoles with aryl iodides (Table 4). For examples, imidazole underwent reactions with a series of aryl iodides having electron donating and -withdrawing substituents to afford the corresponding *N*-arylimidazoles in 60-90 % yield (Table 4, entries 1-6). In addition, 2-methylimidazole and benzimidazole proceeded reaction with iodobenzene to give the cross-coupled products in 70 % and 72 % yield, respectively.

Table 3. *N*-Arylation of Amides with Aryl Iodides[a]

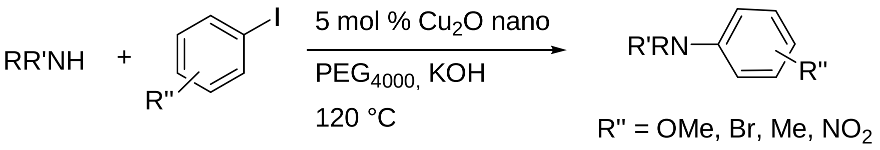


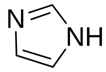
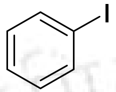
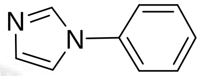
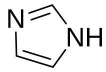
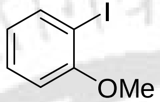
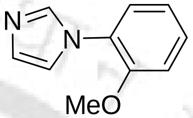
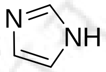
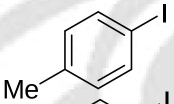
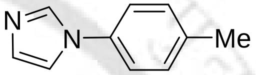
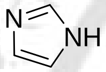
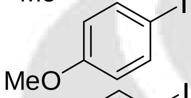
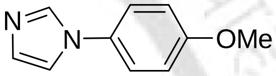
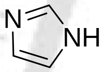
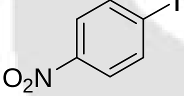
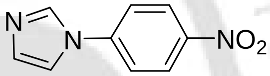
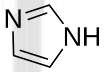
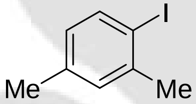
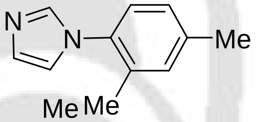
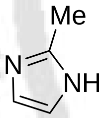
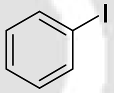
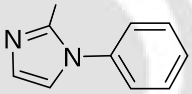
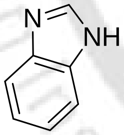
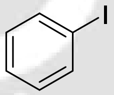
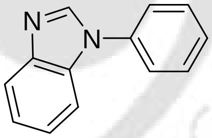
Entry		Aryl iodide	Time (h)	Product	Yield (%)[b]
1			10		73
2			17		70
3			12		76
4			12		75
5			15		75
6			16		72
7			12		80
8			3		75
9			3		70
10			5		75

[a] Amide (1.2 mmol), aryl iodide (1 mmol), CuI (10 mol %) and KOH (1.5 mmol) were stirred at 120 °C in PEG_{4000} (1 g) under nitrogen atmosphere.

[b] Isolated yield.

Table 4. *N*-Arylation of Imidazoles with Aryl Iodides[a]



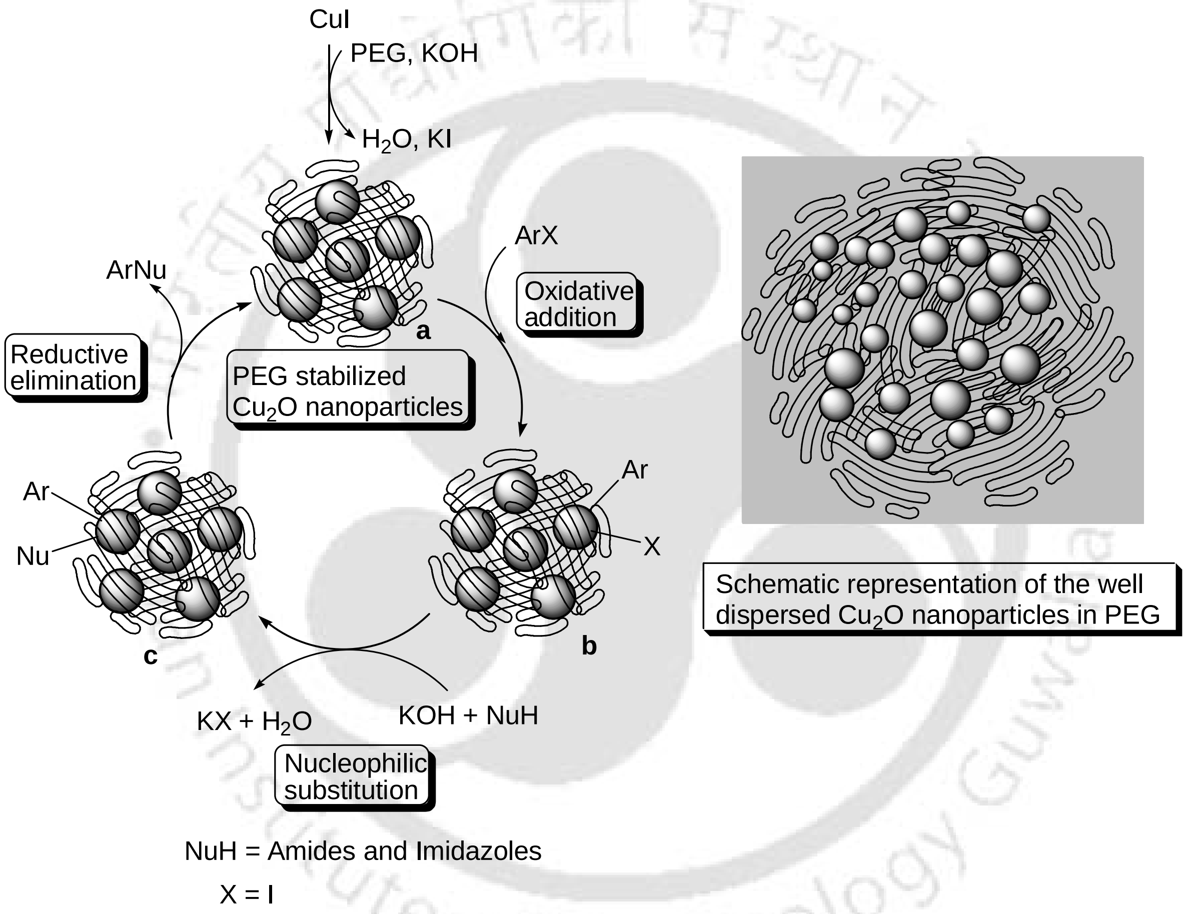
Entry	RR'NH	Aryl iodide	Time (h)	Product	Yield (%)[b]
1			12		90
2			15		60
3			12		85
4			18		88
5			6		85
6			16		65
7			15		70
8			14		72

[a] Imidazole (1.2 mmol), aryl iodide (1 mmol), CuI (10 mol %) and KOH (1.5 mmol) were stirred at 120 °C in PEG_{4000} (1 g) under nitrogen atmosphere.

[b] Isolated yield.

In these reactions, CuI undergoes reaction with KOH in PEG to give spherical Cu_2O nanoparticle in 100 % conversion and selectivity that catalyzes the reaction (Eq. 1).[8] PEG facilitates the formation and stabilization of nanoparticles. The sizes 7-10 nm of the Cu_2O nanoparticles were determined by transmission electron microscopy (TEM) (Figure 1) and their identities were established using the powder X-ray diffraction analysis (Figure 2).[9] The proposed catalytic cycle for the cross-coupling reactions is shown in scheme 10. The PEG stabilized dispersed Cu_2O nanoparticles ***a*** may undergo oxidative addition with aryl iodide to give intermediate ***b*.** Reaction of the nitrogen nucleophiles with intermediate ***b*** can lead to ***c*** which can complete the catalytic cycle by reductive elimination of the cross-coupled product.

$$\mathrm{CuI} \xrightarrow[\text{- KI}]{\text{+ KOH}} \mathrm{Cu(OH)} \xrightarrow{-{}^{1}/_{2}\,H_2O} -{}^{1}/_{2}\,\mathrm{Cu_2O\ nanoparticles} \qquad \text{Eq. 1}$$



***Scheme 10*.** Proposed Catalytic Cycle

The Cu_2O nanoparticles can be recovered and recycled without loss of activity. After completion of the reaction of benzamide with 1-iodo-4-methylbenzene, the reaction material was treated with ethyl acetate (10 mL) and water (5 mL). The aqueous layer having the Cu_2O nanoparticles were centrifuged and the precipitate was washed with deionized water (3 x 2 mL) and acetone (3 x 2 mL). After drying in vacuum, the Cu_2O nanoparticles were reused for the fresh reaction of benzamide with 1-iodo-4-methylbenzene. This process repeated for three runs and the results are presented in table 5. As above, the reactions proceeded well to afford the *C-N* cross-coupled product in 78 % yield. The TEM micrograph and powder X-ray diffraction analysis of the Cu_2O nanoparticles recovered from third run were identical to that of the first run which clearly suggests that the shape and size of the nanoparticles remain intact during the recyclability (Figure 1-2). Thus, the catalyst is recyclable without loss of activity and selectivity.

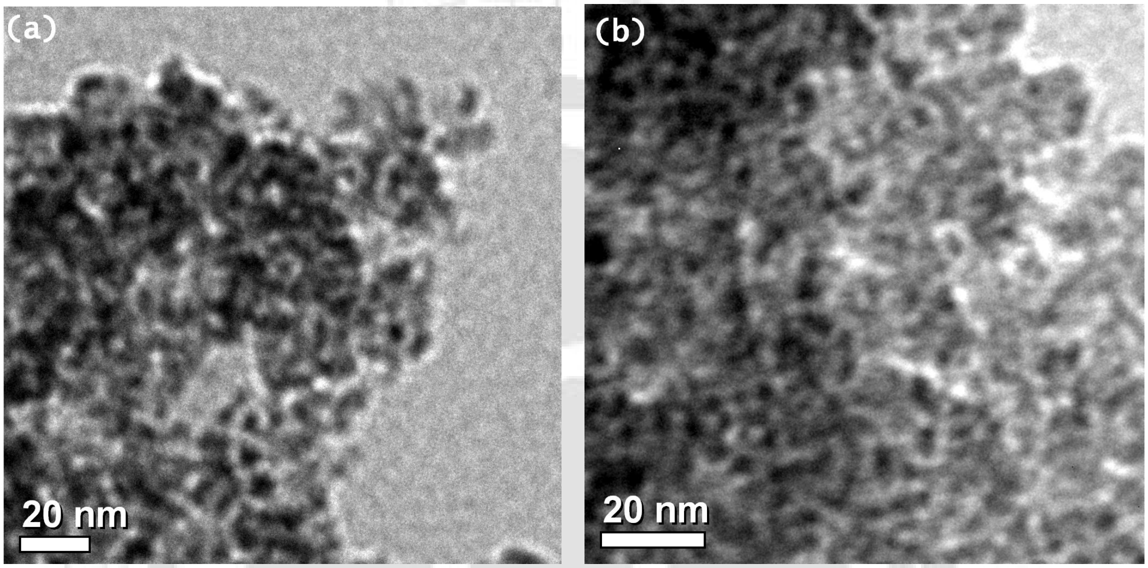


Figure 1. TEM Images of Cu_2O Nanoparticles of PEG_{4000} Reaction after (a) First Cycle and (b) Third Cycle.

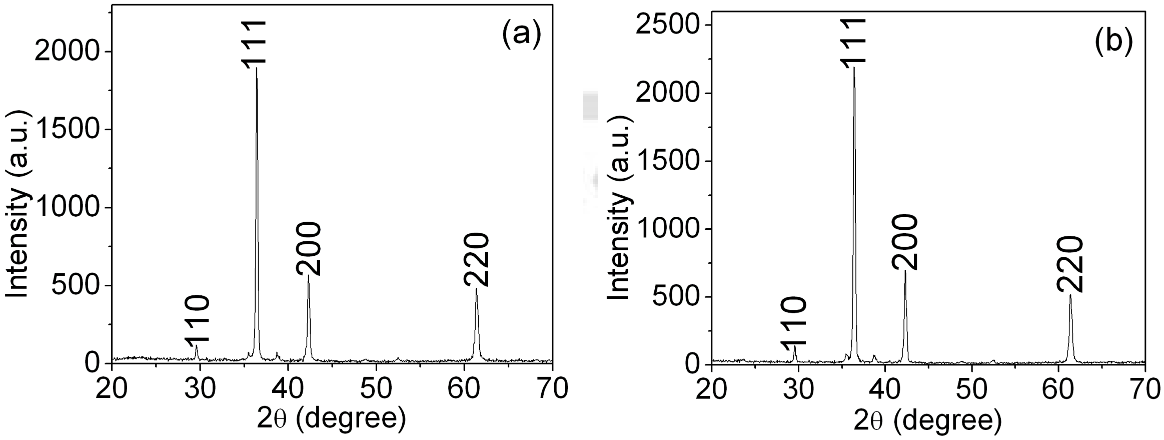
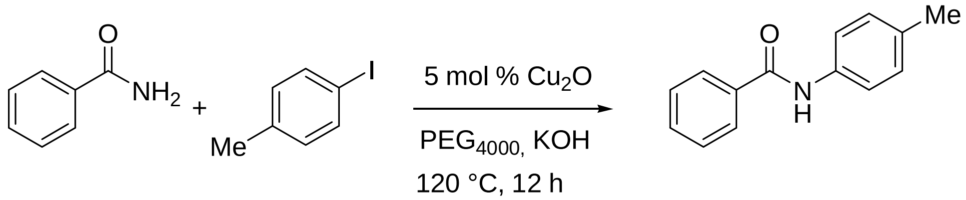


Figure 2. Powder XRD Pattern of Cu_2O Nanoparticles of PEG_{4000} Reaction after (a) First Cycle and (b) Third Cycle.

Table 5. Recycling of the Cu_2O Nanoparticles[a]



Run	1	2[b]	3[b]
Product (%)	79	78	78

[a] Benzamide (6 mmol), 1-iodo-4-methylbenzene (5 mmol), CuI (10 mol %) and KOH (7.5 mmol) were stirred at 120 °C in PEG_{4000} (5 g) under nitrogen atmosphere.

[b] Recovered Cu_2O nanoparticles used.

In summary, we have developed a one pot procedure for the formation and catalysis of Cu_2O nanoparticles for the cross-coupling reactions of amides and imidazoles with aryl iodides in PEG_{4000} in the absence of additional chelating ligand. The significant advantages of this procedure are simplicity of the operation and compatibility with the variety of substituents, general applicability to the synthesis of *N*-arylamides and *N*-arylimidazoles, high yields and recyclability of the catalyst.

Experimental Section

General. CuI (98 %), Cu_2O (<5 μm), CuO (~33 nm), $CuSO_4{\cdot}5H_2O$ (98 %), $CuCl_2{\cdot}2H_2O$ (99 %), Cs_2CO_3 (99 %), K_3PO_4 (98 %), amides, imidazoles and iodobenzene (98 %) were purchased from Sigma-Aldrich. PEG, KOH, NaOH and K_2CO_3 were purchased from Merck. All reagents were used as received. 2-Methoxy-, 4-bromo-, 4-methyl-, 4-methoxy-, 2,4-dimethyl-, naphthyl- and 4-aminoaryl iodides were prepared according to the literature.[10a] Cu_2O nanoparticles were characterized using JEOL JEM 2100 transmission electron microscopy operating at 200 kv and Bruker D8 advance X-ray diffractometer with a Cu-Kα source in the 2θ range of 10 to 70. Samples for TEM analyses were prepared on carbon coated 300 mesh Cu grids. A drop of the reaction mixture was dispersed in 2-propanol (1 mL) then loaded on Cu grid and dried at room temperature in air. The NMR (400 MHz for

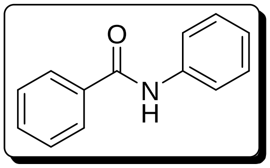
^{1}H and 100 MHz for ^{13}C) spectra of the cross-coupled products were analyzed using DRX 400 Varian spectrometer using $CDCl_3$ and DMSO-d_6 as solvents and Me_4Si as internal standard. Melting points were determined using Buchi B-540 melting point apparatus and were uncorrected. Elemental analysis of the cross-coupled products were carried out using Perkin Elmer-2400 CHNS analyzer.

General Procedure for *C-N* Cross-Coupling Reactions

Aryl iodide (1 mmol), amide or imidazole (1.2 mmol) and CuI (10 mol %) were stirred at 120 ^{o}C in the presence of KOH (1.5 mmol) in PEG_{4000} (1 g) under N_2 atmosphere. Progress of the reaction was monitored by TLC. After completion, the reaction flask was cooled to room temperature and the reaction mixture was treated with ethyl acetate (10 mL). The resulting solution was washed with water (3 x 2 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on a short pad of silica gel using hexane and ethyl acetate as eluent.

Recyclability Experiment

1-Iodo-4-methylbenzene (1.08 g, 5 mmol), benzamide (0.870 g, 6 mmol) and CuI (0.095 g, 10 mol %) were stirred at 120 °C in the presence of KOH (0.420 g, 7.5 mmol) in PEG_{4000} (5 g) under N_2 atmosphere. After the reaction, the reaction material was treated with ethyl acetate (10 mL) and water (5 mL). The aqueous layer having the Cu_2O nanoparticles were centrifuged and the precipitate was washed with deionized water (3 x 2 mL), EtOH (3 x 2 mL) and acetone (3 x 2 mL). After drying in vacuum, the Cu_2O nanoparticles were reused for the fresh reaction of benzamide with 1-iodo-4-methylbenzene.



***N*-Phenylbenzamide** (Table 3, entry 1).[6d] A mixture of iodobenzene (203 mg, 1 mmol), benzamide (145 mg, 1.2 mmol), CuI (19 mg, 10 mol %), KOH (84 mg, 1.5 mmol) and PEG_{4000} (1 g) was subjected to the reaction conditions described in the general procedure for 10 h and the residue was purified on silica gel column chromatography to give the title compound (143 mg, 73 %) as white solid.

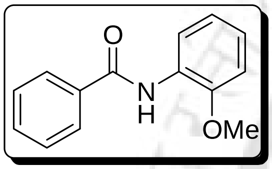
Mp: 162-163 °C.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.86 (d, *J* = 7.2 Hz, 2H), 7.78 (br s, 1H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 2H), 7.36 (t, *J* = 8.0 Hz, 2H), 7.14 (t, *J* = 7.2 Hz, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 166.0, 138.1, 135.2, 132.0, 129.3, 128.9, 127.2, 124.8, 120.5.

FT-IR (KBr): ν 3310, 2995, 1659, 1604, 1533, 1420, 1315, 1233, 1185, 1090, 1023 cm^{-1}.

Anal. Calcd for $C_{13}H_{11}NO$: C, 79.16; H, 5.62; N, 7.10. Found: C, 79.21; H, 5.60; N, 7.15.



***N*-(2-Methoxyphenyl)benzamide** (Table 3, entry 2).[10b] A mixture of 1-iodo-2-methoxybenzene (233 mg, 1 mmol), benzamide (145 mg, 1.2 mmol), CuI (19 mg, 10 mol %), KOH (84 mg, 1.5 mmol) and PEG$_{4000}$ (1 g) was subjected to the reaction conditions shown in the general procedure for 17 h and the residue was purified on silica gel column chromatography to afford the title compound (158 mg, 70 %) as white solid.

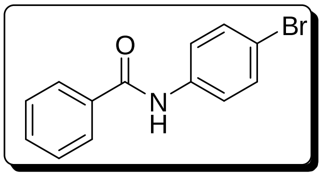
Mp: 58-59 °C.

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.54 (br s, 1H), 8.52-8.50 (dd, *J* = 1.6, 8 Hz, 1H), 7.89-7.86 (m, 2H), 7.55-7.45 (m, 3H), 7.09-7.05 (m, 1H), 7.02-6.98 (m, 1H) 6.90 (dd, *J* = 1.6, 8 Hz, 1H), 3.91 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 165.5, 148.4, 135.6, 131.9, 128.9, 128.0, 127.3, 124.1, 121.5, 120.1, 110.2, 56.0.

FT-IR (KBr): ν 3438, 2928, 1661, 1602, 1519, 1459, 1289, 1253, 1029 cm^{-1}.

Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.06; H, 5.75; N, 6.20.



***N*-(4-Bromophenyl)benzamide** (Table 2, entry 3).[10c] A mixture of

1-bromo-4-iodobenzene (282 mg, 1 mmol), benzamide (145 mg, 1.2 mmol), CuI (19 mg, 10 mol %), KOH (84 mg, 1.5 mmol) and PEG_{4000} (1 g) was subjected to the reaction conditions reported in the general procedure for 12 h and the residue was purified on silica gel column chromatography to provide the title compound (208 mg, 76 %) as white solid.

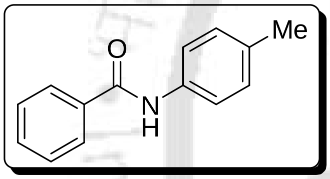
Mp: 202-203 °C.

^{1}H NMR (400 MHz, DMSO:$CDCl_3$ = 1:3): δ 9.45 (br s, 1H), 7.65 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.24 (t, J = 8 Hz, 1H), 7.18 (d, J = 8 Hz, 2H), 7.16-7.12 (m, 2H).

^{13}C NMR (100 MHz, DMSO:$CDCl_3$ = 1:3): δ 166.1, 137.9, 134.8, 131.2, 131.1, 128.0, 127.4, 121.9, 115.9.

FT-IR (KBr): ν 3355, 3057, 2923, 2844, 1644, 1585, 1577, 1545, 1486, 1433, 1319, 1263, 1082, 1077, 1015 cm^{-1}.

Anal. Calcd for $C_{13}H_{10}BrNO$: C, 56.55; H, 3.65; N, 5.07. Found: C, 56.63; H, 3.67; N, 5.09.



***N*-(4-Methylphenyl)benzamide** (Table 3, entry 4).[10d] A mixture of 1-iodo-4-methylbenzene (217 mg, 1 mmol), benzamide (145 mg, 1.2 mmol), CuI (19 mg, 10 mol %), KOH (84 mg, 1.5 mmol) and PEG_{4000} (1 g) was subjected to the reaction conditions described in the general procedure for 12 h and the residue was purified on silica gel column chromatography to give the title compound (150 mg, 75 %) as white solid.

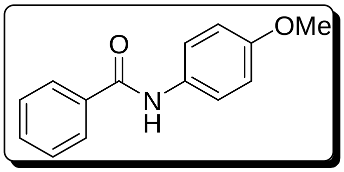
Mp: 158-159 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, J = 8.4 Hz, 2H), 7.74 (br s, 1H), 7.54-7.44 (m, 5H), 7.16 (d, J = 8.4 Hz, 2H), 2.32 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 135.6, 135.3, 134.4, 131.9, 129.8, 128.9, 127.2, 120.5, 21.1.

FT-IR (KBr): ν 3309, 2963, 2926, 2857, 1647, 1596, 1579, 1531, 1491, 1404, 1317, 1296, 1262, 1095, 1022 cm^{-1}.

Anal. Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.66; H, 6.23; N, 6.66.



***N*-(4-Methoxyphenyl)benzamide** (Table 3, entry 5).[10e] A mixture of 1-iodo-4-methoxybenzene (217 mg, 1 mmol), benzamide (145 mg, 1.2 mmol), CuI (19 mg, 10 mol %), KOH (84 mg, 1.5 mmol) and PEG_{4000} (1 g) was subjected to the reaction conditions shown in the general procedure for 15 h and the residue was purified on silica gel column chromatography to afford the title compound (170 mg, 75 %) as white solid.

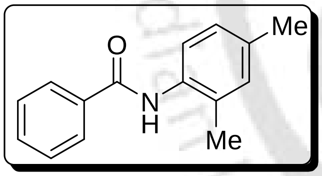
Mp: 157-158 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, *J* = 8.0 Hz, 2H), 7.76 (s, 1H), 7.53-7.43 (m, 5H), 6.90 (d, *J* = 8.8 Hz, 2H), 3.79 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 156.9, 135.2, 131.9, 131.3, 128.9, 127.2, 122.4, 114.5, 55.7.

FT-IR (KBr): ν 3330, 2963, 2926, 1646, 1514, 1469, 1413, 1261, 1095, 1026, 800 cm^{-1}.

Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.04; H, 5.76; N, 6.22.



***N*-(2,4-Dimethylphenyl)benzamide** (Table 3, entry 6). A mixture of 1-iodo-2,4-dimethylbenzene (231 mg, 1 mmol), benzamide (145 mg, 1.2 mmol), CuI (19 mg, 10 mol %), KOH (84 mg, 1.5 mmol) and PEG_{4000} (1 g) was subjected to the reaction conditions reported in the general procedure for 16 h and the residue was purified on silica gel column chromatography to provide the title compound (162 mg, 72 %) as white solid.

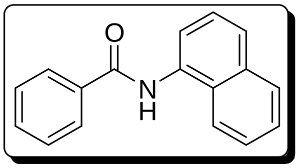
Mp: 193-194 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 7.2 Hz, 2H), 7.73 (d, *J* = 7.6 Hz, 1H), 7.58 (s, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 2.30 (s, 3H), 2.27 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 135.4, 135.2, 133.3, 131.9, 131.4, 129.9, 128.9, 127.6, 127.3, 123.8, 21.1, 17.9.

FT-IR (KBr): ν 3266, 2955, 2921, 2853, 1640, 1601, 1578, 1521, 1505, 1497, 1310, 1278, 1228, 1075, 1027 cm^{-1}.

Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 80.04; H, 6.75; N, 6.28.



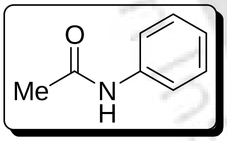
***N*-(1-Napthalenyl)benzamide** (Table 3, entry 7).[10f] A mixture of 1-iodo-naphthalene (253 mg, 1 mmol), benzamide (145 mg, 1.2 mmol), CuI (19 mg, 10 mol %), KOH (84 mg, 1.5 mmol) and PEG_{4000} (1 g) was subjected to the reaction conditions described in the general procedure for 12 h and the residue was purified on silica gel column chromatography to provide the title compound (197 mg, 80 %) as white solid.

Mp: 159 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (br s, 1H), 8.02 (d, J = 7.2 Hz, 1H) 7.97 (d, J = 7.6 Hz, 2H), 7.89-7.87 (m, 2H), 7.73 (d, J = 8 Hz, 1H), 7.59-7.50 (m, 5H), 7.23-7.21 (m,1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5, 135.1, 134.4, 132.6, 132.2, 129.1, 127.6, 127.4, 126.7, 126.3, 126.0, 121.4, 120.8, 109.9, 126.0.

Anal. Calcd for $C_{17}H_{13}NO$: C, 82.57; H, 5.30; N, 5.66. Found: C, 82.62; H, 5.32; N, 5.69.



***N*-Phenylacetamide** (Table 3, entry 8).[5o] A mixture of iodobenzene (203 mg, 1 mmol), acetamide (72 mg, 1.2 mmol), CuI (19 mg, 10 mol %), KOH (84 mg, 1.5 mmol) and PEG_{4000} (1 g) was subjected to the reaction conditions shown in the general procedure for 3 h and the residue was purified on silica gel column chromatography to afford the title compound (101 mg, 75 %) as white solid.

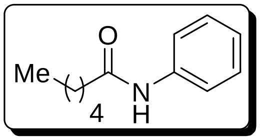
Mp: 161-163 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (br s, 1H), 7.50 (d, J = 8 Hz, 2H), 7.30-7.25 (m, 2H), 7.10-7.07 (m, 1H), 2.14 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 138.2, 129.1, 124.5, 120.2, 24.7.

FT-IR (KBr): ν 3294, 3260, 3194, 3136, 3059, 3021, 2925, 2854, 2802, 1660, 1599, 1557, 1500, 1488, 1435, 1369, 1323, 1264, 1041, 1013 cm^{-1}.

Anal. Calcd for C_8H_9NO: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.15; H, 6.74; N 10.35.



***N*-Phenylhexanamide** (Table 3, entry 9).[10g] A mixture of iodobenzene (203 mg, 1 mmol), hexanamide (138 mg, 1.2 mmol), CuI (19 mg, 10 mol %), KOH (84 mg, 1.5 mmol) and PEG_{4000} (1 g) was subjected to the reaction conditions described in the general procedure for 3 h and the residue was purified on silica gel column chromatography to give the title compound (134 mg, 70 %) as white solid.

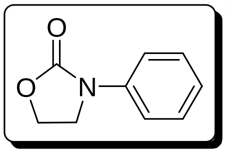
Mp: 93-94 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (d, *J* = 7.6 Hz, 2H), 7.29 (t, *J* = 7.8 Hz, 2H), 7.14 (s, 1H), 7.07 (t, *J* = 8.0 Hz, 1H), 2.33 (t, *J* = 8.0 Hz, 2H), 1.73 (m, 2H), 1.34-1.33 (m, 4H), 0.90-0.87 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 138.2, 129.2, 124.4, 120.0, 38.0, 31.6, 25.5, 22.6, 14.1.

FT-IR (KBr): ν 3305, 3266, 3201, 3144, 3092, 2955, 2931, 2858, 1660, 1618, 1554, 1499, 1464, 1443, 1412, 1375, 1325, 1303, 1259, 1188 cm^{-1}.

Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.40; H, 8.95; N, 7.36.



3-Phenyl-2-oxazolidinone (Table 3, entry 10).[6d] A mixture of iodobenzene (203 mg, 1 mmol), 2-oxazolidinone (104 mg, 1.2 mmol), CuI (19 mg, 10 mol %), KOH (84 mg, 1.5 mmol) and PEG_{4000} (1 g) was subjected to the reaction conditions reported in the general procedure for 5 h and the residue was purified on silica gel column chromatography to provide the title compound (123 mg, 75 %) as white solid.

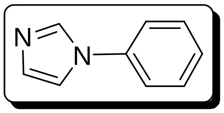
Mp: 120-121 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.8 Hz, 2H), 7.13 (t, *J* = 7.2 Hz, 1H), 4.45 (t, *J* = 8.2 Hz, 2H), 4.03 (t, *J* = 8.0 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5, 138.4, 129.2, 124.2, 118.4, 61.5, 45.3.

FT-IR (KBr): ν 2923, 1736, 1610, 1520, 1500, 1404, 1316, 1262, 1122, 1089, 1020 cm^{-1}.

Anal. Calcd for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.32; H, 5.58; N, 8.61.



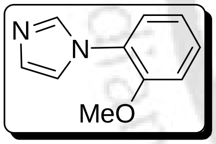
1-Phenyl-1H-imidazole (Table 4, entry 1).[5o] A mixture of iodobenzene (203 mg, 1 mmol), imidazole (81 mg, 1.2 mmol), CuI (19 mg, 10 mol %), KOH (84 mg, 1.5 mmol) and PEG_{4000} (1 g) was subjected to the reaction conditions described in the general procedure for 12 h and the residue was purified on silica gel column chromatography to afford the title compound (129 mg, 90 %) as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (br s, 1H), 7.47-7.43 (m, 2H), 7.36-7.33 (m, 3H), 7.26 (br s, 1H), 7.18 (br s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.5, 135.8, 130.5, 130.1, 127.7, 121.7, 118.5.

FT-IR (KBr): ν 3120, 3060, 1605, 1514, 1311, 1252, 1117, 1063, 968, 901, 811 cm^{-1}.

Anal. Calcd for $C_9H_8N_2$: C, 74.98; H, 5.59; N, 19.43. Found: C, 75.00; H, 5.58; N, 19.43.



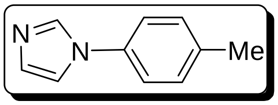
1-(2-Methoxyphenyl)-1H-imidazole (Table 4, entry 2).[6p] A mixture of 1-iodo-2-methoxybenzene (233 mg, 1 mmol), imidazole (81 mg, 1.2 mmol), CuI (19 mg, 10 mol %), KOH (84 mg, 1.5 mmol) and PEG_{4000} (1 g) was subjected to the reaction conditions shown in the general procedure for 15 h and the residue was purified on silica gel column chromatography to provide the title compound (104 mg, 60 %) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (s, 1H), 7.35-7.30 (m, 1H), 7.25-7.23 (m, 1H), 7.15 (d, *J* = 14.8 Hz, 2H), 7.03-6.98 (m, 2H), 3.81 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 152.8, 137.9, 129.2, 128.8, 126.6, 125.7, 121.2, 120.5, 112.5, 55.9.

FT-IR (KBr): ν 3398, 2924, 2851, 1600, 1516, 1454, 1382, 1283, 1251, 1179, 1029 cm^{-1}.

Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.98; H, 5.81; N, 16.12.



1-(4-Methylphenyl)-1H-imidazole (Table 4, entry 3).[6p] A mixture of 1-iodo-4-methylbenzene (217 mg, 1 mmol), imidazole (81 mg, 1.2 mmol), CuI (19 mg, 10 mol %), KOH (84 mg, 1.5 mmol) and PEG_{4000} (1 g) was subjected to the reaction conditions reported in the general procedure for 12 h and the residue was purified on silica gel column chromatography to provide the title compound (134 mg, 85 %) as yellow solid.

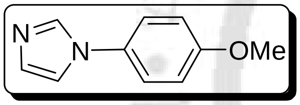
Mp: 45-47 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (s, 1H), 7.28-7.26 (m, 5H), 7.19 (s, 1H), 2.41 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.7, 135.9, 135.3, 130.6, 130.4, 121.7, 118.6, 21.2.

FT-IR (KBr): ν 3419, 2927, 2851, 1599, 1518, 1454, 1380, 1300, 1251, 1229, 1174, 1034 cm^{-1}.

Anal. Calcd for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.95; H, 6.36; N, 17.72.



1-(4-Methoxyphenyl)-1H-imidazole (Table 4, entry 4).[5o] A mixture of 1-iodo-4-methoxybenzene (233 mg, 1 mmol), imidazole (81 mg, 1.2 mmol), CuI (19 mg, 10 mol %), KOH (84 mg, 1.5 mmol) and PEG_{4000} (1 g) was subjected to the reaction conditions described in the general procedure for 18 h and the residue was purified on silica gel column chromatography to afford the title compound (153 mg, 88 %) as white solid.

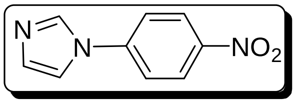
Mp: 62-63 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (br s, 1H), 7.28 (d, J = 8.8 Hz, 2H), 7.20 (br s, 2H), 6.96 (d, J = 9.2 Hz, 2H), 3.82 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2, 136.0, 130.9, 130.1, 123.4, 119.0, 115.1, 55.8.

FT-IR (KBr): ν 3325, 2924, 2846, 1599, 1519, 1462, 1382, 1300, 1251, 1182, 1059, 1028 cm^{-1}.

Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.98; H, 5.80; N, 16.14.



1-(4-Nitrophenyl)-1H-imidazole (Table 4, entry 5).[6p] A mixture of 1-iodo-4-nitrobenzene (249 mg, 1 mmol), imidazole (81 mg, 1.2 mmol), CuI (19 mg, 10 mol

%), KOH (84 mg, 1.5 mmol) and PEG$_{4000}$ (1 g) was subjected to the reaction conditions shown in the general procedure for 6 h and the residue was purified on silica gel column chromatography to give the title compound (160 mg, 85 %) as yellow solid.

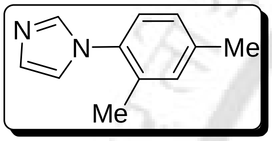
Mp: 203-205 °C.

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.36 (d, *J* = 8.8 Hz, 2H), 7.96 (br s, 1H), 7.56 (d, *J* = 8.8 Hz, 2H), 7.36 (br s, 1H), 7.26 (br s, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 146.4, 142.1, 135.6, 131.8, 125.9, 121.2, 117.8.

FT-IR (KBr): ν 3106, 2962, 2851, 1599, 1511, 1340, 1306, 1262, 1108, 1052 cm^{-1}.

Anal. Calcd for $C_9H_7N_3O_2$: C, 57.14; H, 3.73; N, 22.21. Found: C, 57.19; H, 3.75; N, 22.27.



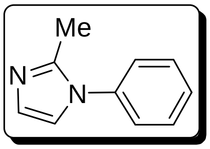
1-(2,4-Dimethylphenyl)-1H-imidazole (Table 4, entry 6). A mixture of 1-iodo-2,4-dimethylbenzene (231 mg, 1 mmol), imidazole (81 mg, 1.2 mmol), CuI (19 mg, 10 mol %), KOH (84 mg, 1.5 mmol) and PEG$_{4000}$ (1 g) was subjected to the reaction conditions reported in the general procedure for 16 h and the residue was purified on silica gel column chromatography to afford the title compound (111 mg, 65 %) as yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.53 (s, 1H), 7.15 (s, 1H), 7.11 (s, 1H), 7.06 (s, 2H), 6.99 (s, 1H), 2.35 (s, 3H), 2.10 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 139.0, 137.8, 134.3, 133.8, 132.1, 129.4, 127.6, 126.6, 120.9, 21.2, 17.7.

FT-IR (KBr): ν 3407, 2923, 2846, 1615, 1516, 1451, 1443, 1380, 1251, 1226, 1033 cm^{-1}.

Anal. Calcd for $C_{11}H_{12}N_2$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.73; H, 7.03; N, 16.25.



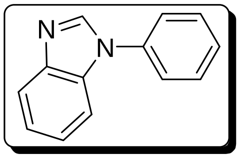
2-Methyl-1-phenyl-1H-imidazole (Table 4, entry 7).[10f] A mixture of iodobenzene (203 mg, 1 mmol), 2-methylimidazole (98 mg, 1.2 mmol), CuI (19 mg, 10 mol %), KOH (84 mg, 1.5 mmol) and PEG$_{4000}$ (1 g) was subjected to the reaction conditions shown in the general procedure for 15 h and the residue was purified on silica gel column chromatography to give the title compound (111 mg, 70 %) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48-7.40 (m, 3H), 7.28-7.24 (m, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 2.34 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.9, 138.1, 129.7, 128.5, 127.6, 125.7, 120.9, 13.9.

FT-IR (KBr): ν 3117, 3059, 1601, 1510, 1309, 1259, 1120, 1075, 989, 918, 801 cm^{-1}.

Anal. Calcd for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.95; H, 6.35; N, 17.70.



1-(Phenyl)-1H-benzimidazole (Table 4, entry 8).[5o] A mixture of iodobenzene (203 mg, 1 mmol), benzimidazole (141 mg, 1.2 mmol), CuI (19 mg, 10 mol %), KOH (84 mg, 1.5 mmol) and PEG_{4000} (1 g) was subjected to the reaction conditions described in the general procedure for 14 h and the residue was purified on silica gel column chromatography to provide the title compound (140 mg, 72 %) as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.87-7.85 (m, 1H), 7.58-7.43 (m, 6H), 7.33-7.31 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 144.0, 142.4, 136.4, 133.8, 130.1, 128.1, 124.1, 123.8, 122.9, 120.6, 110.6.

FT-IR (KBr): ν 3406, 3065, 2927, 2846, 1599, 1503, 1454, 1382, 1319, 1286, 1248, 1231, 1201, 1028 cm^{-1}.

Anal. Calcd for $C_{13}H_{10}N_2$: C, 80.39; H, 5.19; N, 14.42. Found: C, 80.41; H, 5.17; N, 14.45.

1.4 References

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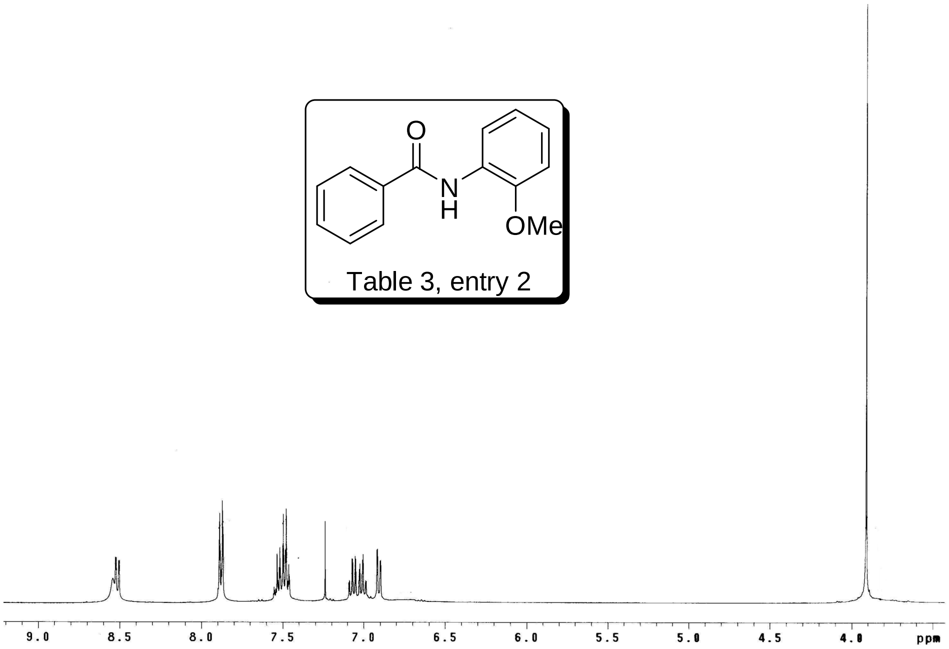
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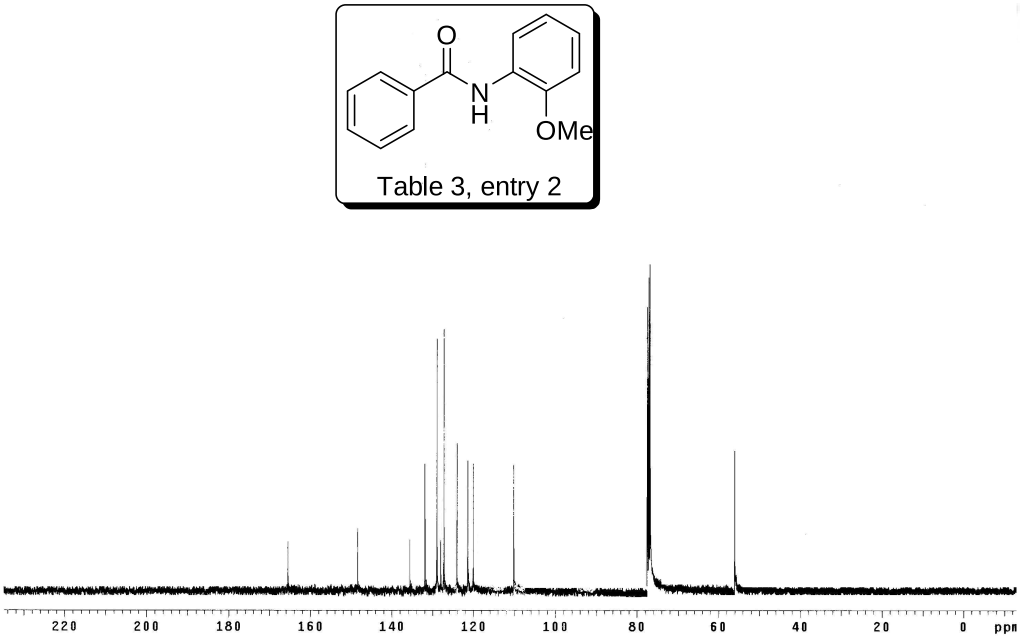
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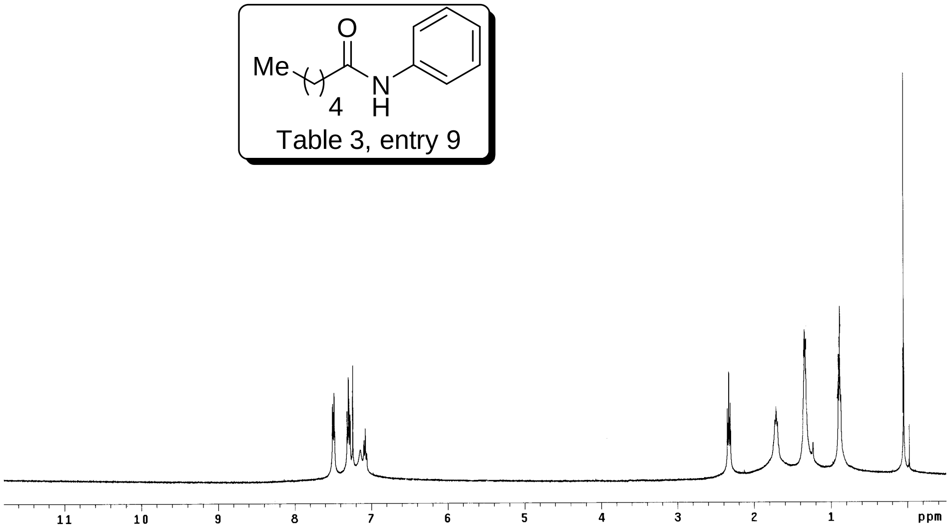
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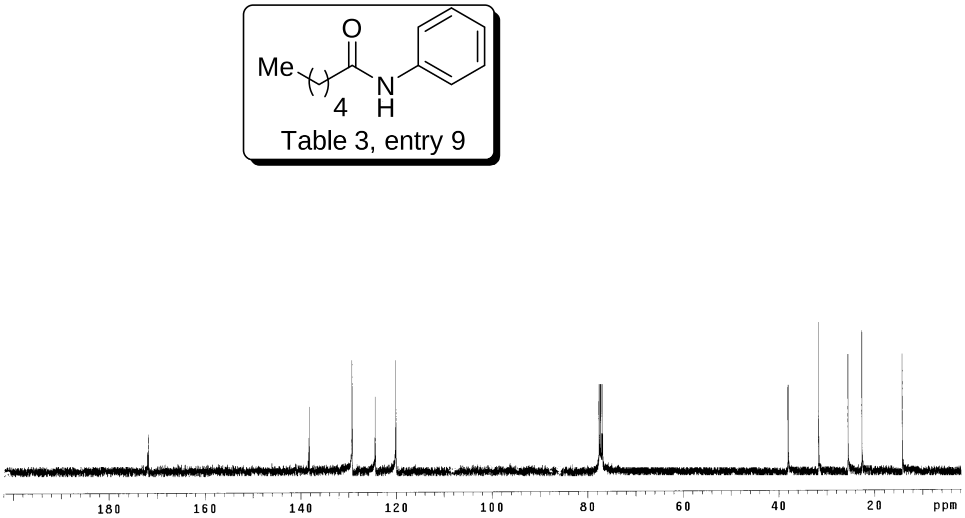
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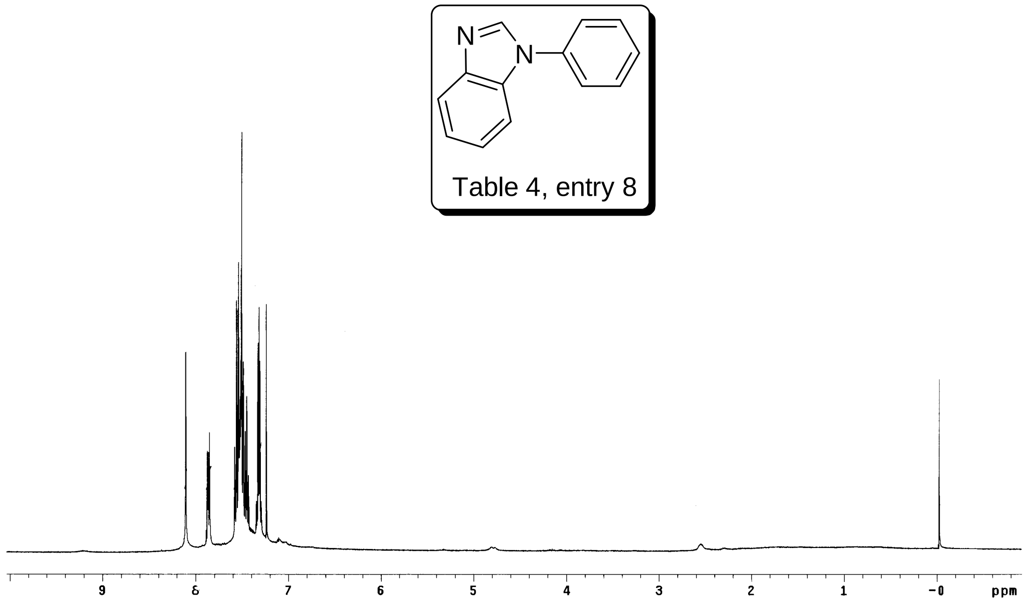
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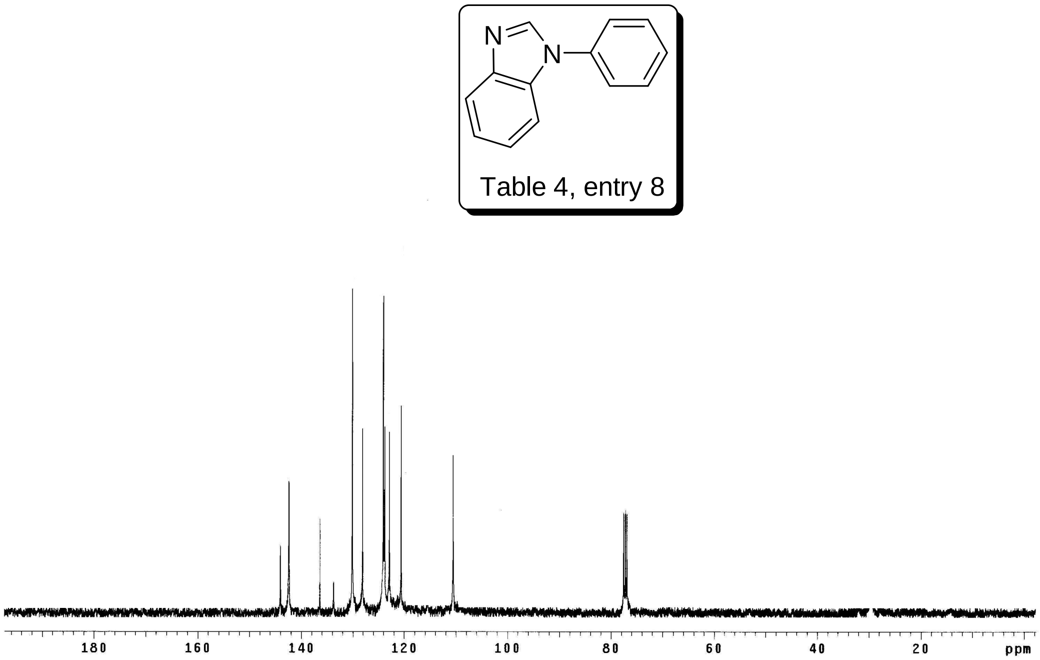
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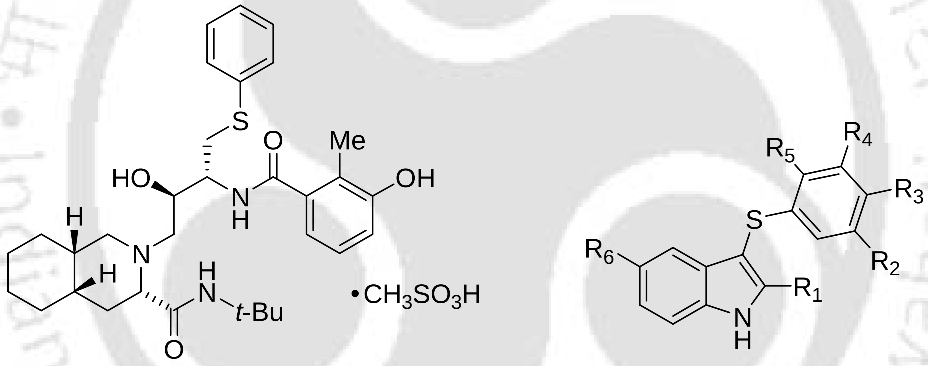
ppm

Chapter I1

Copper(I) Oxide Nanoparticles Catalyzed *S*-Arylation of Thiols

The cross-coupling of thiols with aryl halides is an important reaction in organic synthesis. The products, substituted sulfides, serve as building blocks for the synthesis of sulfur containing compounds in medicinal, material and biological sciences (Scheme 1).[1] Traditional methods for the formation of *C-S* bond often require harsh reaction conditions. For examples, use of polar solvents such as HMPA, temperature around 200 °C, reduction of sulfones or sulfoxides by DIBAL-H or $LiAlH_4$[2] and designing of ligands with *ortho* carbonyl groups that are both electron withdrawing and capable of chelating copper limit their application in industry. Thus, considerable attention has been recently focused to develop catalytic systems for this reaction.



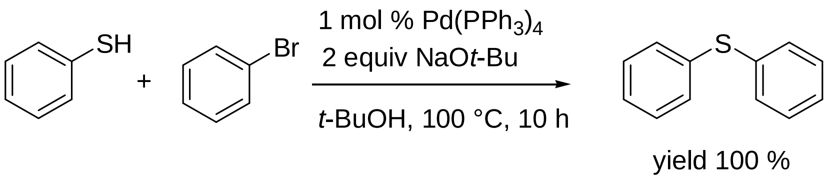
Nelfinavir mesylate
HIV-1 protease inhibitor

Arylthioindoles (ATIs)
R_1 = ester, R_2-R_6 = H, Cl, OMe
Anti-cancer agent

Scheme 1

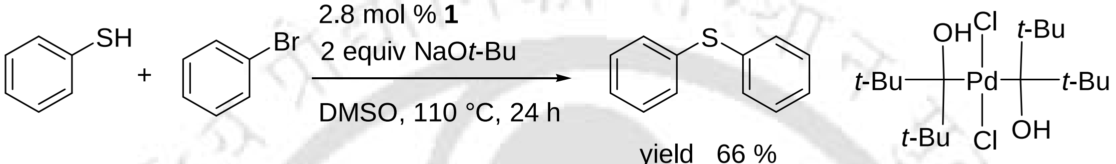
2.1 Palladium Catalysts

Palladium based catalysts are widely studied for *C-S* cross-coupling reactions.[3] In 1980, Migita and co-workers first reported the cross-coupling of thiols with aryl halides using $Pd(PPh_3)_4$ in the presence of NaO*t*-Bu in *t*-BuOH (Scheme 2).[3a-b] Aryl iodide and –bromide are compatible with this catalytic system affording the cross-coupled products in high yield.



Scheme 2

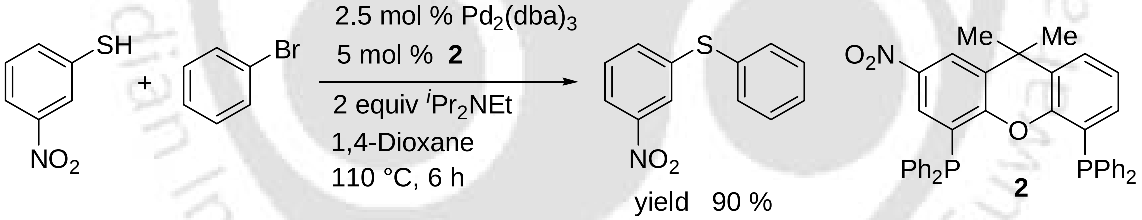
The coupling of thiols with aryl chlorides and -bromides is subsequently studied using palladium(II) complex **1** in the presence of NaO*t*-Bu (Scheme 3).[3c] These reaction conditions are also suitable for the reactions of aryl halides with amines and alkenes.



1

Scheme 3

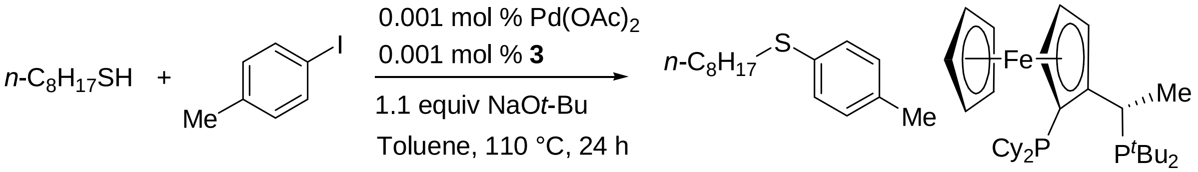
Itoh and Mase reported the cross-coupling of thiols with aryl bromides by the combined use of $Pd_2(dba)_3$ and xantphos **2** in the presence of ${}^iPr_2NEt$ in 1,4-dioxane (Scheme 4).[3e] These reaction conditions are also compatible for the coupling of aryl chlorides with thiols.



2

Scheme 4

Hartwig and co-workers showed the coupling of thiols with aryl halides using $Pd(OAc)_2$ and ligand **3** in the presence of NaO*t*-Bu in toluene (Scheme 5).[3f] Under these conditions, aryl iodides and –bromides undergo reaction with high turnovers.

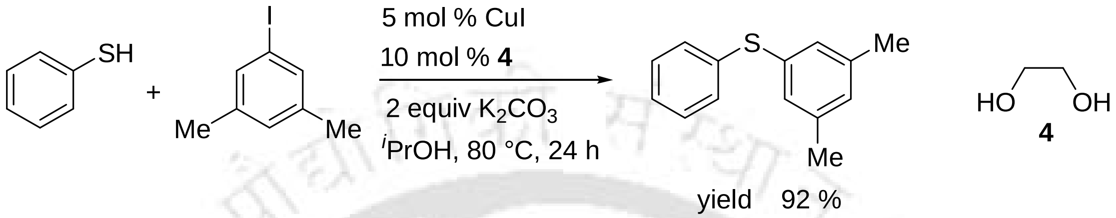


3

Scheme 5

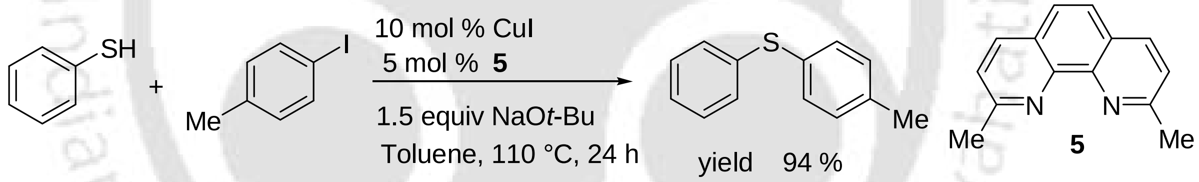
2.2 Copper Catalysts

Following the palladium catalyzed reactions, copper based catalytic systems are considerably studied for *C*-*S* cross-coupling reactions.[4] CuI-1,2-ethylene glycol is used for the coupling of thiols with aryl iodides in the presence of K_2CO_3 in 2-propanol (Scheme 6).[4d] The reaction of aryl iodides having electron withdrawing and –donating groups is demonstrated.



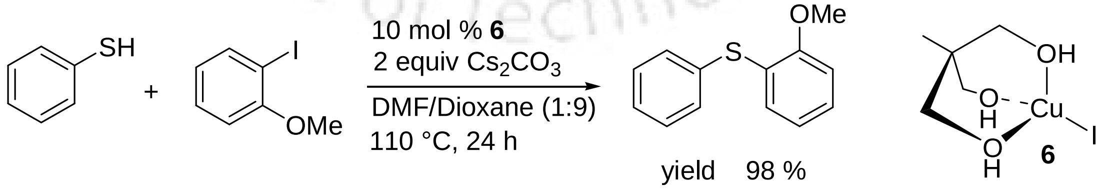
Scheme 6

Venkataraman and co-workers have demonstrated the coupling of aryl thiols with aryl iodides using CuI and neocuproine **5** in the presence of NaO*t*-Bu in toluene (Scheme 7).[4e] Using this procedure the coupling of thiophenol with 1-iodo-4-methylbenzene is accomplished in 94 % yield.



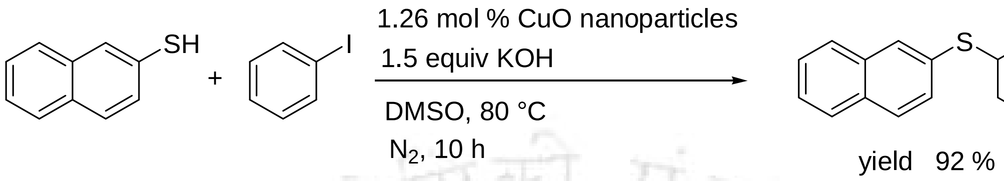
Scheme 7

Copper(I) complex **6** is used for the coupling of aromatic thiols with aryl iodides in the presence of Cs_2CO_3 in 1:9 DMF/dioxane (Scheme 8).[4i] These reaction conditions are also effective for *C*-*O* cross-coupling reactions.



Scheme 8

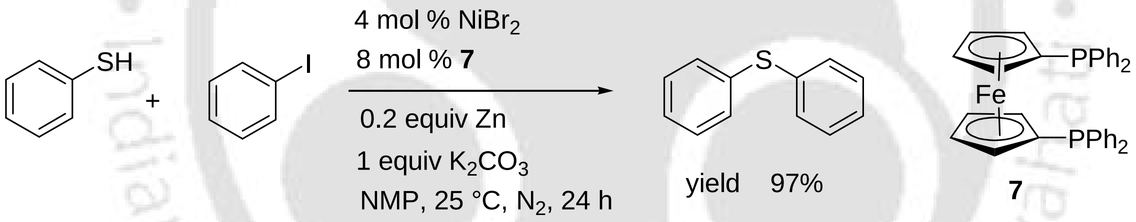
Recently, we have reported CuO nanoparticle catalyzed *C*-*S* cross coupling reactions of thiols with aryl iodides in presence of KOH at moderate temperature (Scheme 9).[4k-l] The procedure is simple, general, ligand-free and efficient to give the cross-coupled products in high yield.



Scheme 9

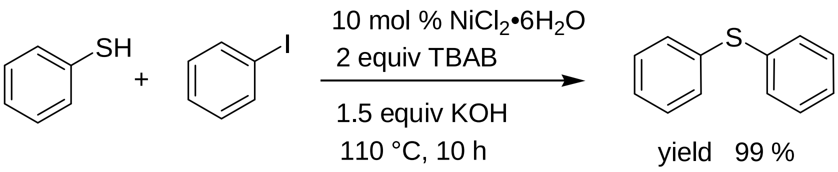
2.3 Nickel Catalysts

Few studies are focused on nickel catalysed *C*-*S* cross coupling reactions.[5] The combination of $NiBr_2$-dppf [dppf =1,1'-bis(diphenylphosphino ferrocene)] and zinc is used for coupling of aromatic thiols with aryl iodides and –bromides in the presence of K_2CO_3 in *N*-methyl-2-pyrrolidone at ambient temperature (Scheme 10).[5c]



Scheme 10

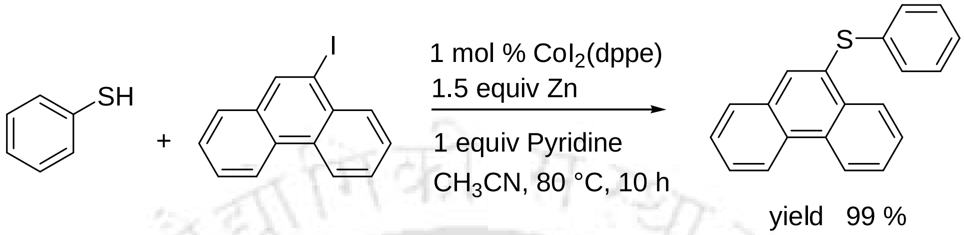
We have reported the coupling of thiols with aryl iodides using $NiCl_2{\cdot}6H_2O$ in TBAB (TBAB = tetrabutylammonium bromide) (Scheme 11).[5b] In these reactions, the products are separated from the solid material by extraction with diethyl ether and the insoluble catalyst can be recycled without loss of activity.



Scheme 11

2.4 Cobalt Catalyst

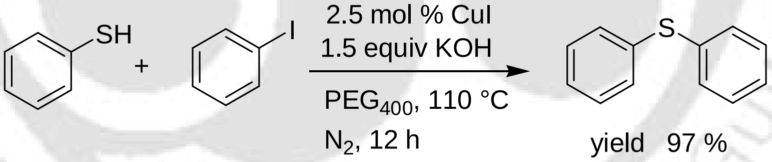
By the combined use of $CoI_2(dppe)_2$ and Zn powder, the cross-coupling of thiols with aryl iodides and –bromides is accomplished in the presence of pyridine (Scheme 12).[6] Under these conditions thiophenol is coupled with 9-iodophenanthrene in 99 % yield.



Scheme 12

2.5 Present Study

Following the success with the *C-N* cross-coupling of amides and imidazoles with aryl iodides, the Cu_2O nanoparticles/PEG system was further studied for the *C-S* cross-coupling of thiols with aryl halides. The reaction conditions were optimized by studying the coupling of thiophenol with iodobenzene as model substrate. The reaction occurred to afford the desired *C-S* cross-coupled product in 97 % yield when the substrates were stirred at 110 ^{o}C in the presence of 5 mol % of CuI and 1.5 equiv of KOH in PEG_{400} (Scheme 13).

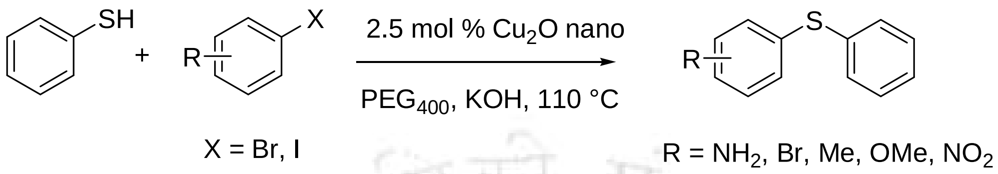


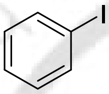
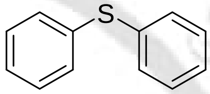
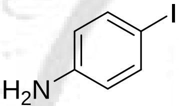
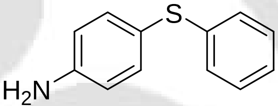
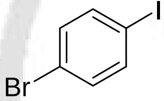
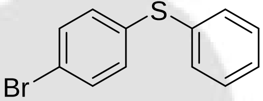
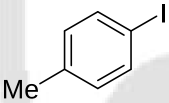
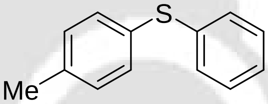
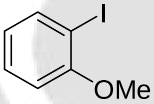
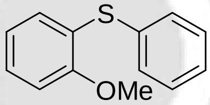
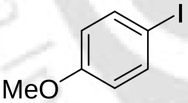
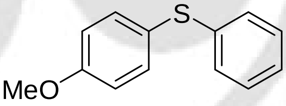
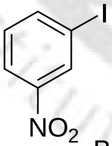
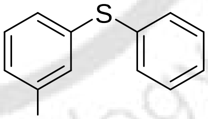
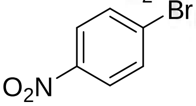
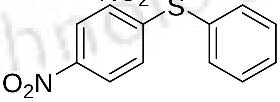
Scheme 13

Next, thiophenol proceeded reaction with a series of substituted aryl iodides having electron donating and -withdrawing substituents on the aromatic ring to give the corresponding aryl thioethers in >81 % yield (Table 1, entries 1-7). Similarly, thiophenol, having electron withdrawing and -donating substituents in the aromatic ring, 2-naphthylthiol and benzylthiol underwent reactions with 1-iodo-4-methoxybenzene to provide the aryl thioethers in >83 % yield (Table 2). Interestingly, the activated 1-bromo-4-nitrobenzene proceeded reaction with thiophenol to afford the respective aryl thioether in 88 % yield

(Table 1, entry 8). These results clearly suggest that both the substituted thiols and aryl iodides can be cross-coupled with high yield.

Table 1. *S*-Arylation of Thiophenol with Aryl halides[a]

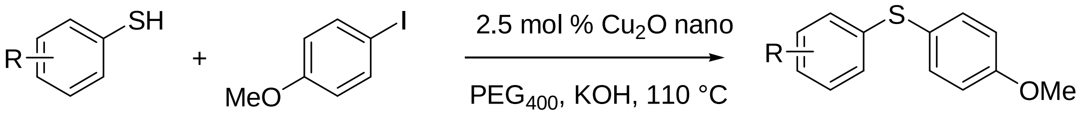


Entry	Aryl halide	Time (h)	Product	Yield (%)[b]
1		12		97
2		15		81
3		12		85
4		14		91
5		17		82
6		15		85
7		15		85
8		12		88

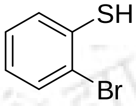
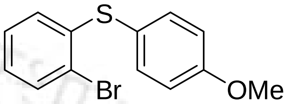
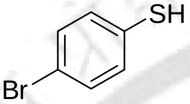
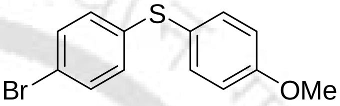
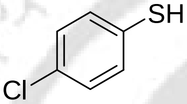
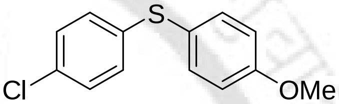
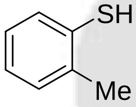
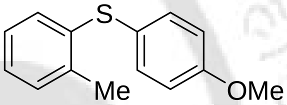
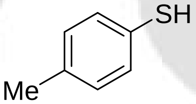
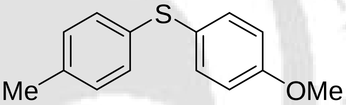
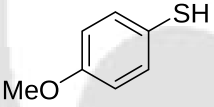
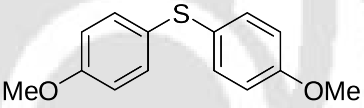
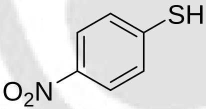
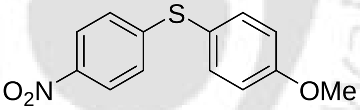
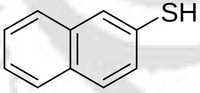
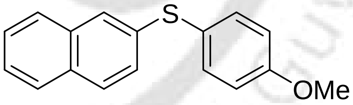
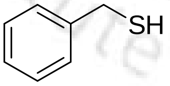
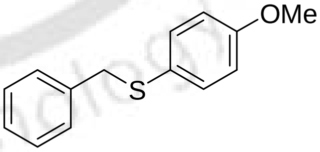
[a] Thiophenol (1 mmol), aryl halide (1.1 mmol), CuI (5 mol %) and KOH (1.5 mmol) were stirred at 110 °C in PEG_{400} (1 g) under nitrogen atmosphere.

[b] Isolated yield.

Table 2. *S*-Arylation of Thiols with 1-Iodo-4-methoxybenzene[a]



R = Br, Cl, Me, OMe, NO_2

Entry	Substrate	Time (h)	Product	Yield (%)[b]
1		15		84
2		10		85
3		8		92
4		15		83
5		14		90
6		8		86
7		16		72
8		12		73
9		14		70

[a] Thiol (1 mmol), 1-iodo-4-methoxybenzene (1.1 mmol), CuI (5 mol %) and KOH (1.5 mmol) were stirred at 110 °C in PEG_{400} (1 g) under nitrogen atmosphere.

[b] Isolated yield.

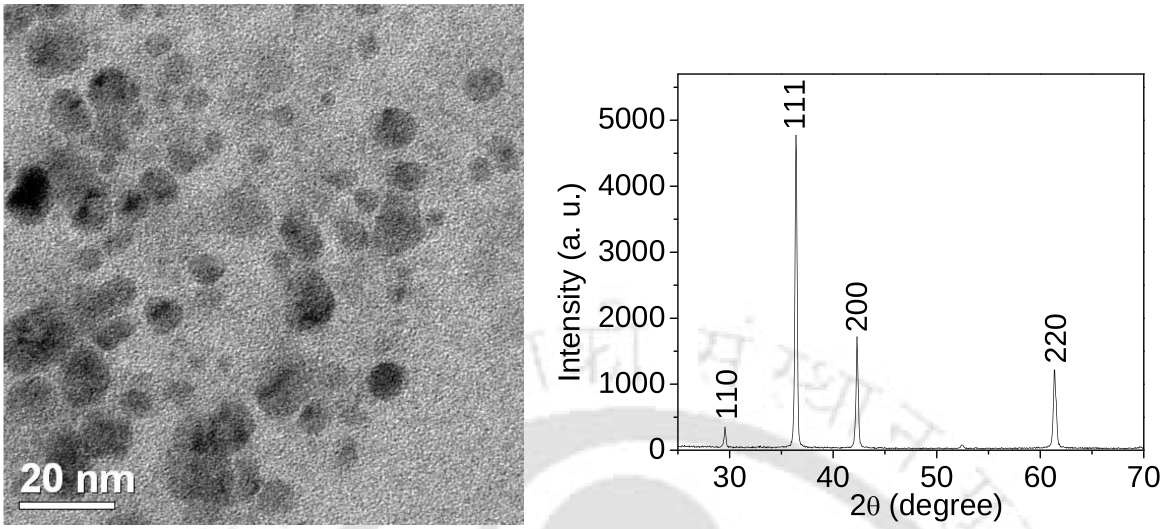


Figure 1. TEM Image and Powder XRD Pattern of Cu_2O Nanoparticles after First Cycle.

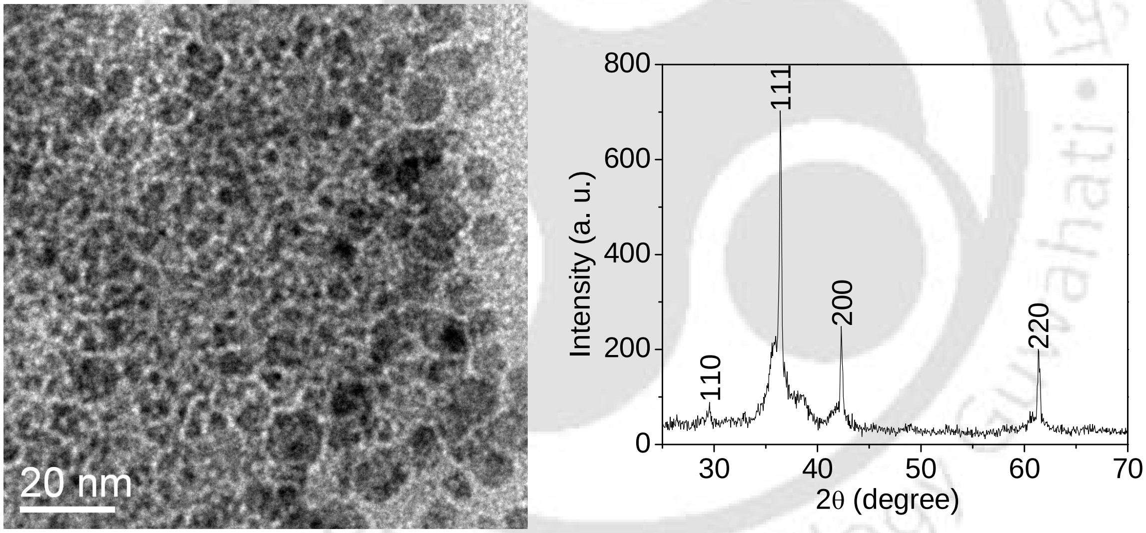


Figure 2. TEM Image and Powder XRD Pattern of Cu_2O Nanoparticles after Fifth Cycle.

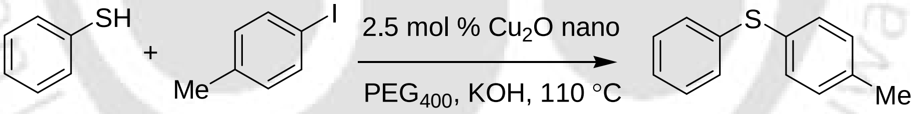
In these reactions, CuI undergoes reaction with KOH in PEG to give spherical Cu_2O nanoparticles in 100 % conversion and selectivity that catalyzes the reaction (Eq. 1).[7] PEG facilitates the formation and stabilization of nanoparticles. The sizes 7-10 nm of the Cu_2O nanoparticles were determined by transmission electron microscopy (TEM) (Figure 1-2) and their identities were established using the powder X-ray diffraction analysis (Figure 1-2).

These *in situ* formed PEG stabilized dispersed Cu_2O nanoparticles catalyze the reaction via oxidative addition followed by reductive elimination process as described in chapter I of the thesis.

$$\text{CuI} \xrightarrow[\text{- KI}]{\text{+ KOH}} \text{Cu(OH)} \xrightarrow{-{}^{1}/_{2}\ H_2O} -{}^{1}/_{2}\ \text{Cu}_2\text{O nanoparticles} \qquad \text{Eq. 1}$$

The Cu_2O nanoparticles can be recovered and recycled without loss of activity. After completion of the reaction of thiophenol with 1-iodo-4-methylbenzene, the product was extracted using Et_2O and the residue having Cu_2O nanparticles and PEG_{400} was reused for the fresh reaction of thiophenol with 1-iodo-4-methylbenzene. This process was repeated for five runs and the results are presented in table 3. As above, the reactions proceeded well to afford the *C*-*S* cross-coupled product in >90 % yield. The TEM micrograph and powder X-ray diffraction analysis of the Cu_2O nanoparticles recovered from the fifth run were identical to that of the first run which clearly suggests that the shape and size of the nanoparticles remain intact during the recyclability (Figure 1-2). Thus, the catalyst and PEG are reusable without loss of activity and selectivity.

Table 3. Recycling of the Cu_2O Nanoparticles[a]



Run	1	2	3	4	5
Product (%)	91	90[b]	90[b]	92[b]	90[b]

[a] Thiophenol (5 mmol), 1-iodo-4-methylbenzene (5.5 mmol), CuI (5 mol %) and KOH (7.5 mmol) were stirred at 110 °C in PEG_{400} (1 g) under nitrogen atmosphere.

[b] Recovered Cu_2O nanoparticles used.

In summary, we have developed a one pot procedure for the formation and catalysis of Cu_2O nanoparticles for the cross-coupling reactions of thiols with aryl iodides in PEG_{400} in the absence of additional chelating ligand. The significant advantages of this procedure are simplicity of the operation and compatibility with the variety of substituents, high yields and recyclability of the catalyst.

Experimental Section

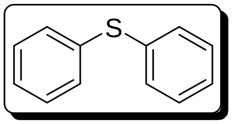
General. CuI (98 %), thiols, iodobenzene (98 %) and 1-bromo-4-nitrobenzene (99 %) were purchased from Sigma-Aldrich. PEG and KOH were purchased from Merck. All reagents were used as received. 2-Methoxy-, 4-bromo-, 4-methyl-, 4-methoxy-, 2,4-dimethyl-, naphthyl- and 4-aminoaryl iodides were prepared according to the literature.[8] Cu_2O nanoparticles were characterized using JEOL JEM 2100 transmission electron microscopy operating at 200 kv and Bruker D8 advance X-ray diffractometer with a Cu-Kα source in the 2θ range of 10 to 70. Samples for TEM analyses were prepared on carbon coated 300 mesh Cu grids. A drop of the reaction mixture was dispersed in 2-propanol (1 mL) then loaded on Cu grid and dried at room temperature in air. The NMR (400 MHz for ^1H and 100 MHz for ^{13}C) spectra of the cross-coupled products were analyzed using DRX 400 Varian spectrometer using $CDCl_3$ as solvent and Me_4Si as internal standard. Melting points were determined using Buchi B-540 melting point apparatus and were uncorrected. Elemental analysis of the cross-coupled products were carried out using Perkin Elmer-2400 CHNS analyzer.

General Procedure for *C-S* Cross-Coupling Reactions

Aryl iodide (1.1 mmol), thiol (1 mmol) and CuI (5 mol %) were stirred at 110 ^oC in the presence of KOH (1.5 mmol) in PEG_{400} (1 g) under N_2 atmosphere. Progress of the reaction was monitored by TLC. After completion, the reaction flask was cooled to room temperature and the reaction mixture was treated with ethyl acetate (10 mL). The resulting solution was washed with water (3 x 2 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was purified on a short pad of silica gel using hexane and ethyl acetate as eluent.

Recyclability Experiment

1-Iodo-4-methylbenzene (1.30 g, 5.5 mmol), thiophenol (0.550 g, 5 mmol) and CuI (0.047 g, 5 mol %) were stirred at 110 °C in the presence of KOH (0.420 g, 7.5 mmol) in PEG_{400} (5 g) under N_2 atmosphere. After completion, the reaction mixture was extracted with Et_2O (3 x 10 mL) and the residue having Cu_2O nanoparticles and PEG_{400} was reused for the fresh reaction of thiophenol with aryl iodide in the presence of KOH.



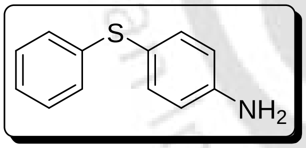
1,1′-Thiobis-benzene (Table 1, entry 1).[4k] Thiophenol (110 mg, 1 mmol), iodobenzene (223 mg, 1.1 mmol), KOH (84 mg, 1.5 mmol), CuI (9.5 mg, 5 mol %) and PEG_{400} (1 g) were subjected to the reaction conditions described in the general procedure for 12 h to afford the title compound (180 mg, 97 %) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.24 (m, 10H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 136.2, 131.4, 129.6, 127.4.

FT-IR (neat): ν 1580, 1475, 1439, 1023 cm^{-1}.

Anal. Calcd for $C_{12}H_{10}S$: C, 77.37; H, 5.41; S, 17.21. Found: C, 77.41; H, 5.39; S, 17.22.



4-(Phenylthio)benzenamine (Table 1, entry 2).[6] Thiophenol (110 mg, 1 mmol), 4-iodo-benzenamine (240 mg, 1.1 mmol), KOH (84 mg, 1.5 mmol), CuI (9.5 mg, 5 mol %) and PEG_{400} (1 g) were subjected to the reaction conditions shown in the general procedure for 15 h to give the title compound (162 mg, 81 %) as colorless solid.

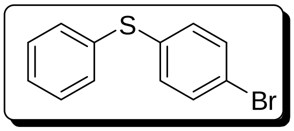
Mp: 88-89 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (d, J = 8.4 Hz, 2H), 7.21-7.17 (m, 2H), 7.11-7.06 (m, 3H), 6.67 (d, J = 8.8 Hz, 2H), 3.74 (br s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.1, 139.7, 136.1, 128.7, 127.3, 125.2, 121.5, 116.0.

FT-IR (neat): ν 3455, 3350, 3321, 1610, 1596, 1489, 1468, 1441, 1290, 1177, 1022 cm^{-1}.

Anal. Calcd for $C_{12}H_{11}NS$: C, 71.60; H, 5.51; N, 6.96; S, 15.93. Found: C, 71.63; H, 5.52; N, 6.98; S, 15.95.



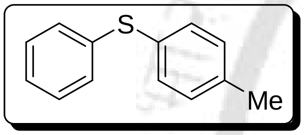
1-Bromo-4-(phenylthio)benzene (Table 1, entry 3).[4k] Thiophenol (110 mg, 1 mmol), 1-bromo-4-iodobenzene (309 mg, 1.1 mmol), KOH (84 mg, 1.5 mmol), CuI (9.5 mg, 5 mol %) and PEG_{400} (1 g) were subjected to the reaction conditions reported in the general procedure for 12 h to provide the title compound (225 mg, 85 %) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (dd, *J* = 6.8, 4.8 Hz, 2H), 7.36 -7.25 (m, 5H), 7.18 -7.16 (dd, *J* = 6.8, 4.8 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 135.9, 132.7, 132.5, 132.0, 129.8, 128.0.

FT-IR (neat): ν 3060, 1591, 1483, 1096, 1014 cm^{-1}.

Anal. Calcd for $C_{12}H_9BrS$: C, 54.35; H, 3.42; S, 12.09. Found: C, 54.43; H, 3.44; S, 12.11.



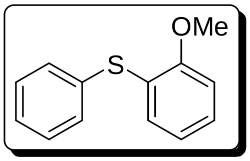
1-Methyl-4-(phenylthio)benzene (Table 1, entry 4).[4k] Thiophenol (110 mg, 1 mmol), 1-iodo-4-methylbenzene (238 mg, 1.1 mmol), KOH (84 mg, 1.5 mmol), CuI (9.5 mg, 5 mol %) and PEG_{400} (1 g) were subjected to the reaction conditions described in the general procedure for 14 h to give the title compound (182 mg, 91 %) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.25 (m, 6H), 7.20-7.12 (m, 3H), 2.31(s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.8, 137.3, 132.4, 131.4, 130.2, 129.9, 129.2, 126.5, 21.3.

FT-IR (neat): ν 3052, 2933, 1589, 1491, 1480, 1442, 1091, 1020 cm^{-1}.

Anal. Calcd for $C_{13}H_{12}S$: C, 77.95; H, 6.04; S, 16.01. Found: C, 77.94; H, 6.05; S, 16.05.



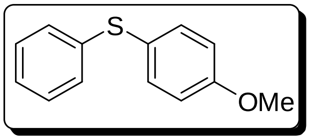
1-Methoxy-2-(phenylthio)benzene (Table 1, entry 5).[6] Thiophenol (110 mg, 1 mmol), 1-iodo-2-methoxybenzene (257 mg, 1.1 mmol), KOH (84 mg, 1.5 mmol), CuI (9.5 mg, 5 mol %) and PEG_{400} (1 g) were subjected to the reaction conditions shown in the general procedure for 17 h to afford the title compound (177 mg, 82 %) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.20 (m, 6H), 7.06 (d, *J* = 8.8 Hz, 1H), 6.90–6.82 (m, 2H), 3.86 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.5, 134.7, 131.7, 131.6, 129.3, 128.5, 127.0, 124.3, 121.4, 111.1, 56.1.

FT-IR (neat): ν 3080, 3048, 2932, 2920, 2813, 1595, 1496, 1428, 1015 cm^{-1}.

Anal. Calcd for $C_{13}H_{12}OS$: C, 72.19; H, 5.59; S, 14.82. Found: C, 72.24; H, 5.61; S, 14.85.



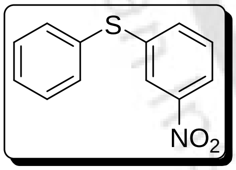
1-Methoxy-4-(phenylthio)benzene (Table 1, entry 6).[4k] Thiophenol (110 mg, 1 mmol), 1-iodo-2-methoxybenzene (257 mg, 1.1 mmol), KOH (84 mg, 1.5 mmol), CuI (9.5 mg, 5 mol %) and PEG_{400} (1 g) were subjected to the reaction conditions reported in the general procedure for 15 h to provide the title compound (183 mg, 85 %) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.37 (dd, *J* = 8.8, 2.8 Hz, 2H), 7.23-7.12 (m, 5H), 6.88-6.85 (dd, *J* = 8.8, 2.4 Hz, 2H), 3.78 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9, 138.7, 135.5, 129.1, 128.3, 125.9, 124.4, 115.1, 55.5.

FT-IR (neat): ν 3085, 3042, 2942, 2919, 2802, 1600, 1485, 1430, 1020 cm^{-1}.

Anal. Calcd for $C_{13}H_{12}OS$: C, 72.19; H, 5.59; S, 14.82. Found: C, 72.26; H, 5.57; S, 14.86.



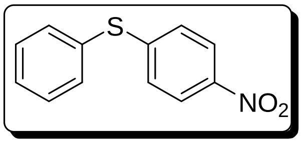
1-Nitro-3-(phenylthio)benzene (Table 1, entry 7).[5b] Thiophenol (110 mg, 1 mmol), 1-iodo-3-nitrobenzene (272 mg, 1.1 mmol), KOH (84 mg, 1.5 mmol), CuI (9.5 mg, 5 mol %) and PEG_{400} (1 g) were subjected to the reaction conditions described in the general procedure for 15 h to give the title compound (196 mg, 85 %) as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00-7.96 (m, 2H), 7.47-7.36 (m, 7H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.8, 140.7, 134.4, 133.6, 132.2, 130.0, 129.8, 129.1, 123.3, 121.1.

FT-IR (neat): ν 3066, 1660, 1622, 1530, 1477, 1334, 1126, 1075, 1034 cm^{-1}.

Anal. Calcd for $C_{12}H_9NO_2S$: C, 62.32; H, 3.92; N, 6.06; S, 13.86. Found: C, 62.35; H, 3.93; N, 6.10; S, 13.90.



1-Nitro-4-(phenylthio)benzene (Table 1, entry 8).[4k] Thiophenol (110 mg, 1 mmol), 1-bromo-4-nitrobenzene (222 mg, 1.1 mmol), KOH (84 mg, 1.5 mmol), CuI (9.5 mg, 5 mol %) and PEG_{400} (1 g) were subjected to the reaction conditions shown in the general procedure for 12 h to afford the title compound (203 mg, 88 %) as yellow solid.

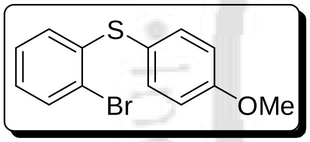
Mp: 54 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (dd, *J* = 8.8, 2.0 Hz, 2H), 7.55-7.53 (m, 2H), 7.47-7.45 (m, 3H), 7.16 (d, *J* = 8.4 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.7, 134.9, 130.5, 130.2, 129.8, 126.8, 124.2.

FT-IR (KBr): ν 3060, 1572, 1511, 1476, 1442, 1333, 1081, 1025 cm^{-1}.

Anal. Calcd for $C_{12}H_9NO_2S$: C, 62.32; H, 3.92; N, 6.06; S, 13.86. Found: C, 62.37; H, 3.90; N, 6.08; S, 13.88.



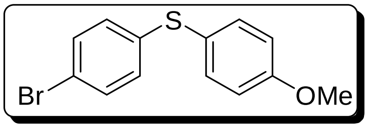
1-Bromo-2-[(4-methoxyphenyl)thio]benzene (Table 2, entry 1).[9a] 2-Bromobenzenethiol (189 mg, 1 mmol), 1-iodo-4-methoxybenzene (257 mg, 1.1 mmol), KOH (84 mg, 1.5 mmol), CuI (9.5 mg, 5 mol %) and PEG_{400} (1 g) were subjected to the reaction conditions reported in the general procedure for 15 h to give the title compound (247 mg, 84 %) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55-7.44 (m, 3H), 7.09-7.05 (m, 1H), 6.96-6.91 (m, 3H), 6.65 (dd, *J* = 8.0, 1.6 Hz, 1H), 3.83 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8, 141.0, 137.2, 132.9, 127.8, 127.5, 126.3, 122.2, 120.9, 115.6, 55.6.

FT-IR (neat): ν 3066, 3022, 2955, 2923, 2804, 1600, 1488, 1090, 1015 cm^{-1}.

Anal. Calcd for $C_{13}H_{11}BrOS$: C, 52.89; H, 3.76; S, 10.86. Found: C, 52.94; H, 3.75; S, 10.90.



1-Bromo-4-[(4-methoxyphenyl)thio]benzene (Table 2, entry

2). 4-Bromobenzenethiol (189 mg, 1 mmol), 1-iodo-4-methoxybenzene (257 mg, 1.1 mmol), KOH (84 mg, 1.5 mmol), CuI (9.5 mg, 5 mol %) and PEG_{400} (1 g) were subjected to the reaction conditions shown in the general procedure for 10 h to give the title compound (250 mg, 85 %) as colorless solid.

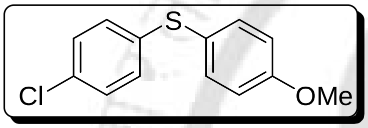
Mp: 66-67 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, *J* = 8.8 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 6.99 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 3.80 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.3, 138.4, 135.8, 132.1, 129.6, 123.6, 119.5, 115.3, 55.6.

FT-IR (neat): ν 3075, 3028, 2964, 2800, 1595, 1480, 1095, 1023 cm^{-1}.

Anal. Calcd for $C_{13}H_{11}BrOS$: C, 52.89; H, 3.76; S, 10.86. Found: C, 52.92; H, 3.78; S, 10.89.



1-Chloro-4-[(4-methoxyphenyl)thio]benzene (Table 2, entry 3). 4-Chlorobenzenethiol (144 mg, 1 mmol), 1-iodo-4-methoxybenzene (257 mg, 1.1 mmol), KOH (84 mg, 1.5 mmol), CuI (9.5 mg, 5 mol %) and PEG_{400} (1 g) were subjected to the reaction conditions described in the general procedure for 8 h to provide the title compound (230 mg, 92 %) as colorless solid.

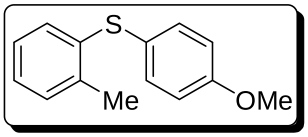
Mp: 60 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, *J* = 8.8 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.0 Hz, 2H), 3.80 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 160.3, 137.6, 135.7, 131.8, 129.5, 129.2, 123.9, 115.3, 55.6.

FT-IR (neat): ν 3080, 3025, 2960, 2810, 1590, 1475, 1090, 1029 cm^{-1}.

Anal. Calcd for $C_{13}H_{11}ClOS$: C, 62.27; H, 4.42; S, 12.79. Found: C, 62.33; H, 4.45; S, 12.85.



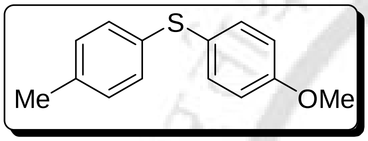
1-[(4-Methoxyphenyl)thio]-2-methyl-benzene (Table 2, entry 4). 2-Methylbenzenethiol (124 mg, 1 mmol), 1-iodo-4-methoxybenzene (257 mg, 1.1 mmol), KOH (84 mg, 1.5 mmol), CuI (9.5 mg, 5 mol %) and PEG_{400} (1 g) were subjected to the reaction conditions described in the general procedure for 15 h to give the title compound (190 mg, 83 %) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (d, *J* = 9.2 Hz, 2H), 7.18 (d, *J* = 7.2 Hz, 1H), 7.11-7.03 (m, 2H), 6.97-6.95 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.90 (d, *J* = 8.0 Hz, 2H), 3.82 (s, 3H), 2.38 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 137.1, 134.8, 130.4, 129.3, 129.2, 126.7, 126.3, 124.6, 115.2, 55.5, 20.5.

FT-IR (neat): ν 3069, 3035, 2930, 2910, 2825, 1599, 1475, 1440, 1085, 1015 cm^{-1}.

Anal. Calcd for $C_{14}H_{14}OS$: C, 73.01; H, 6.13; S, 13.92. Found: C, 73.07; H, 6.12; S, 13.98.



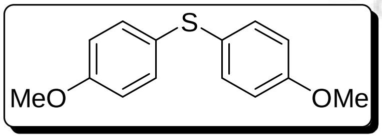
1-Methyl-4-[(4-methoxyphenyl)thio]benzene (Table 2, entry 5).[4l] 4-Methylbenzenethiol (124 mg, 1 mmol), 1-iodo-4-methoxybenzene (257 mg, 1.1 mmol), KOH (84 mg, 1.5 mmol), CuI (9.5 mg, 5 mol %) and PEG_{400} (1 g) were subjected to the reaction conditions reported in the general procedure for 14 h to provide the title compound (207 mg, 90 %) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.33 (d, *J* = 8.8 Hz, 2H), 7.12-7.10 (d, *J* = 8 Hz, 2H), 7.06-7.04(d, *J* = 8.4 Hz, 2H), 6.86-6.84 (d, *J* = 8 Hz, 2H), 3.79 (s, 3H), 2.28 (s, 3H).

^{13}C NMR(100 MHz, $CDCl_3$): δ 159.6, 136.2, 134.5, 129.9, 127.5, 125.7, 115.0, 55.5, 21.1.

FT-IR (neat): ν 3078, 3044, 2925, 2914, 2812, 1592, 1485, 1438, 1089, 1014 cm^{-1}.

Anal. Calcd for $C_{14}H_{14}OS$: C, 73.01; H, 6.13; S, 13.92. Found: C, 73.08; H, 6.16; S, 13.97.



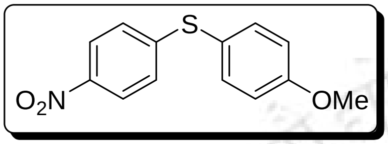
1,1′-Thiobis[4-methoxy-benzene] (Table 2, entry 6).[3e] 4-Methoxybenzenethiol (140 mg, 1 mmol), 1-iodo-4-methoxybenzene (257 mg, 1.1 mmol), KOH (84 mg, 1.5 mmol), CuI (9.5 mg, 5 mol %) and PEG_{400} (1 g) were subjected to the reaction conditions described in the general procedure for 8 h to give the title compound (211 mg, 86 %) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (d, *J* = 8.8 Hz, 4H), 6.84 (d, *J* = 8.8 Hz, 4H), 3.79 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2, 132.9, 127.6, 114.9, 55.5.

FT-IR (neat): ν 3081, 3035, 2940, 2912, 2865, 1599 cm^{-1}.

Anal. Calcd for $C_{14}H_{14}O_2S$: C, 68.26; H, 5.73; S, 13.02. Found: C, 68.30; H, 5.76; S, 13.05.



1-Nitro-4-[(4-methoxyphenyl)thio]benzene (Table 2, entry 7).[4k] 4-Nitrobenzenethiol (155 mg, 1 mmol), 1-iodo-4-methoxybenzene (257 mg, 1.1 mmol), KOH (84 mg, 1.5 mmol), CuI (9.5 mg, 5 mol %) and PEG_{400} (1 g) were subjected to the reaction conditions described in the general procedure for 16 h to give the title compound (187 mg, 72 %) as yellow solid

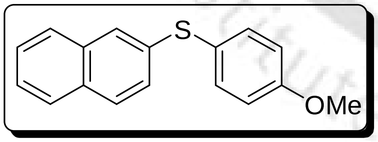
Mp: 61-62 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (dd, *J* = 8.8, 2.8 Hz, 2H), 7.41 (dd, *J* = 6.8, 2.0 Hz, 2H), 7.01 (dd, *J* = 6.4, 4.8 Hz, 2H), 6.93 (dd, *J* = 9.2, 7.2 Hz, 2H), 3.79 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 161.3, 150.2, 137.3, 125.7, 124.1, 120.3, 115.8, 55.6.

FT-IR (neat): ν 3075, 3033, 2940, 2922, 2810, 1589, 1480, 1442, 1090, 1032 cm^{-1}.

Anal. Calcd for $C_{13}H_{11}NO_3S$: C, 59.73; H, 4.24; N, 5.36; S, 12.27. Found: C, 59.79; H, 4.22; N, 5.40; S, 12.32.



2-[(4-Methoxyphenyl)thio]naphthalene (Table 2, entry 8).[9b] 2-Naphthalenethiol (160 mg, 1 mmol), 1-iodo-4-methoxybenzene (257 mg, 1.1 mmol), KOH (84 mg, 1.5 mmol), CuI (9.5 mg, 5 mol %) and PEG_{400} (1 g) were subjected to the reaction conditions shown in the general procedure for 12 h to provide the title compound (191 mg, 73 %) as colorless solid.

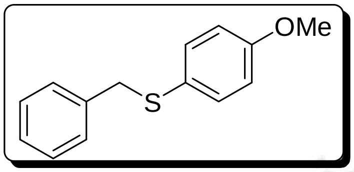
Mp: 67-69 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77-7.65 (m, 3H), 7.59 (s, 1H), 7.47-7.38 (m, 4H), 7.30-7.25 (m, 1H), 6.92 (d, *J* = 8.8 Hz, 2H), 3.83 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 160.1, 136.3, 135.5, 134.0, 132.0, 128.8, 127.9, 127.4, 126.9, 126.7, 125.9, 124.6, 115.3, 55.60.

FT-IR (neat): ν 3077, 3045, 2935, 2920, 2808, 1595, 1485, 1430, 1020 cm^{-1}.

Anal. Calcd for $C_{17}H_{14}OS$: C, 76.66; H, 5.30; S, 12.04. Found: C, 76.70; H, 5.28; S, 12.09.



1-Methoxy-4-[(phenylmethyl)thio]benzene (Table 2, entry 9).[9c] Benzylthiol (124 mg, 1 mmol), 1-iodo-4-methoxybenzene (257 mg, 1.1 mmol), KOH (84 mg, 1.5 mmol), CuI (9.5 mg, 5 mol %) and PEG$_{400}$ (1 g) were subjected to the reaction conditions reported in the general procedure for 14 h to give the title compound (140 mg, 70 %) as colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.26-7.18 (m, 7H), 6.80-6.78 (dd, *J* = 2.4, 6.8 Hz, 2H), 3.98 (s, 2H), 3.79 (s, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 159.4, 138.3, 134.3, 129.1, 128.5, 127.2, 126.2, 114.6, 55.5, 41.4.

FT-IR (neat): ν 3440, 1600, 1510, 1480, 1435, 1304, 1255, 1180, 1035 cm^{-1}.

Anal. Calcd for $C_{14}H_{14}OS$: C, 73.01; H, 6.13; S, 13.92. Found: C, 73.08; H, 6.16; S, 13.95.

2.6 References

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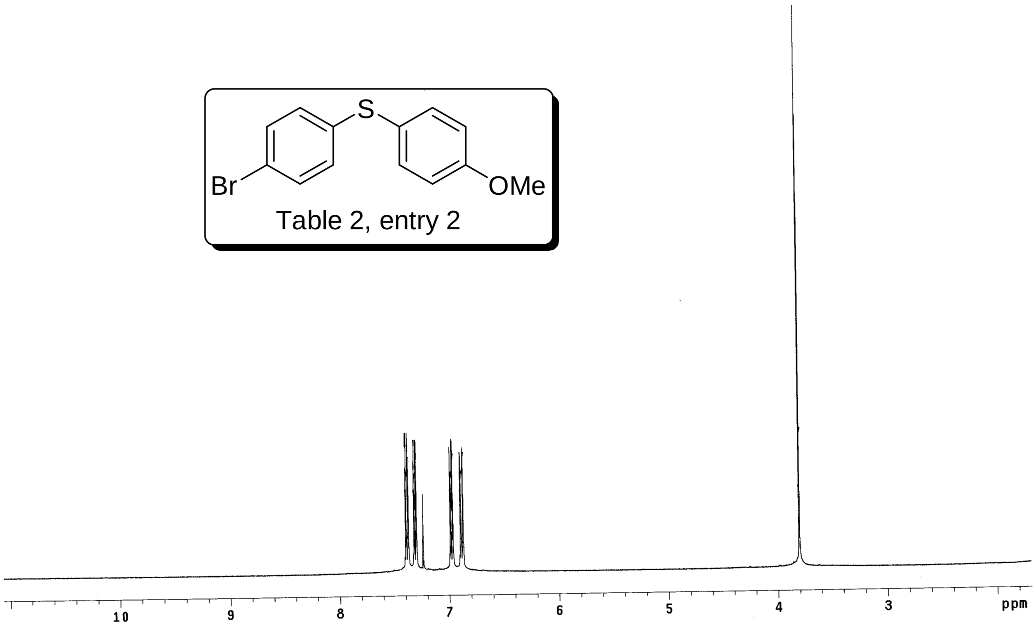
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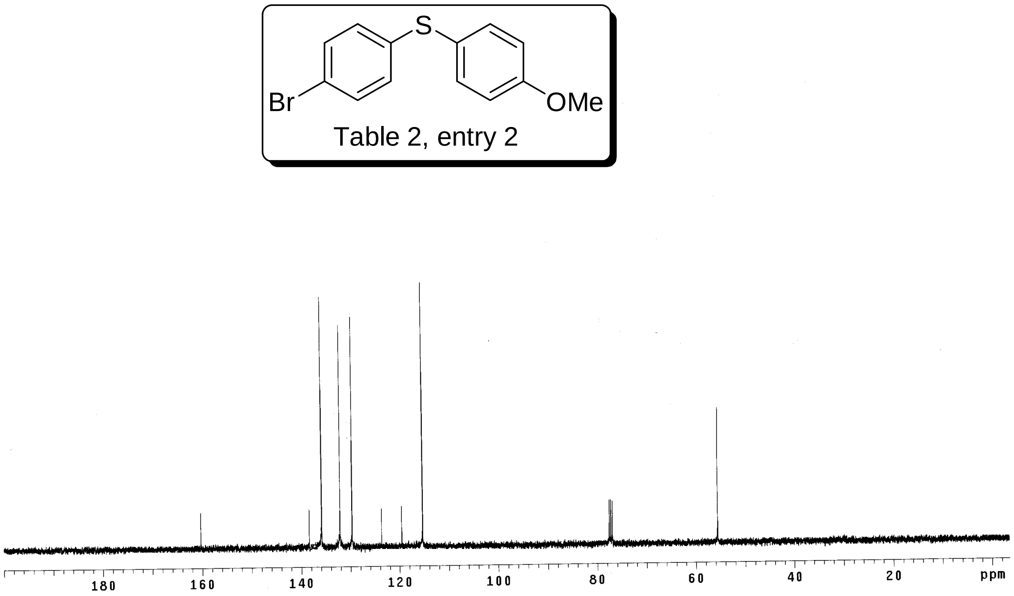
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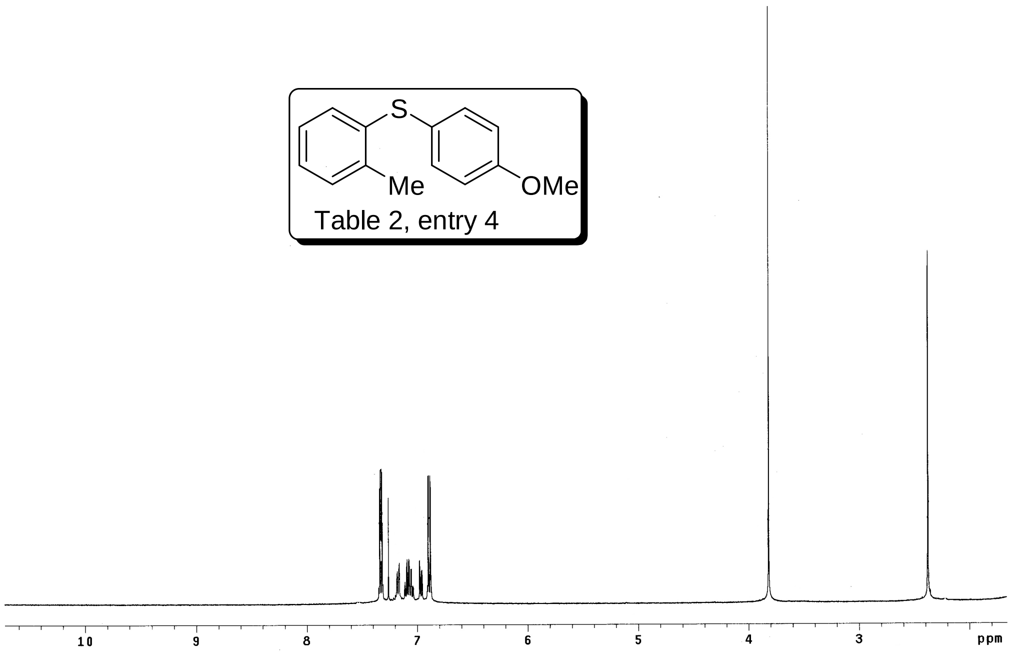
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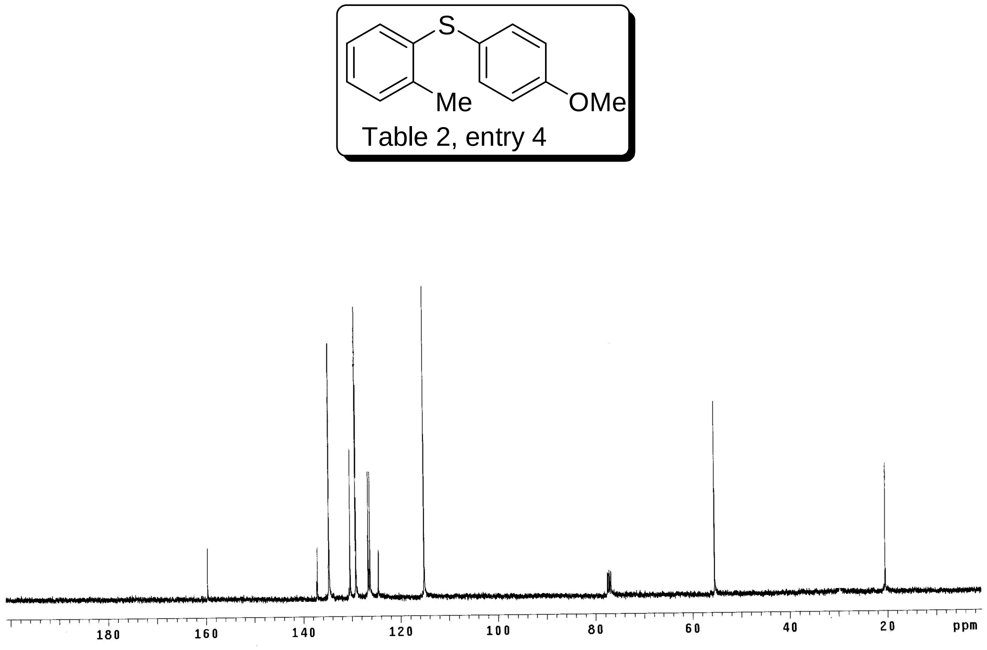
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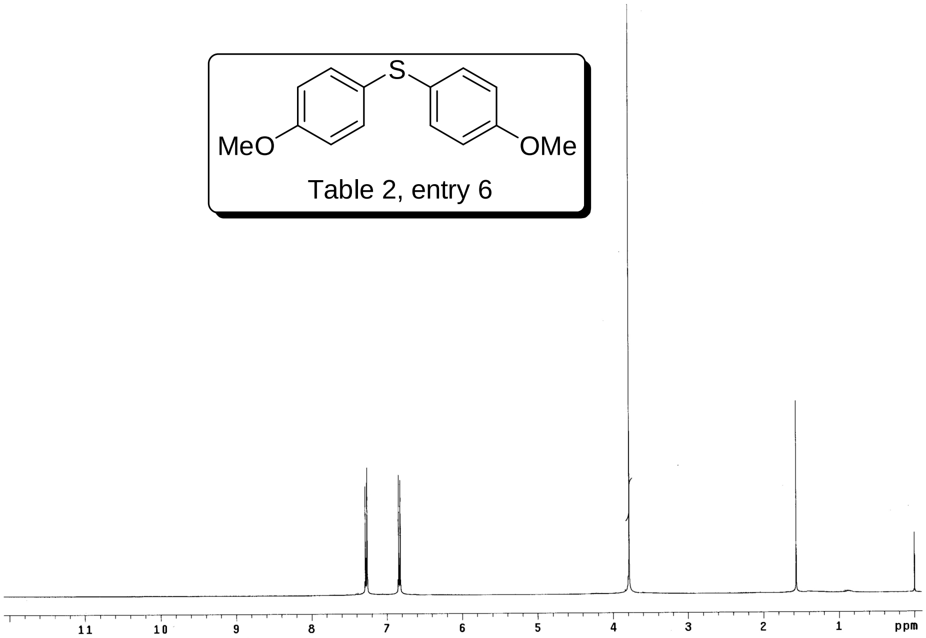
ppm


S
MeO
OMe
Table 2, entry 6
11
10
9
8
7
6
5
4
3
2
1
ppm

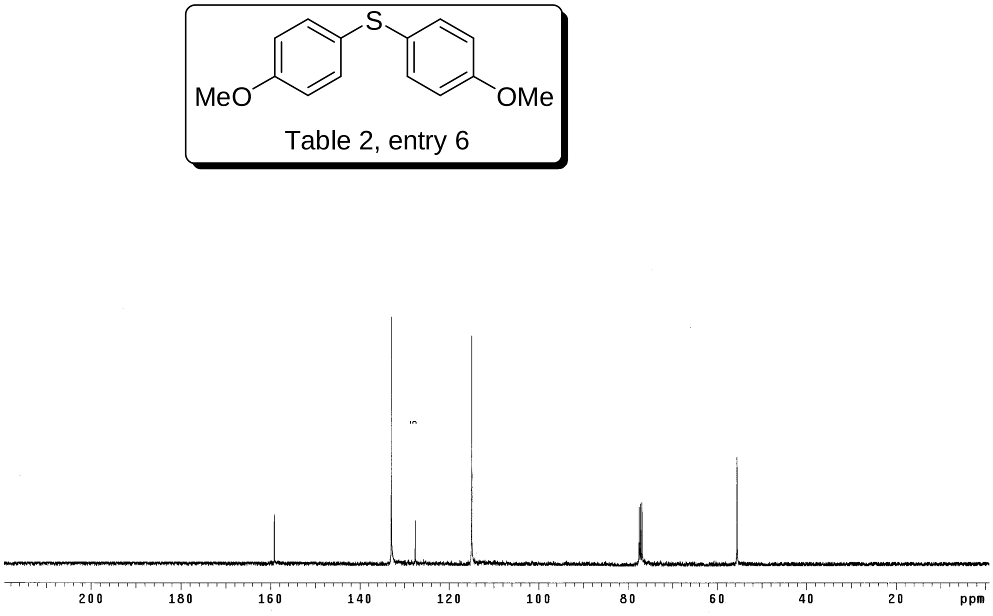

S
MeO
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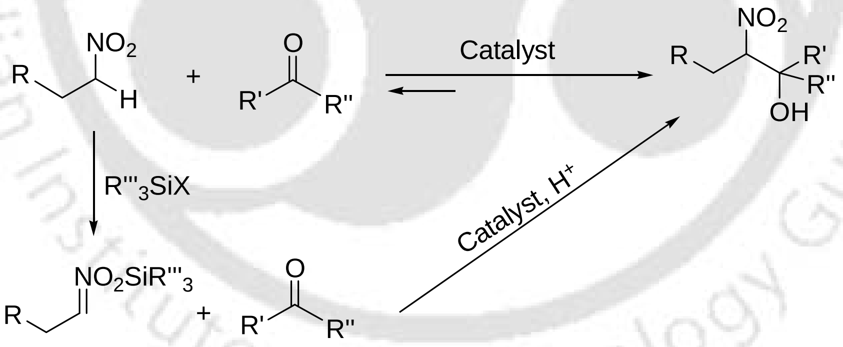
Table 2, entry 6
200
180
160
140
120
100
80
60
40
20
ppm

Chapter I11

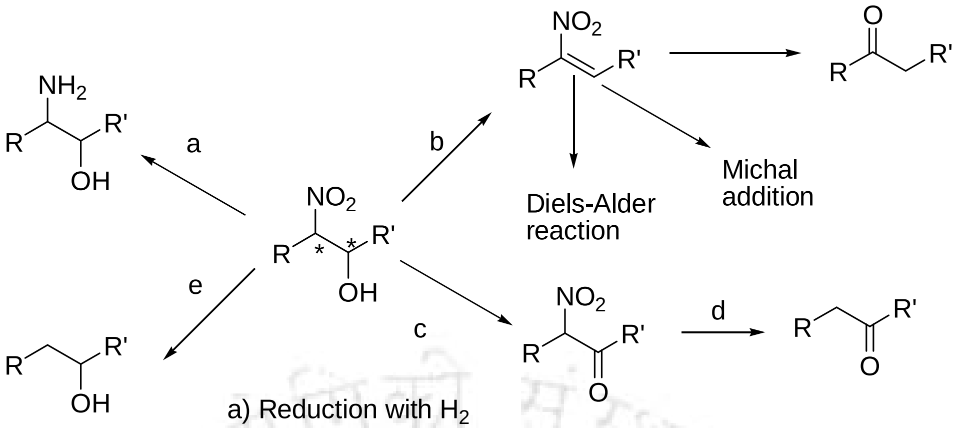
Chiral Binuclear Copper(II) Catalyzed Asymmetric Nitroaldol Reaction

Carbon-carbon bond formation is the essence of organic synthesis. The nitroaldol (Henry) reaction, an aldol type reaction, represents one of the classical *C-C* bond-forming processes. The reaction involves, the coupling of a reactive nitronate species (nucleophile) with a carbonyl electrophile.[1] The nucleophile nitronate can be generated *in situ* as part of the catalytic cycle through the action of a suitable catalyst or alternatively, preformed nitronates, particularly silyl nitronate species, can be used (Scheme 1).[2] The diversity of the transformation of the adducts, such as reduction to amines,[3] Nef reaction to form carbonyl compounds,[4] dehydration to nitroalkenes,[5] or nucleophilic displacement of the nitro group by various carbon- and heteroatom –centered nucleophiles,[6] affords numerous applications for this reaction in organic chemistry for the synthesis of natural products and pharmaceuticals (Scheme 2-3).[7]



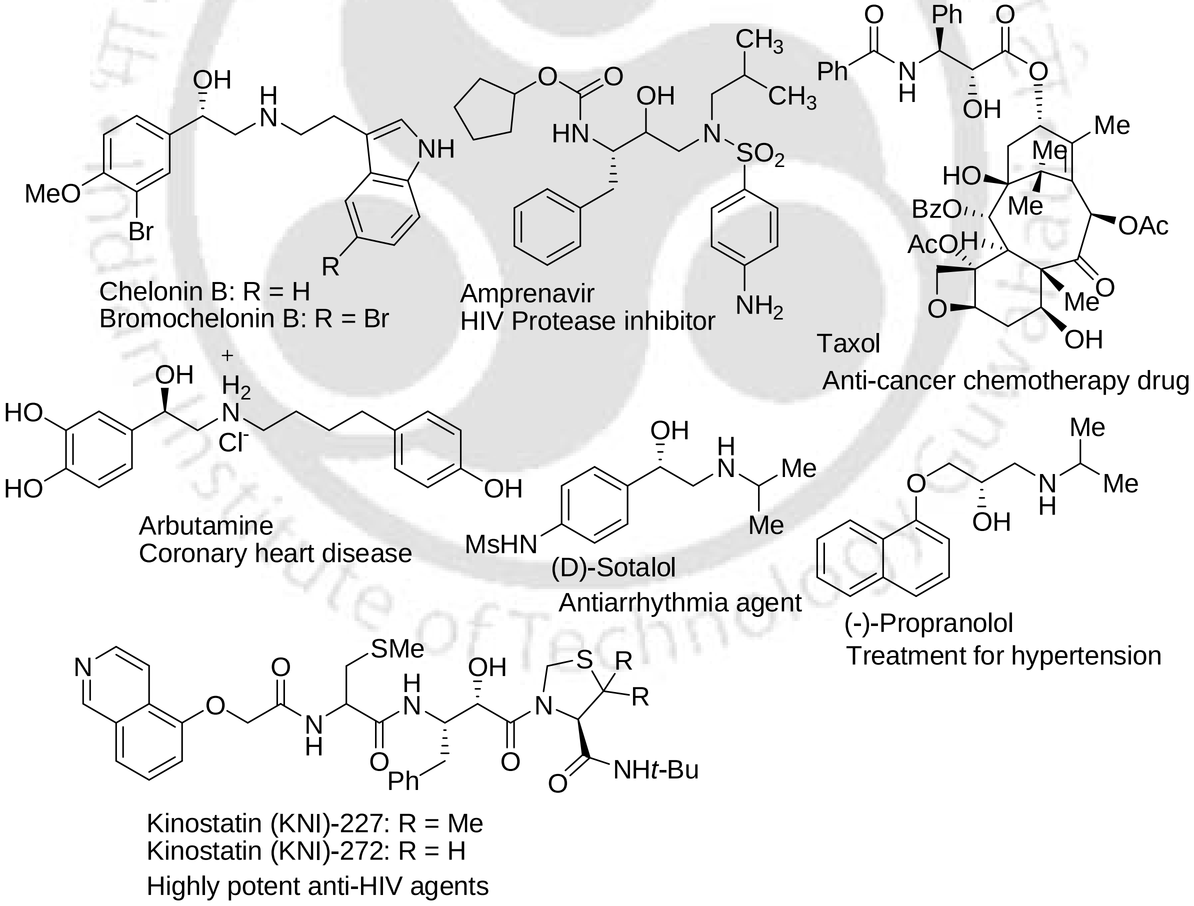
Scheme 1

The catalytic methods studied for the enantioselective nitroaldol reaction can be broadly divided into two parts: i) asymmetric nitroaldol reaction using unmodified nitroalkanes and ii) asymmetric nitroaldol reaction with modified nitroalkanes.



a) Reduction with H_2
b) Dehydration with DCC
c) Oxidation with PCC
d) Nef reaction with $TiCl_3$
e) Denitration with $Bu_3SnH/AIBN$

Scheme 2



Scheme 3. Natural Products and Drugs

3.1 Asymmetric Nitroaldol Reaction using Unmodified Nitroalkanes

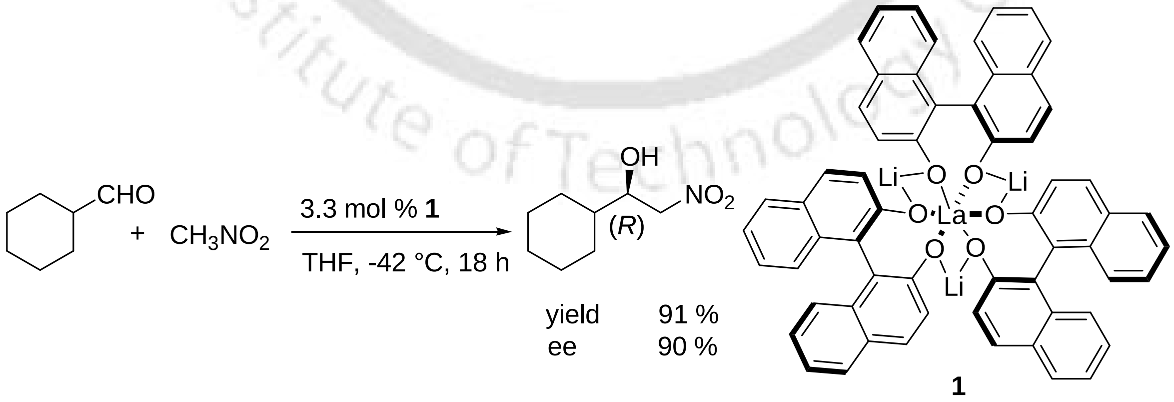
Methods that use unmodified nitroalkanes and acceptor carbonyls (aldehydes or ketones) to produce the product *β*–nitro alcohols in a single synthetic operation through the action of a catalytic species are preferable for obvious reasons. In these methods, nitroalkane activation by base promoted hydrogen transfer must necessarily be part of the catalytic cycle, together with the activation of the acceptor carbonyl through the coordination to an acidic centre. The breakthrough in this area came from Shibasaki's laboratory in 1992 and was based on bifunctional multimetallic catalysis.[8a] In recent years, purely organic molecules acting as catalysts and are capable of catalyzing the chemical transformation (organocatalysis), usually working in the context of a cooperative activation principle model, have also appeared. Both the approaches, metal catalysis and organocatalysis, have been successfully applied in nitroaldol reaction and very recently biocatalytic nitroaldol reaction has been developed.

3.1.1 Chiral Metal Catalysis

Methods belong to the chiral metal complex catalyzed reactions can be categorized according to the metal involved.

3.1.1.1 Chiral Rare Earth Metal Catalysts

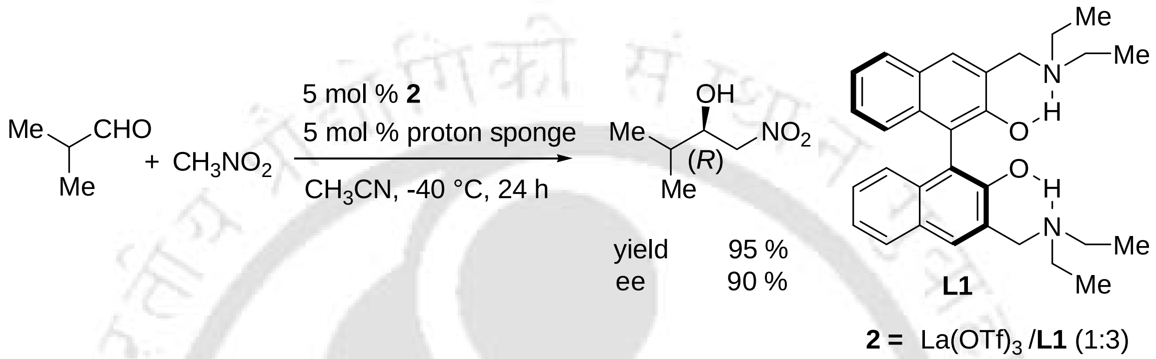
Shibasaki's group has developed the rare earth metal based asymmetric nitroaldol reaction.[8] Lanthanum alkoxide complex **1** has been shown to catalyze the reaction of nitroalkanes with aldehydes with up to 90 % ee (Scheme 4).[8a] The lanthanum and the phenoxy-Li groups act as



Scheme 4

the Lewis acid and the Brønsted base, respectively. Further refinement of the catalyst through insertion of substituent's at the 6,6′-positions of the BINOL skeleton led to an improvement in the enantio- and *syn*/*anti* selectivities.

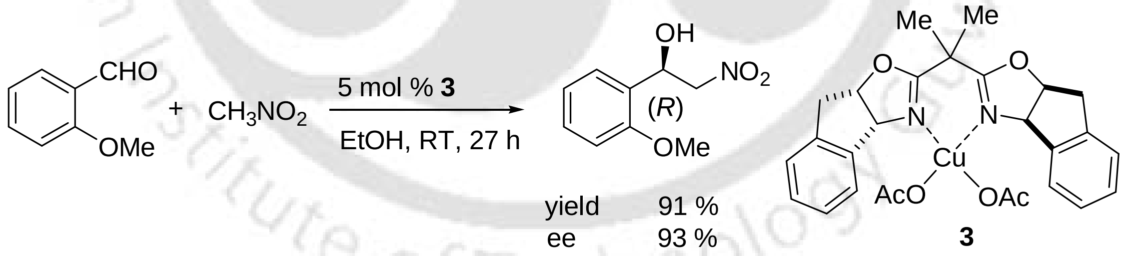
Recently, Saa and co-workers have described the lanthanum-based bifunctional catalyst **2** for nitroaldol reaction (Scheme 5).[8h] In this method aliphatic aldehydes show the best results compared to aromatic and *α,β*-unsaturated aldehydes.



Scheme 5

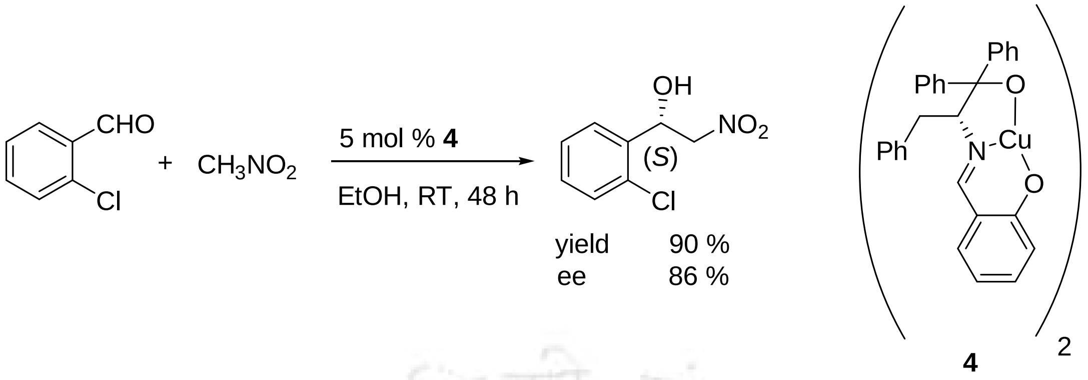
3.1.1.2 Chiral Copper Catalysts

Chiral copper catalyzed asymmetric nitroaldol reaction is an active topic.[9] Evans and co-workers have employed copper(II)-bisoxazoline **3** for the reaction of aldehydes with nitromethane at room temperature with up to 94 % ee (Scheme 6).[9e]



Scheme 6

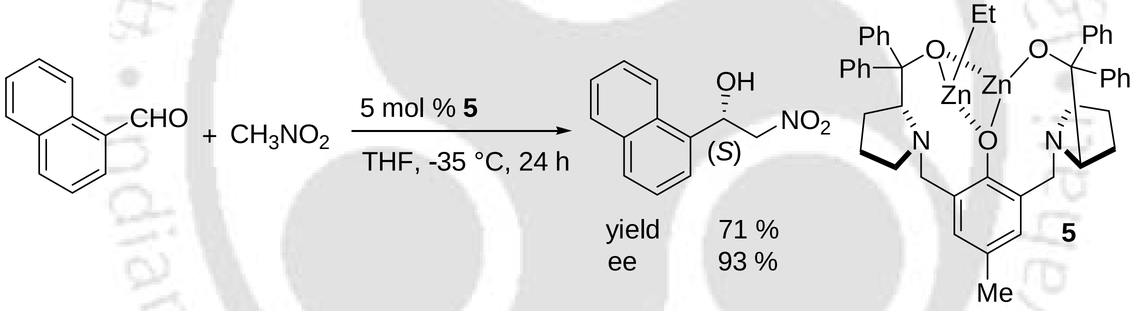
Zhou and co-workers have investigated binuclear copper(II) complex **4** for nitroaldol reaction. These reactions have been studied in the absence of either the base or additive to afford the nitroaldol products in moderate enantioselectivity (Scheme 7).[9f]



Scheme 7

3.1.1.3 Chiral Zinc Catalyst

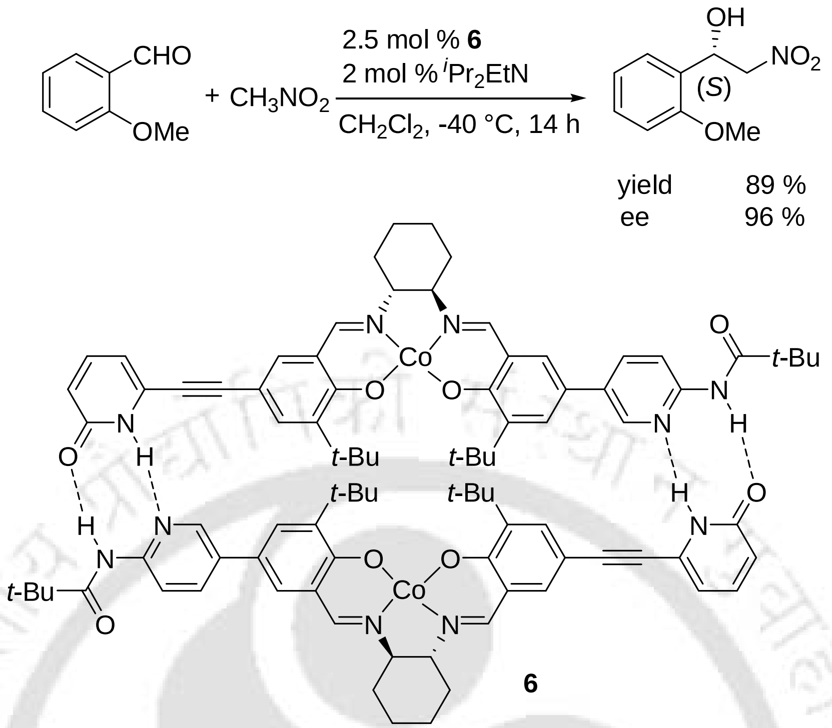
Trost and Yeh have studied the chiral dinuclear zinc complex **5** for the asymmetric nitroaldol reaction. The reaction has occurred efficiently to provide the nitroaldol product with up to 93 % ee (Scheme 8).[10]



Scheme 8

3.1.1.4 Chiral Cobalt Catalysts

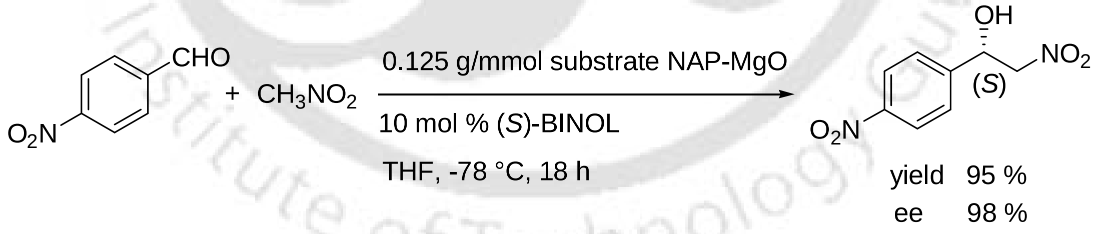
Chiral cobalt complexes are known to have considerable catalytic potential due to their Lewis acidic nature. Yamada and co-workers have developed chiral ketoamino cobalt complexes for the nitroaldol reaction.[11a] Later they have used the commercially available chiral cobalt salen complexes for nitroaldol reaction.[11b] Subsequently, Hong and co-workers have found the self-assembled chiral bimetallic cobalt(II)-salen **6** with diisopropylethylamine to catalyze the nitroaldol reaction with up to 96 % ee (Scheme 9).[11c] The self-assembly of **6** through hydrogen bonding is confirmed by X-ray structure which results in significant rate acceleration as well as high enantioselectivity of the reaction.



Scheme 9

3.1.1.5 Chiral Magnesium Catalyst

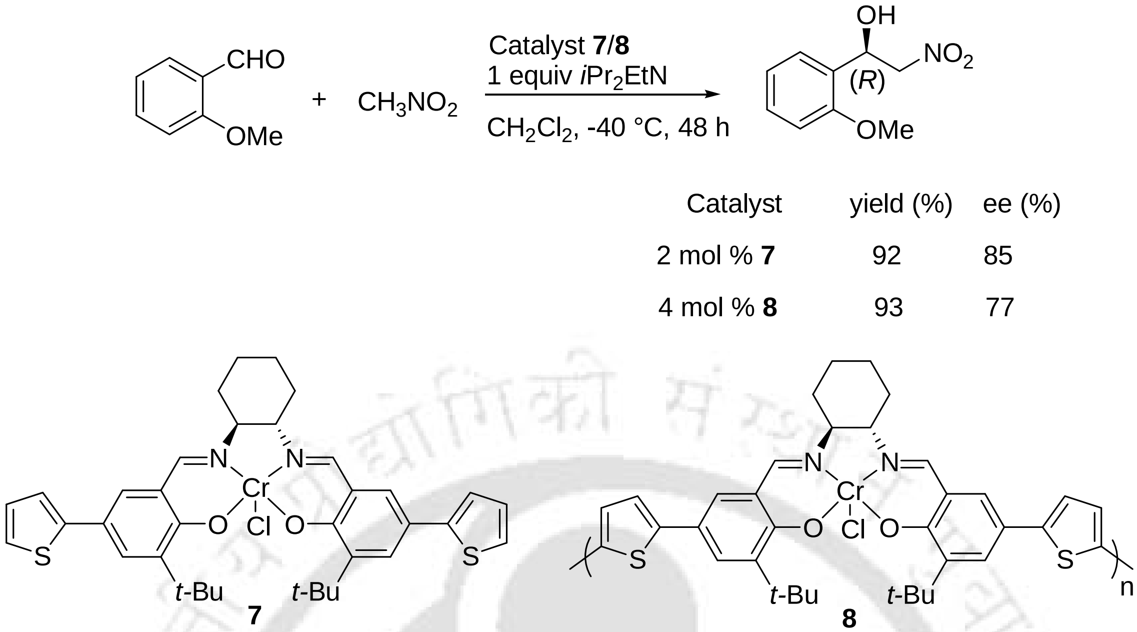
Choudary and co-workers have described the nanocrystalline MgO-BINOL as heterogeneous catalytic system for nitroaldol reaction at -78 °C in THF. Both aliphatic and aromatic aldehydes undergo reaction with up to 98 % ee (Scheme 10).[12]



Scheme 10

3.1.1.6 Chiral Chromium Catalysts

Schulz and co-workers have studied chiral chromium(III)-salen **7** in its monomeric form as a soluble catalyst for nitroaldol reaction with up to 85 % ee. Anodic polymerization of **7** led to an insoluble polymer **8** that has been successfully used as a heterogeneous catalyst with up to 77 % ee. The catalyst **8** is recyclable without loss of activity and selectivity (Scheme 11).[13]



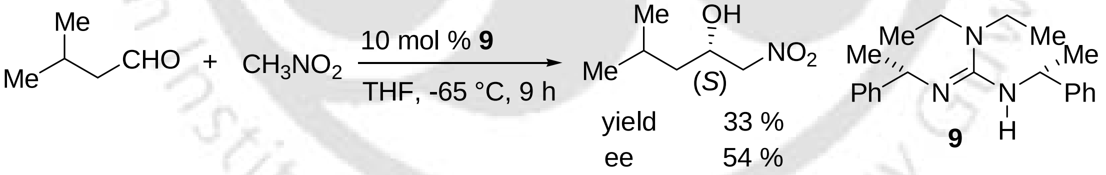
Catalyst	yield (%)	ee (%)
2 mol % **7**	92	85
4 mol % **8**	93	77

7 **8**

Scheme 11

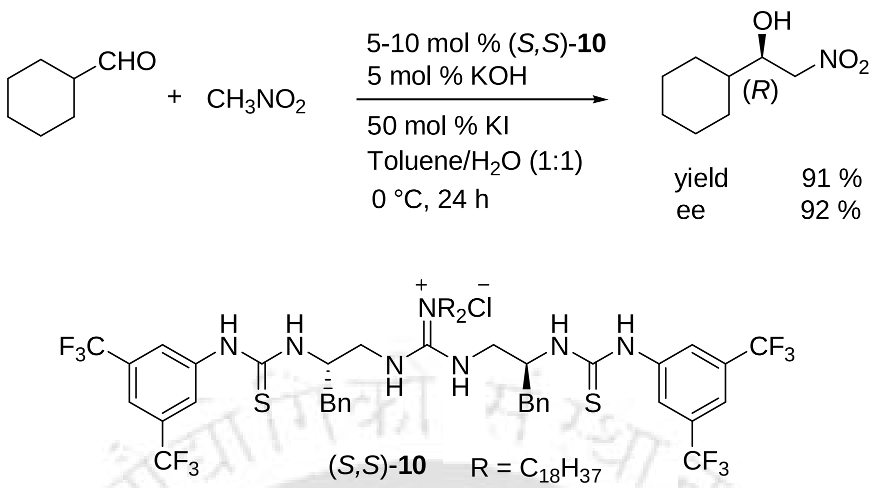
3.1.2 Organocatalysis

The study of organocatalysis for nitroaldol reaction has been active topic in recent years.[14,15] In 1994, Nájera and co-workers documented the first organocatalytic asymmetric nitroaldol reaction using guanidine derivatives with up to 54 % ee (Scheme 12).[15a] This has brought a new concept to the asymmetric nitroaldol reaction.



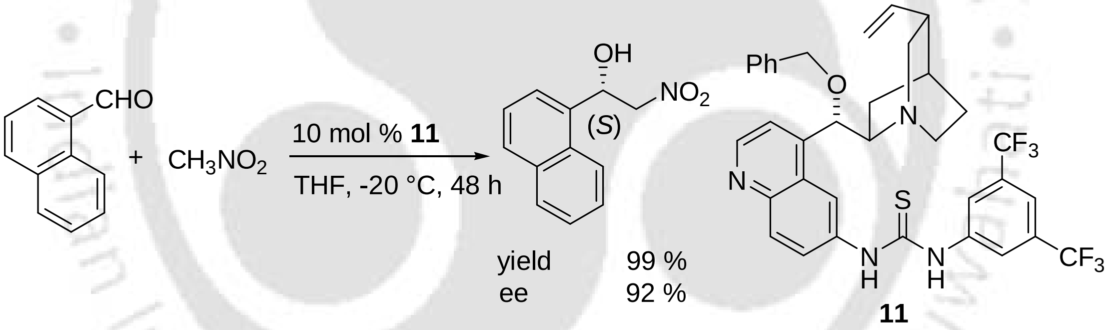
Scheme 12

Nagasawa and co-workers have reported linear guanidine-thiourea based bifunctional catalysts, with guanidine and thiourea linked to a chiral spacer (phenylalanine), for an enantio- and diastereoselective nitroaldol reaction. Under the optimal conditions, 10 mol % of the octadecyl substituted **10** with KI as an additive in a biphasic system of toluene and aqueous KOH promotes the reaction between nitromethane and aliphatic α-branched aldehydes with up to 92 % ee (Scheme 13).[15c]



Scheme 13

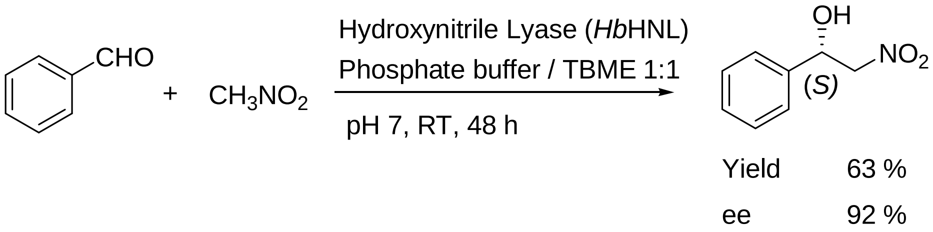
Hiemstra and co-workers have introduced *Cinchona* derived bifunctional catalyst **11** for nitroaldol reaction. The reactions of series of substrates have been studied with up to 92 % ee (Scheme 14).[15e]



Scheme 14

3.1.3 Biocatalysis

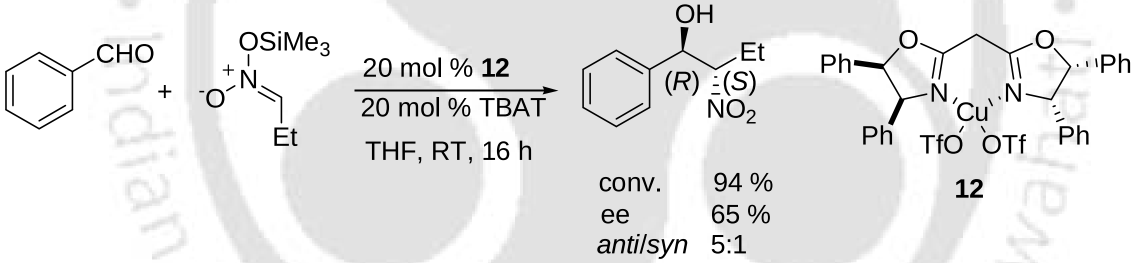
Griengl and co-workers have developed the first example for biocatalytic asymmetric nitroaldol reaction using hydroxynitrile lyase from *Heavea brasiliensis* (HbHNL). The reactions have occurred with reasonable to high enantioselectivity. In the case of the reaction with nitroethane, two stereocenters are generated simultaneously with good diastereo- and enantioselectivity (Scheme 15).[16a]



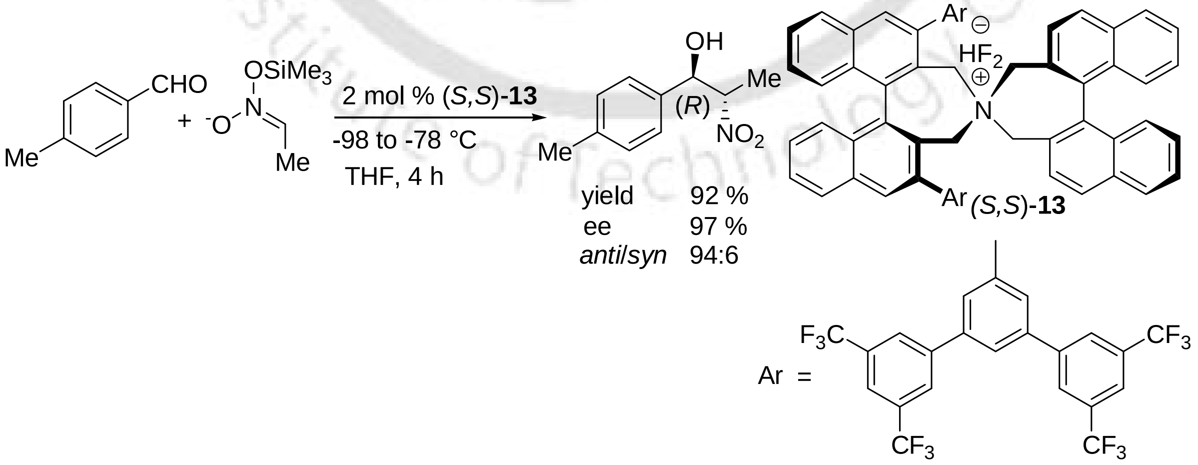
Scheme 15

3.2 Asymmetric Nitroaldol Reaction with Modified Nitroalkanes

Silyl nitronates are activated nitroalkanes which are generated prior to the nucleophilic attack of the nitro compound on the carbonyl group of an aldehyde or ketone.[2] This approach offers a good platform for asymmetric implementation. An asymmetric version of this reaction is first reported by Jørgensen and co-workers using chiral bisoxazoline copper(II) complex **12** in combination with tetrabutylammonium triphenylsilyl difluorosilicate (TBAT) as fluoride ion source for the addition of trimethyl silyl nitronates to aromatic aldehydes with up to 65 % ee (Scheme 16).[17a]



Scheme 16

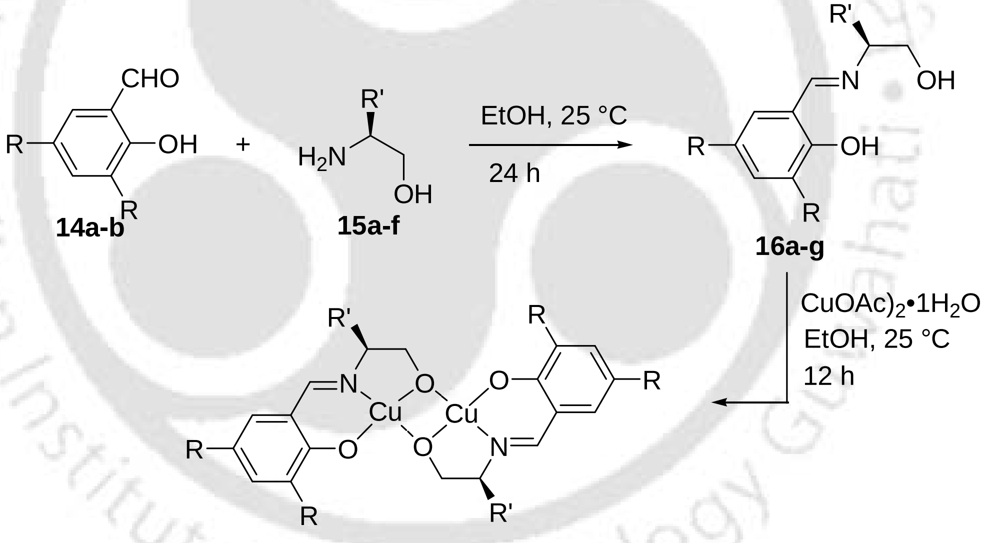


Scheme 17

Maruoka and co-workers have showed the addition of trimethylsilyl nitronates to aromatic aldehydes in the presence of *N*-spiro *C*$_2$-symmetric quaternary ammoniumbifluoride **13** in THF at -98 to -78 °C to give nitroaldol adduct with 94:6 *anti/syn* and > 90 % ee (Scheme 17).[17b] Under these conditions, aliphatic aldehydes do not give acceptable levels of diastereo- and enantioselectivity.

3.3 Present Study

Copper is an abundant element in earth crust. It is also present in proteins such as tyrosinase, hemocyanins and copper oxidases.[18] Many of these proteins are believed to contain the copper ions in dissymmetric ligand arrangements and therefore modeling the structural aspects of this dissymmetric ligand environment around copper is currently of great interest.[19] Chiral binuclear complexes of copper(II) have received special attention because of their importance in molecular recognition.[20,21] In this chapter, we describe the synthesis



17	R	R'	Yield (%)
a	*t*-Bu	Me	76
b	*t*-Bu	*i*-Pr	88
c	*t*-Bu	*s*-Bu	79
d	*t*-Bu	*i*-Bu	90
e	*t*-Bu	*t*-Bu	95
f	*t*-Bu	Bn	82
g	H	*t*-Bu	70

Scheme 18. Synthesis of the Binuclear Copper(II) Complexes **17a-g**

and application of chiral binuclear copper(II) complexes for addition of nitroalkanes to aldehydes. The reactions are free from the addition of an additive or base and the complexes **17a–g** act as bifunctional catalyst. Both the aryl and alkyl aldehydes are compatible with this protocol providing the nitroaldol products in high yield. Nitromethane is more reactive compared to nitroethane and nitropropane.

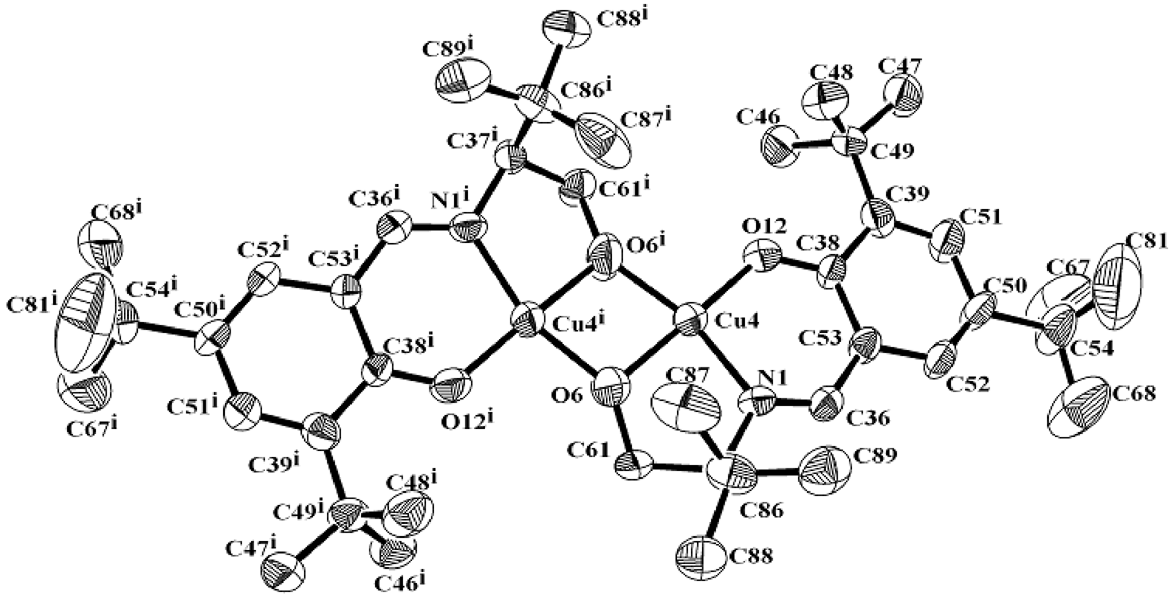
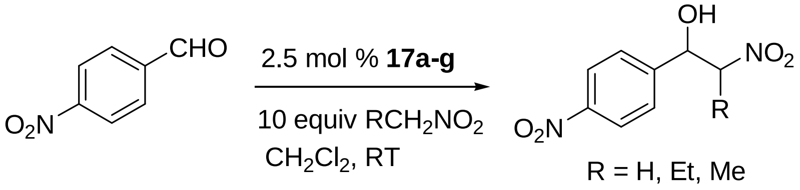


Figure 1. *ORTEP* Diagram of **17e** with Thermal Ellipsoid Set to 50 % Probability. H-Atoms are Omitted for Clarity.

Aldehydes **14a-b** were reacted with (*S*)-amino alcohols **15a–f** in EtOH to provide Schiff bases **16a–g** in high yield. The latter were then treated with $Cu(OAc)_2 \cdot 1H_2O$ in EtOH to give the complexes **17a–g** as green powder (Scheme 18). During recrystallization in a mixture of MeOH and CH_2Cl_2, the complex **17e** yielded single crystals whose X-ray analysis showed it as a binuclear complex having Cu–O–Cu bridge with the alkyl OH group (Figure 1). The copper(II) atoms are tetracoordinated with a distorted square planar geometry. The Cu–Cu distances (2.853–2.907 Å), bond lengths of the bridged (1.856–1.939 Å) and terminal (1.835–1.876 Å) Cu–O, Cu–N (1.886–1.927 Å) and the bond angles of Cu–O–Cu (96.04°–101.50°) agree with the reported data.[22] The five-membered rings, arising from the coordination of the bridged O and imine N of **17e** with Cu(II), exist in envelope conformation.

Table 1. Reaction of 4-Nitrobenzaldehyde: Screening of Complexes **17a–g** and Nitroalkanes



Entry	Catalyst	RCH_2NO_2	Product Yield (%)[a]	Product er[d]	Product Config[e]
1	**17a**	$MeNO_2$	55	53:47	*S*
2	**17b**	$MeNO_2$	86	58:42	*S*
3	**17c**	$MeNO_2$	77	57:43	*S*
4	**17d**	$MeNO_2$	75	56:44	*S*
5	**17e**	$MeNO_2$	90	66:34	*S*
6	**17f**	$MeNO_2$	82	53:47	*S*
7	**17g**	$MeNO_2$	75	45:55	*S*
8	**17e**	$EtNO_2$	78 (11:9)[b,c]	56:44, 64:36	nd
9	**17e**	$PrNO_2$	45 (11:9)[b,c]	55:45, 59:41	nd
10	**17e**	*i*-$PrNO_2$	nr	-	-

[a] 4-Nitrobenzaldehyde (0.5 mmol), **17a–g** (2.5 mol %), and nitroalkane (5 mmol) stirred for 24 h in CH_2Cl_2 (1 mL).

[b] *syn*/*anti* ratio.

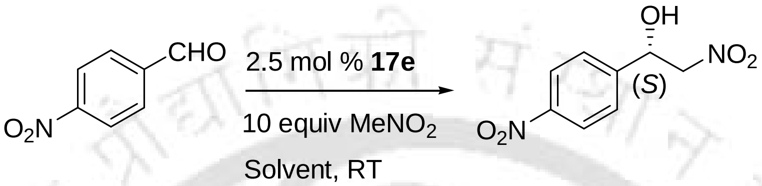
[c] Reaction time = 48 h.

[d] Determined by HPLC with Chiralcel OD-H column using hexane/isopropanol (85:15).

[e] Determined from sign of optical rotation. nr = no reaction. nd = not detected.

The catalytic activity of the complexes **17a–g** was studied for the addition of nitroalkanes to aldehydes.[8-13,15-17,23] The optimization of the reaction conditions was carried out with the addition of nitromethane to *p*-nitrobenzaldehyde as a model substrate (Table 1). The best results observed when substrates were stirred for 24 h in the presence of 2.5 mol % of **17e** at ambient temperature. Nitroethane and nitropropane showed less reactivity compared to nitromethane. No reaction was observed with 2-nitropropane. Of the solvents studied, CH_2Cl_2, EtOH, THF, CH_3CN, and toluene, the former was found to be the choice for these reactions (Table 2). The complex **17e** provided the best results compared to **17a–d** and **17f-g**.

Table 2. Reaction of 4-Nitrobenzaldehyde with Nitromethane using **17e**: Solvent Effect



Entry	Solvent	Product		
		Yield (%)[a]	er[b]	Config.[c]
1	EtOH	40	61:39	*S*
2	THF	53	57:43	*S*
3	CH_3CN	20	56:44	*S*
4	Toluene	49	60:40	*S*
5	$CHCl_3$	84	60:40	*S*

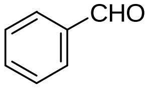
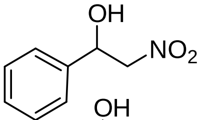
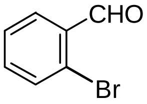
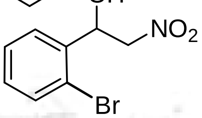
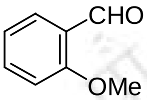
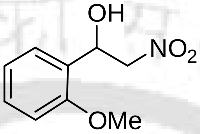
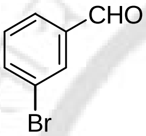
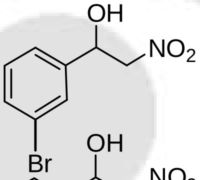
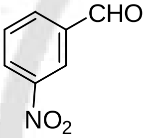
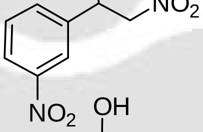
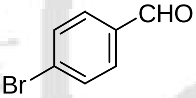
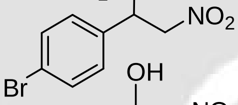
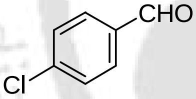
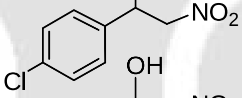
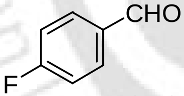
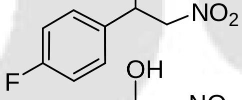
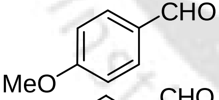
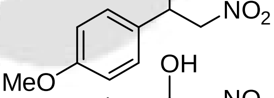
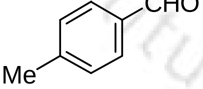
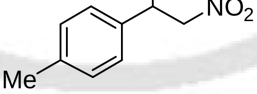
[a] 4-Nitrobenzaldehyde (0.5 mmol), catalyst **17e** (2.5 mol %) and nitromethane (5 mmol) were stirred for 24 h in appropriate solvent (1 mL).

[b] Determined by HPLC analysis with chiralcel OD-H column using hexane/isopropanol (85:15).

[c] Determined from sign of optical rotation.

Next, the scope of the reaction was studied (Table 3-4). Benzaldehyde underwent reaction with 60:40 er. Similar results observed with 2-bromo-, 2-methoxy-, 3-bromo-, 3-nitro-, 4-bromo-, 4-chloro-, 4-fluoro-, 4-methoxy-, and 4-methylbenzaldehydes (Table 3). 2-Naphthaldehyde, 2-thiophenecarboxaldehyde, 2-furaldehyde, cyclohexanecarboxaldehyde,

Table 3. Reaction of Aryl Aldehydes with Nitromethane

Entry	Substrate	Time (h)	Product	Yield (%)[a,b]	er[c]	Config.[d]
1		28		92	60:40	*S*
2		20		93	55:45	*S*
3		34		89	65:35	*S*
4		30		85	60:40	nd
5		26		90	76:24	nd
6		24		95	58:42	nd
7		23		90	54:46	*S*
8		22		94	55:45	*S*
9		38		84	66:34	*S*
10		30		90	64:36	*S*

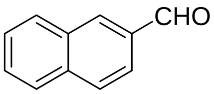
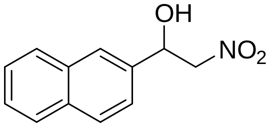
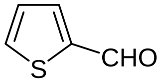
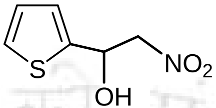
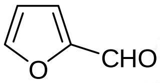
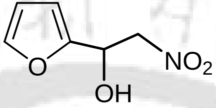
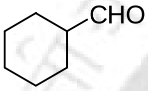
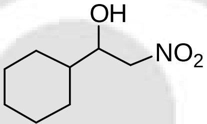
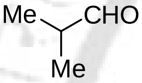
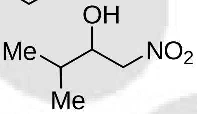
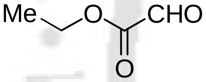
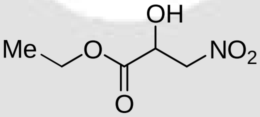
[a] Substrate (0.5 mmol), catalyst **17e** (2.5 mol %) and nitromethane (5 mmol) were stirred in CH_2Cl_2 (1 mL) at ambient temperature.

[b] Isolated yield.

[c] Determined by HPLC analysis using chiralcel OD-H column with hexane/isopropanol.

[d] Determined from sign of optical rotation. nd = not detected.

Table 4. Reaction of 2-Naphthyl, Hetero Aryl and Alkyl Aldehydes with Nitromethane

Entry	Substrate	Time (h)	Product	Yield (%)^{a,b}	er^{c}	Config.^{d}
1		36		81	61:39	*S*
2		30		65	54:46	*S*
3		16		74	55:45	*S*
4		24		89	68:32	*S*
5		20		86	64:36	*S*
6		30		55	57:43	nd

[a] Substrate (0.5 mmol), catalyst **17e** (2.5 mol %) and nitromethane (5 mmol) were stirred in CH_2Cl_2 (1 mL) at ambient temperature.

[b] Isolated yield.

[c] Determined by HPLC analysis using chiralcel OD-H (for entries 1-2 and 6) and chiralpak AD-H (for entries 3-5) columns with hexane/isopropanol.

[d] Determined from sign of optical rotation.

isobutyraldehyde, and ethyl glyoxalate underwent reaction to give nitroaldol products with up to 68:32 er (Table 4). In aryl aldehydes, the substrates bearing electron-withdrawing groups exhibited greater reactivity compared to that having electron-donating groups.

The observed experimental results suggest that the complexes **17** act as bifunctional catalysts in these reactions: first, as Brønsted base, and then, as Lewis acid. To reveal the mechanism, the complex **17e** was titrated with HCl whose electronic spectra showed that the intensity of the bands at 384 nm and 283 nm decreased with respect to increasing concentra-

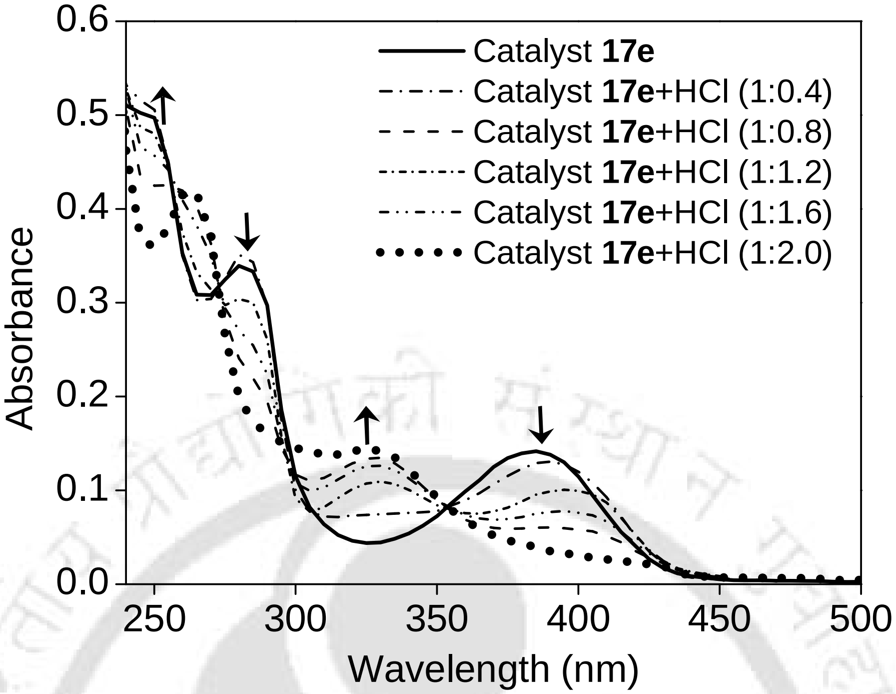


Figure 2. UV-vis Spectra of **17e** (3.3×10^{-2} mM) with an Increasing Concentration of HCl (0.0 to 6.6×10^{-2} mM) in CH_2Cl_2.

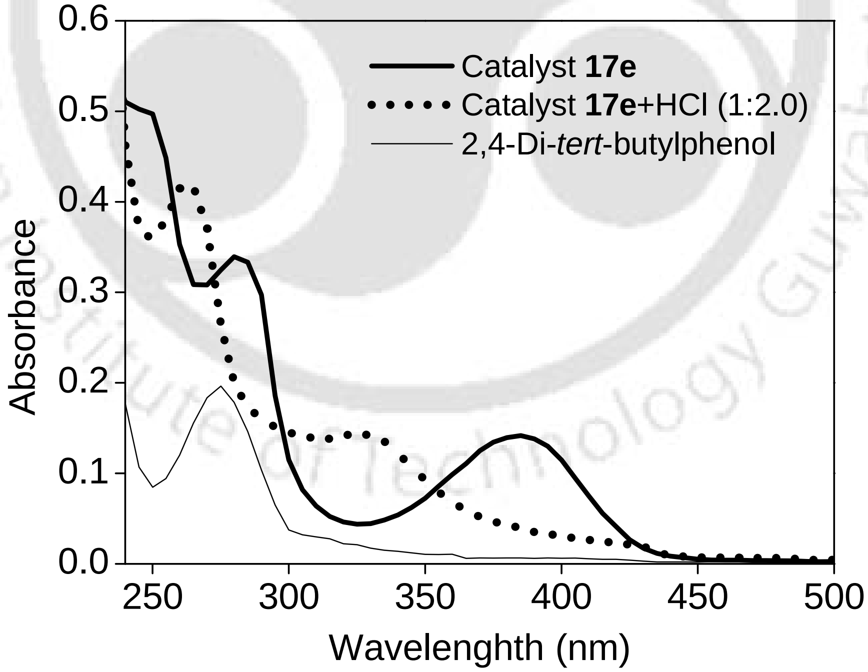
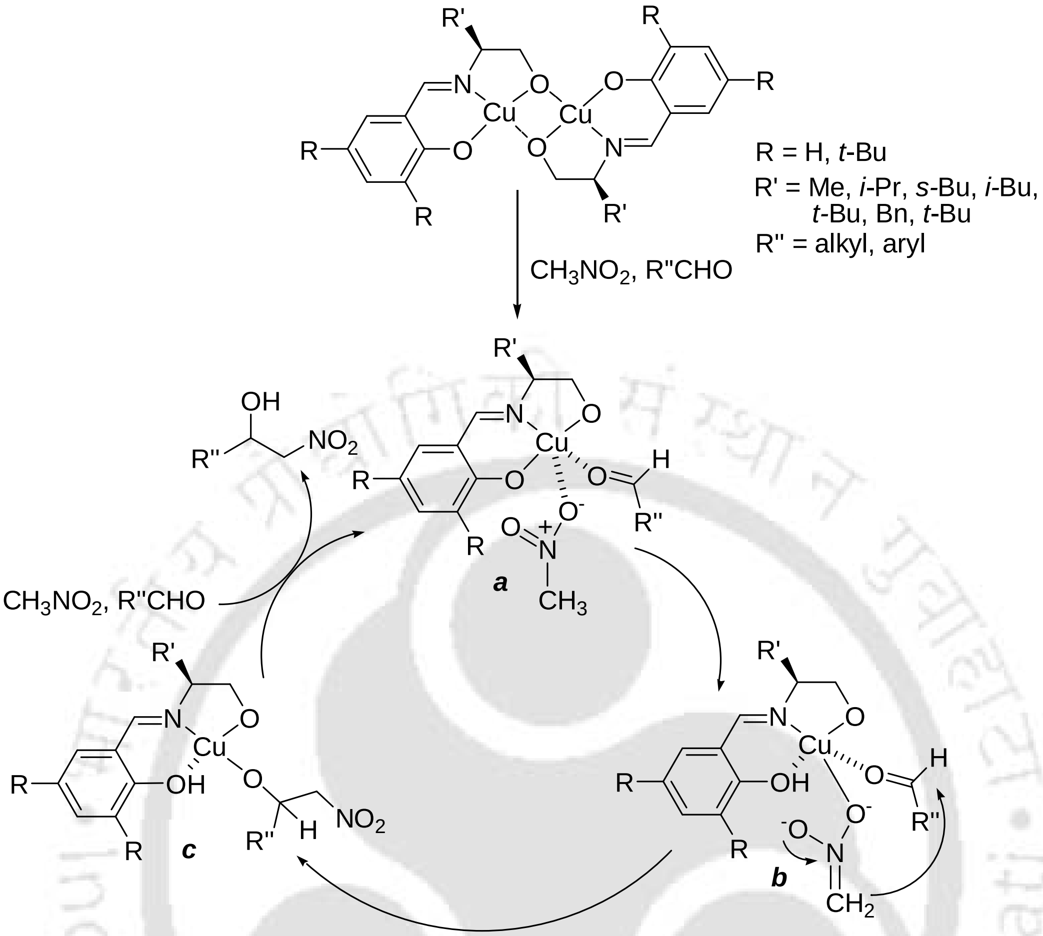


Figure 3. UV-vis Spectra of **17e**, **17e**+HCl and 2,4-Di-*tert*-butylphenol in CH_2Cl_2 (in all Cases the Concentration of Sample is 3.3×10^{-2} mM).



Scheme 18. Proposed Catalytic Cycle

tion of HCl, and shifted to lower wavelength at 327 nm and 263 nm, respectively (Figure 2).[24] These studies clearly reveal that phenolate oxygen is selectively protonated (Figure 3). Thus, the phenolate oxygen acts as a stronger base compared to alcoholic oxygen under these conditions. Hence, the reaction of complex **17** with nitroalkane and aldehyde can generate monomeric complex ***a*** that could transform to intermediate ***c*** via intramolecular addition of nitronate to aldehyde ***b*** followed by reaction with fresh nitroalkane. The intermediate ***c*** can complete the catalytic cycle by reaction with fresh aldehyde and nitromethane (Scheme 18).

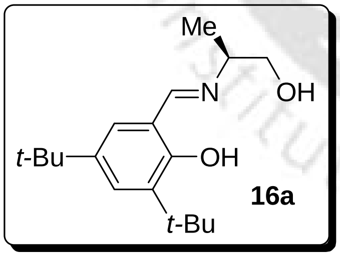
In summary, the synthesis of chiral copper(II) Schiff base complexes **17a–g** has been accomplished in high yield. They have been studied for the addition of nitroalkanes to aldehydes as bifunctional catalysts with 76:24 *er*.

Experimental Section

General. L-Amino acids, 2,4-di-*tert*-butylphenol (98 %), aldehydes, nitroalkanes, and $Cu(OAc)_2{\cdot}1H_2O$ (>99 %) purchased from Aldrich. (*S*)-Amino alcohols obtained by reduction of amino acids according to the literature.[25a] 3,5-Di-*tert*-butylsalicylaldehyde prepared from 2,4-di-*tert*-butylphenol.[25b] NMR spectra recorded using Varian-400 spectrometer. FT-IR spectra was recorded on Nicolet-410 spectrometer. HPLC analysis was carried out on a Waters-2478 with chiral stationary phase columns (chiralcel OD-H and chiralpak AD-H). UV–vis spectra obtained from Perkin–Elmer Lambda-25 spectrophotometer. EPR spectra recorded using JES-FA-200 spectrometer. Melting points were determined using Buchi B-540 melting point apparatus and uncorrected. X-ray data collected on Bruker SMARTAPEX equipped with CCD area detector using Mo-Kα radiation. The structure solved using SHELXL-97 Göttingen, Germany. Column chromatography performed on 60–120 mesh silica gel. Elemental analysis carried using Perkin–Elmer-2400 CHNS analyzer.

General Procedure for the Preparation of 16a–g

Aldehydes **14a-b** (5 mmol) and (*S*)-amino alcohols **15a–f** (5 mmol) were stirred in EtOH (10 mL) for 24 h at ambient temperature. Removal of the solvent provided a residue, which was purified on silica gel column chromatography using ethyl acetate and hexane (1:19) to give **16a–g** as yellow compounds.



16a

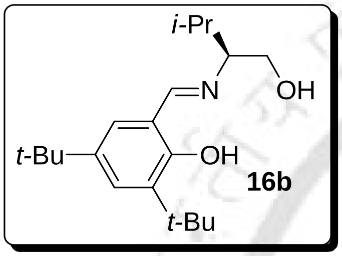
2,4-Bis(1,1-dimethylethyl)-6-[[[(1*S*)-2-hydroxy-1-methylethyl] imino]methyl]-phenol 16a.[26a] A mixture of 3,5-di-*tert*-butylsalicylaldehyde (1.17 g, 5 mmol) and (*S*)-alaninol (0.375 g, 5 mmol) in EtOH (10 mL) was subjected to the reaction conditions described in the general procedure to give **16a** (1.19 g, 82 %) as yellow liquid.
$[\alpha]_D^{25}$ = - 37.6 (c = 0.516, CH_2Cl_2).

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.32 (s, 1H), 7.30 (d, *J* = 2.0 Hz, 1H), 7.02 (d, *J* = 2.4 Hz, 1H), 3.55 (d, *J* = 6.8 Hz, 2H), 3.33 (m, 1H), 1.35 (s, 9H), 1.26 (s, 9H), 1.13 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 166.4, 158.3, 140.4, 136.9, 127.3, 126.3, 117.9, 67.4, 66.8, 35.2, 34.3, 31.8, 29.6, 18.5.

FT-IR (neat): ν 3391, 2966, 2879, 1634, 1470, 1373, 1271, 1102, 1035 cm^{-1}.

Anal. Calcd for $C_{18}H_{29}NO_2$: C, 74.18; H, 10.03; N, 4.81. Found: C, 74.28; H, 10.10; N, 4.88.



16b

2,4-Bis(1,1-dimethylethyl)-6-[[[(1*S*)-1-hydroxymethyl-2-ethylpropyl]imino]methyl]-phenol 16b.[26b] A mixture of 3,5-di-*tert*-butylsalicylaldehyde (1.17 g, 5 mmol) and (*S*)-valinol (0.515 g, 5 mmol) in EtOH (10 mL) was subjected to the reaction conditions shown in the general procedure to give **16b** (1.44 g, 90 %) as yellow solid.

Mp: 102-105 °C.

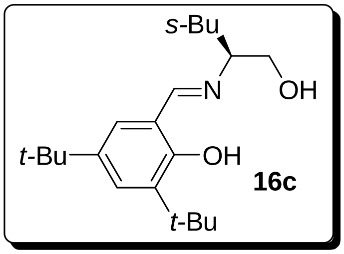
$[\alpha]_D^{25}$ = -12.2 (c = 0.416, CH_2Cl_2).

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.36 (s, 1H), 7.39 (d, *J* = 2.0 Hz, 1H), 7.12 (d, *J* = 1.2 Hz, 1H), 3.79-3.74 (m, 2H), 3.01-2.99 (m, 1H), 1.93-1.89 (m, 1H), 1.43 (s, 9H), 1.30 (s, 9H), 0.93 (d, *J* = 5.6 Hz, 6H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 167.3, 158.3, 140.3, 136.9, 127.3, 126.3, 117.8, 78.1, 64.9, 35.2, 34.3, 31.8, 29.9, 20.0, 19.0.

FT-IR (neat): ν 3385, 2970, 2868, 1638, 1477, 1370, 1261, 1100, 1042 cm^{-1}.

Anal. Calcd for $C_{20}H_{33}NO_2$: C, 75.19; H, 10.41; N, 4.38. Found: C, 75.23; H, 10.45; N, 4.43.



16c

2,4-Bis(1,1-dimethylethyl)-6-[[[(1S,2S)-1-(hydroxymethyl)-2-methylbutyl]imino]methyl]-phenol 16c.[26c] A mixture of 3,5-di-tert-butylsalicylaldehyde (1.17 g, 5 mmol) and (*S*)-isoleucinol (0.585 g, 5 mmol) in EtOH (10 mL) was subjected to the reaction conditions reported in the general procedure to yield **16c** (1.46 g, 88 %) as yellow liquid.

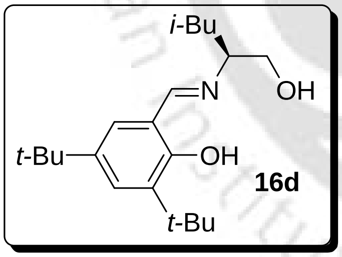
$[\alpha]_D^{25}$ = - 12.9 (c = 0.592, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (s, 1H), 7.38 (d, *J* = 2.4 Hz, 1H), 7.11 (d, *J* = 2.0 Hz, 1H), 3.83-3.73 (m, 2H), 3.11-3.06 (m, 1H), 2.0 (s, 1H), 1.69-1.65 (m, 1H), 1.42 (s, 9H), 1.14-1.09 (m, 2H), 1.30 (s, 9H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.87 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 67.1, 158.3, 140.3, 136.9, 127.3, 126.3, 117.8, 79.9, 64.5, 37.0, 35.2, 34.3, 31.6, 29.6, 25.6, 16.0, 11.5.

FT-IR (neat): ν 3389, 2956, 2868, 1644, 1469, 1372, 1275, 1109, 1044 cm^{-1}.

Anal. Calcd for $C_{21}H_{35}NO_2$: C, 75.63; H, 10.58; N, 4.20. Found: C, 75.75; H, 10.59; N, 4.24.



16d

2,4-Bis(1,1-dimethylethyl)-6-[[[(1*S*)-1-(hydroxymethyl)-3-methylbutyl]imino]methyl]-phenol 16d.[26a] A mixture of 3,5-di-*tert*-butylsalicylaldehyde (1.17 g, 5 mmol) and (*S*)-leucinol (0.585 g, 5 mmol) in EtOH (10 mL) was subjected to reaction conditions described in the general procedure to afford **16d** (1.53 g, 92 %) as yellow liquid.

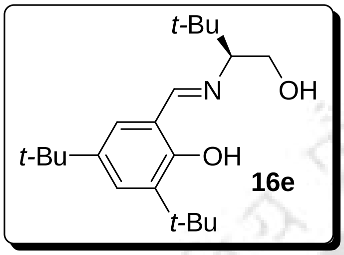
$[\alpha]_D^{25}$ = - 23.3 (c = 0.316, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (s, 1H), 7.40 (d, *J* = 2.4 Hz, 1H), 7.13 (d, *J* = 2.4 Hz, 1H), 3.72–3.64 (m, 2H), 3.40–3.36 (m, 1H), 1.63–1.53 (m, 3H), 1.44 (s, 9H), 1.28 (s, 9H), 0.91–0.99 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 158.3, 140.4, 136.9, 127.3, 126.3, 117.8, 70.2, 66.8, 41.1, 35.2, 34.4, 31.7, 29.6, 24.6, 23.8, 21.7.

FT-IR (neat): ν 3412, 2960, 2868, 1633, 1457, 1396, 1360, 1251, 1171, 1097, 1045, 1017 cm^{-1}.

Anal. Calcd for $C_{21}H_{35}NO_2$: C, 75.63; H, 10.58; N, 4.20. Found: C, 75.73; H, 10.60; N, 4.31.



16e

2,4-Bis(1,1-dimethylethyl)-6-[[[(1S)-1-(hydroxymethyl)-2,2-dimethylpropyl]imino]methyl]-phenol 16e.[26b] A mixture of 3,5-di-*tert*-butylsalicylaldehyde (1.17 g, 5 mmol) and (*S*)-*tert*-leucinol (0.585 g, 5 mmol) in EtOH (10 mL) was subjected to the reaction conditions described in the general procedure to give **16e** (1.58 g, 95 %) as yellow liquid.

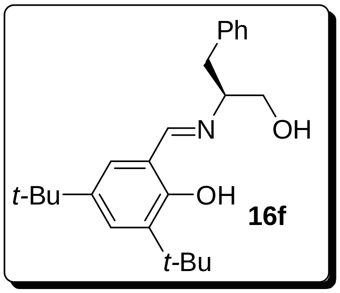
$[\alpha]_D^{25}$ = - 37 (c = 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (s, 1H), 7.38 (d, *J* = 2.0 Hz, 1H), 7.10 (d, *J* = 2.0 Hz, 1H), 3.71-3.94 (m, 2H), 2.91 (dd, *J* = 2.8, 9.6 Hz, 1H), 1.44 (s, 9H), 1.31 (s, 9H), 0.98 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 157.9, 140.0, 136.6, 126.9, 126.0, 117.5, 81.4, 62.6, 35.1, 34.2, 33.3, 31.6, 29.6, 27.2.

FT-IR (neat): ν 3391, 2966, 2879, 1634, 1470, 1373, 1271, 1102, 1035 cm^{-1}.

Anal. Calcd for $C_{21}H_{35}NO_2$: C, 75.63; H, 10.58; N, 4.20. Found: C, 75.68; H, 10.55; N, 4.29.



16f

β-[[[3,5-Bis(1,1-dimethylethyl)-2-hydroxyphenyl]-

methylene]amino]-(βS)-benzenepropanol 16f.[26d] A mixture of 3,5-di-*tert*-butylsalicylaldehyde (1.17 g, 5 mmol) and (*S*)-phenylalaninol (0.756 g, 5 mmol) in EtOH (10 mL) was subjected to reaction conditions described in the general procedure to give **16f** (1.47 g, 80 %) as yellow liquid.

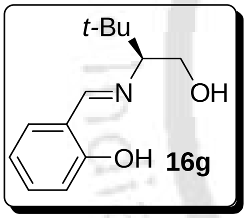
$[\alpha]_D^{25}$ = - 17.2 (c = 0.28, CH_2Cl_2).

^1H NMR (400 MHz, $CDCl_3$): δ 8.19 (s, 1H), 7.40 (s, 1H), 7.29–7.25 (m, 2H), 7.21–7.16 (m, 3H), 7.01 (s, 1H), 3.81–3.75 (m, 2H), 3.53–3.50 (m, 1H), 2.97–2.89 (m, 2H), 1.46 (s, 9H), 1.28 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.4, 158.2, 140.4, 138.2, 136.8, 129.7, 128.7, 127.4, 126.6, 126.4, 117.8, 73.4, 66.1, 39.4, 35.3, 34.3, 31.7, 29.6.

FT-IR (neat): ν 3395, 3055, 2960, 2875, 1644, 1503, 1475, 1386, 1275, 1245, 1165, 1053, 1028 cm^{-1}.

Anal. Calcd for $C_{24}H_{33}NO_2$: C, 78.43; H, 9.05; N, 3.81. Found: C, 78.58; H, 9.10; N, 3.79.



16g

2-[[[(1S)-1-(Hydroxymethyl)-2,2-dimethylpropyl]-imino]methyl]-phenol 16g.[26e] A mixture of salicylaldehyde (0.610 g, 5 mmol) and (*S*)-*tert*-leucinol (0.585 g, 5 mmol) in EtOH (10 mL) was subjected to the reaction conditions shown in the general procedure to provide **16g** (1.02 g, 92 %) as yellow liquid.

$[\alpha]_D^{25}$ = - 22 (c = 0.5, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$): δ 8.34 (s, 1H), 7.33–7.26 (m, 2H), 6.96–6.87 (m, 2H), 3.94 (d, *J* = 10.8 Hz, 1H), 3.72 (t, *J* = 9.6 Hz, 1H), 2.95 (d, *J* = 9.2 Hz, 1H), 0.97 (s, 9H).

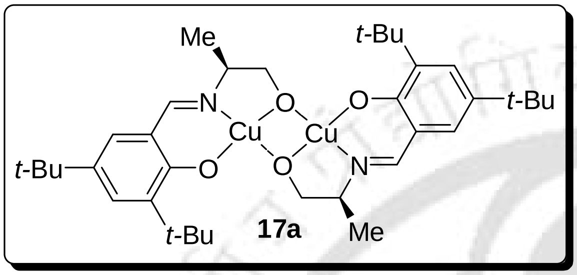
^{13}C NMR (100 MHz, $CDCl_3$): δ 196.9, 166.1, 161.6, 132.6, 131.7, 118.8, 117.2, 81.2, 62.5, 33.3, 27.2.

FT-IR (neat): ν 3365, 2958, 2871, 1633, 1469, 1390, 1361, 1274, 1252, 1173, 1062, 1047 cm^{-1}.

Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.63; H, 8.69; N, 6.35.

General Procedure for the Preparation of 17a–g

The ligands **16a–g** (3 mmol) were reacted with $Cu(OAc)_2{\cdot}1H_2O$ (3 mmol) in EtOH (10 mL) for 12 h at ambient temperature. The solvent was evaporated under reduced pressure and the residue was purified on silica gel column chromatography using ethyl acetate and hexane to give **17a–g** as a green colored powder.



17a

Complex 17a. A mixture of **16a** (0.874 g, 3 mmol) and $Cu(OAc)_2{\cdot}1H_2O$ (0.598 g, 3 mmol) in EtOH (10 mL) was subjected to the reaction conditions described in the general procedure and product **17a** was purified on silica gel column chromatography using 9:1 hexane/ethyl acetate with 76 % yield (1.61 g) as green powder.

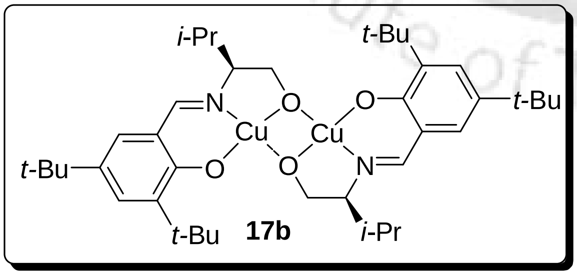
$[\alpha]_D^{25} = +\ 520$ (c = 0.02, CH_2Cl_2).

FT-IR (KBr): ν 2957, 1627, 1530, 1433, 1325, 1255, 1167, 1054, 874, 690, 626, 520 cm^{-1}.

UV-vis (CH_2Cl_2): λ_{max} (ε) 610 (7931), 388 nm (14,981 mol^{-1} dm^3 cm^{-1}).

EPR (MeOH): liquid N_2 temp; $g_{\parallel} = 2.12$, $g_{\perp} = 2.03$, $A_{\parallel} = 316$ mT.

Anal. Calcd for $C_{36}H_{54}N_2O_4Cu_2$: C, 61.25; H, 7.71; N, 3.97. Found: C, 61.36; H, 7.72; N, 4.01.



17b

Complex 17b. A mixture of **16b** (0.958 g, 3 mmol) and $Cu(OAc)_2{\cdot}1H_2O$ (0.598 g, 3 mmol) in EtOH (10 mL) was subjected to the reaction condition described in the general procedure and the residue was purified on silica gel column chromatography using 17:3 hexane/ethyl acetate to give **17b** (2.01 g, 88 %) as green powder.

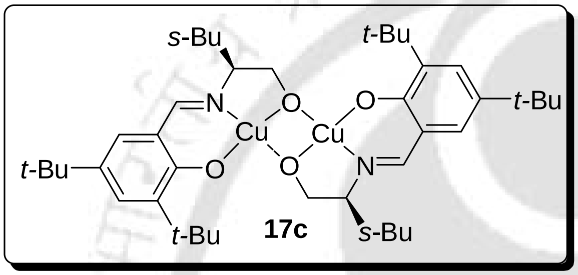
$[\alpha]_D^{25} = + 492$ (c = 0.02, CH_2Cl_2).

FT-IR (KBr): ν 2958, 1626, 1528, 1433, 1323, 1255, 1164, 1054, 837, 525 cm^{-1}.

UV-vis (CH_2Cl_2): $\lambda_{max}(\varepsilon)$ 597 (3352), 382 nm (25,832 mol^{-1} dm^3 cm^{-1}).

EPR (MeOH): liquid N_2 temp; $g_{\parallel} = 2.05$, $g_{\perp} = 2.01$, $A_{\parallel} = 317$ mT.

Anal. Calcd for $C_{40}H_{62}N_2O_4Cu_2$: C, 63.05; H, 8.20; N, 3.68. Found: C, 63.12; H, 8.22; N, 3.75.



17c

Complex 17c. A mixture of **16c** (1.0 g, 3 mmol) and $Cu(OAc)_2 \cdot 1H_2O$ (0.598 g, 3 mmol) in EtOH (10 mL) was subjected to the reaction conditions reported in the general procedure and the residue was purified on silica gel column chromatography using 19:1 hexane/ethyl acetate to yield **17c** (1.87 g, 79 %) as green powder.

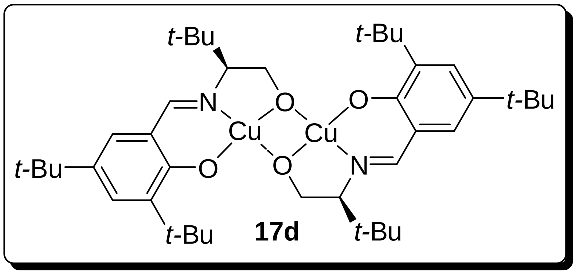
$[\alpha]_D^{25} = + 476$ (c = 0.02, CH_2Cl_2).

FT-IR (KBr): ν 2959, 1625, 1528, 1459, 1432, 1324, 1255, 1166, 1057, 837, 526 cm^{-1}.

UV-vis (CH_2Cl_2): $\lambda_{max}(\varepsilon)$ 605 (9282), 382 nm (29,270 mol^{-1} dm^3 cm^{-1}).

EPR (MeOH): liquid N_2 temp; $g_{\parallel} = 2.13$, $g_{\perp} = 2.04$, $A_{\parallel} = 320$ mT.

Anal. Calcd for $C_{42}H_{66}N_2O_4Cu_2$: C, 63.85; H, 8.42; N, 3.55. Found: C, 63.80; H, 8.50; N, 3.59.



17d

Complex 17d. A mixture of **16d** (1.0 g, 3 mmol) and $Cu(OAc)_2 \cdot 1H_2O$ (0.598 g, 3 mmol) in EtOH (10 mL) was subjected to the reaction conditions described in the general procedure and the residue was purified on silica gel column chromatography using 9:1 hexane/ethyl acetate to give **17d** (2.13 g, 90 %) as a green powder.

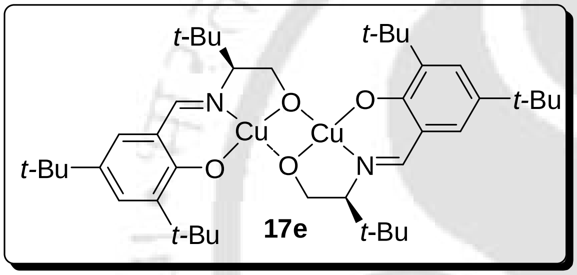
$[\alpha]_D^{25}$ = + 395 (c = 0.02, CH_2Cl_2).

FT-IR (KBr): ν 2959, 1625, 1528, 1459, 1432, 1324, 1255, 1164, 1057, 837, 526 cm^{-1}.

UV-vis (CH_2Cl_2): $\lambda_{max}(\varepsilon)$ 613 (8492), 384 nm (18,723 mol^{-1} dm^3 cm^{-1}).

EPR (MeOH): liquid N_2 temp; $g_{\parallel}$ = 2.10, $g_{\perp}$ = 2.02, $A_{\parallel}$ = 313 mT.

Anal. Calcd for $C_{42}H_{66}N_2O_4Cu_2$: C, 63.85; H, 8.42; N, 3.55. Found: C, 63.79; H, 8.45; N, 3.59.



17e

Complex 17e. A mixture of **16e** (1.0 g, 3mmol) and $Cu(OAc)_2 \cdot 1H_2O$ (0.598 g, 3 mmol) in EtOH (10 mL) was subjected to the reaction conditions described in the general procedure and the residue was purified on silica gel column chromatography using 19:1 hexane/ethyl acetate to give **17e** (2.25 g, 95 %) as a green powder.

$[\alpha]_D^{25}$ = + 400 (c = 0.02, CH_2Cl_2).

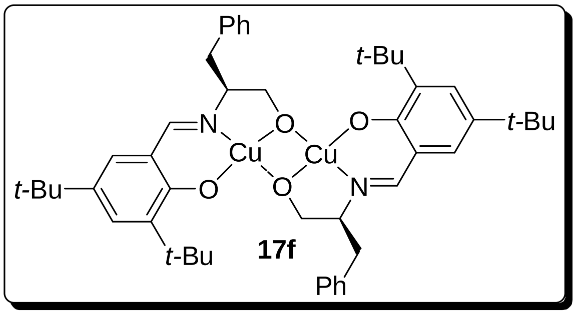
FT-IR (KBr): ν 2960, 1619, 1537, 1260, 1163, 1076, 840, 554, 426 cm^{-1}.

UV-vis (CH_2Cl_2): $\lambda_{max}(\varepsilon)$ 385 (4272), 281 nm(10,303 $mol^{-1}dm^3$ cm^{-1}).

EPR (MeOH): liquid N_2 temp; $g_{\parallel}$ = 2.28, $g_{\perp}$ = 2.02, $A_{\parallel}$ = 317 mT.

μ_{eff} (powder, 298 K): 1.58 μ_B/Cu.

Anal. Calcd for $C_{42}H_{66}N_2O_4Cu_2$: C, 63.85; H, 8.42; N, 3.55. Found: C, 63.75; H, 8.53; N, 3.68.



17f

Complex 17f. A mixture of **16f** (1.10 g, 3 mmol) and Cu(OAc)$_2$·1H$_2$O (0.598 g, 3 mmol) in EtOH (10 mL) was subjected to the reaction conditions described in the general procedure and the residue was purified on silica gel column chromatography using 9:1 hexane/ethyl acetate to afford **17f** (2.11 g, 82 %) as green powder.

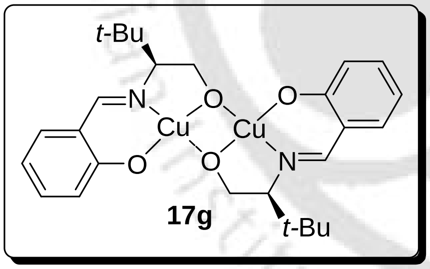
$[\alpha]_D^{25}$ = + 320 (c = 0.02, CH$_2$Cl$_2$).

FT-IR (KBr): ν 2966, 1635, 1540, 1441, 1322, 1266, 1178, 1076, 890, 855, 564, 446 cm^{-1}.

UV-vis (CH$_2$Cl$_2$): $\lambda_{max}(\varepsilon)$ 615 (9137), 390 nm (12,526 mol^{-1} dm^3 cm^{-1}).

EPR (MeOH): liquid N$_2$ temp; $g_{\parallel}$ = 2.13, $g_{\perp}$ = 2.06, $A_{\parallel}$ = 314 mT.

Anal. Calcd for $C_{48}H_{62}N_2O_4Cu_2$: C, 67.18; H, 7.28; N, 3.26. Found: C, 67.30; H, 7.35; N, 3.29.



17g

Complex 17g. A mixture of **16g** (0.664 g, 3 mmol) and Cu(OAc)$_2$·1H$_2$O (0.598 g, 3 mmol) in EtOH (10 mL) was subjected to the reaction conditions described in the general procedure and the residue was purified on silica gel column chromatography using 19:1 hexane/ethyl acetate to provide **17g** (1.18 g, 70 %) as a green powder.

$[\alpha]_D^{25}$ = + 430 (c = 0.02, CH$_2$Cl$_2$).

FT-IR (KBr): ν 2961, 1631, 1536, 1447, 1348, 1194, 1072, 1016, 902, 852, 760, 671, 582, 544, 461 cm^{-1}.

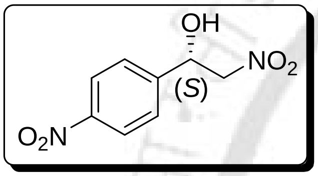
UV-vis (CH$_2$Cl$_2$): $\lambda_{max}(\varepsilon)$ 614 (4943), 385 nm (9859 mol^{-1} dm^3 cm^{-1}).

EPR (MeOH): liquid N_2 temp; $g_{\parallel} = 2.14$, $g_{\perp} = 2.05$, $A_{\parallel} = 315$ mT.

Anal. Calcd for $C_{26}H_{34}N_2O_4Cu_2$: C, 55.21; H, 6.06; N, 4.95. Found: C, 55.32; H, 6.09; N, 5.07.

General Procedure for Nitroaldol Reaction

Aldehyde (0.5 mmol), nitroalkane (5 mmol), and complex **17a–g** (2.5 mol %) were stirred in appropriate solvent (1 mL) at ambient temperature. The progress of the reaction was monitored by TLC. After completion, the solvent was evaporated and the residue was purified on silica gel column chromatography using ethyl acetate and hexane as eluent.



(*S*)-(+)-2-Nitro-1-(4-nitrophenyl)ethanol (Table 1, entry 5).[27a] A mixture of 4-nitrobenzaldehyde (75.5 mg, 0.5 mmol), nitromethane (305.2 mg, 5 mmol), and catalyst **17e** (9.8 mg, 2.5 mol %) in CH_2Cl_2 (1 mL) was subjected to the reaction conditions reported in the general procedure for 24 h and the residue was purified on silica gel column chromatography using 4:1 hexane/ethyl acetate to give the title compound (95.6 mg, 90 %) as colorless solid.

Mp: 84–85 °C.

$[\alpha]_D^{20} = +8.4$ (c = 1.0, CH_2Cl_2).

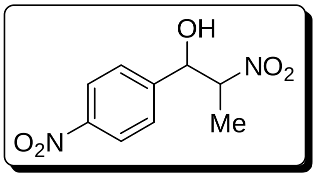
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, *J* = 8.4 Hz, 2H), 7.61 (d, *J* = 8.8 Hz, 2H), 5.60 (m, 1H), 4.58 (m, 2H), 3.28 (d, *J* = 4.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.2, 145.2, 127.1, 124.3, 80.8, 70.1.

FT-IR (KBr): ν 3534, 1557, 1521, 1348 cm^{-1}.

Anal. Calcd for $C_8H_8N_2O_5$: C, 45.29; H, 3.80; N, 13.20. Found: C, 45.34; H, 3.83; N, 13.25.

HPLC: Chiralcel OD-H column, n-hexane/isopropanol (85:15), wavelength: 215 nm, flow rate: 1 mL/min, retention time: 14.7 min, 18.1 min; 66:34 er.



2-Nitro-1-(4-nitrophenyl)propanol (Table 1, entry 8).[27a] A mixture of 4-nitrobenzaldehyde (75.5 mg, 0.5 mmol), nitroethane (375.3 mg, 5 mmol), and catalyst **17e** (9.8 mg, 2.5 mol %) in CH_2Cl_2 (1 mL) was subjected to the reaction conditions shown in the general procedure for 48 h and the residue was purified on silica gel column chromatography using 4:1 hexane/ethyl acetate to provide the title compound (88.2 mg, 78 %, *syn*/*anti* 55:45) as colorless solid.

Mp: 92–94 °C.

$[\alpha]_D^{20}$ = - 0.3 (c = 0.4, CH_2Cl_2).

Syn isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23-8.19 (m, 2H), 7.58-7.54 (m, 2H), 5.16 (d, *J* = 8.4 Hz, 1H), 4.79-4.67 (m, 1H), 3.24 (s, 1H), 1.35 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.2, 145.5, 128.1, 124.2, 87.9, 75.2, 16.3.

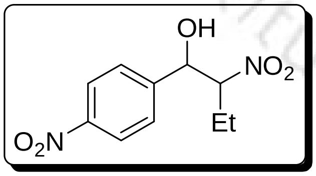
Anti isomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23-8.19 (m, 2H), 7.58-7.54 (m, 2H), 5.53 (d, *J* = 3.2 Hz, 1H), 4.76-4.67 (m, 1H), 3.24 (s, 1H), 1.46 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.1, 145.7, 127.2, 124.0, 86.9, 73.0, 12.0.

FT-IR (KBr): ν 3448, 1556, 1522, 1344 cm^{-1}.

Anal. Calcd for $C_9H_{10}N_2O_5$: C, 47.79; H, 4.46; N, 12.39. Found: C, 47.85; H, 4.47; N, 12.43.

HPLC: Chiralcel OD-H column, n-hexane/isopropanol (85:15), wavelength: 215 nm, flow rate: 0.3 mL/min, retention time: 32.6 min, 38.2 min, 41.0 min, 42.5 min; 56:44, 64:36 er.



2-Nitro-1-(4-nitrophenyl)butanol (Table 1, entry 9). A mixture of 4-nitrobenzaldehyde (75.5 mg, 0.5 mmol), 1-nitropropane (445.4 mg, 5 mmol), and catalyst **17e** (9.8 mg, 2.5 mol %) in CH_2Cl_2 (1 mL) was subjected to the reaction conditions described in the general procedure for 48 h and the residue was purified on silica gel column chromatography using 4:1 hexane/ethyl acetate to afford the title compound (54.0 mg, 45 %, *syn*/*anti* 55:45) as colorless solid.

Mp: 97–98 ˚C.

$[\alpha]_D^{20} = -0.2$ (c = 0.28, CH_2Cl_2).

Syn isomer: ^1H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, *J* = 8.8 Hz, 2H), 7.57 (d, *J* = 8.8 Hz, 2H), 5.17-5.13 (m, 1H), 4.61-4.56 (m, 1H), 2.96 (d, *J* = 0.8 Hz, 1H), 1.50-1.41 (m, 2H), 0.90 (t, *J* = 0.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.4, 145.8, 128.0, 124.3, 94.7, 74.4, 24.0, 10.5.

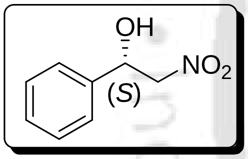
Anti isomer: ^1H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, *J* = 8.8 Hz, 2H), 7.57 (d, *J* = 8.8 Hz, 2H), 5.17-5.13 (m, 1H), 4.61-4.56 (m, 1H), 2.96 (d, *J* = 0.8 Hz, 1H), 1.94-1.84 (m, 2H), 0.90 (t, *J* = 0.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.4, 145.8, 127.4, 128.0, 94.3, 73.4, 21.4, 10.2.

FT-IR (KBr): ν 3460, 1557, 1520, 1345 cm^{-1}.

Anal. Calcd for $C_{10}H_{12}N_2O_5$: C, 50.00; H, 5.04; N 11.66. Found: C, 50.03; H, 5.05; N, 11.70.

HPLC: Chiralcel OD-H column, n-hexane/isopropanol (85:15), wavelength: 215 nm, flow rate: 0.3 mL/min, retention time: 29.6 min, 32.2 min, 33.5 min, 35.2 min; 55:45, 59:41 er.



(*S*)-(+)-2-Nitro-1-phenylethanol (Table 3, entry 1).[27a] A mixture of benzaldehyde (53.0 mg, 0.5 mmol), nitromethane (305.2 mg, 5 mmol), and catalyst **17e** (9.8 mg, 2.5 mol %) in CH_2Cl_2 (1 mL) was subjected to the reaction conditions reported in the general procedure for 28 h and the residue was purified on silica gel column chromatography using 4:1 hexane/ethyl acetate to yield the title compound (76.8 mg, 92 %) as yellow oil.

$[\alpha]_D^{20} = +10$ (c = 0.1, CH_2Cl_2).

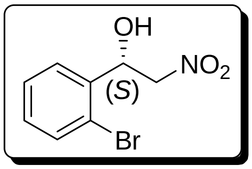
^1H NMR (400 MHz, $CDCl_3$): δ 7.39 (m, 5H), 5.46 (m, 1H), 4.63-4.48 (m, 2H), 3.03 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.3, 129.1, 129.0, 126.1, 81.3, 71.0.

FT-IR (neat): ν 3430, 1555, 1347 cm^{-1}.

Anal. Calcd for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.53; H, 5.45, N, 8.44.

HPLC: Chiralcel OD-H column, n-hexane/isopropanol (85:15), wavelength: 215 nm, flow rate: 0.6 mL/min, retention time: 34.1 min, 39.5 min; 60:40 er.



(*S*)-(+)-2-Nitro-1-(2-bromophenyl)ethanol (Table 3, entry 2).[27b,c] A mixture of 2-bromobenzaldehyde (92.5 mg, 0.5 mmol), nitromethane (305.2 mg, 5 mmol), and catalyst **17e** (9.8 mg, 2.5 mol %) in CH_2Cl_2 (1 mL) was subjected to the reaction conditions shown in the general procedure for 20 h and the residue was purified on silica gel column chromatography using 4:1 hexane/ethyl acetate to provide the title compound (144.4 mg, 93 %) as colorless oil.

$[\alpha]_D^{20}$ = + 3.5 (c = 1, $CHCl_3$).

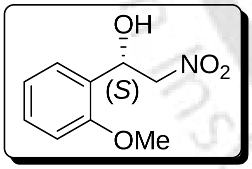
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67-7.65 (m, 1H), 7.57 (d, *J* = 8 Hz, 1H), 7.42-7.38 (t, *J* = 7.2 Hz, 1H), 7.26-7.21 (m, 1H), 5.82-5.79 (m, 1H), 4.71-4.66 (m, 1H), 4.46- 4.39 (m, 1H), 3.16 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.0, 134.3, 133.1, 130.4, 128.3, 127.9, 79.5, 75.3.

FT-IR (neat): ν 3445, 1563, 1340 cm^{-1}.

Anal. Calcd for $C_8H_8NO_3Br$: C, 39.05; H, 3.28; N, 5.69. Found: C, 39.12; H, 3.30; N, 5.74.

HPLC: Chiralcel OD-H column, n-hexane/isopropanol (85:15), wavelength: 215 nm, flow rate: 0.8 mL/min, retention time: 11.43 min, 12.14 min; 55:45 er.

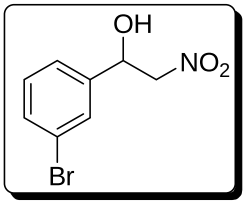


(*S*)-(+)-2-Nitro-1-(2-methoxyphenyl)ethanol (Table 3, entry 3).[27c] A mixture of 2-methoxybenzaldehyde (68.07 mg, 0.5 mmol), nitromethane (305.2 mg, 5 mmol), and catalyst **17e** (9.8 mg, 2.5 mol %) in CH_2Cl_2 (1 mL) was subjected to the reaction conditions reported in the general procedure for 34 h and the residue was purified on silica gel column chromatography using 4:1 hexane/ethyl acetate to afford the title compound (87.7 mg, 89 %) as yellow oil.

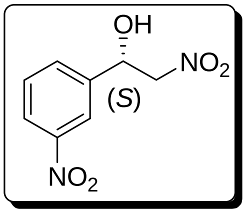
$[\alpha]_D^{20}$ = + 12 (c = 1.06, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 7.4 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.02 (t, *J* = 7.0 Hz, 1H), 6.92 (d, *J* = 8.2 Hz, 1H), 5.67-5.61 (m, 1H), 4.67-4.56 (m, 1H), 3.91(s, 3H), 3.10 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.5, 156.6, 131.1, 128.3, 122.3, 111.6, 80.7, 68.6, 56.1.
FT-IR (neat): ν 3432, 1570, 1365 cm^{-1}.
Anal. Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.90; H, 5.65; N, 7.17.
HPLC: Chiralcel OD-H column, n-hexane/isopropanol (85:15), wavelength: 215 nm, flow rate: 0.8 mL/min, retention time: 12.5 min, 14.3 min; 65:35 er.



(+)-2-Nitro-1-(3-bromophenyl)ethanol (Table 3, entry 4).[27d] A mixture of 3-bromobenzaldehyde (92.5 mg, 0.5 mmol), nitromethane (305.2 mg, 5 mmol), and catalyst **17e** (9.8 mg, 2.5 mol %) in CH_2Cl_2 (1 mL) was subjected to the reaction conditions described in the general procedure for 30 h and the residue was purified on silica gel column chromatography using 4:1 hexane/ethyl acetate to give the title compound (104.5 mg, 85 %) as yellow oil.
$[\alpha]_D^{20}$ = + 2 (c = 1, CH_2Cl_2).
^1H NMR (400 MHz, $CDCl_3$): δ 7.58 (s, 1H), 7.50-7.47 (m, 1H), 7.33-7.25 (m, 2H), 5.45-5.42 (m, 1H), 4.60-4.48 (m, 2H), 3.1 (s, 1H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 140.5, 132.1, 130.7, 129.2, 124.7, 123.1, 81.1, 70.3.
FT-IR (neat): ν 3437, 1557, 1343 cm^{-1}.
Anal. Calcd for $C_8H_8NO_3Br$: C, 39.05; H, 3.28; N, 5.69. Found: C, 39.08, H, 3.30; N, 5.73.
HPLC: Chiralcel OD-H column, n-hexane/isopropanol (85:15), wavelength: 215 nm, flow rate: 1 mL/min, retention time: 17.45 min, 23.1 min. 60:40 er.



(*S*)-(+)-2-Nitro-1-(3-nitrophenyl)ethanol (Table 3, entry 5).[27a] A mixture of 3-nitrobenzaldehyde (75.5 mg, 0.5 mmol), nitromethane (305.2 mg, 5 mmol), and catalyst **17e** (9.8 mg, 2.5 mol %) in CH_2Cl_2 (1 mL) was subjected to the reaction conditions shown in the general procedure for 26 h and the residue was purified on silica gel column chromatography using 4:1 hexane/ethyl acetate to give the title compound (94.5 mg, 90 %) as yellow oil.

$[\alpha]_D^{20} = + 14$ (c = 0.4, CH_2Cl_2).

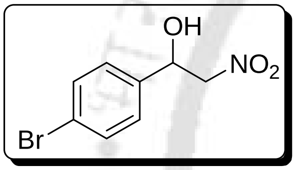
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (s, 1H), 8.21 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.61 (t, *J* = 8.0 Hz, 1H), 5.61 (m, 1H), 4.67-4.57 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.6, 140.4, 132.2, 130.3, 123.9, 121.3, 80.9, 70.0.

FT-IR (KBr): ν 3539, 1566, 1520, 1355 cm^{-1}.

Anal. Calcd for $C_8H_8N_2O_5$: C, 45.29; H, 3.80; N, 13.20. Found: C, 45.37; H, 3.78; N, 13.25.

HPLC: Chiralcel OD-H column, n-hexane/isopropanol (85:15), wavelength: 215 nm, flow rate: 1 mL/min, retention time: 21.8 min, 24.4 min; 76:24 er.



(+)-2-Nitro-1-(4-bromophenyl)ethanol (Table 3, entry 6).[27e] A mixture of 4-bromobenzaldehyde (92.5 mg, 0.5 mmol), nitromethane (305.2 mg, 5 mmol), and catalyst **17e** (9.8 mg, 2.5 mol %) in CH_2Cl_2 (1 mL) was subjected to the raction conditions reported in the general procedure for 24 h and the residue was purified on silica gel column chromatography using 4:1 hexane/ethyl acetate to give the title compound (116.8 mg, 95 %) as yellow oil.

$[\alpha]_D^{20} = + 1.5$ (c = 0.5, CH_2Cl_2).

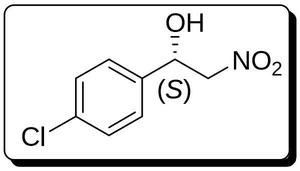
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54-7.52 (m, 2H), 7.30-7.25 (m, 2H), 5.45-5.42 (m, 1H), 4.59-4.46 (m, 2H), 3.00 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.5, 132.7, 128.1, 123.4, 81.4, 70.8.

FT-IR (neat): ν 3445, 1558, 1349 cm^{-1}.

Anal. Calcd for $C_8H_8NO_3Br$: C, 39.05; H, 3.28; N, 5.69. Found: C, 39.10; H, 3.29; N, 5.72.

HPLC: Chiralcel OD-H column, n-hexane/isopropanol (85:15), wavelength: 215 nm, flow rate: 0.8 mL/min, retention time: 15.7 min, 18.9 min; 58:42 er.



(*S*)-(+)-2-Nitro-1-(4-chlorophenyl)ethanol (Table 3, entry 7).[27a] A mixture of 4-chlorobenzaldehyde (70.2 mg, 0.5 mmol), nitromethane (305.2 mg, 5 mmol), and catalyst **17e** (9.8 mg, 2.5 mol %) in CH_2Cl_2 (1 mL) was subjected to the reaction conditions described in the general procedure for 23 h and the residue was purified on silica gel column chromatography using 4:1 hexane/ethyl acetate to give the title compound (90.7 mg, 90 %) as yellow oil.

$[\alpha]_D^{20}$ = + 2 (c = 0.5, CH_2Cl_2).

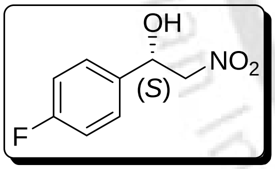
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.32 (m, 4H), 5.44-5.41 (m, 1H), 4.59-4.46 (m, 2H), 3.28 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 136.7, 134.7, 129.2, 127.4, 81.1, 70.3.

FT-IR (neat): ν 3430, 1560, 1378 cm^{-1}.

Anal. Calcd for $C_8H_8NO_3Cl$: C, 47.66; H, 4.00; N, 6.95. Found: C, 47.75, H 4.01, N 7.06.

HPLC: Chiralcel OD-H column, n-hexane/isopropanol (85:15), wavelength: 215 nm, flow rate: 0.8 mL/min, retention time: 12.8 min, 16.09 min; 54:46 er.



(*S*)-(+)-2-Nitro-1-(4-fluorophenyl)ethanol (Table 3, entry 8).[27f] A mixture of 4-fluorobenzaldehyde (62.0 mg, 0.5 mmol), nitromethane (305.2 mg, 5 mmol), and catalyst **17e** (9.8 mg, 2.5 mol %) in CH_2Cl_2 (1 mL) was subjected to the reaction conditions shown in the general procedure for 22 h and the residue was purified on silica gel column chromatography using 4:1 hexane/ethyl acetate to give the title compound (87.0 mg, 94 %) as yellow oil.

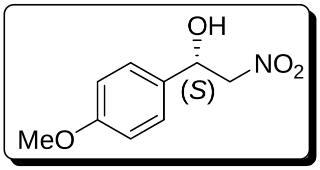
$[\alpha]_D^{20}$ = + 1.7 (c = 0.8, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.37 (m, 2H), 7.10-7.05 (m, 2H), 5.46-5.42 (dd, J = 3.2, 5.2 Hz, 1H), 4.59-4.45 (m, 2H), 2.90 (s, 1H).

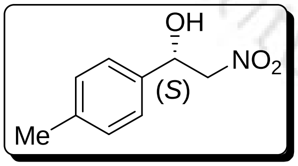
^{13}C NMR (100 MHz, $CDCl_3$): δ 128.0, 127.9, 116.3, 116.1, 81.3, 70.5.

FT-IR (neat): ν 3425, 1557, 1511, 1342 cm^{-1}.

Anal. Calcd for $C_8H_8NO_3F$: C, 51.90; H, 4.36; N, 7.56. Found: C, 51.97; H, 4.38; N, 7.60.
HPLC: Chiralcel OD-H column, n-hexane/isopropanol (85:15), wavelength: 215 nm, flow rate: 0.8 mL/min, retention time: 12.1 min, 14.0 min; 55:45 er.



(*S*)-(+)-2-Nitro-1-(4-methoxyphenyl)ethanol (Table 3, entry 9).[27c] A mixture of 4-methoxybenzaldehyde (68.0 mg, 0.5 mmol), nitromethane (305.2 mg, 5 mmol), and catalyst **17e** (9.8 mg, 2.5 mol %) in CH_2Cl_2 (1 mL) was subjected to the reaction conditions reported in the general procedure for 38 h and the residue was purified on silica gel column chromatography using 4:1 hexane/ethyl acetate to give the title compound (82.8 mg, 84 %) as yellow oil.
$[\alpha]_D^{20}$ = + 10 (c = 1.4, CH_2Cl_2).
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 5.40 (d, *J* = 9.2 Hz, 1H), 4.61-4.44 (m, 2H), 3.79 (s, 3H), 2.73 (d, *J* = 3.2 Hz, 1H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 130.4, 127.4, 114.5, 81.4, 70.8, 55.5.
FT-IR (neat): ν 3445, 1559, 1377 cm^{-1}.
Anal. Calcd for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 54.87; H, 5.64; N, 7.15.
HPLC: Chiralcel OD-H column, n-hexane/isopropanol (85:15), wavelength: 215 nm, flow rate: 0.8 mL/min, retention time: 16.9 min, 21.7 min; 66:34 er.



(*S*)-(+)-2-Nitro-1-(4-methylphenyl)ethanol (Table 3, entry 10).[27g] A mixture of 4-methylbenzaldehyde (60.0 mg, 0.5 mmol), nitromethane (305.2 mg, 5 mmol), and catalyst **17e** (9.8 mg, 2.5 mol %) in CH_2Cl_2 (1 mL) was subjected to the reaction conditions described in the general procedure for 30 h and the residue was purified on silica gel column chromatography using 4:1 hexane/ethyl acetate to give the title compound (81.5 mg, 90 %) as colorless oil.
$[\alpha]_D^{20}$ = + 8 (c = 1, CH_2Cl_2).

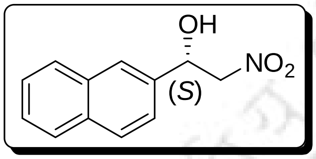
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29-7.19 (m, 4H), 5.44-5.41 (dd, *J* = 9.6, 2.4 Hz, 1H), 4.63-4.46 (m, 2H), 2.90 (s, 1H), 2.36 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 139.0, 135.3, 129.8, 126.0, 81.4, 71.0, 21.3.

FT-IR (neat): ν 3422, 1557, 1380 cm^{-1}.

Anal. Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.72; H, 6.13; N, 7.77.

HPLC: Chiralcel OD-H column, n-hexane/isopropanol (90:10), wavelength: 215 nm, flow rate: 0.8 mL/min, retention time: 16.5 min, 21.2 min; 64:36 er.



(*S*)-(+)-2-Nitro-1-naphthylethanol (Table 4, entry 1).[27g] A mixture of naphthaldehyde (78.0 mg, 0.5 mmol), nitromethane (305.2 mg, 5 mmol), and catalyst **17e** (9.8 mg, 2.5 mol %) in CH_2Cl_2 (1 mL) was subjected to the reaction conditions shown in the general procedure for 36 h and the residue was purified on silica gel column chromatography using 4:1 hexane/ethyl acetate to yield the title compound (87.9 mg, 81 %) as yellow oil.

$[\alpha]_D^{20}$ = + 10 (c = 1, CH_2Cl_2).

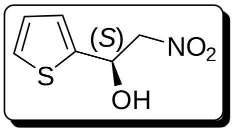
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88-7.84 (m, 4H), 7.54-7.51 (m, 2H), 7.47-7.44 (m, 1H), 5.62-5.59 (m, 1H), 4.71-4.56 (m, 2H), 3.11 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 135.6, 133.6, 133.4, 129.2, 128.3, 128.0, 126.9, 126.9, 125.5, 123.4, 81.4, 71.3.

FT-IR (neat): ν 3422, 1555, 1512, 1342 cm^{-1}.

Anal. Calcd for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.43; H, 5.12; N, 6.46.

HPLC: Chiralcel OD-H column, n-hexane/isopropanol (85:15), wavelength: 215 nm, retention time: 34.4 min, 49.7 min; flow rate: 0.8 mL/min, 61:39 er.



(*S*)-(-)-2-Nitro-1-(2-thiophenyl)ethanol (Table 4, entry 2).[27h] A mixture of 2-thiophenecarboxaldehyde (56.0 mg, 0.5 mmol), nitromethane (305.2 mg, 5 mmol), and catalyst **17e** (9.8 mg, 2.5 mol %) in CH_2Cl_2 (1 mL) was subjected to the reaction conditions reported in the general procedure for 30 h and the residue was purified on silica gel column chromatography using 4:1 hexane/ethyl acetate to give the title compound (56.2 mg, 65 %) as yellow oil.

$[\alpha]_D^{20}$ = - 2.5 (c = 0.2, CH_2Cl_2).

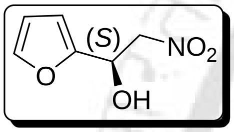
^1H NMR (400 MHz, $CDCl_3$): δ 7.33-7.31 (m, 1H), 7.06-7.04 (m, 1H), 7.01-6.99 (m, 1H), 5.72-5.70 (m, 1H), 4.73-4.57 (m, 2H), 3.00 (d, J = 4.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 141.5, 127.3, 126.2, 125.1, 81.0, 67.2.

FT-IR (neat): ν 3416, 1618, 1557, 1415, 1380 cm^{-1}.

Anal. Calcd for $C_6H_7NO_3S$: C, 41.61; H, 4.07; N, 8.09. Found: C, 41.66; H, 4.08; N, 8.15.

HPLC: Chiralcel OD-H column, n-hexane/isopropanol (85:15), wavelength: 215 nm, flow rate: 1 mL/min, retention time: 9.6 min, 10.4 min; 54:46 er.



(*S*)-(-)-2-Nitro-1-(2-furanyl)ethanol (Table 4, entry 3).[27h] A mixture of 2-furaldehyde (48.01 mg, 0.5 mmol), nitromethane (305.2 mg, 5 mmol), and catalyst **17e** (9.8 mg, 2.5 mol %) in CH_2Cl_2 (1 mL) was subjected to the reaction conditions reported in the general procedure for 16 h and the residue was purified on silica gel column chromatography using 4:1 hexane/ethyl acetate to provide the title compound (58.1 mg, 74 %) as yellow oil.

$[\alpha]_D^{20}$ = - 7 (c = 0.5, CH_2Cl_2).

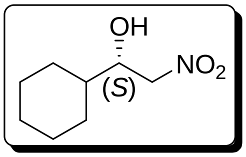
^1H NMR (400 MHz, $CDCl_3$): δ 7.39 (t, J = 0.8 Hz, 1H), 6.38-6.35 (m, 2H), 5.47-5.44 (m, 1H), 4.79-4.63 (m, 2H), 2.94 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 151.0, 143.3, 110.8, 108.3, 78.6, 65.0.

FT-IR (neat): ν 3430, 1615, 1563, 1410, 1385 cm^{-1}.

Anal. Calcd for $C_6H_7NO_3S$: C, 45.86; H, 4.49; N, 8.91. Found: C, 45.95; H, 4.50; N, 8.96.

HPLC: Chiralpak AD-H column, n-hexane/isopropanol (95:5), wavelength: 215 nm, flow rate: 1 mL/min, retention time: 26.6 min, 28.1 min; 55:45 er.



(*S*)-(+)-2-Nitro-1-cyclohexylethanol (Table 4, entry 4).[27f] A mixture of cyclohexanecarboxaldehyde (56.08 mg, 0.5 mmol), nitromethane (305.2 mg, 5 mmol), and catalyst **17e** (9.8 mg, 2.5 mol %) in CH_2Cl_2 (1 mL) was subjected to the reaction conditions shown in the general procedure for 24 h and the residue was purified on silica gel column chromatography using 4:1 hexane/ethyl acetate to give the title compound (77.0 mg, 89 %) as yellow oil.

$[\alpha]_D^{20}$ = + 3.5 (c = 2, CH_2Cl_2).

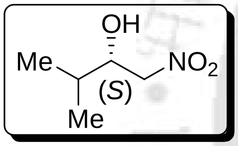
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.51-4.40 (m, 2H), 4.10-4.09 (m, 1H), 2.51-2.49 (d, *J* = 5.2 Hz, 1H), 1.85-1.03 (m, 11H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 79.5, 73.0, 41.6, 29.0, 28.1, 26.2, 26.1, 25.9.

FT-IR (neat): ν 3432, 1550, 1384 cm^{-1}.

Anal. Calcd for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09. Found: C, 55.52; H, 8.79; N, 8.17.

HPLC: Chiralpak AD-H column, n-hexane/isopropanol (97:3), wavelength: 215 nm, flow rate: 0.8 mL/min, retention time: 33.2 min, 35.8 min; 68:32 er.



(*S*)-(+)-3-Methyl-1-nitro-2-butanol (Table 4, entry 5).[27a] A mixture of isobutyraldehyde (36.0 mg, 0.5 mmol), nitromethane (305.2 mg, 5 mmol), and catalyst **17e** (9.8 mg, 2.5 mol %) in CH_2Cl_2 (1 mL) was subjected to the reaction conditions described in the general procedure for 20 h and the residue was purified on silica gel column chromatography using 4:1 hexane/ethyl acetate to give the title compound (57.2 mg, 86 %) as colorless oil.

$[\alpha]_D^{20}$ = + 1.2 (c = 0.45, CH_2Cl_2).

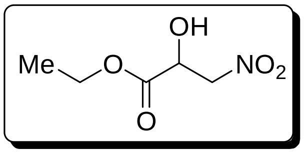
^{1}H NMR (400 MHz, $CDCl_3$): δ 4.49-4.38 (m, 2H), 4.11 (m, 1H), 2.48 (s, 1H), 1.83-1.78 (m, 1H), 1.01-0.98 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 79.4, 73.5, 31.9, 18.6, 17.6.

FT-IR (neat): ν 3420, 1558, 1380 cm^{-1}.

Anal. Calcd for $C_5H_{11}NO_3$: C, 45.10; H, 8.33; N, 10.52. Found: C, 45.16; H, 8.35; N, 10.58.

HPLC: Chiralpak AD-H column, n-hexane/isopropanol (95:5), wavelength: 215 nm, flow rate: 1 mL/min, retention time: 11.5 min, 15.6 min; 64:36 er.



(-)-2-Hydroxy-3-nitropropanoic acid ethyl ester (Table 4, entry 6).[27i] A mixture of ethyl glyoxalate (51.0 mg, 0.5 mmol), nitromethane (305.2 mg, 5 mmol), and catalyst **17e** (9.8 mg, 2.5 mol %) in CH_2Cl_2 (1 mL) was subjected to the reaction conditions shown in the general procedure for 30 h and the residue was purified on silica gel column chromatography using 4:1 hexane/ethyl acetate to afford the title compound (4.8 mg, 55 %) as colorless solid.

$[\alpha]_D^{20}$ = - 0.5 (c = 0.38, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.75-4.74 (m, 2H), 4.60 (m, 1H), 4.37-4.28 (m, 2H), 3.35 (s, 1H), 1.31 (t, J = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 77.0, 67.6, 62.8, 13.9.

FT-IR (neat): ν 3417, 1555, 1385 cm^{-1}.

Anal. Calcd for $C_5H_9NO_5$: C, 36.81; H, 5.56; N, 8.59. Found: C, 36.86. H, 5.55; N, 8.65.

HPLC: Chiralcel OD-H column, n-hexane/isopropanol (85:15), wavelength: 215 nm, flow rate: 1 mL/min, retention time: 8.1 min, 8.6 min; 57:43 er.

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Crystal Structure and Analysis of complex 17e

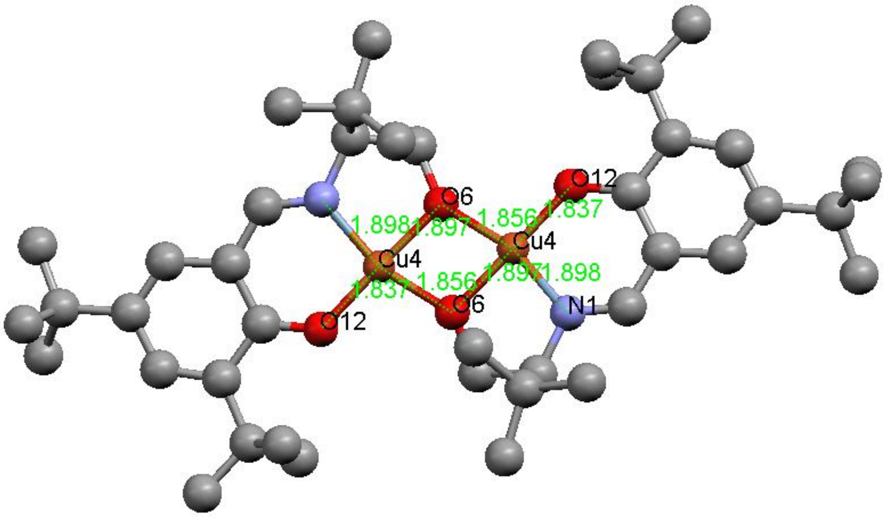


Figure 4. Ball and Stick Model of Complex **17e** Showing Bond Distances.

Cu4-O6 = 1.856 (bridged) Cu4-O12 =1.837(terminal) Cu4-N1 = 1.898 (terminal)

Cu4 - O6 = 1.897(bridged) Cu4-Cu4 = 2.907 Å

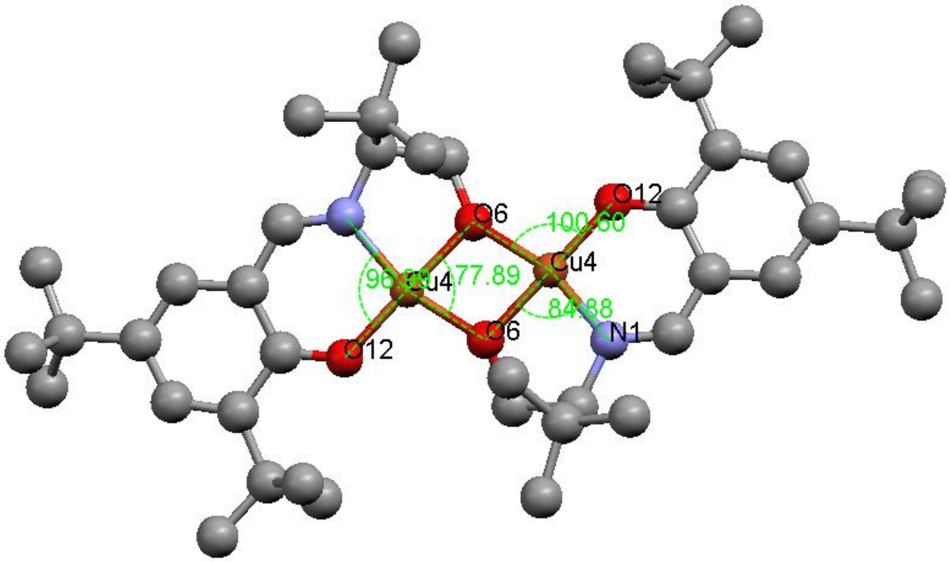


Figure 5. Ball and Stick Model of Complex **17e** Showing Bond Angles.

N1-Cu4-O12 = 96.99° O6-Cu4-O6 =77.89° Cu4-O6-Cu4 =101.5° O6-Cu4-O12 =100.6°

N1- Cu4-O6 =84.88°

Crystal Data and Structure Refinement of 17e

Identification code	tp04_0m	
Empirical formula	$C_{42}H_{66}Cu_2N_2O_4$	
Formula weight	790.05	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C_2	
Unit cell dimensions	a = 31.671(5) Å	α= 90°.
	b = 10.5061(16) Å	β= 112.432(9)°.
	c = 28.397(4) Å	γ = 90°.
Volume	8734 (2) $Å^3$	
Z	8	
Density (calculated)	1.202 Mg/m^3	
Absorption coefficient	1.012 mm^{-1}	
F(000)	3376	
Crystal size	0.51 x 0.20 x 0.11 mm^3	
Theta range for data collection	1.39 to 28.38°.	
Index ranges	-39<=h<=42, -14<=k<=13, -33<=l<=37	
Reflections collected	24401	
Independent reflections	14718 [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	14718 / 1 / 938	
Goodness-of-fit on F^2	0.864	
Final R indices [I>2sigma(I)]	R1 = 0.0646, wR2 = 0.1608	
R indices (all data)	R1 = 0.1107, wR2 = 0.1858	
Absolute structure parameter	0.025(18)	
Extinction coefficient	0.00129(14)	
Largest diff. peak and hole	0.742 and -0.550 e.$Å^{-3}$	

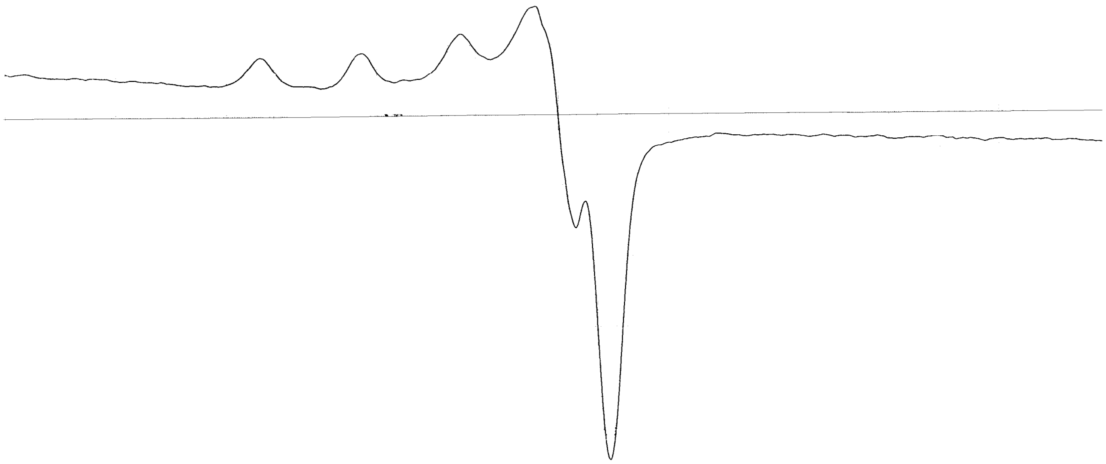


Figure 6. EPR Spectrum of Complex **17e** Recorded at Liquid N_2 Temperature in MeOH.

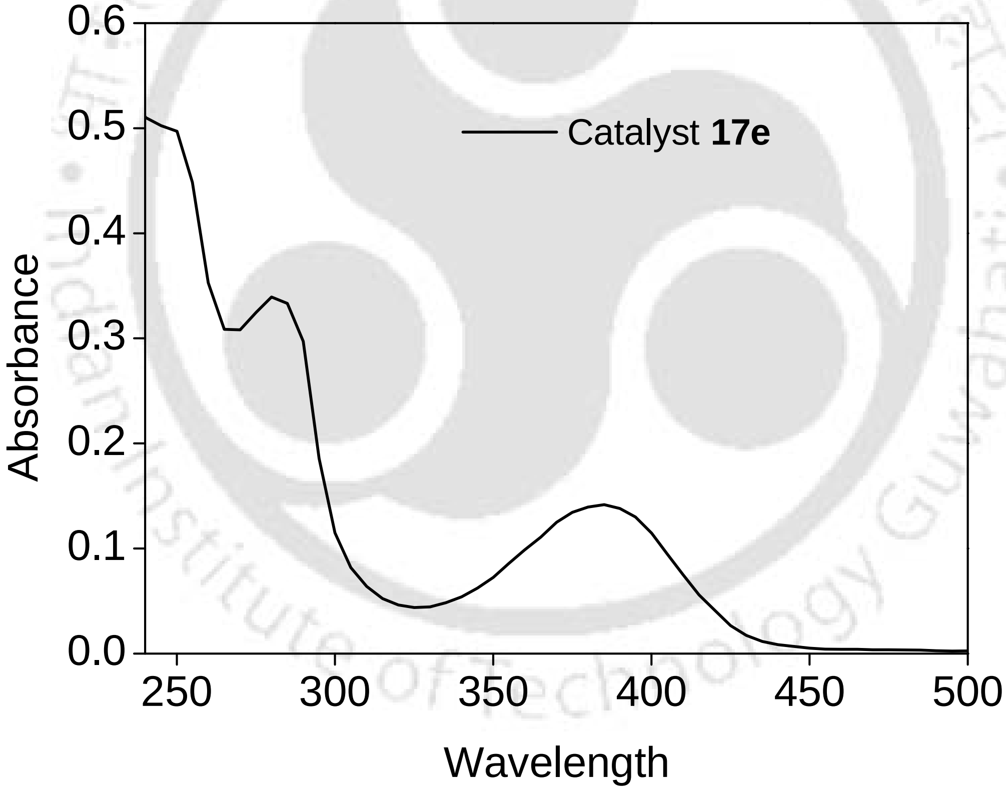
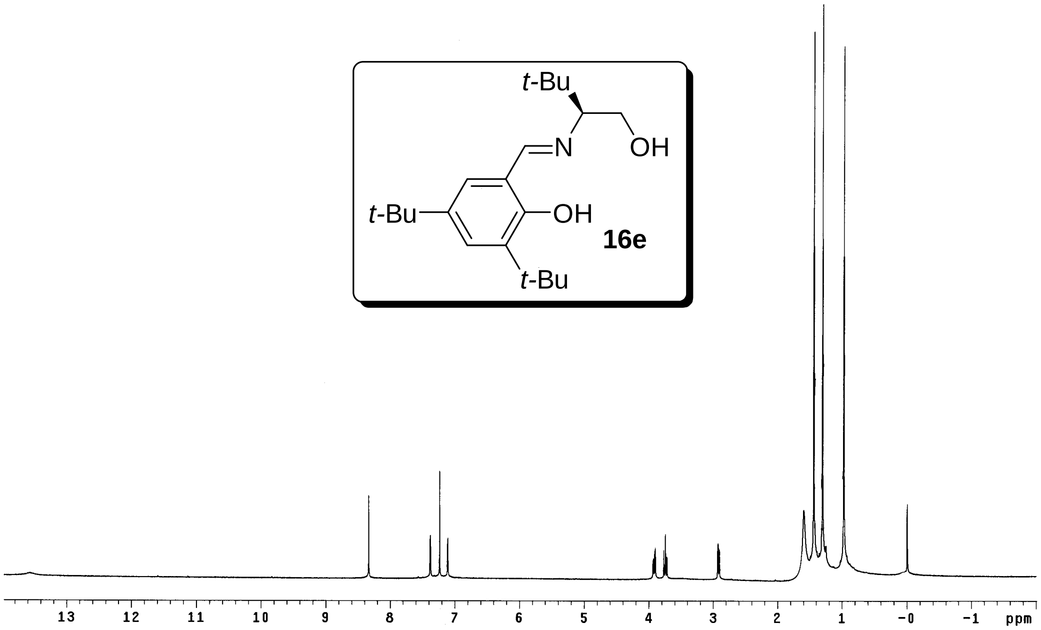


Figure 7. UV-vis Spectrum of **17e** in CH_2Cl_2.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7
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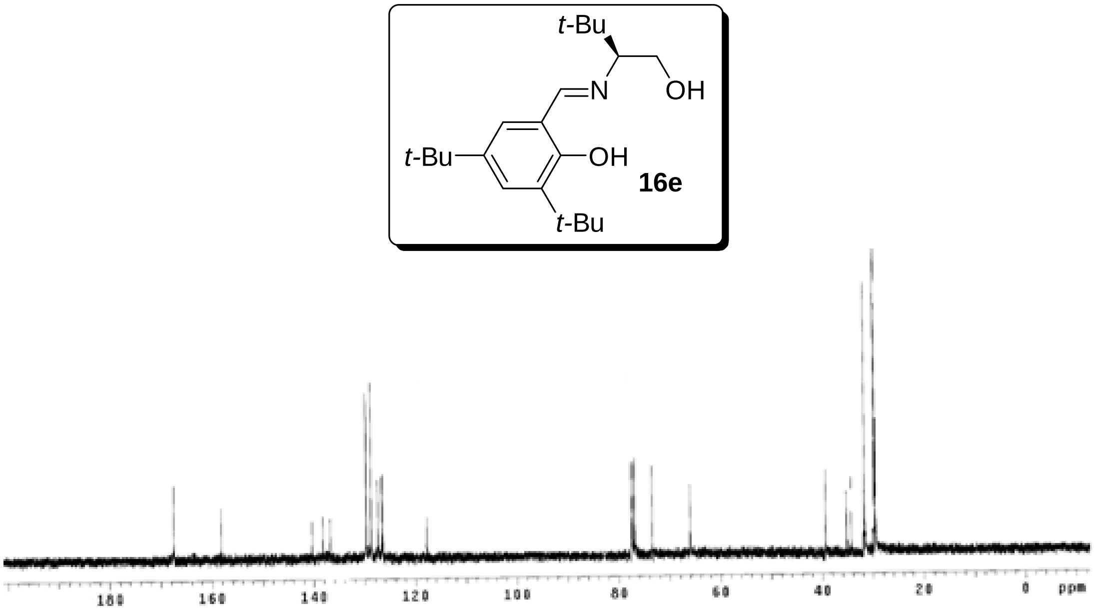
1
-0
-1
ppm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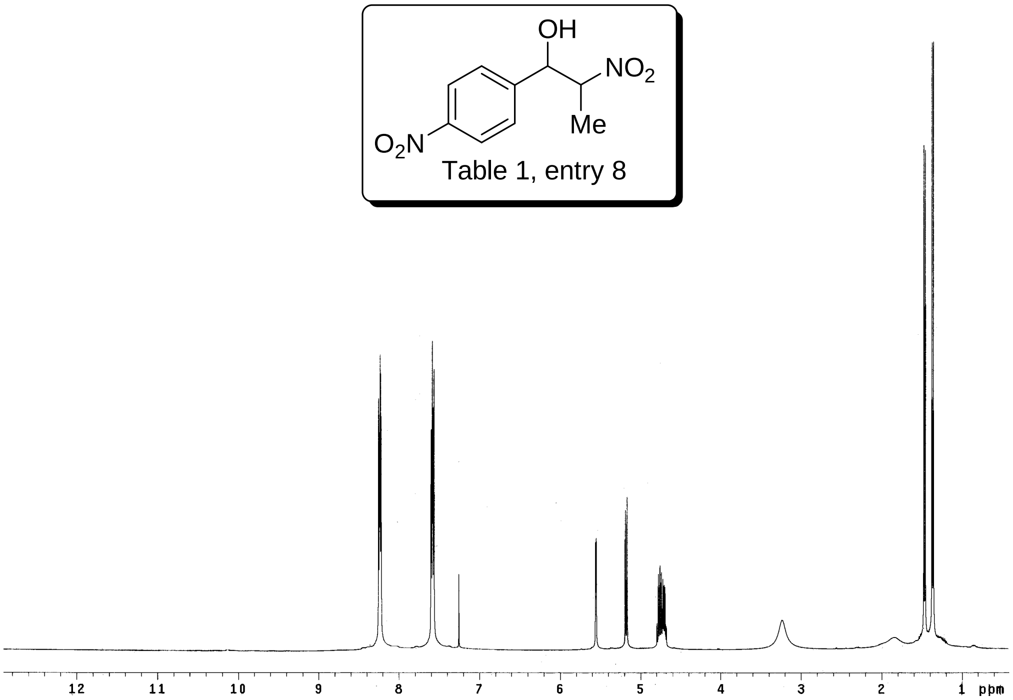
ppm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7
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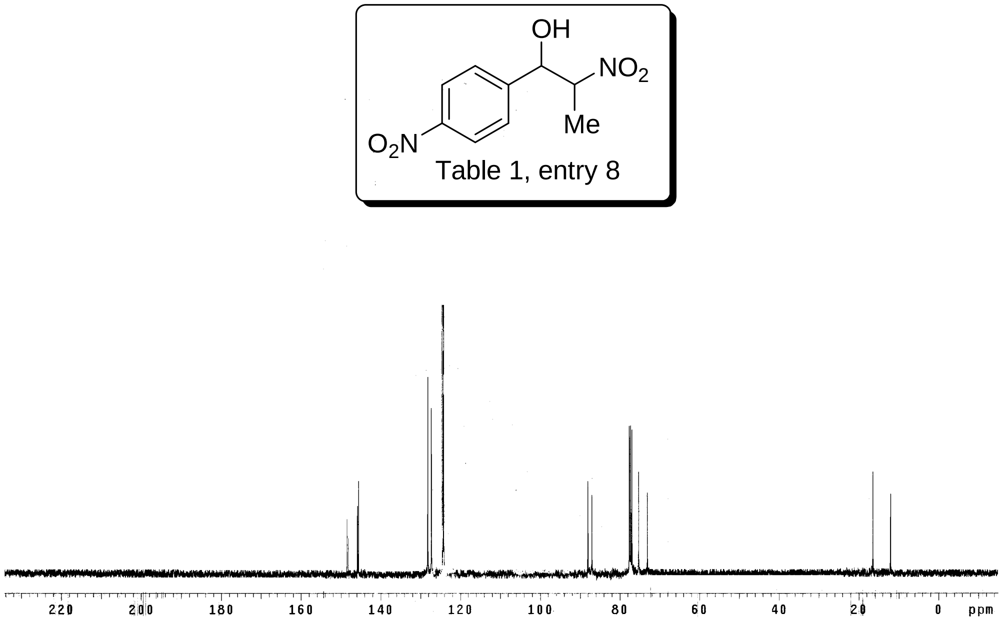
1
ppm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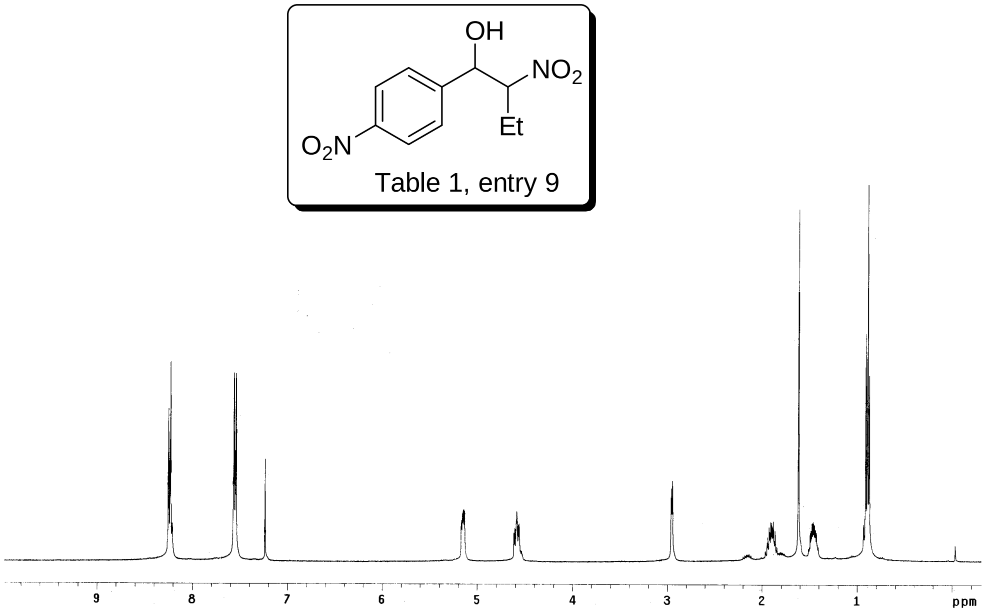
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4
3
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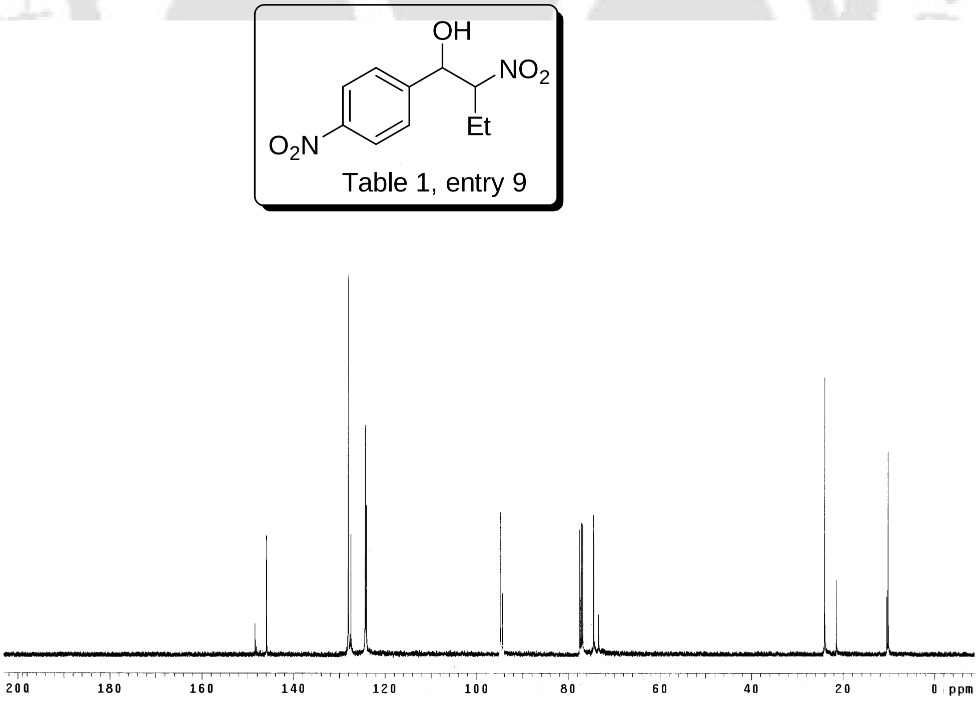
1
ppm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Et
O2N
Table 1, entry 9
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180
160
140
120
100
80
60
40
20
0 ppm

Chapter IV

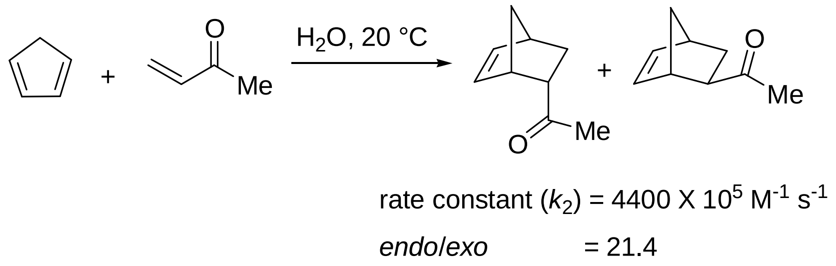
Self-Assembly and Application of Copper(II) Complexes for Acceleration of Nitroaldol Reaction "On Water"

"Green Chemistry" is a central issue, in both academia and industry, with regard to chemical synthesis in the 21st century. To ensure compatibility with conservation of global environment, chemical processes are required to be changed to green processes, which include atom economy, use of safer solvents, reagents and processes. Most of the organic solvents are flammable or toxic. Hence the process, which avoids the use of volatile organic solvents, will gain importance in modern days.

Water plays an essential role in life processes and is the solvent of choice for nature to carry out her synthesis. In contrast, its use as a solvent for organic synthesis has been limited. Indeed, it is fair to say that most of the organic reactions commonly used both in academic laboratories and industry fail in the presence of water or oxygen, despite the fact that water possesses many unique physical and chemical properties: a large temperature window in which it remains in the liquid state, extensive hydrogen bonding, high heat capacity, large dielectric constant and optimum oxygen solubility to maintain aquatic life forms. These distinctive properties are the consequence of the unique structure of water.[1] The structure and properties of water have been studied by scientists representing almost all fields of knowledge, and new theoretical models continue to emerge.[2] Water is also non-toxic, safer, more abundant, cheap and known to affect the rates and selectivity of a wide variety of organic reactions.[3] In spite of these potential advantages, water is still not commonly used as a sole solvent for organic synthesis, because most organic compounds do not dissolve in water to a significant extent, and solubility is generally considered a prerequisite for reactivity. The use of water as a medium for organic reactions is therefore one of the latest challenges for modern organic chemists. The solubility of reacting species and products in water can range from complete to partial to practically none, so that reaction mixtures can be both homogeneous and heterogeneous. The amount of water can also range widely, from substoichiometric quantities to a large volume in which the reactants are suspended or dissolved. Several terms have been used in the literature to describe reactions in aqueous media. *In water*, *in the presence of water*, and *on water* are commonly found in the recent publications and are often used interchangeably to describe reactions that proceed under very different conditions.[4] The field of aqueous organic synthesis has been regularly and comprehensively reviewed.[3b,5] In addition, recent reviews focusing on microwave-assisted organic synthesis in water,[6] reactions in near-critical water[7] and biocatalysis in water[8] have been published. This section of the thesis describes different organic reactions performed "on water" from literature of the past few years under the conditions defined by Sharpless and co-workers: when insoluble reactant(s) are stirred in aqueous emulsions or suspensions without the addition of any organic co-solvent.[9]

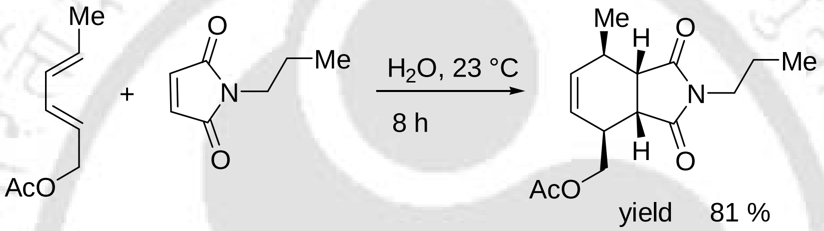
4.1 Diels-Alder Reaction

Diels-Alder reaction has proven to be of great synthetic value, forming a key-step in the construction of compounds containing six-membered rings. In 1939, Hopff and Rautenstrauch disclosed that Diels-Alder reaction can be efficiently carried out in an aqueous media.[10a] In 1980, Rideout and Breslow achieved both rate enhancement and excellent selectivity of Diels-Alder reaction between cyclopentadiene and butanone in water. The authors also studied the effect of different additives like lithium chloride, guanidinium chloride and cyclodextrins on this reaction. Among these additives, they have found that the reaction was accelerated in 4.86 M LiCl solution (Scheme 1).[10b] This observed rate increase is due to hydrophobic association of diene with dienophile. In subsequent study,[10c] the same authors demonstrated that, in addition to the enhanced rate of the reaction, the *endo* selectivity of the cycloaddition between the cyclopentadiene and butanone was also much higher in water than in ethanol as well as in the absence of a solvent. These reactions were performed at a higher concentration (0.15 M for both reactants) to keep the reaction mixture as heterogeneous in water. This could be the first example for on water reaction for which a significant rate enhancement and a much higher selectivity were achieved simply by using water to support the reaction of two insoluble substances.



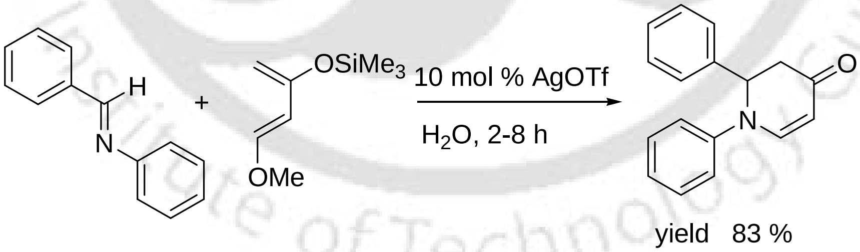
Scheme 1

In 2005, Sharpless and co-workers demonstrated the “on water” effect on the Diels-Alder reaction of *trans*,*trans*-2,4-hexadienyl acetate with *N*-propylmaleimide. The reaction shows enhanced reactivity on water compared to that in organic solvent (Scheme 2).[10d]



Scheme 2

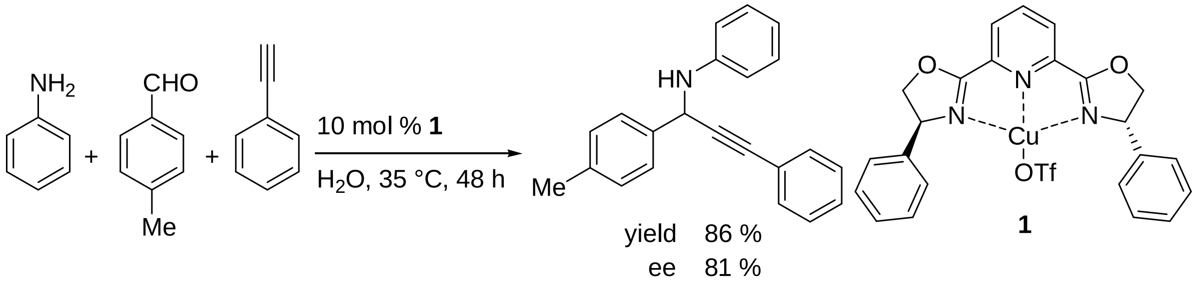
Kobayashi and co-workers have reported aza-Diels-Alder reaction of silver triflate activated imines with Danishefsky’s diene on water in good yield (Scheme 3).[10e]



Scheme 3

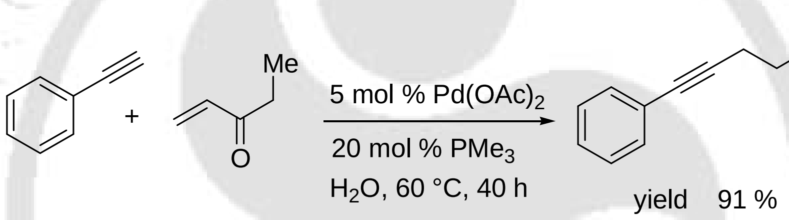
4.2 Transformations Catalyzed by Transition Metals

Li and co-workers have used chiral copper(I)-bis(oxazolinyl)pyridine **1** for asymmetric aldehyde-alkyne-amine (AA^3) coupling reaction on water. This three-component asymmetric (AA^3) coupling reaction provides propargyl amines with up to 81 % ee (Scheme 4).[11]



Scheme 4

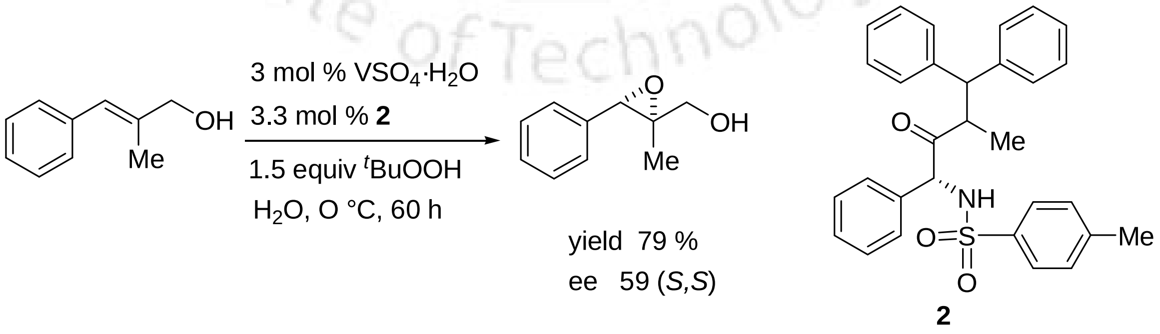
Chen and Li have reported the "on water" reaction of Pd-catalyzed 1,4-additions of terminal alkynes to α,β-unsaturated ketones. The process is experimentally simple, proceed well on water and could be performed in the presence of oxygen, leading to a wide range of γ,δ-alkynyl ketones (Scheme 5).[12]



Scheme 5

4.3 Oxidation and Reduction Reactions

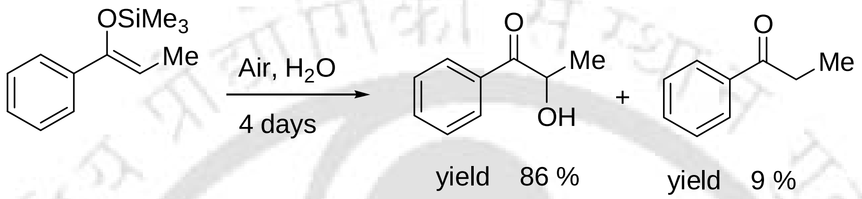
Water is a relatively redox inert molecule. In addition to being difficult to oxidize, it is supportive of a variety of chemical and electrochemical oxidants as well as transition metal catalysts. Hence, it could be a useful solvent for oxidation and reduction of organic compounds.



Scheme 6

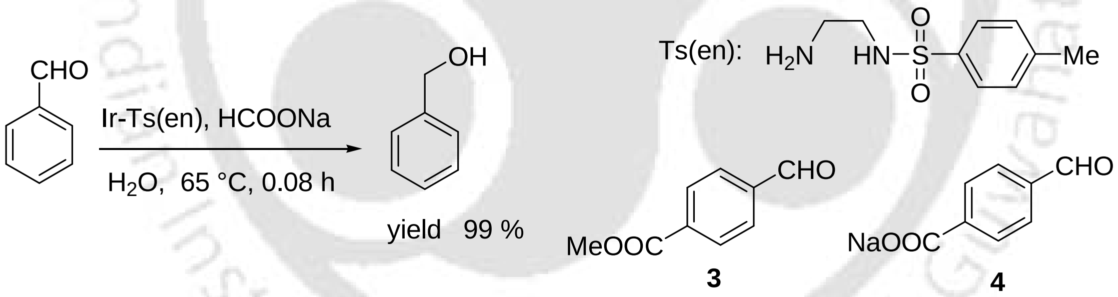
In a recent report, Malkov and Bourhani have developed a vanadium catalyzed epoxidation of allylic alcohols with *t*-BuOOH. This single atom transfers reaction has been successfully performed on water with moderate to good yield (Scheme 6).[13a,b]

Li and co-workers have disclosed a catalyst-free on water oxidation of aromatic silyl enol ethers. The substrates are converted to *α*-hydroxy ketones in good to excellent yields simply by stirring on water in the presence of air. These oxidations fail in most of the organic solvents (Scheme 7).[13c]



Scheme 7

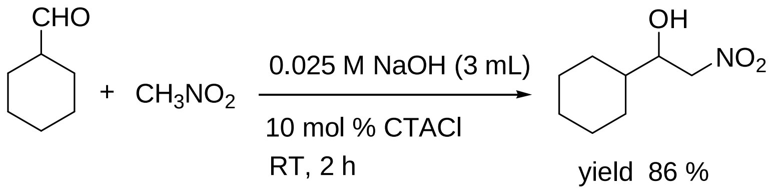
Xiao and co-workers have reported iridium catalyzed chemoselective hydrogenation on water. Under these conditions, the water insoluble aldheyde **3** is reduced quantitatively, while the water soluble aldehyde **4** showed no reaction (Scheme 8).[13d]



Scheme 8

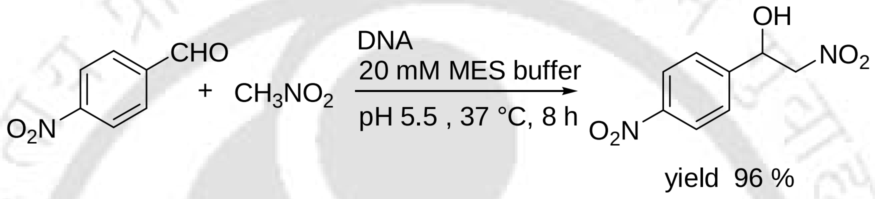
4.4 Nitroaldol Reaction

The classical nitroaldol (Henry) reaction is usually performed in presence of base in organic solvents and very few reports have involved water as the reaction medium. In 1997, Ballini and Bosica first reported the nitroaldol reaction in 0.025 M NaOH solution in the presence of cetyl trimethylammonium chloride (CTACl) as cationic surfactant. Under these conditions, aliphatic aldehydes shows greater reactivity compared to aromatic aldehydes (Scheme 9).[14a]



Scheme 9

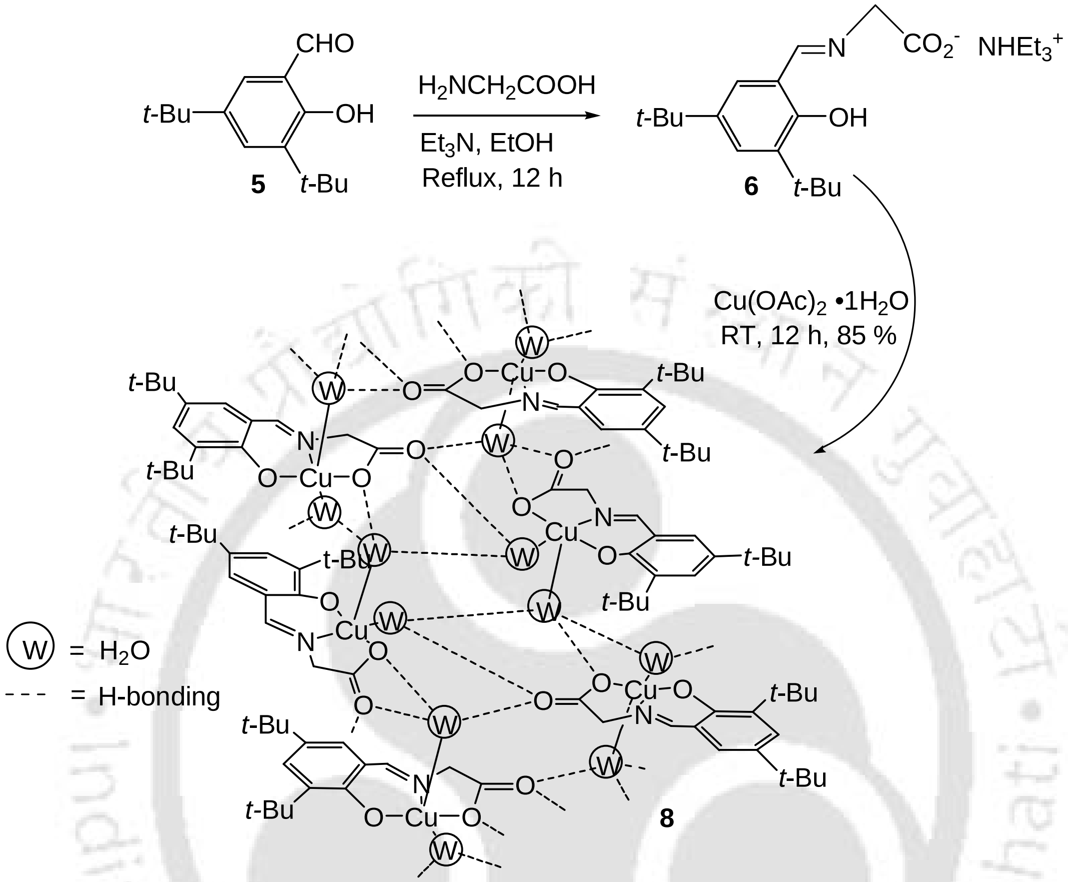
More recently, Li and co-workers have employed DNA as catalyst for nitroaldol reaction in water. The reactions are studied using 20 mM MES buffer solution (pH = 5.5). The catalyst, DNA, can be recycled without loss activity (Scheme 10).[14b]



Scheme 10

4.5 Present Study

Chemical self-assembly is an active interdisciplinary research topic with potential applications in molecular recognition, catalysis, gas storage, ion exchange and magnetic materials.[15] Indeed, nature utilizes the self-assembling processes in many interesting chemical and biomolecular systems.[16] In addition, the principles of self-assembly constitute a novel strategy for the rational design and development of supramolecular architectures, especially for the preparation of extended metal-organic frameworks (MOFs).[17] Polynuclear metal clusters have attracted considerable interest because of their relevance to multi-electron transfer centers in biological systems, and their interesting catalytic and magnetic properties.[18] Of these, metal cubane complexes are a well-studied class of compounds,[19] in which the four metal ions are bridged by hydroxy, alkoxo, azido, sulfide or iminato groups.[20] Many alkoxo-bridged copper(II) cubanes have been prepared and have been reported to have intracluster ferromagnetic interactions.[21] In this chapter, we describe the synthesis, structure and application of self-assembled copper(II) aqua complex **8** and tetranuclear copper(II) open cubane complex **9** for the acceleration of nitroaldol reaction on water. The water insoluble copper(II) complexes **8** and **9** float on water and accelerate the addition of nitroalkanes to aldehydes in high yields. These are heterogeneous processes, no additive is involved and the catalysts **8** and **9** can be filtered and recycled without loss of activity.



Scheme 11. Synthesis of Complex **8**

The synthesis of complex **8** is shown in scheme 11. The reaction of 3,5-di-*tert*-butyl salicylaldehyde **5** with glycine in the presence of Et_3N in EtOH provided Schiff base **6** that was treated with $Cu(OAc)_2 \cdot 1H_2O$ *in situ* to give copper(II) aqua complex **8** as a green colored powder. During purification on silica gel column chromatography using 1:9 MeOH and CH_2Cl_2 as an eluent, the complex **8** underwent crystallization to afford single crystals whose X-ray analysis showed that the complex **8** is self-assembled through aqua ligands (Figure 1-3). The aqua ligands having tetrahedral (axial) and trigonal (equatorial) geometries exhibited an intermolecular H-bond interaction with the oxygen of carboxylate and aqua ligand of another molecule to provide staircase like self-assembled structure.

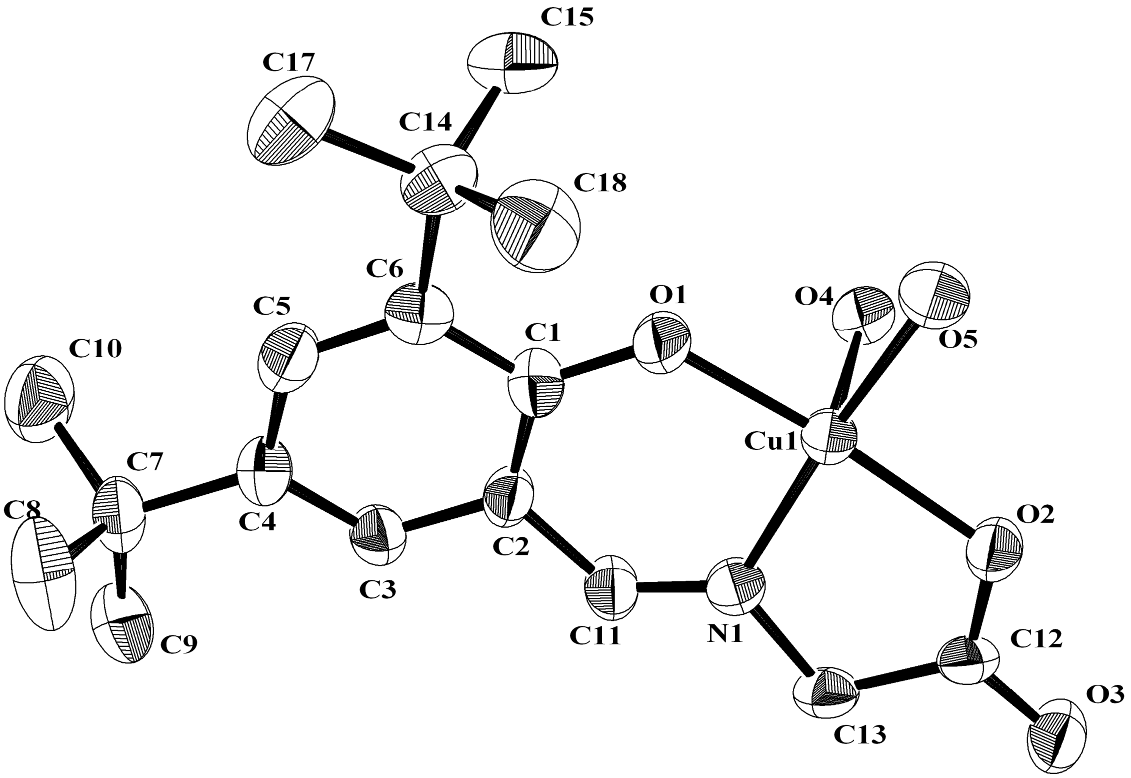


Figure 1. ORTEP Diagram of **8** with 50 % Probability. H-Atoms Omitted for Clarity.

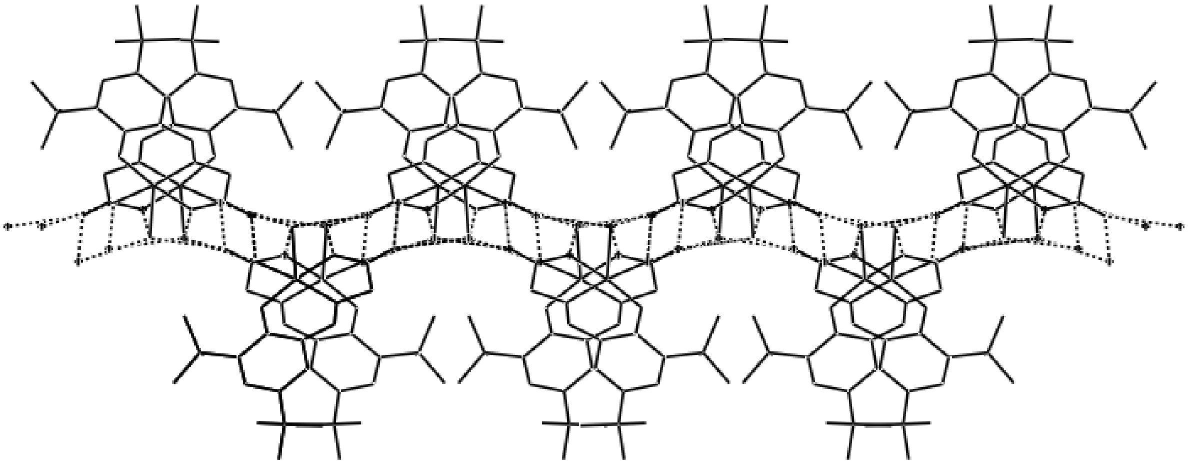


Figure 2. H-bonded Network of **8** Viewing Down "c" Flipping 90° Around an Axis Perpendicular to Screen.

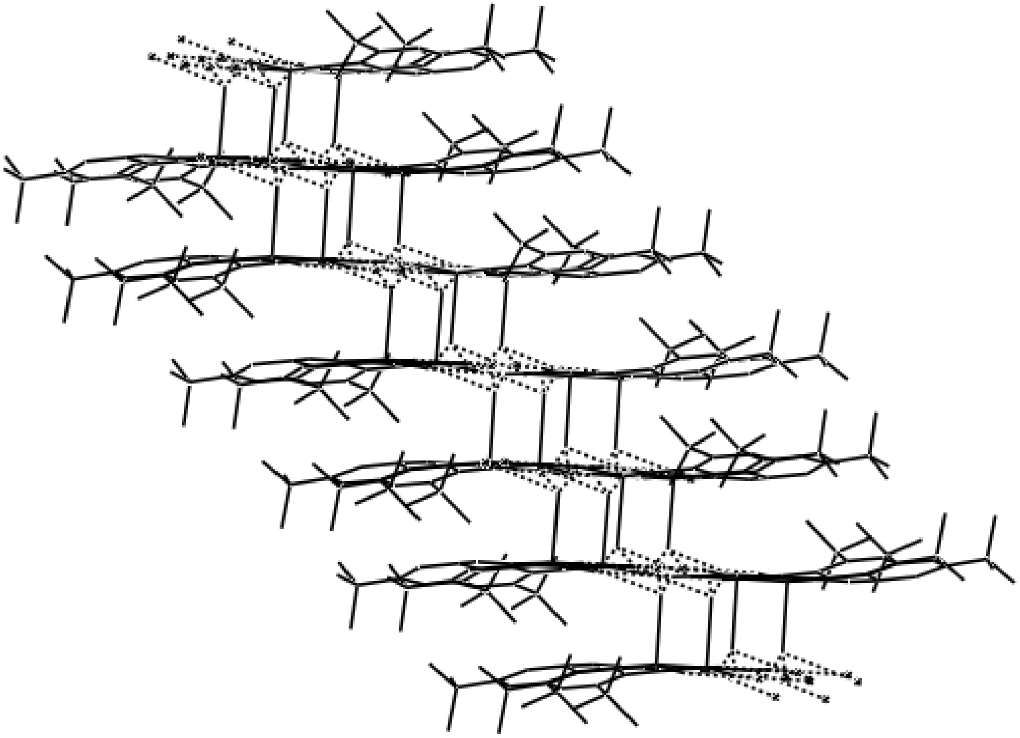
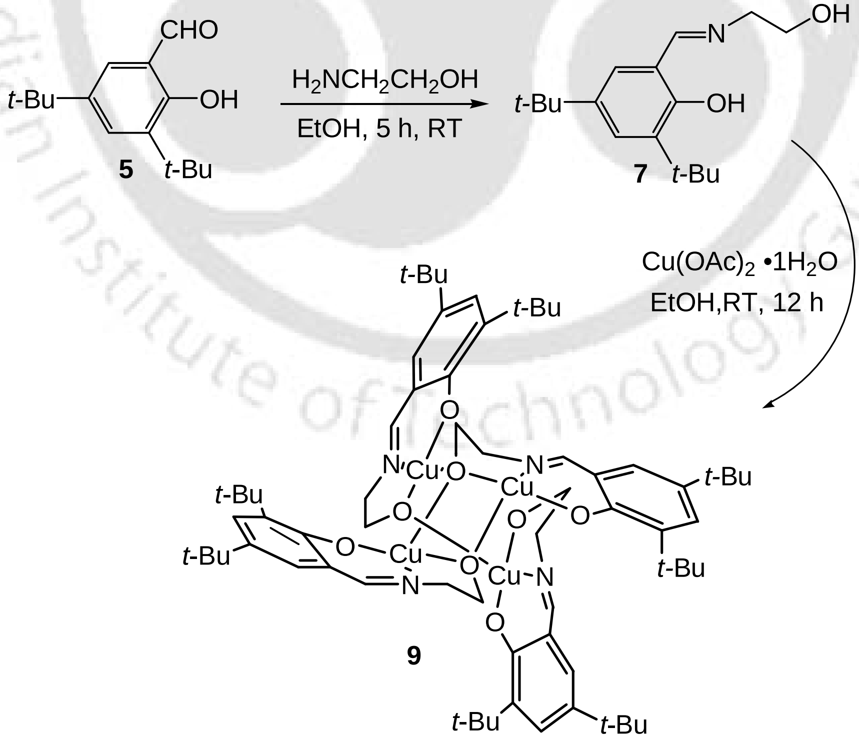


Figure 3. Self-Assembly of **8** with a Staircase-Like Structure.



Scheme 12. Synthesis of Complex **9**

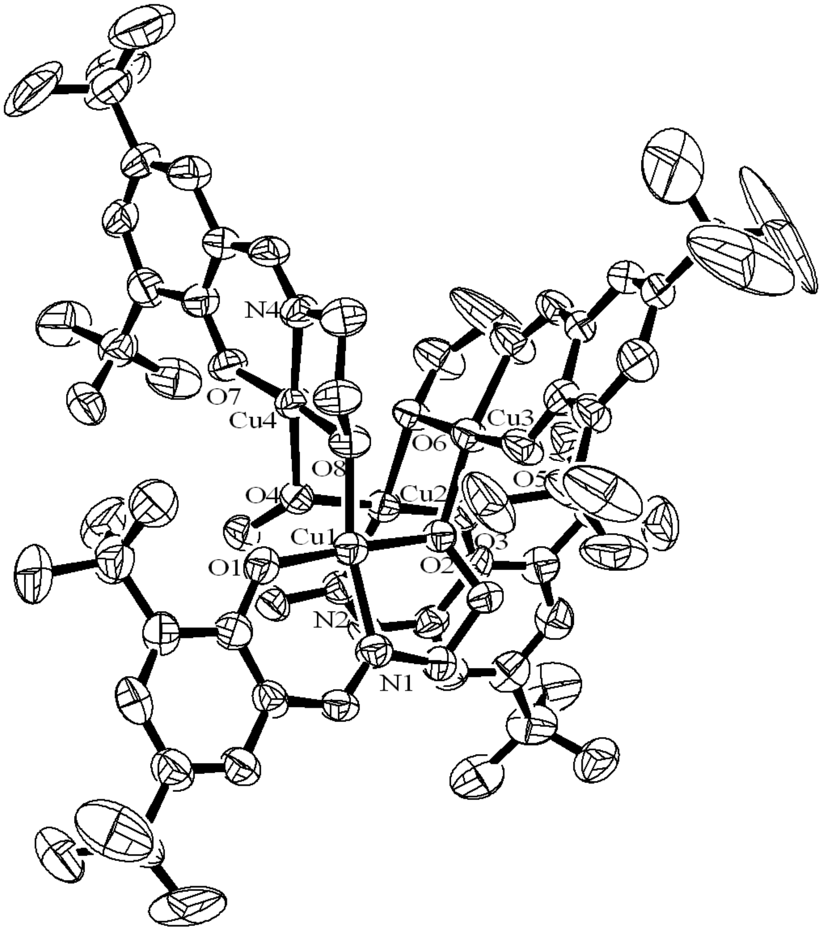


Figure 4. ORTEP Diagram of **9** with 50 % Probability. H-Atoms Omitted for Clarity.

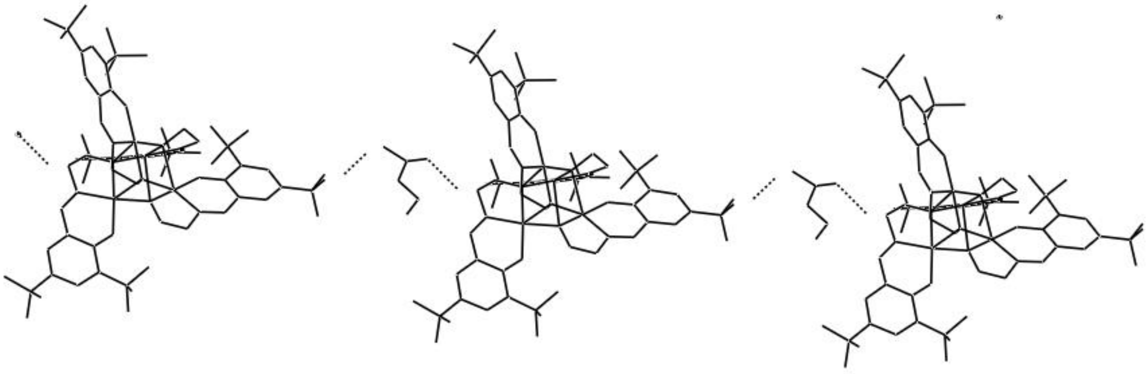


Figure 5. Copper(II) Cluster **9** Stabilized by EtOAc and H_2O Molecules.

Table 1. Reaction of 4-Nitrobenzaldehyde with Nitroalkanes on Water using **8** and **9**

Entry	Nitroalkane (mmol)	H_2O (mL)	Time (h)	Conv. (%)[a-c]
1	CH_3NO_2 (1)	1	3	15
2	CH_3NO_2 (2.5)	1	3	25
3	CH_3NO_2 (5)	1	3	25
4	CH_3NO_2 (7.5)	1	3	30
5	CH_3NO_2 (1)	3	3	35
6	CH_3NO_2 (2.5)	3	3	44
7	CH_3NO_2 (5)	3	3	77
8	CH_3NO_2 (7.5)	3	3	>99
9	CH_3NO_2 (5)	3	1.5	>99[d]
10	CH_3NO_2 (7.5)	-	3	nr
11	$C_2H_5NO_2$ (7.5)	3	30	50 (55:45)[e]
12	*n*-$C_3H_7NO_2$ (7.5)	3	30	15 (54:46)[e]
13	*i*-$C_3H_7NO_2$ (7.5)	3	30	nr

[a] 4-Nitrobenzaldehyde (1 mmol), catalyst **8** (5 mol %) and nitroalkane (1-7.5 mmol) were stirred on water (1-3 mL).

[b] Determined from 400 MHz ^{1}H NMR.

[c] Heterogeneous process.

[d] 4-Nitrobenzaldehyde (1 mmol), catalyst **9** (2.5 mol %) and nitromethane (5 mmol) were stirred on water (3 mL).

[e] Diastereomeric ratio (*syn/anti*) determined from 400 MHz ^{1}H NMR. nr = no reaction.

Next, the synthesis of copper(II) cubane complex **9** was pursued (Scheme 12). The aldehyde **5** was treated with $H_2NCH_2CH_2OH$ in EtOH to give Schiff base **7** as yellow solid in 90 % yield. The latter underwent reaction with $Cu(OAc)_2{\cdot}1H_2O$ in EtOH to afford the cluster **9** as a green powder. During purification on silica gel column chromatography with EtOAc and hexane, the cluster **9** provided single crystals in 80 % yield. Their X-ray analysis revealed that the cluster **9** contains an open cubane structure (Figure 4). In the crystal lattice EtOAc exhibits interaction with adjacent cluster molecules (Figure 5). The five membered rings containing the copper(II) ion, alkoxo oxygen and imine nitrogen exist with half-chair conformation.

Complexes **8** and **9** are well soluble in common organic solvents such as CH_2Cl_2, THF, diethyl ether, $CHCl_3$ and toluene, but insoluble in water due to hydrophobic *t*-butyl groups. Since complex **8** is self-assembled through aqua ligands, and complex **9** contains water molecules in its lattice,[16,22] we were interested to study their catalysis for organic reactions on water.[9,14,23] First, we studied the addition of nitroalkanes to aldehydes.[14,24]

Table 2. Reaction of 4-Nitrobenzaldehyde with Nitromethane on Water: Screening of Copper Source

Entry	Catalyst	Conv. (%)$^{a-c}$
1	$CuSO_4{\cdot}5H_2O$	7
2	$Cu(OAc)_2{\cdot}1H_2O$	14
3	$CuCl_2{\cdot}2H_2O$	13
4	$Cu(ClO_4)_2{\cdot}6H_2O$	15
5	$Cu(NO_3)_2{\cdot}3H_2O$	16
6	**8**	>99[d]
7	**9**	>99[d,e]
8	-	<5

[a] 4-Nitrobenzaldehyde (1 mmol), catalyst (5 mol %), nitromethane (7.5 mmol) and solvent (3 mL) were stirred for 3 h.

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

[c] Homogeneous process.

[d] Heterogeneous process.

[e] 4-Nitrobenzaldehyde (1 mmol), catalyst (2.5 mol %), nitromethane (5 mmol) and solvent (3 mL) were stirred for 1.5 h.

The optimization of the reaction conditions was pursued with 4-nitrobenzaldehyde and nitromethane as model substrates (Table 1). The reaction occurred efficiently to afford the desired nitroaldol product in high yield when the substrates were stirred for 3 h with 5 mol %

of **8** on water. The same conversion was achieved in 1.5 h with 2.5 mol % of **9** on water. The reactions were heterogeneous exhibiting a greater reactivity compared to the copper(II) salts catalyzed homogeneous process (Table 2). The reaction was accelerated on water in comparison to those in organic solvents (Table 3).[9,23d,23h] A control experiment without catalysts **8** and **9** showed <5 % conversion. However, the neat reaction having substrates and catalyst showed no reaction. Nitromethane was more reactive compared to nitroethane and nitropropane. No reaction was observed with 2-nitropropane.

Table 3. Reaction of 4-Nitrobenzaldehyde with Nitromethane using **8**: Effect of Solvent

Entry	Solvent	Conversion (%)[a-c]
1	H_2O	>99[d]
2	CH_2Cl_2	12
3	$CHCl_3$	14
4	THF	25
5	Toluene	18
6	EtOH	40
7	CCl_4	14
8	$(CH_2)_2Cl_2$	16
9	Et_2O	20

[a] 4-Nitrobenzaldehyde (1 mmol), complex **8** (5 mol %) and nitromethane (7.5 mmol) and solvent (3 mL) were stirred for 3 h.

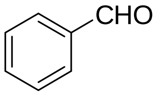
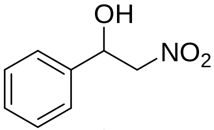
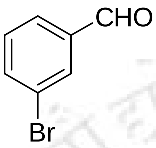
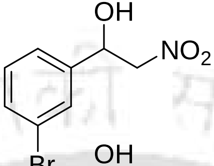
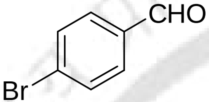
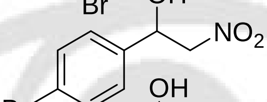
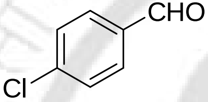
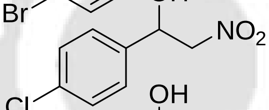
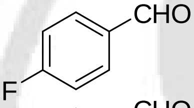
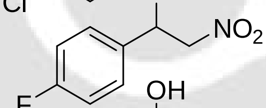
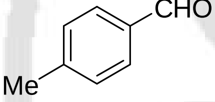
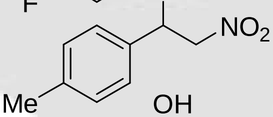
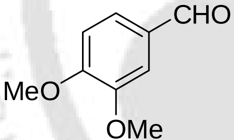
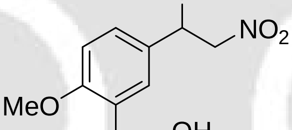
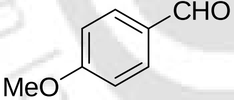
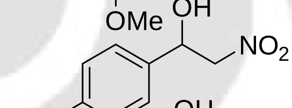
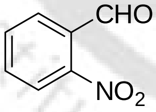
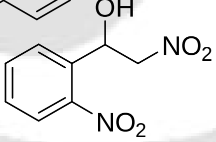
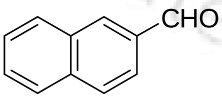
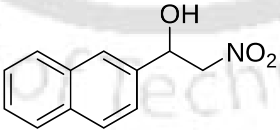
[b] Determined from 400 MHz ^{1}H NMR.

[c] Homogeneous process.

[d] Heterogeneous process.

Next, the reactions of other aldehydes were investigated with nitromethane (Table 4-5). Benzaldehyde underwent reaction with 97 % yield. Similar results observed with aryl aldehydes having 3-bromo-, 4-bromo-, 4-chloro-, 4-fluoro-, 4-methyl-, 3,4-dimethoxy and 4-methoxy substituents (Table 4). Aldehyde with electron withdrawing groups showed greater

Table 4. Reaction of Aryl Aldehydes with Nitromethane using **8** and **9** on Water

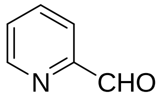
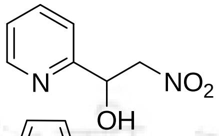
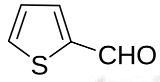
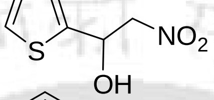
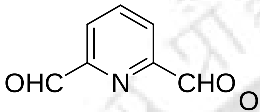
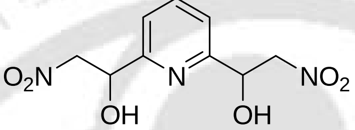
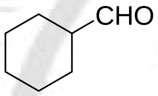
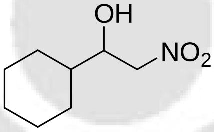
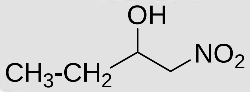
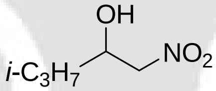
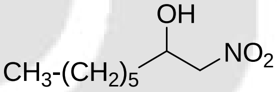
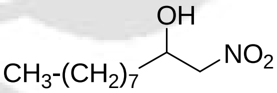
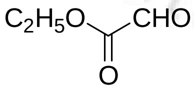
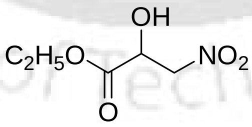
Entry	Substrate	Product	Catalyst [a,b]	Time (h)	Yield (%)[c]
1			**8**	2.5	97
			9	2	92
2			**8**	24	72
			9	12	88
3			**8**	7	98
			9	4	89
4			**8**	14	76
			9	6	85
5			**8**	15	82
			9	8	90
6			**8**	12	89
			9	4	85
7			**8**	12	82
			9	12	81
8			**8**	24	75
			9	12	77
9			**8**	15	81
			9	5	80
10			**8**	24	54
			9	12	68

[a] Substrate (1 mmol), complex **8** (5 mol %) and nitromethane (7.5 mmol) were stirred on water (3 mL).

[b] Substrate (1 mmol), complex **9** (2.5 mol %) and nitromethane (5 mmol) were stirred on water (3 mL).

[c] Isolated yield.

Table 5. Reaction of Hetero Aryl and Alkyl Aldehydes with Nitromethane using **8** and **9** on Water

Entry	Substrate	Product	Catalyst [a,b]	Time (h)	Yield (%)[c]
1			**8**	5	92
			9	1	95
2			**8**	20	70
			9	10	90
3			**8**	24	62
			9	12	75
4			**8**	8	91
			9	6	88
5	$CH_3\text{-}CH_2\text{-}CHO$		**8**	6	88
			9	4	92
6	$i\text{-}C_3H_7\text{-}CHO$		**8**	12	85
			9	8	82
7	$CH_3\text{-}(CH_2)_5\text{-}CHO$		**8**	24	75
			9	12	78
8	$CH_3\text{-}(CH_2)_7\text{-}CHO$		**8**	24	68
			9	12	72
9			**8**	24	70
			9	12	85

[a] Substrate (1 mmol), complex **8** (5 mol %) and nitromethane (7.5 mmol) were stirred on water (3 mL).

[b] Substrate (1 mmol), complex **9** (2.5 mol %) and nitromethane (5 mmol) were stirred on water (3 mL).

[c] Isolated yield.

reactivity compared to that having electron donating groups. These reaction conditions were also suitable for the reactions of 2-naphthaldehyde and heterocyclic aldehydes, 2-pyridinecarboxaldehyde and 2-thiophenecarboxaldehyde, to afford the nitroaldols in 54-95 % yield. In case of 2,6-pyridinedicarboxaldehyde, both the CHO groups underwent reaction with 75 % yield. Likewise, aliphatic substrates, cyclohexanecarboxaldehyde, propanal, 2-methylpropanal, 1-heptanal, 1-nonanal and ethyl glyoxalate underwent reaction to provide the nitroaldols in 68-92 % yield (Table 5).

Table 6. Reaction of 4-Nitrobenzalehdyde with Nitromethane on Water using **8** and **9**: Recyclability Experiments

Run	Recovery of Catalyst **(**%)	Product (conv. %)[a-c]
1	99	>99
2	97	>99[d]
3	97	>99[d]

[a] 4-Nitrobenzaldehyde (10 mmol), complex **8** (5 mol %) and nitromethane (75 mmol) stirred on water (30 mL) for 3 h.

[b] 4-Nitrobenzaldehyde (10 mmol), complex **9** (5 mol %) and nitromethane (50 mmol) stirred on water (30 mL) for 1.5 h.

[c] Determined from 400 MHz ^{1}H NMR.

[d] Recovered **8 or 9** used.

The catalysts were recyclable without loss of activity. After completion of the addition of nitromethane to 4-nitrobenzaldehyde, the catalyst was recovered by filtration and reused for the reaction of fresh nitromethane with 4-nitrobenzaldehyde. This process was repeated up to three runs and no loss of activity was observed (Table 6). In addition, to study the leaching of the catalyst in water, the catalysts were stirred on water in the presence, as well as in the absence of nitromethane for 7 h and filtered. The filtrates were independently investigated for the addition of nitromethane to benzaldehyde. Both experiments provided the corresponding nitroaldol in <5 % conversion, which is similar to that of blank reaction. Furthermore, the filtrates were analyzed using a UV-vis spectrophotometer and no absorption peak was observed for the presence of the catalysts. These results clearly suggest that no leaching of the metal complex is involved and the reaction is a heterogeneous process.

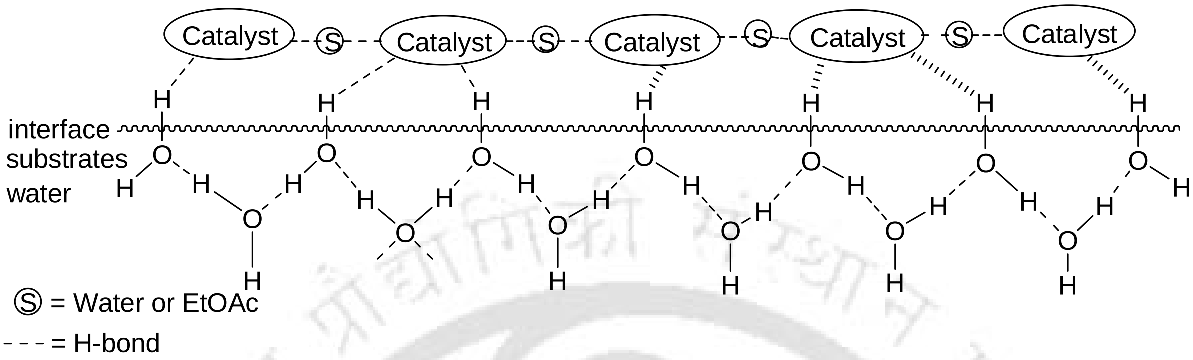
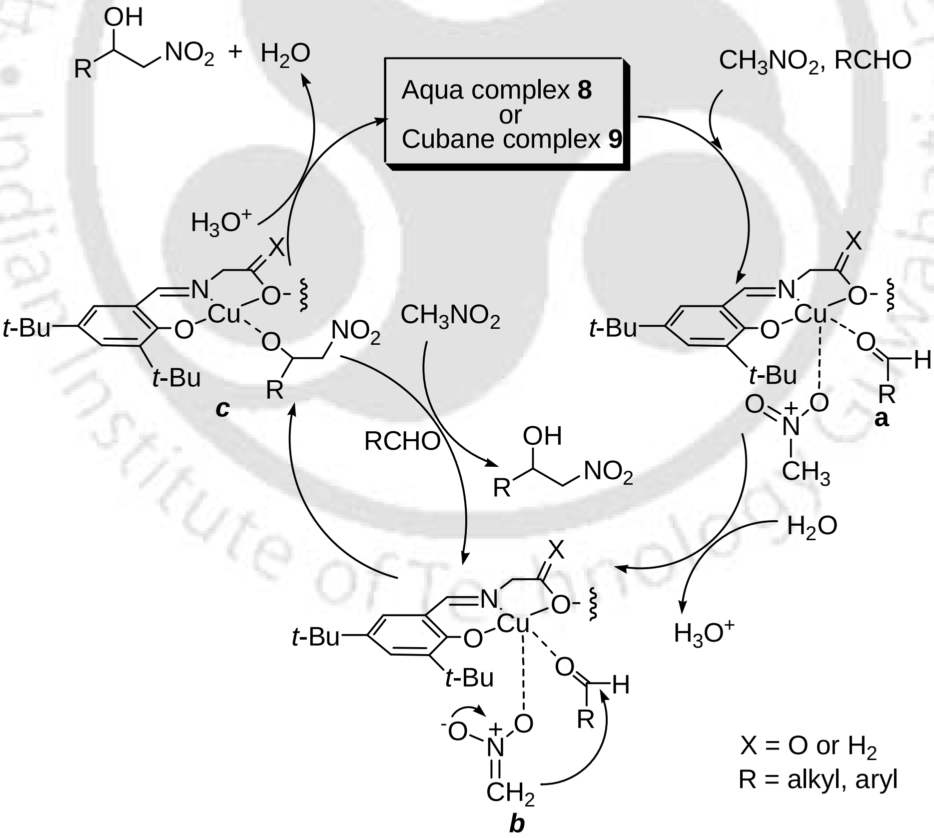


Figure 6. Proposed Henry Reaction on Water.



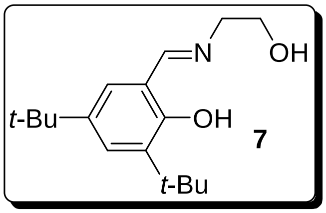
Scheme 13. Proposed Catalytic Cycle for Nitroaldol Reaction

The enhanced reactivity of the heterogeneous process using **8** and **9** on water compared to the homogeneous systems in organic solvents could be attributed to the occurrence of the reaction at the solid-liquid interface of water droplets (Figure 6).[9,23d,23h] The coordination of the nitroalkane on the surface of the catalyst **8** or **9** can generate intermediate ***a*,** which can undergo reaction with water to generate intermediate ***b***. Intramolecular 1,2-addition of the nitronate to the coordinated aldehyde can generate the intermediate ***c***, which can complete the catalytic cycle by reaction with fresh nitroalkane or water, giving the nitroaldol product (Scheme 13).

In conclusion, the synthesis, crystal structure and application of a self-assembled copper(II) aqua complex **8** and an alkoxo-bridged tetranuclear copper(II) open cubane complex **9** have been described for acceleration of the nitroaldol reaction on water. It is a heterogeneous process, involves no additive or base, and the catalysts can be recycled without loss of activity.

Experimental Section

General. Aldehydes, nitroalkanes, glycine (>99 %), ethanolamine, 2,4-di-*tert*-butylphenol (98 %) and Cu(OAc)$_2$·1H$_2$O (>99 %) purchased from Aldrich. 3,5-Di-*tert*-butyl salicylaldehyde prepared from 2,4-di-*tert*-butylphenol.[25] NMR spectra recorded using Varian-400 spectrometer. UV-vis spectra obtained from Perkin Elmer Lambda-25 spectrophotometer. FT-IR spectra obtained from Nicolet-410 spectrometer. EPR spectrum recorded using JES-FA-200 spectrometer. X-Ray data collected on Bruker SMART APEX equipped with CCD area detector using Mo-Kα radiation. The structure solved using SHELXL-97 Göttingen, Germany. Column chromatography performed on 60-120 mesh silica gel. Elemental analysis obtained from Perkin Elmer-2400 CHNS analyzer.



2,4-Bis(1,1-dimethylethyl)-6-[[(2-hydroxyethyl)imino] methyl]-phenol 7. 3,5-Di-*tert*-butyl salicylaldehyde (234 mg, 1 mmol) and NH$_2$CH$_2$CH$_2$OH (61 mg, 1 mmol) stirred for 5 h in EtOH (5 mL). Evaporation of the solvent gave a residue that was purified on silica gel column chromatography using 9:1 hexane and ethyl acetate to afford **7** as yellow solid in 90 % (249.3 mg) yield.

M.p: 63-65 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (s, 1H), 7.38 (s, 1H), 7.10 (s, 1H), 3.91 (t, *J* = 5.2 Hz, 2H), 3.73 (t, *J* = 5.6 Hz, 2H), 2.0 (s, 1H), 1.32 (s, 9H), 1.29 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 158.3, 140.2, 136.8, 127.2, 126.2, 117.9, 62.2, 61.7, 31.6, 29.6.

FT-IR (KBr): ν 3365, 2958, 2871, 1734, 1633, 1469, 1441, 1390, 1361, 1274, 1252, 1201, 1173, 1063, 1047, 878 cm^{-1}.

UV-vis (CH_2Cl_2): λ_{max} 342 (ε = 6022), 263 nm (ε = 20639 mol^{-1} dm^3 cm^{-1}).

Anal. Calcd for $C_{17}H_{27}NO_2$: C, 73.61; H, 9.81; N, 5.05. Found: C, 73.70; H, 9.85; N, 5.08.

Preparation of Copper(II) Complex 8. 3,5-Di-*tert*-butyl salicylaldehyde (234 mg, 1 mmol), glycine (75 mg, 1 mmol) and Et_3N (101 mg, 1 mmol) were refluxed for 12 h in EtOH (5 mL). The reaction mixture was then treated with $Cu(OAc)_2·1H_2O$ (199 mg, 1 mmol) and the stirring continued for over night at ambient temperature. The solvent was evaporated under reduced pressure and the residue was purified on silica gel column chromatography using CH_2Cl_2 and MeOH (9:1) as eluent to afford **8** as green colored needles in 85 % yield.

FT-IR (KBr): ν 3421, 3004, 2961, 2867, 2366, 2346, 1633, 1610, 1528, 1459, 1437, 1419, 1379, 1167, 787, 753, 536 cm^{-1}.

UV-vis (CH_2Cl_2): λ_{max} (ε) 397 (916), 283 nm (2669 mol^{-1} dm^3 cm^{-1}).

EPR (MeOH): $g_{\parallel}$ = 2.139, $g_{\perp}$ = 2.049.

Anal. Calcd for $C_{17}H_{27}O_5NCu$: C, 52.50; H, 7.00; N, 3.60. Found: C, 52.56; H, 7.03; N, 3.66.

Preparation of the Copper(II) Cubane Complex 9. Schiff base **7** (277 mg, 1 mmol) and $Cu(OAc)_2·1H_2O$ (199 mg, 1 mmol) were stirred in EtOH (5 mL) for 12 h at ambient temperature. The solvent was evaporated and the residue was purified on silica gel column chromatography using 9:1 hexane and ethyl acetate to give **9** as green colored crystals in 80 % (257.6 mg) yield.

FT-IR (KBr): ν 2957, 2905, 2866, 1740, 1633, 1528, 1459, 1434, 1323, 1256, 1165, 1057, 911, 872, 638, 616, 513 cm^{-1}.

UV-vis (CH_2Cl_2): λ_{max} (ε) 384 (25303), 278 nm (79848 mol^{-1} dm^3 cm^{-1}).

EPR (Solid): g = 2.04, A = 330 mT.

Anal. Calcd for $C_{72}H_{110}N_4O_{11}Cu_4$: C, 59.16; H, 7.58; N, 3.83. Found: C, 59.25; H, 7.62; N, 3.88.

General Procedure for Nitroaldol Reaction using Catalyst 8

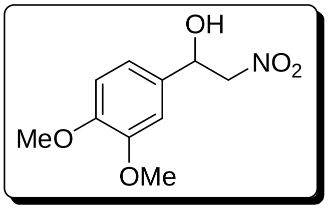
Aldehyde (1 mmol), nitroalkane (7.5 mmol) and catalyst **8** (5 mol %) were stirred on water (3 mL) at ambient conditions. The progress of the reaction was monitored using TLC. After completion, the catalyst **8** was filtered and the filtrate was extracted with ethyl acetate (2 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was passed through a short pad of silica gel using ethyl acetate and hexane as eluent to afford analytically pure nitroaldol product.

General Procedure for Nitroaldol Reaction using Catalyst 9

A mixture of aldehyde (1 mmol), nitroalkane (5 mmol) and cluster **9** (2.5 mol %) was stirred on water (3 mL). Progress of the reaction was monitored by TLC. After completion, the cluster **9** was filtered and the filtrate was extracted with EtOAc (2 x 25 mL). Drying (Na_2SO_4) and evaporation of the solvent gave a residue that was passed through a short pad of silica gel using ethyl acetate and hexane as eluent to provide analytically pure nitroaldols in high yield.

Recycling Experiment

The suspension, which contains 4-nitrobenzaldehyde (1.51g, 10 mmol), catalyst **8** (0.194 g, 10 mmol) and nitromethane (4.56 g, 75 mmol) was stirred for 3 h on water (30 mL). Catalyst **8** was then filtered and the filtrate was extracted with ethyl acetate (2 x 50 mL). The recovered **8** was reused for the new reaction for three runs. The reactions occurred without loss of activity to afford the desired nitroaldol product in >99 % conversion.



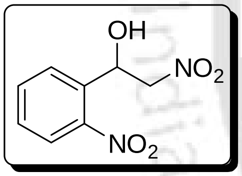
2-Nitro-1-(3,4-dimethoxyphenyl)ethanol (Table 4, entry 10).[26a] A mixture of 3,4-dimethoxybenzaldehyde (227 mg, 1 mmol), nitromethane (305.2 mg, 5 mmol), cluster **9** (35.5 mg, 2.5 mol %) and water (3 mL) was subjected to the reaction conditions described in the general preocedure for 12 h and the residue was purified on silica gel column chromatography using 4:1 hexane/ethyl acetate to give the title compound (183 mg, 81 %) as yellow oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ 6.92-6.82 (m, 3H), 5.39-5.37 (m, 1H), 4.62-4.46 (m, 2H), 3.87 (s, 6H), 3.22 (s, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 149.4, 130.9, 118.4, 111.3, 108.9, 81.4, 70.9, 56.0.

FT-IR (neat): ν 3570, 1565, 1348 cm^{-1}.

Anal. Calcd for $C_{10}H_{13}NO_5$: C, 52.86; H, 5.77; N, 6.16. Found: C, 52.90; H, 5.76; N, 6.25.



2-Nitro-1-(2-nitrophenyl)ethanol (Table 4, entry 9). A mixture of 2-nitrobenzaldehyde (151 mg, 1 mmol), nitromethane (305.2 mg, 5 mmol), cluster **9** (35.5 mg, 2.5 mol %) and water (3 mL) was subjected to the reaction conditions reported in the general procedure for 5 h and the residue was purified on silica gel column chromatography using 4:1 hexane/ethyl acetate to afford the title compound (170 mg, 80 %) as colorless solid.

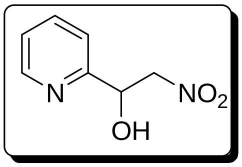
Mp: 66-67 ˚C.

^{1}H NMR (400 MHz, CDCl$_3$): δ 8.09 (d, *J* = 8.0 Hz, 1H), 7.97 (d, *J* = 8.0 Hz, 1H), 7.77 (t, *J* = 7.2 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 6.06-6.04 (m, 1H), 4.89-4.85 (m, 1H), 4.59-4.53 (m, 1H), 3.39 (s, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 147.2, 134.6, 134.3, 129.8, 128.9, 125.2, 80.3, 66.9.

FT-IR (KBr): ν 3554, 1568, 1528, 1356 cm^{-1}.

Anal. Calcd for $C_8H_8N_2O_5$: C, 45.29; H, 3.80; N, 13.20. Found: C, 45.35; H, 3.83; N, 13.24.



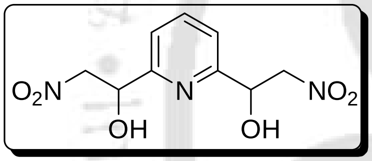
2-Nitro-1-(2-pyridyl)ethanol (Table 5, entry 1).[26b] A mixture of 2-pyridinecarboxaldehyde (107 mg, 1 mmol), nitromethane (305.2 mg, 5 mmol), cluster **9** (35.5 mg, 2.5 mol %) and water (3 mL) was subjected to the reaction conditions shown in the general procedure for 1 h and the residue was purified on silica gel column chromatography using 4:1 hexane/ethyl acetate to give the title compound (159 mg, 95 %) as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.58-8.57 (d, J = 4.8 Hz, 1H), 7.79-7.75 (m, 1H), 7.45 (d, J = 6.0 Hz, 1H), 7.32-7.26 (m, 1H), 5.48-4.80 (m, 1H), 4.80-4.62 (m, 2H), 4.42 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 157.1, 148.9, 137.7, 123.7, 121.1, 80.7, 70.6.

FT-IR (neat): ν 3349, 2917, 1557, 1432, 1381 cm^{-1}.

Anal. Calcd for $C_7H_8N_2O_3$: C, 50.00; H, 4.80; N, 16.66. Found: C, 50.09; H, 4.81; N, 16.70.



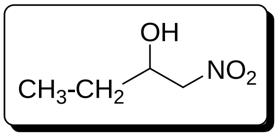
2,6-Pyridine-di-2-nitro-1-ethanol (Table 5, entry 3). A mixture of 2,6-pyridinedicarboxaldehyde (135 mg, 1 mmol), nitromethane (305.2 mg, 5 mmol), cluster **9** (35.5 mg, 2.5 mol %) and water (3 mL) was subjected to the reaction conditions described in the general procedure for 12 h and the residue was purified on silica gel column chromatography using 4:1 hexane/ethyl acetate to provide the title compound (192 mg, 75 %) as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87-7.83 (t, J = 8.0 Hz, 1H), 7.52 (d, J = 8.0 Hz, 2H), 5.44 (m, 2H), 4.84-4.80 (m, 2H), 4.71-4.65 (m, 2H), 3.73 (s, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 156.3, 139.1, 121.0, 80.2, 70.6.

FT-IR (neat): ν 3394, 1554, 1380 cm^{-1}.

Anal. Calcd for $C_9H_{11}N_3O_6$: C, 42.03; H, 4.31; N, 16.34. Found: C, 42.08; H, 4.30; N, 16.45.



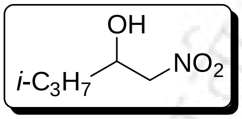
1-Nitro-2-butanol (Table 5, entry 5).[26a] A mixture of propanal (57 mg, 1 mmol), nitromethane (305.2 mg, 5 mmol), cluster **9** (35.5 mg, 2.5 mol %) and water (3 mL) was subjected to the reaction conditions described in the general procedure for 4 h and the residue was purified on silica gel column chromatography using 4:1 hexane/ethyl acetate to provide the title compound (109 mg, 92 %) as colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ 4.46-4.38 (m, 2H), 4.25 (m, 1H), 2.54 (d, *J* = 4.8 Hz, 1H), 1.59 (m, 2H), 1.04 (t, *J* = 6.8, 8.4 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 80.5, 70.1, 27.0, 9.7.

FT-IR (neat): ν 3349, 1556, 1385 cm^{-1}.

Anal. Calcd for $C_4H_9NO_3$: C, 40.33; H, 7.62; N, 11.76. Found: C, 40.41; H, 7.63; N, 11.84.



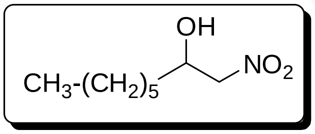
3-Methyl-1-nitro-2-butanol (Table 5, entry 6).[26c] A mixture of 2-methylpropanal (72 mg, 1 mmol), nitromethane (305.2 mg, 5 mmol), cluster **9** (35.5 mg, 2.5 mol %) and water (3 mL) was subjected to the reaction conditions reported in the general procedure for 8 h and the residue was purified on silica gel column chromatography using 4:1 hexane/ethyl acetate to give the title compound (109 mg, 82 %) as colorless oil.

^{1}H NMR (400 MHz, CDCl$_3$): δ 4.49-4.38 (m, 2H), 4.11 (m, 1H), 2.48 (s, 1H), 1.83-1.78 (m, 1H), 1.01-0.98 (m, 6H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 79.4, 73.5, 31.9, 18.6, 17.6.

IR (neat): ν 3420, 1558, 1380 cm^{-1}.

Anal. Calcd for $C_5H_{11}NO_3$: C, 45.10; H, 8.33; N, 10.52. Found: C, 45.18; H, 8.36; N, 10.50.



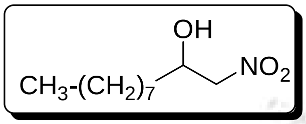
1-Nitro-2-octanol (Table 5, entry 7). A mixture of 1-heptanal (114 mg, 1 mmol), nitromethane (305.2 mg, 5 mmol), cluster **9** (35.5 mg, 2.5 mol %) and water (3 mL) was subjected to the reaction conditions described in the general procedure for 12 h and the residue was purified on silicagel column chromatography using 4:1 hexane/ethyl acetate to give the title compound (136 mg, 78 %) as colorless oil.

^1H NMR (400 MHz, $CDCl_3$): δ 4.42-4.31 (m, 2H), 4.29-4.26 (m, 1H), 2.30 (s, 1H), 1.52-1.43 (m, 4H), 1.36-1.21 (m, 6H), 0.85 (t, J = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 80.8, 68.9, 33.8, 31.7, 29.0, 25.2, 22.5, 14.0.

FT-IR (KBr): ν 3400, 2931, 2857, 1556, 1517, 1458, 1383, 1252, 1091, 835, 743 cm^{-1}.

Anal. Calcd for $C_8H_{17}NO_3$: C, 54.84; H, 9.78; N, 7.99. Found: C, 54.88; H, 9.80; N, 8.04.



1-Nitro-2-decanol (Table 5, entry 8). A mixture of 1-nonanal (142 mg, 1 mmol), nitromethane (305.2 mg, 5 mmol), cluster **9** (35.5 mg, 2.5 mol %) and water (3 mL) was subjected to the reaction conditions shown in the general procedure for 12 h and the residue was purified on silica gel column chromatography using 4:1 hexane/ethyl acetate to afford the title compound (172 mg, 85 %) as colorless oil.

^1H NMR (400 MHz, $CDCl_3$): δ 4.41-4.30 (m, 2H), 4.27 (s, 1H), 2.83 (s, 1H), 1.51-1.38 (m, 4H), 1.31-1.23 (m, 10H), 0.84 (t, *J* = 6.0 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 80.9, 68.9, 33.9, 31.9, 29.5, 29.5, 29.3, 25.3, 22.7, 14.2.

FT-IR (KBr): ν 3416, 2926, 2856, 1557, 1518, 1464, 1383, 1252, 1093, 835, 742 cm^{-1}.

Anal. Calcd for $C_{10}H_{21}NO_3$: C, 59.08; H, 10.41; N, 6.89. Found: C, 59.15; H, 10.40; N, 6.93.

Please see the analytical deta for nitroaldol products 2-Nitro-1-phenylethanol (Table 4, entry1), 2-Nitro-1-(3-bromophenyl)ethanol (Table 4, entry 2), 2-Nitro-1-(4-bromophenyl)ethanol (Table 4, entry 3), 2-Nitro-1-(4-chlorophenyl)ethanol (Table 4, entry 4), 2-Nitro-1-(4-fluorophenyl)ethanol (Table 4, entry5), 2-Nitro-1-(4-methylphenyl)ethanol (Table 4, entry 6), 2-Nitro-1-(4-methoxyphenyl)ethanol (Table 4, entry 8), 2-Nitro-1-naphthylethanol (Table 4, entry 10), 2-Nitro-1-(2-thiophenyl)ethanol (Table 5, entry 2), 2-Nitro-1-cyclohexylethanol (Table 5, entry 9) in chapter III.

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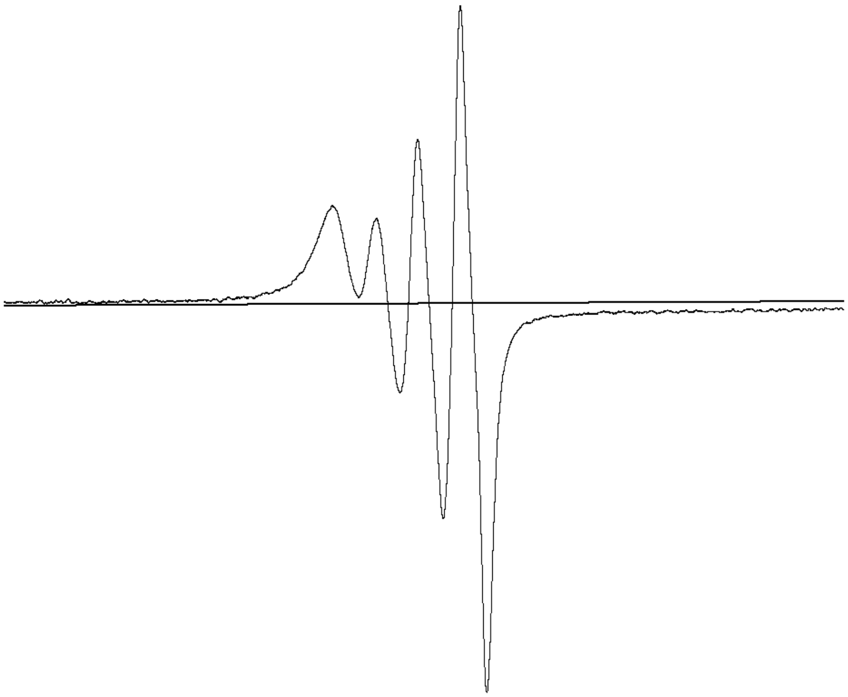


Figure 7. EPR Spectrum of complex **8** Recorded at Room Temperature in MeOH.

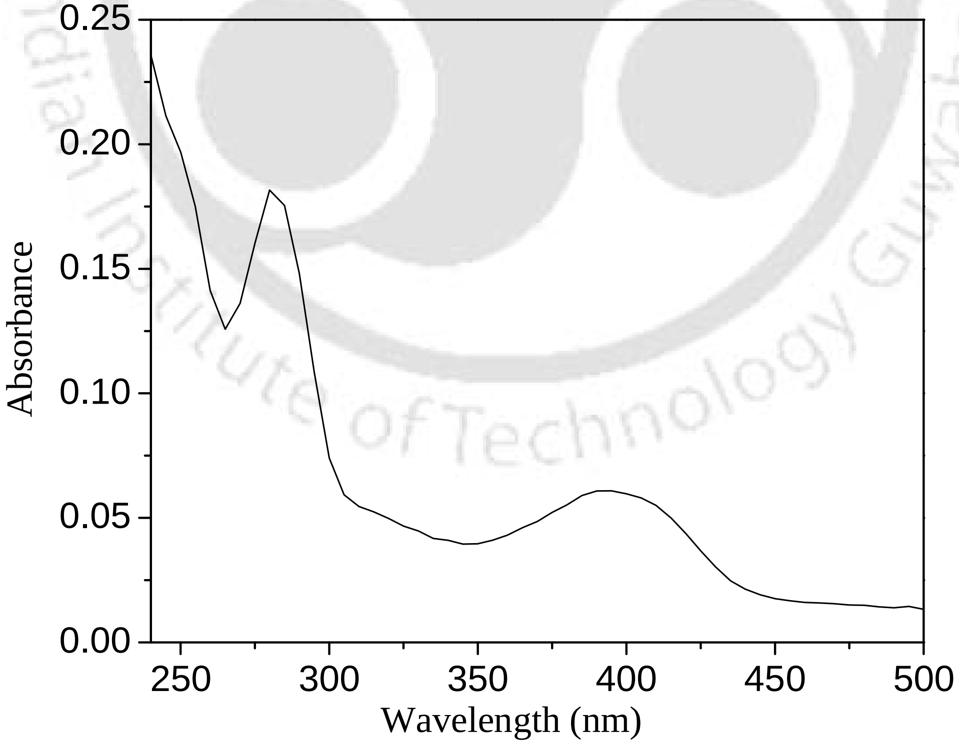


Figure 8. UV-vis Spectrum of **8** in CH_2Cl_2.

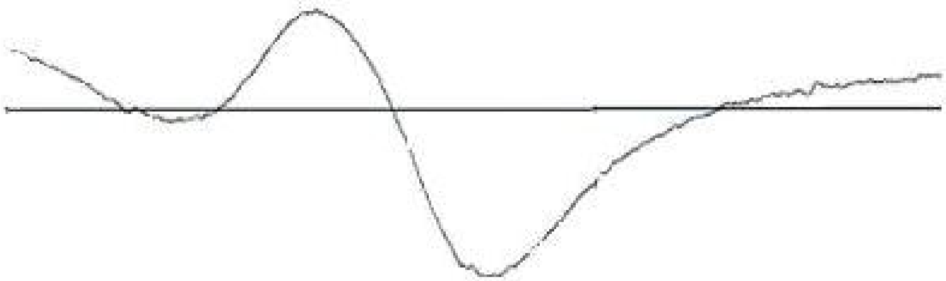


Figure 7. EPR Spectrum of complex **9** Recorded at Room Temperature (Solid).

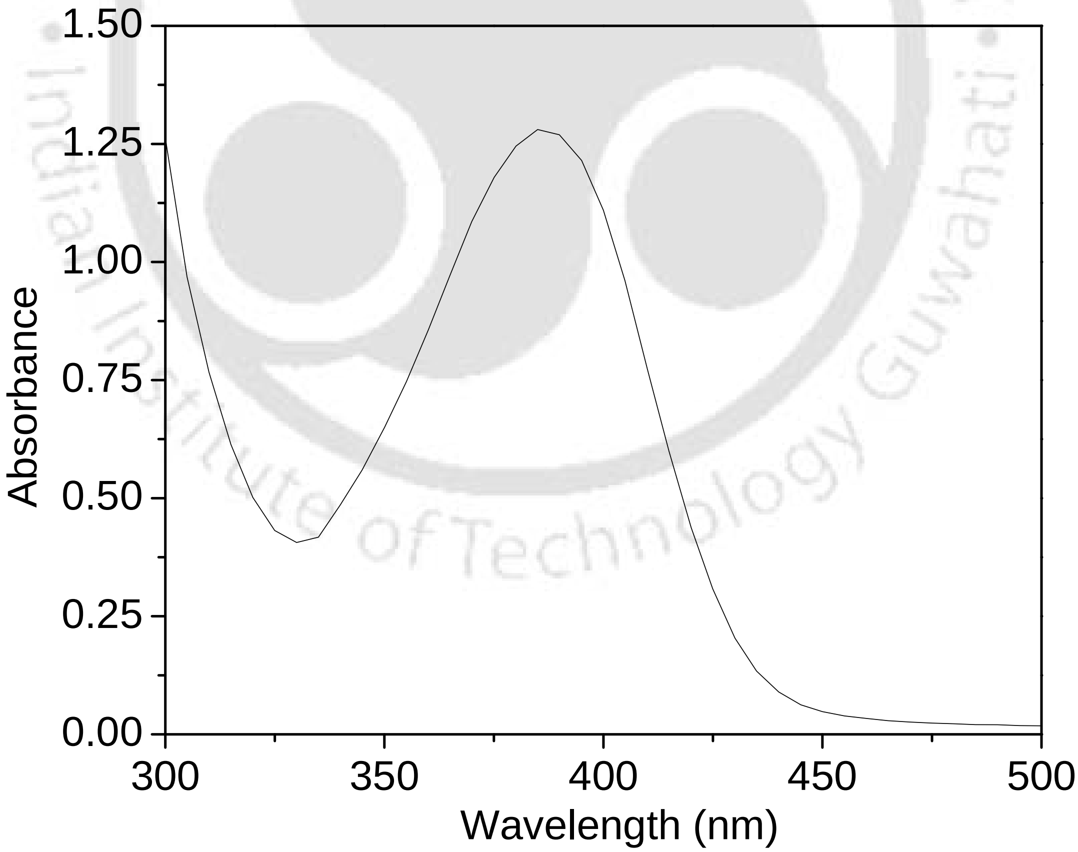


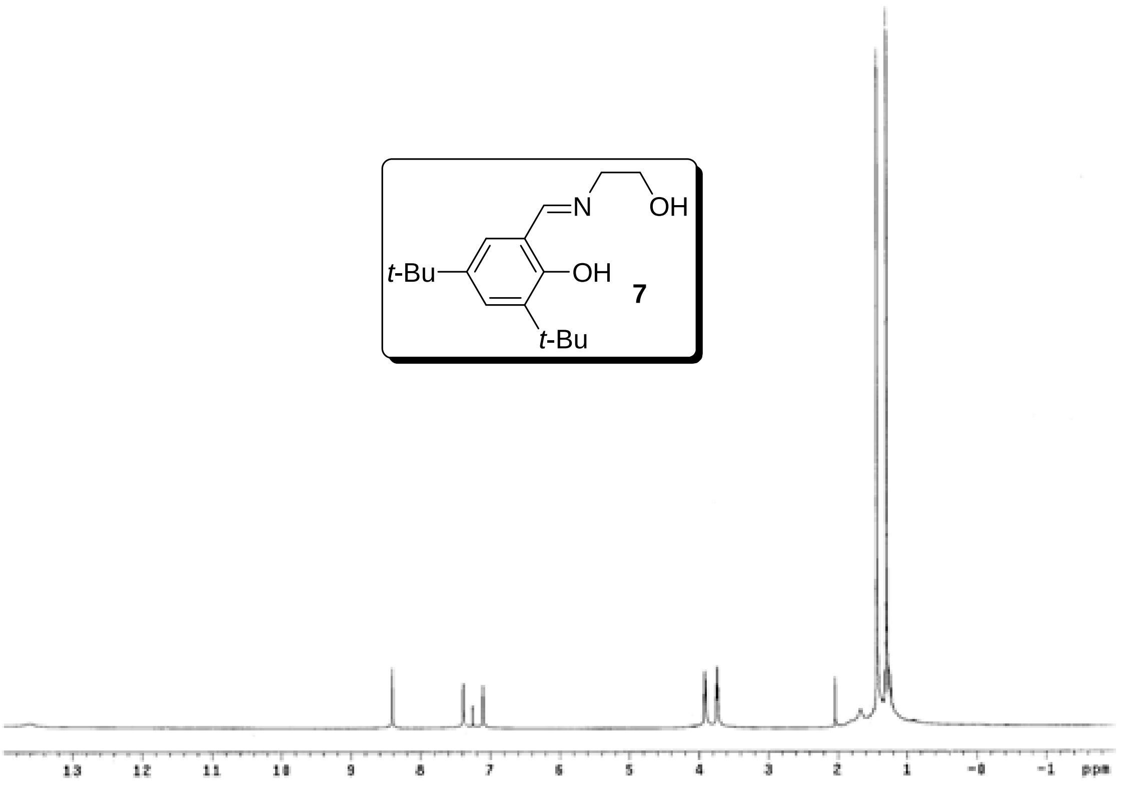
Figure 8. UV-vis Spectrum of **9** in CH_2Cl_2.

Crystal Data and Structure Refinement for Complex 8

Identification code	sj-9R2	
Empirical formula	$C_{17}H_{23}CuNO_5$	
Formula weight	384.90	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 17.1751(10) Å	α= 90°.
	b = 10.4512(6) Å	β= 98.769(4)°.
	c = 10.4495(6) Å	γ = 90°.
Volume	1853.76(19) Å^3	
Z	4	
Density (calculated)	1.379 Mg/m^3	
Absorption coefficient	1.202 mm^{-1}	
F(000)	804	
Crystal size	0.48 x 0.24 x 0.10 mm^3	
Theta range for data collection	1.20 to 28.31°.	
Index ranges	-22<=h<=22, -13<=k<=13, -13<=l<=13	
Reflections collected	19526	
Independent reflections	4187 [R(int) = 0.0519]	
Completeness to theta = 28.31°	96.1 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4187 / 0 / 223	
Goodness-of-fit on F^2	1.026	
Final R indices [I>2sigma(I)]	R1 = 0.0810, wR2 = 0.3409	
R indices (all data)	R1 = 0.1253, wR2 = 0.3486	
Largest diff. peak and hole	1.215 and -1.209 e.Å^{-3}	

Crystal Data and Structure Refinement for Cluster 9

Identification code	sj-27r2	
Empirical formula	$C_{144} H_{216} Cu_8 N_8 O_{21}$	
Formula weight	2903.57	
Temperature	296(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 14.868(3) Å	α= 90°.
	b = 29.556(5) Å	β= 101.441(9)°.
	c = 18.797(3) Å	γ = 90°.
Volume	8096(2) $Å^3$	
Z	2	
Density (calculated)	1.191 Mg/m^3	
Absorption coefficient	1.089 mm^{-1}	
F(000)	3072	
Crystal size	0.48 x 0.26 x 0.18 mm^3	
Theta range for data collection	1.30 to 27.96°.	
Index ranges	-19<=h<=18, -38<=k<=38, -24<=l<=24	
Reflections collected	99235	
Independent reflections	18024 [R(int) = 0.1383]	
Completeness to theta = 27.96°	96.5 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	18024 / 0 / 843	
Goodness-of-fit on F^2	0.996	
Final R indices [I>2sigma(I)]	R1 = 0.0743, wR2 = 0.1896	
R indices (all data)	R1 = 0.2304, wR2 = 0.2388	
Largest diff. peak and hole	0.681 and -0.449 e.$Å^{-3}$	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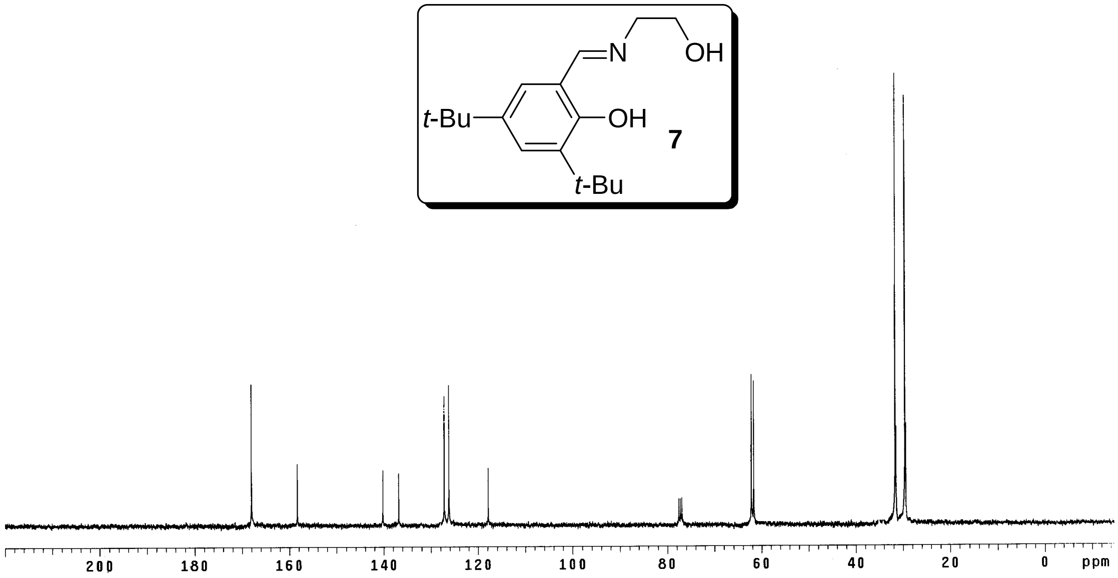
ppm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40
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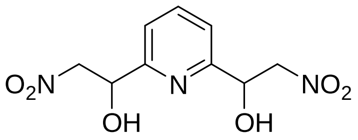
ppm



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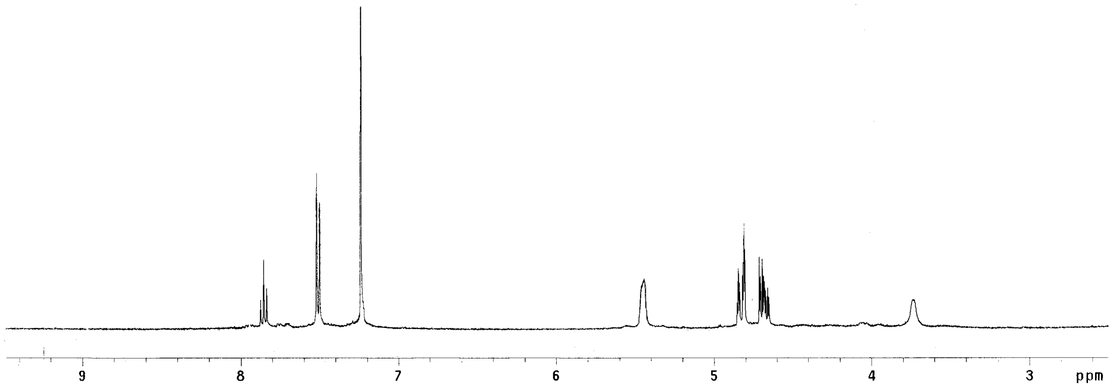

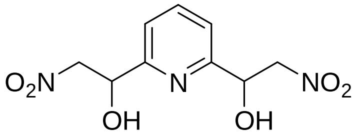

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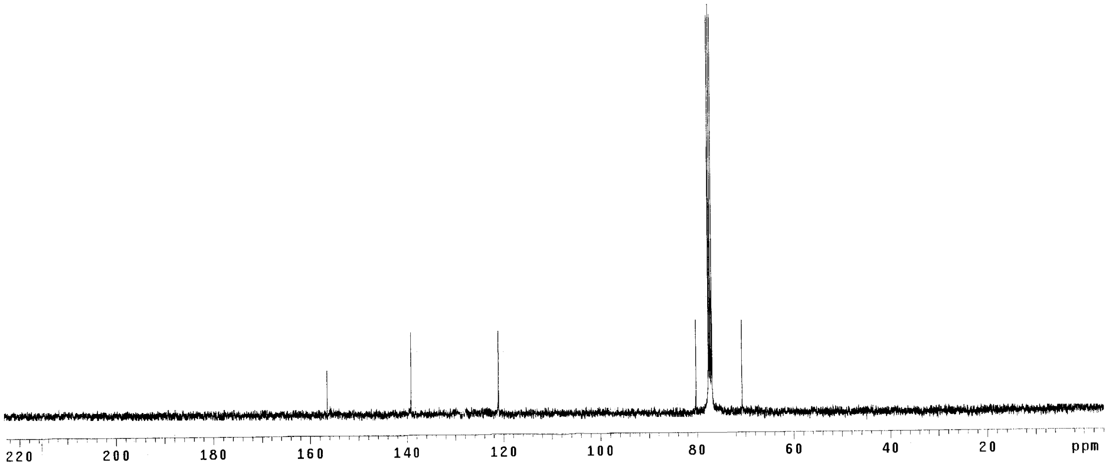

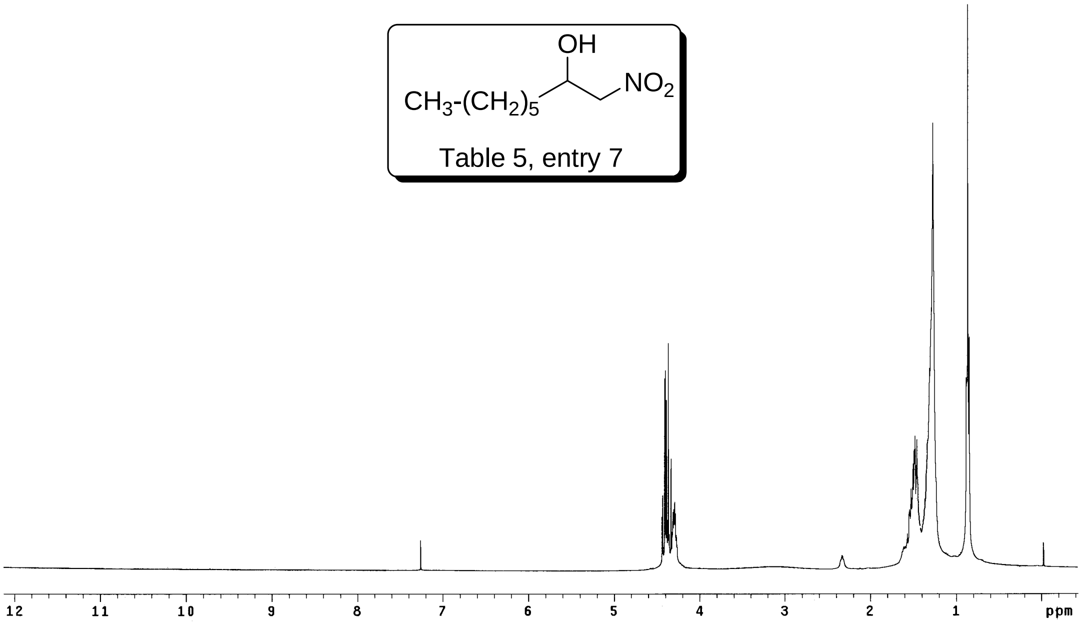
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NO2
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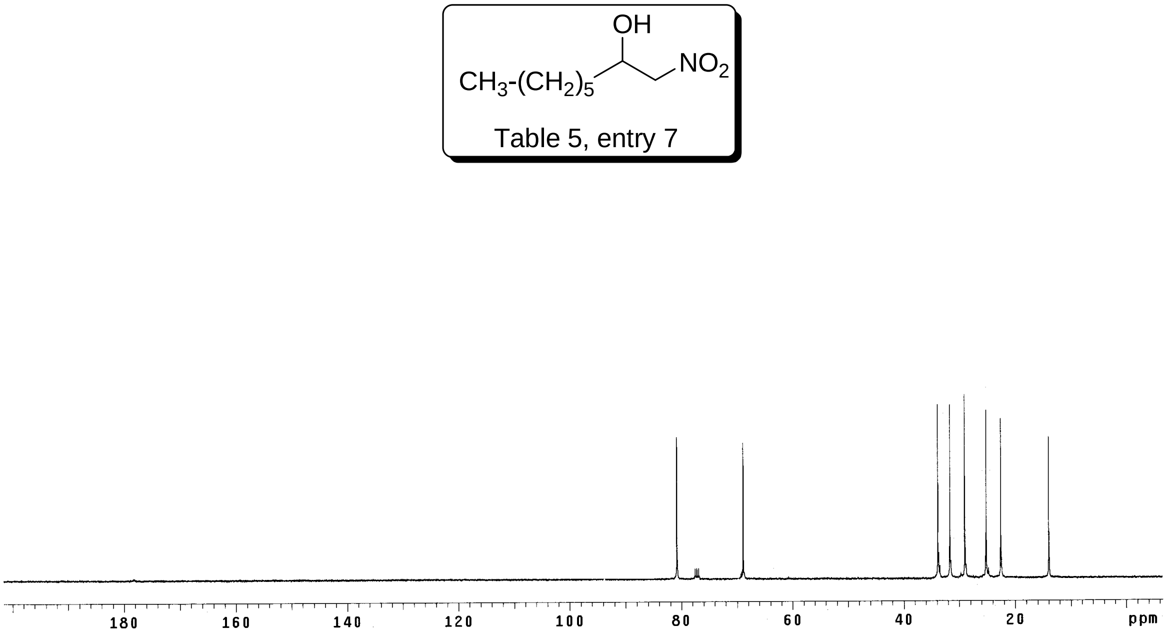
11
10
9
8
7
6
5
4
3
2
1
ppm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NO2
Table 5, entry 7
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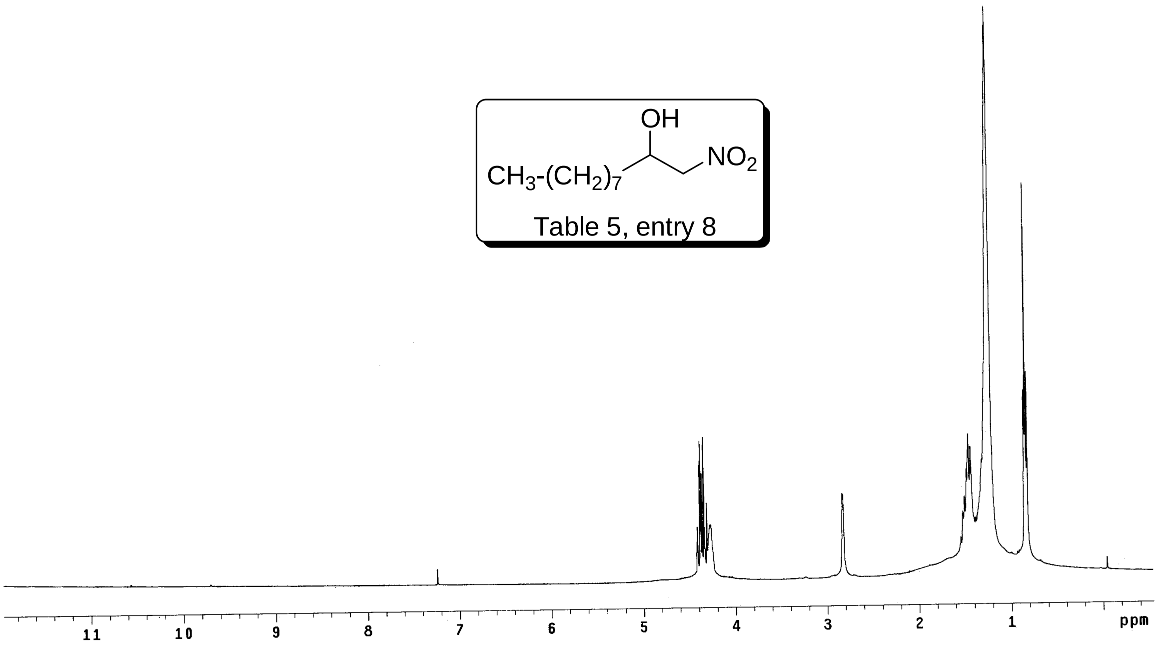
160
140
120
100
80
60
40
20
ppm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NO_2
Table 5, entry 8
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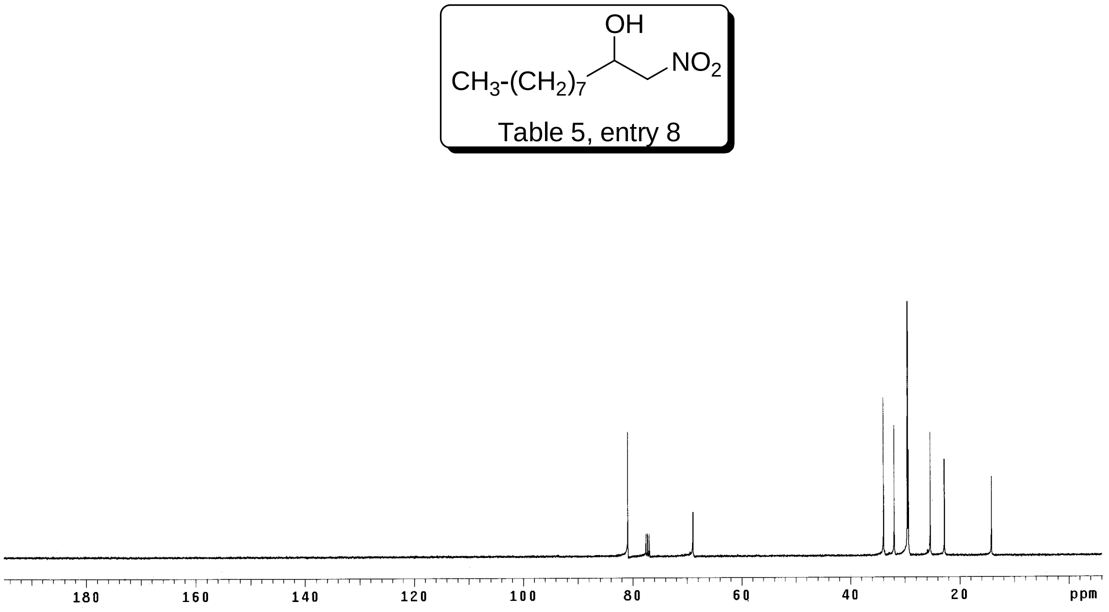
9
8
7
6
5
4
3
2
1
ppm

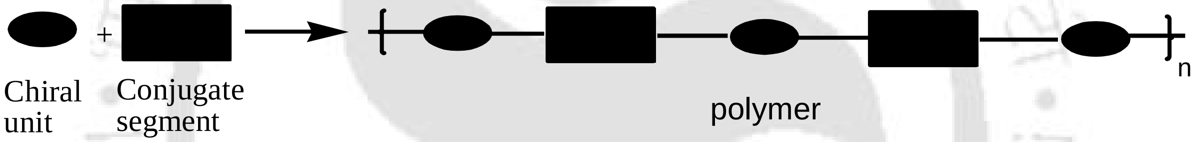

OH
CH_3-$(CH_2)_7$
NO_2
Table 5, entry 8
180
160
140
120
100
80
60
40
20
ppm

Chapter V

Synthesis of New Chiral Main Chain Polymers with (1*R*,2*R*)-1,2-Diamines

Asymmetric catalysis, an ideal method for synthesizing optically active molecules, constitutes one of the most important subjects in chemistry. But still, the application of such methodologies in chemical industry is rather limited due to the high cost of chiral ligands and use of noble metals in such transformations, which have to be separated from the reaction mixture after use. Additionally, sometimes the final products contain high levels of metal contaminants derived from catalyst decomplexation or degradation phenomena, which can become a serious drawback if the metal is toxic for pharmaceutical and food industries. The crucial goal for the world wide synthetic organic chemists is to overcome the above drawbacks and to transfer the asymmetric catalysis methodology to large scale synthesis technology. In this context, scientists are involved in the development of recyclable macromolecular stereoselective catalysts.[1] Generally, these catalysts may be divided into two classes. One is insoluble macromolecular stereoselective catalysts, and the other is soluble macromolecular stereoselective catalysts. The former type of catalysts catalyze the reactions under heterogeneous conditions and the latter type of catalysts catalyze the reactions in homogeneous conditions.

Stereochemical and chemical efficiencies of a certain transformation are in principle better reproduced and predicted in homogeneous catalysis than in heterogeneous catalysis. The presence of the heterogeneous support in a reaction vessel, in some cases, can make the results unpredictable (negative vs novel positive effects).[1a] The choice of the heterogeneous support for the catalysis is a crucial decision. Some properties of the support like high thermal, chemical and physical stabilities, chemical inertia, and homogeneous like behavior are highly desirable. Diffusion of molecules inside a matrix adds a delaying contribution to the kinetics of reaction. In heterogeneous catalysis these phenomena are a sum of two contributions: diffusion of molecules inside the solvent (which is also present in homogeneous catalysis) and diffusion of molecules inside the porous structure of the supporting matrix. Based on this, homogeneous catalysis theoretically has advantages over heterogeneous catalysis. But in heterogeneous catalysis, the catalyst is easily recovered using just filtration or extraction techniques that are impossible to apply in homogeneous catalysis. Inorganic supports[2a] such as silica, zeolite, alumina, zirconia, ZnO, clay etc., and highly cross linked organic polymers[2b] are the standard supports for the synthesis of insoluble macromolecular stereoselective catalysts. Soluble macromolecules like oligomeric or soluble polymers having low cross link, PEG, and dendrimers are the standard supports for the synthesis of soluble macromolecular stereoselective catalysts. The alternative method for the synthesis of soluble macromolecular stereoselective catalysts is co-polymerization of monomeric chiral unit with a suitable conjugate segment (Scheme 1). We can combine the advantages of homogeneous and heterogeneous systems by running reactions with soluble macromolecular stereoselective catalysts. These macromolecular homogeneous catalysts can be precipitated at the end of the reaction by addition of a co-solvent and recovered like a heterogeneous system.

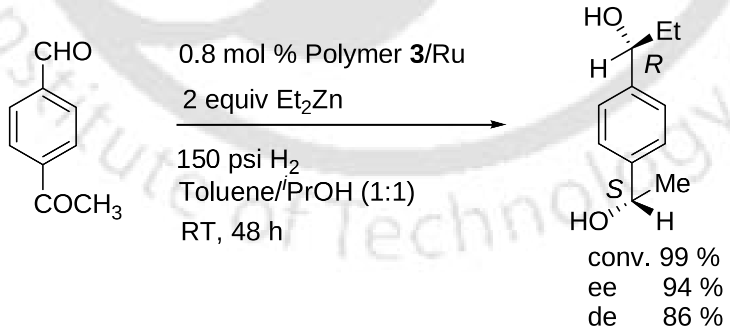


Scheme 1

The study of π-conjugated stereoregular organic polymers is an active topic due to their remarkable electronic and optical properties.[3,4] Much effort has been made to control the bulk properties of these materials by a design strategy based on molecular engineering.[5] π-Conjugated chiral main chain organic polymers are potentially useful materials. For example, they can be used in areas such as photo- or electroluminescence, non-linear optics, chiral sensor and asymmetric catalysis. These materials can be classified into two types: i) polymers incorporating inherently the chiral units in the main chain[6] and ii) polymers having either chiral side chains or chiral dopants.[7] Both these types have received growing research attention in recent years.

5.1 Binapthyl Based Chiral Main Chain Polymers

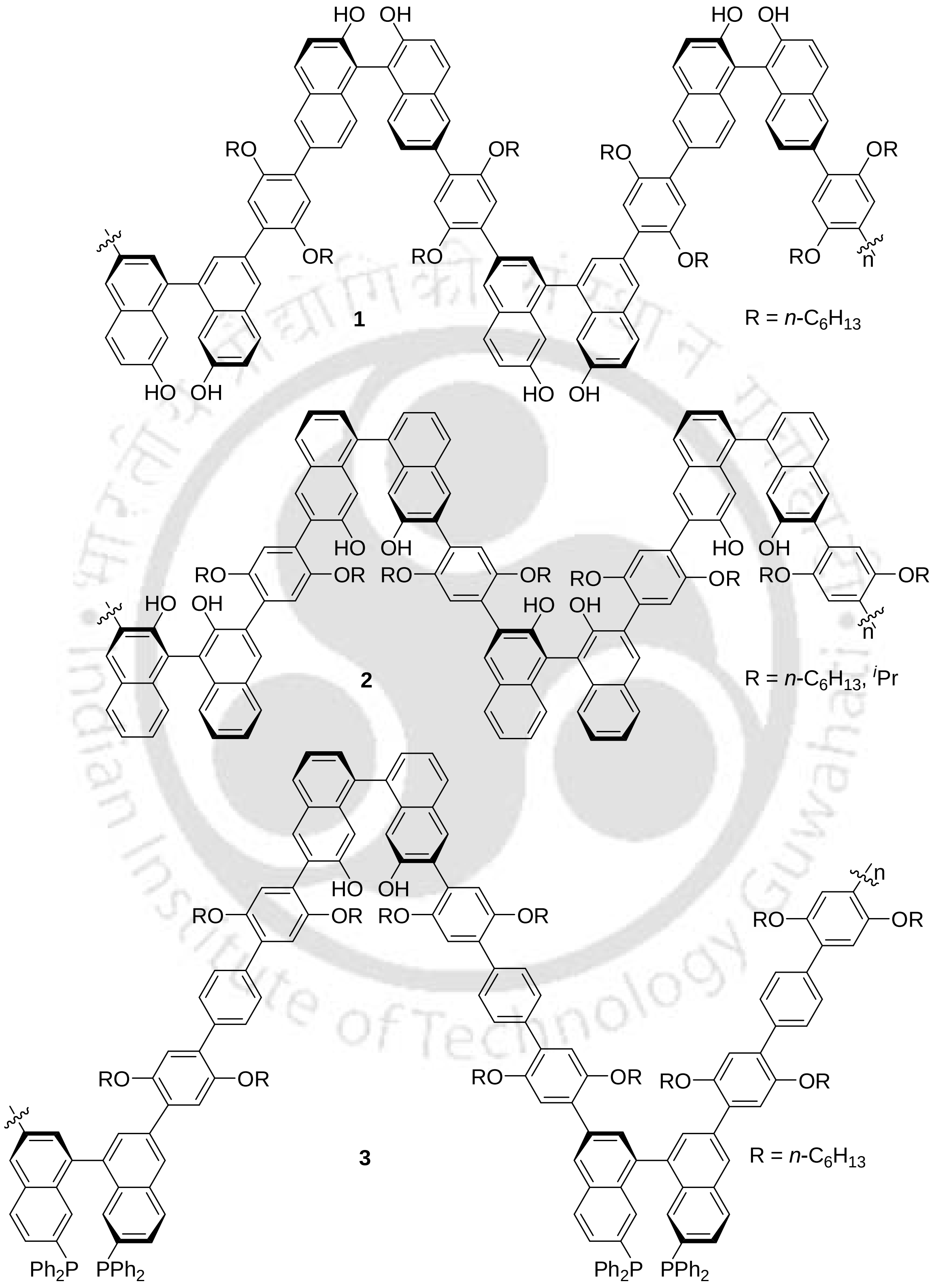
Binaphthyl based chiral main chain polymers have been developed by Lin Pu group.[8] They have used optically active binaphthyl compounds to construct a series of main chain chiral conjugated polymers as novel electrical and optical materials and new generation of polymeric catalysts (Scheme 3). The polyhydroxyl groups of these polymers allow the introduction of different Lewis acid metal centres to prepare novel soluble macromolecular chiral catalysts for asymmetric transformations like enantioselective diethylzinc addition to aldehydes, asymmetric Diels-Alder reactions and asymmetric hydrogenation reactions. In these polymeric complexes, the catalytic sites are expected to be highly organized along the rigid and sterically regular backbone. This is different from most of the polymer-supported catalysts where flexible and sterically irregular polymers are used. The rigidity and stereoregularity of the chiral conjugated binaphthyl polymers make it possible to systematically adjust the microenvironment of the catalytic sites for the development of enantioselective polymeric catalysts. For an example, the polymer **3** containing two distinctively different catalytic sites, BINOL and BINAP, has shown excellent stereoselectivity in tandem asymmetric reactions involving the diethylzinc addition to the aldehydes and hydrogenation of the ketones (Scheme 2).[8n] It demonstrates that the rigid polybinaphthyl structure not only can preserve the catalytic properties of a monomer catalyst but can also allow distinctively different catalytic sites to function independently in the polymer chain to conduct different asymmetric reactions. The alkoxy chain in the polymers enhances the solubility in common organic solvents such as CH_2Cl_2, $CHCl_3$, toluene and THF. After the reaction the polymer complex was recovered from the organic solution by precipitation with methanol.



Scheme 2

5.2 (*1R,2R*)-1,2-Diaminocyclohexane Based Chiral Main Chain Polymers

Moreau and co-workers have developed a quite general route for the synthesis of diamine based chiral main chain polymers with readily available C_2 symmetric chiral (*1R,2R*)-1,2-di-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RO
OR
RO
OR
OR
RO
RO
OR
n
HO OH
HO OH
1
R = n-C6H13
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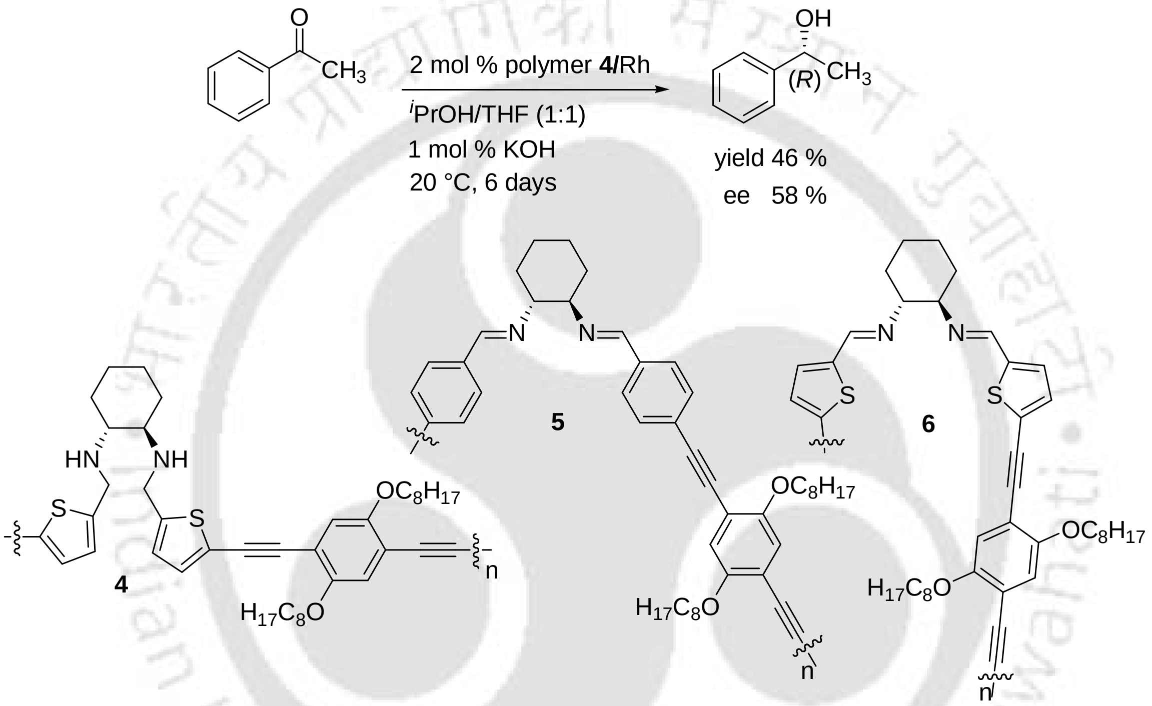
HO OH
RO
OR
RO
OR
RO
OR
RO
OR
HO OH
HO OH
n
2
R = n-C6H13, iPr
HO OH
RO
OR
RO
OR
RO
OR
RO
OR
RO
OR
RO
OR
n
3
R = n-C6H13
Ph2P PPh2
Ph2P PPh2

Scheme 3

aminocyclohexane and conjugated 1,4-diethynyl-2,5-bis(alkyloxy)benzene using palladium catalyzed Sonogashira cross-coupling reaction (Scheme 4).[6d-e] These chiral π-conjugated polymers are soluble in common organic solvents and showed very high optical rotations, photoluminescence properties, strong Cotton effect and low crystallinity. In these polymers the chiral unit can serve as a ligand. For example, the polymer **4** with rhodium catalyzes the asymmetric hydrogen-transfer to ketone with enhanced selectivity of (58 % ee) compared to the monomer (32 % ee) (Scheme 4).[6d]

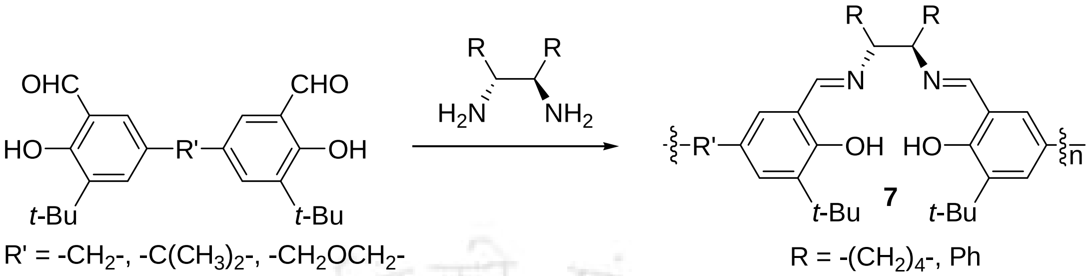


Scheme 4

5.3 Soluble Macromolecular Stereoselective Catalysts Containing Salen

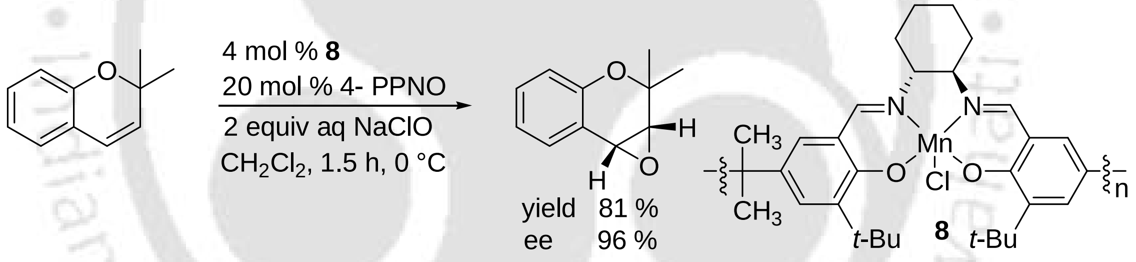
Metal complexes derived from chiral salen are the most successful enantioselective catalysts in asymmetric catalysis. This is due to the high enantiomeric excesses that can be achieved and their general applicability to many different reaction types.[9] One general trend in catalysis is the transformation of successful homogeneous catalysts into recoverable catalytic systems for obvious reasons. Following this general trend, the development of reusable chiral metal-salen complexes appears to be of great interest. This section describes some of the approaches to synthesize soluble polymeric chiral salen catalysts and their use in asymmetric catalysis as recoverable catalysts.

The most general approach to synthesize a soluble polymer with salen repeating units **7** is the Schiff's base formation of bis(*o*-hydroxybenzaldehyde) with diamine (Scheme 5).[10]



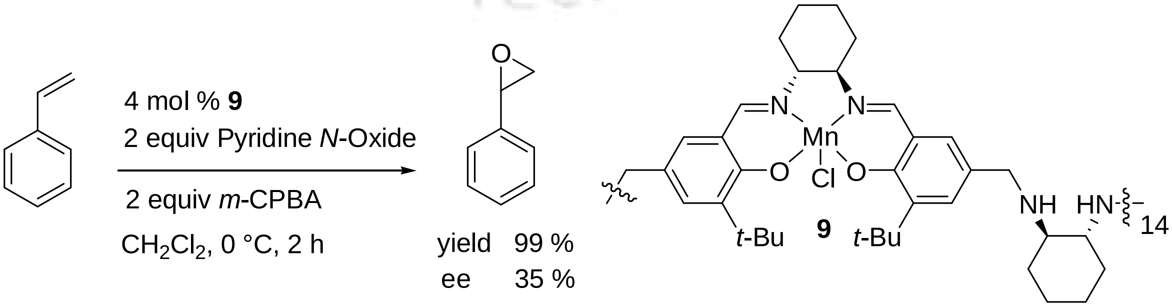
Scheme 5

Zheng and co-workers have studied the chiral manganese(III)-salen **8** as a soluble catalyst for asymmetric epoxidation of unfunctionalized olefins along with 4-phenylpyridine *N*-oxide (4-PPNO) with up to 97 % ee (Scheme 6).[10a] The catalyst **8** is recyclable without loss of activity and selectivity. In addition, the catalyst **8** exhibits activities and enantioselectivities as good as the Jacobsen homogeneous catalyst.[10b]



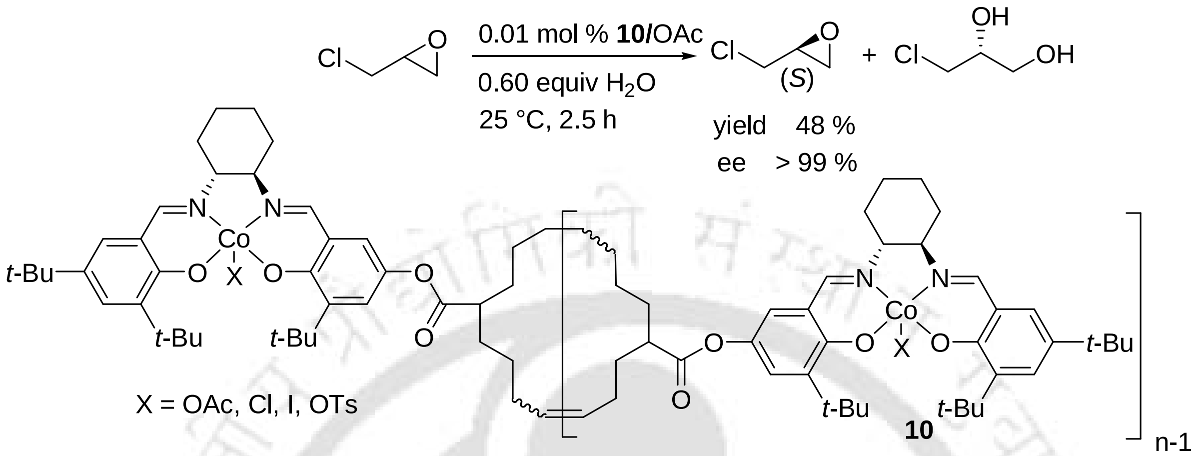
Scheme 6.

Yu and co-workers have used chiral manganese(III) salen **9** for epoxidation of styrene (Scheme 7).[11] However, the recovered catalyst shows less reactivity and selectivity compared to the fresh catalyst.



Scheme 7

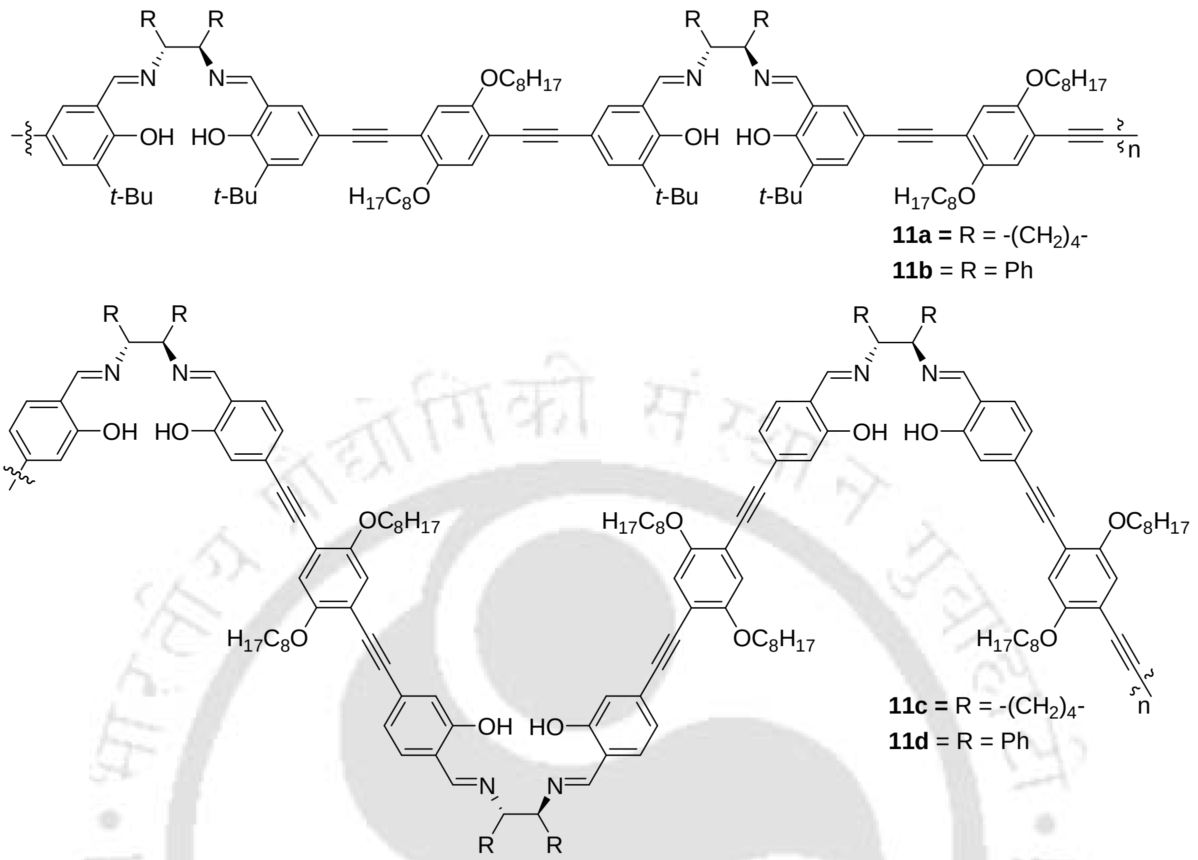
Weck and co-workers have developed cobalt(III)-salen **10** for kinetic resolution of racemic terminal epoxides (Scheme 8). The catalyst is recyclable without loss of activity and selectivity.[12]



Scheme 8

5.4 Present Study

The application of optically active 1,2-diamine derivatives in asymmetric catalysis has attracted very extensive attention.[9] These molecules have demonstrated excellent chiral induction in a number of organic transformations when used either as chiral auxiliary or chiral ligand.[9] Thus, the design and development of stereoregular main chain polymers with optically active 1,2-diamine derivatives will be valuable for enantioseletive catalysis because these materials provide the advantages of simplified product isolation, easy recovery of the chiral catalysts, and potential use for continuous production. From an environmental and economic standpoint, these studies are attractive since the cost and environmental impact (E-factor) of the process can be lowered. In this chapter, we describe the synthesis, characterization and application of new π-conjugated chiral 1,2-diamine based main chain polymers **11** (Scheme 9) from (*1R,2R*)-1,2-diamines **12** and dialdehydes **13 -14** by Schiff's base formation (Scheme 10).

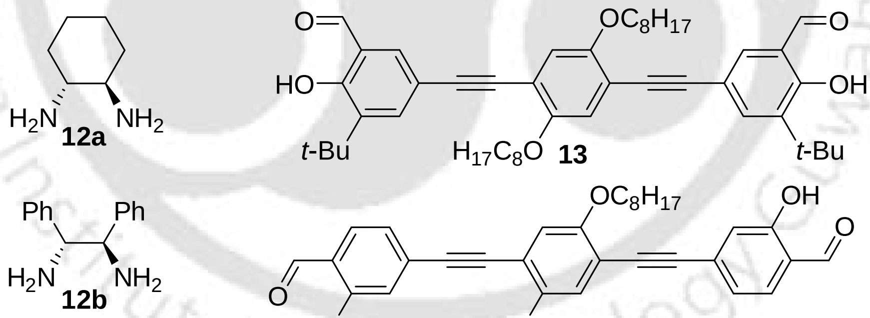


11a = R = -(CH$_2$)$_4$-
11b = R = Ph

11c = R = -(CH$_2$)$_4$-
11d = R = Ph

11

Scheme 9

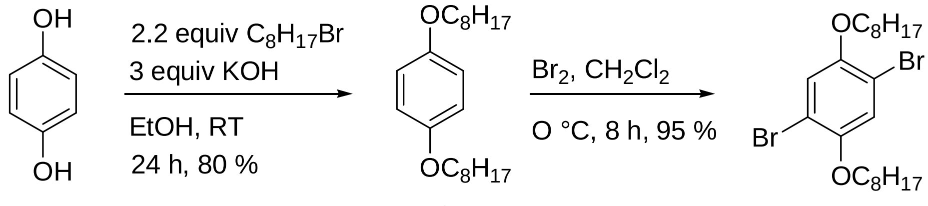


12a **13**

12b

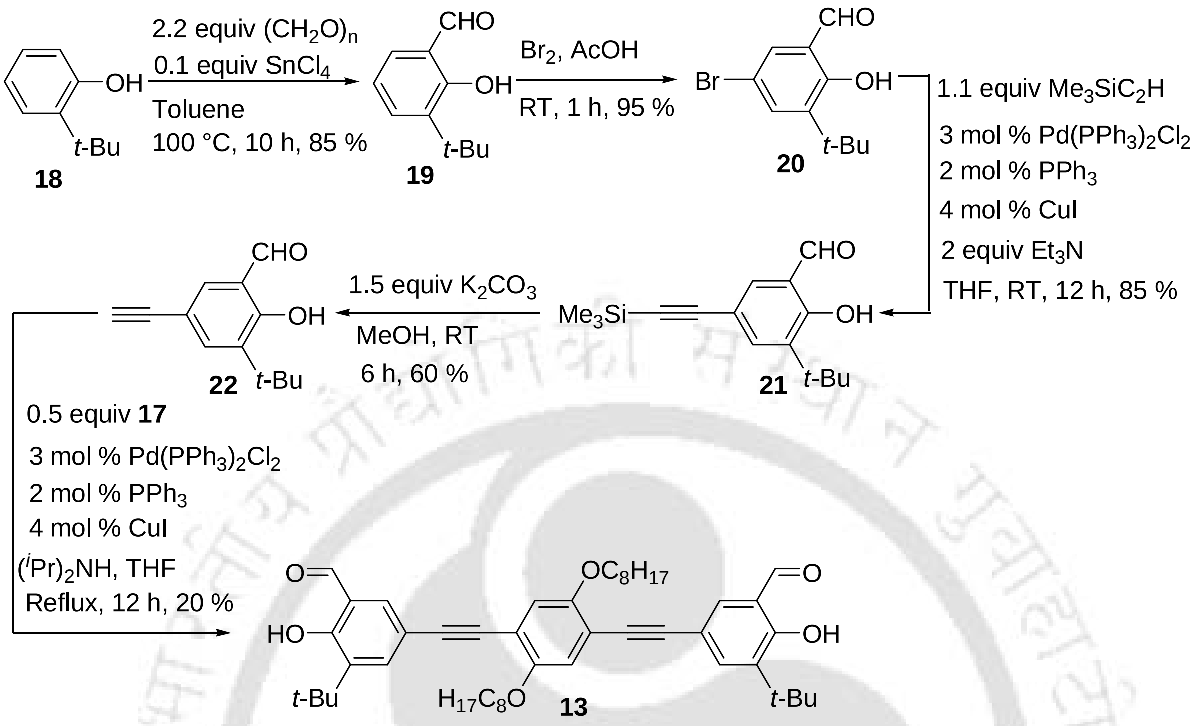
12 **14**

Scheme 10

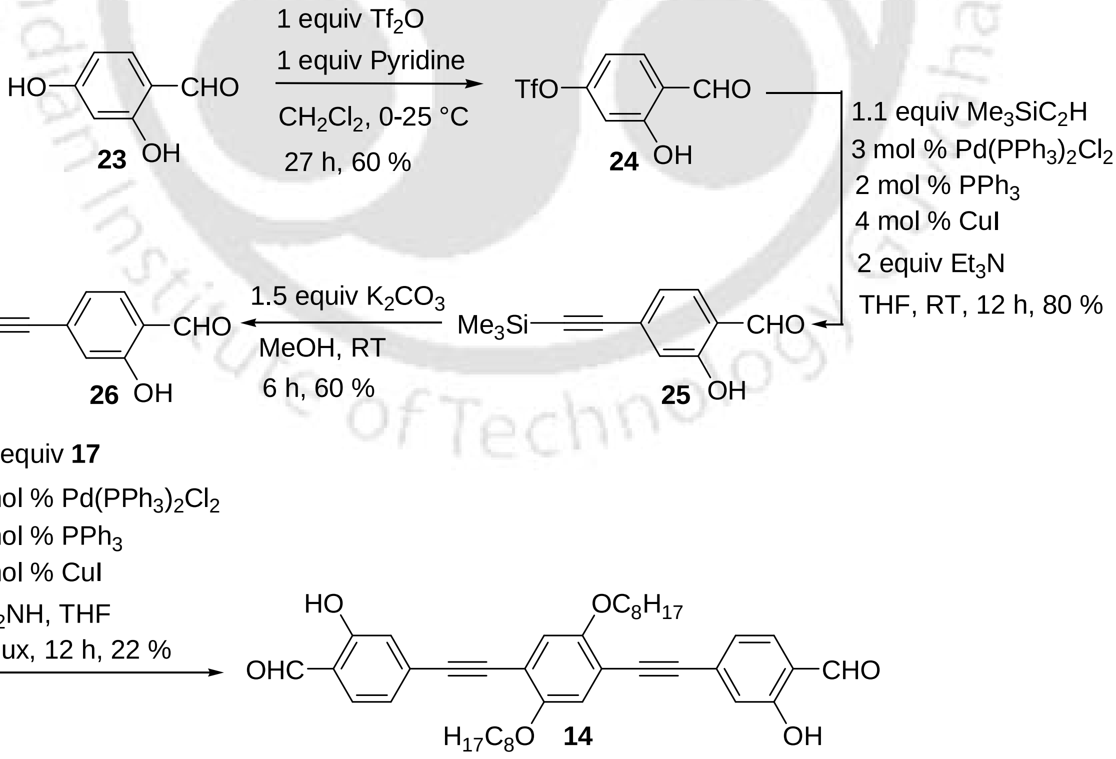


15 **16** **17**

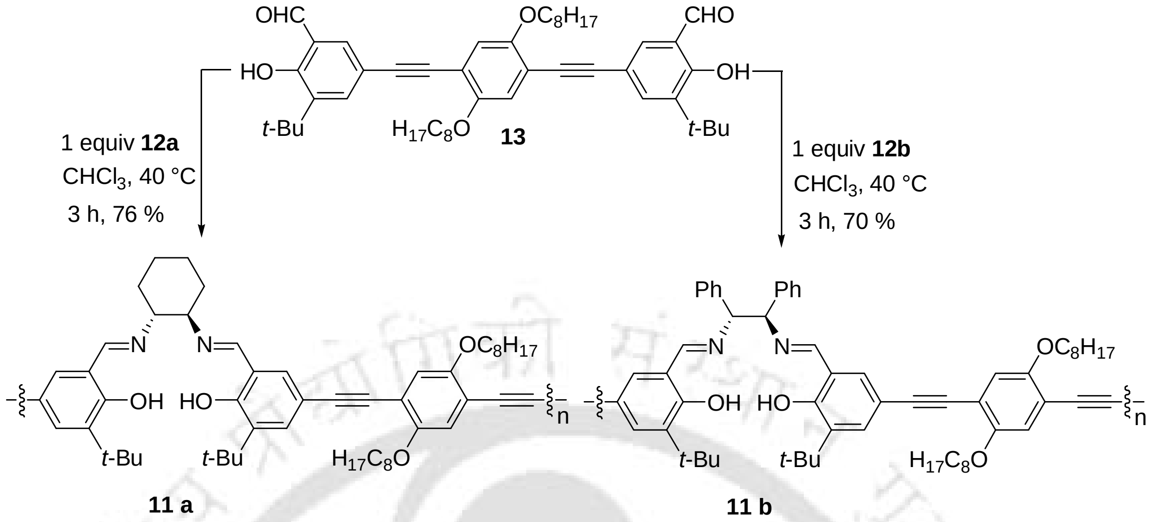
Scheme 11



Scheme 12



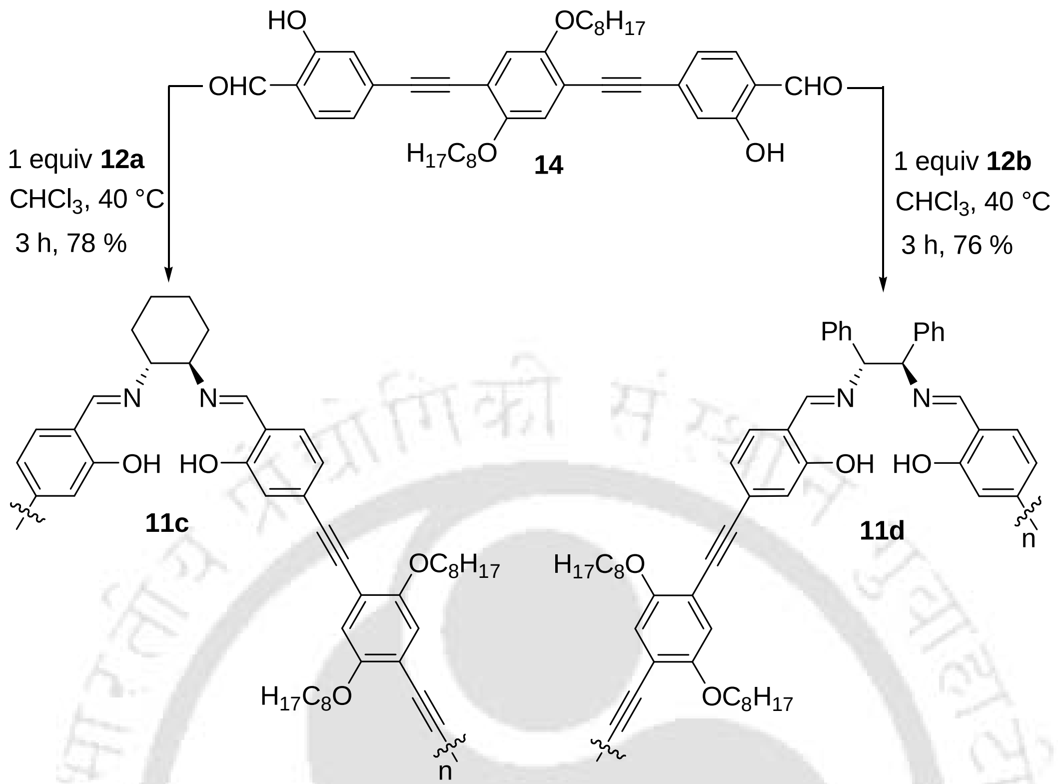
Scheme 13



Scheme 14

The synthesis of dialdehyde **13** is shown in scheme 12. The reaction of 2-*tert*-butylphenol **18** with paraformaldehyde in the presence of $SnCl_4$ followed by bromination with Br_2 in acetic acid afforded 5-bromo-3-*tert*-butylsalicylaldehyde **20** as a yellow solid.[13] Aldehyde **20** was transformed into silyl derivative **21** by coupling with trimethylsilylacetylene using $Pd(PPh_3)_2Cl_2$ and CuI in the presence of Et_3N in THF. Desilylation of **21** with K_2CO_3 in MeOH gave ethynyl derivative **22**, which was coupled with 1,4-dibromo-2,5-dioctyloxybenzene **17** using $Pd(PPh_3)_2Cl_2$ and CuI to afford dialdehyde **13** as a yellow solid (Scheme 11).

The synthesis of the dialdehyde **14** is shown in scheme 13. The reaction of 2,4-dihydroxybenzaldehyde **23** with trifluoromethanesulfonic anhydride in the presence of pyridine gave the triflate **24** in 60 % yield.[14a,b] The C-C cross-coupling of **24** with trimethylsilylacetylene using $Pd(PPh_3)_2Cl_2$ and CuI afforded the silyl derivative **25** in 80 % yield. The latter was transformed to the aldehyde **14** via desilylation using K_2CO_3 in MeOH followed by C-C cross-coupling with 1,4-dibromo-2,5-dioctyloxybenzene **17** in the presence of $Pd(PPh_3)_2Cl_2$ and CuI.[14c]



Scheme 15

The synthesis of the polymers **11a-d** is shown in scheme 14-15. The reactions of the aldehyde **13** and **14** with optically active (1*R*,2*R*)-1,2-diaminocyclohexane **12a** and (1*R*,2*R*)-1,2-diphenylethylenediamine **12b** in $CHCl_3$ provided the polymers **11a-d** as yellow powder in 76-78 % yield. These polymers were soluble in toluene, THF, CH_2Cl_2 and $CHCl_3$ and insoluble in MeOH. Solutions of **11a-d** in $CHCl_3$ showed the specific rotations, $[\alpha]_D^{20}$ +376 (c = 0.1, $CHCl_3$), $[\alpha]_D^{20}$ +166 (c = 0.1, $CHCl_3$), $[\alpha]_D^{20}$ = -797 (*c* = 0.1, $CHCl_3$) and $[\alpha]_D^{20}$ = -244 (*c* = 0.1, $CHCl_3$), respectively. GPC analysis with polystyrene as internal standard and THF as the eluent exhibited the molecular weights correspond to *ca* 21 repeating units for **11a** (M_w = 18512, M_w/M_n = 1.27), *ca* 5 repeating units for **11b** (M_w = 4864, M_w/M_n = 1.4), *ca.* 17 repeating units for **11c** (M_w = 12102 and $M_\mathrm{w}/M_\mathrm{n}$ = 1.27) and ca. 27 repeating units for **11d** (M_w = 22157 and $M_\mathrm{w}/M_\mathrm{n}$ = 1.49). The ^{1}H NMR spectra recorded at 400 MHz and FT-IR spectra of **11a-d** were consistent with the polymers structures.

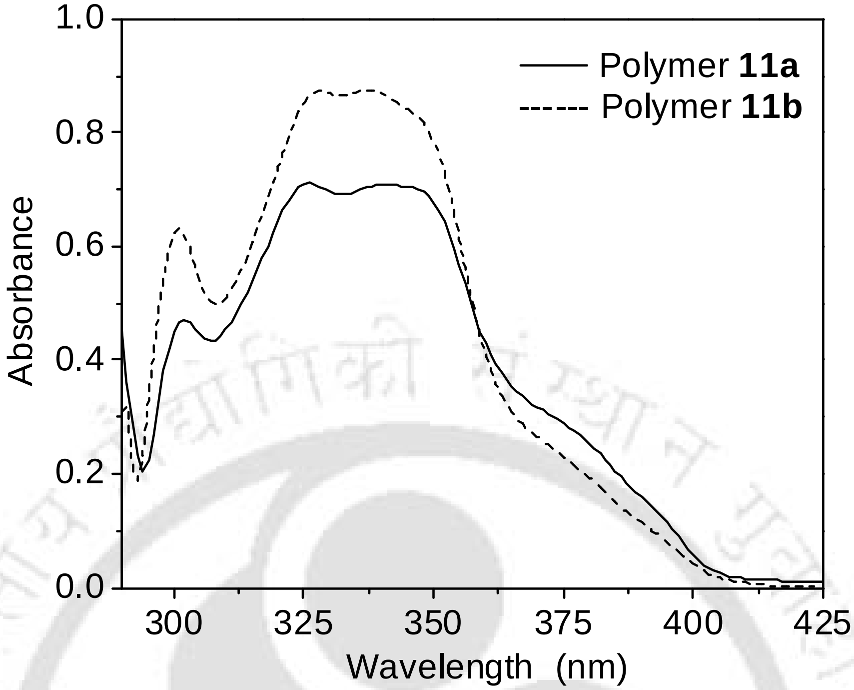


Figure 1. UV-vis Spectra of the Polymers **11a-b** in THF.

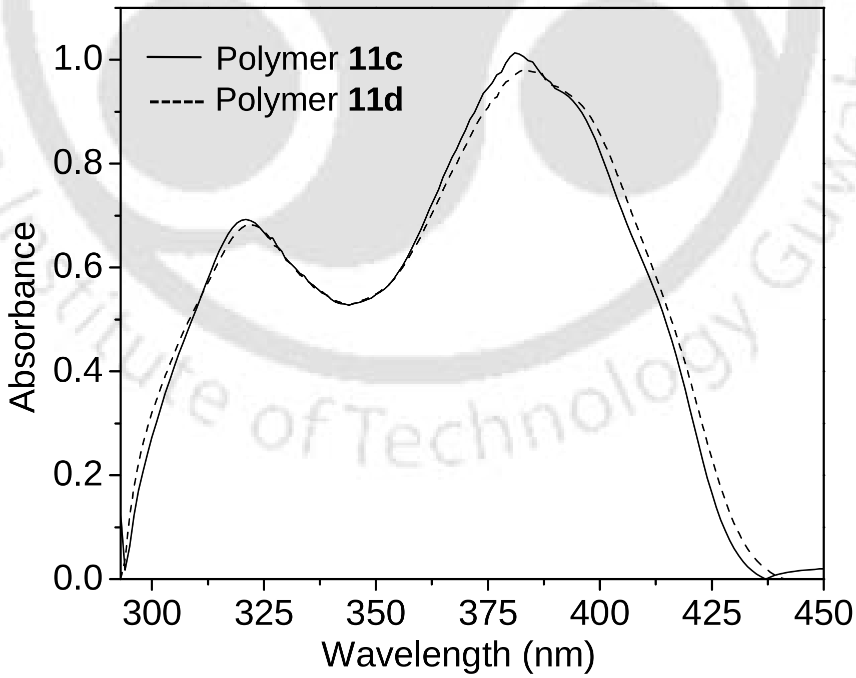


Figure 2. UV-vis Spectra of the Polymers **11c-d** in THF and on Thin Film.

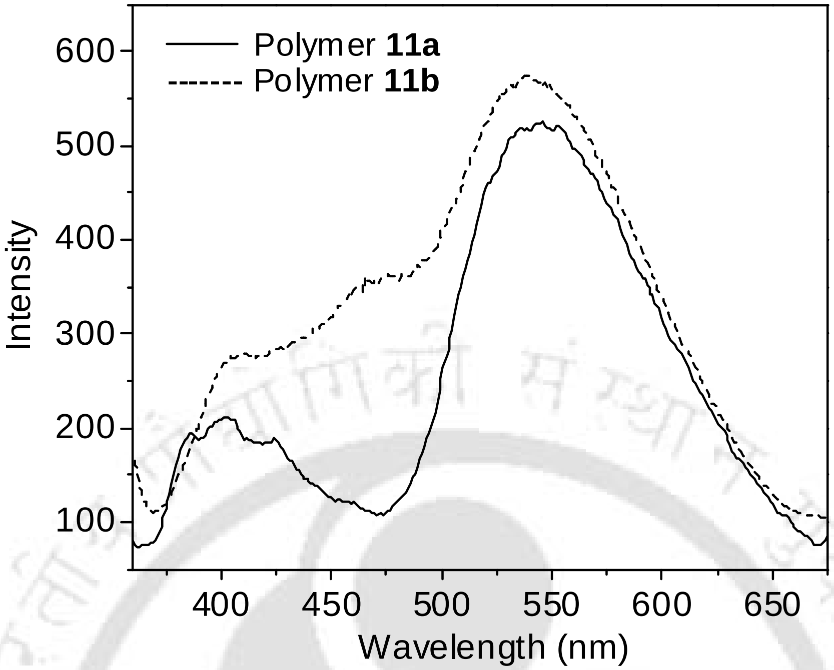


Figure 3. Fluorescence Spectra of the Polymers **11a -b** ($\lambda_{excitation}$ = 340 nm) in THF.

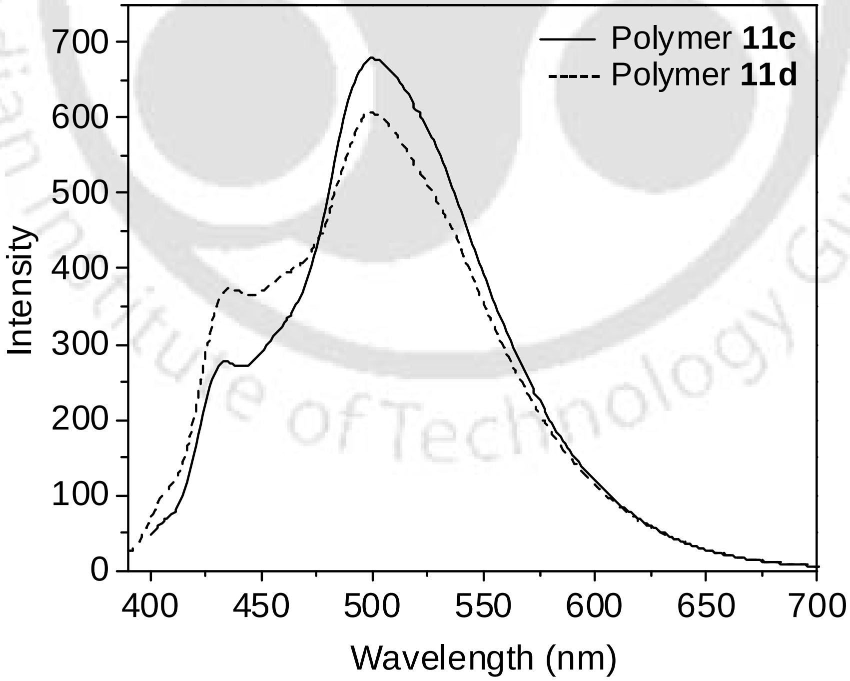


Figure 4. Fluorescence Spectra of the Polymers **11c -d** ($\lambda_{excitation}$ = 380 nm) in THF.

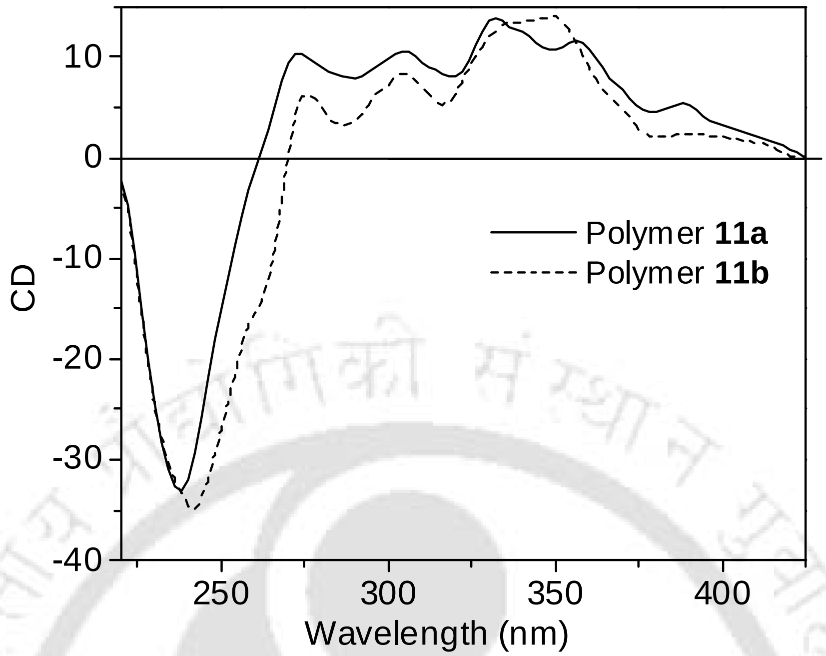


Figure 5. CD Spectra of the Polymers in $CHCl_3$ [C = 1.99 x 10^{-5} M for **11a** and C = 8.45 x 10^{-5} M for **11b**].

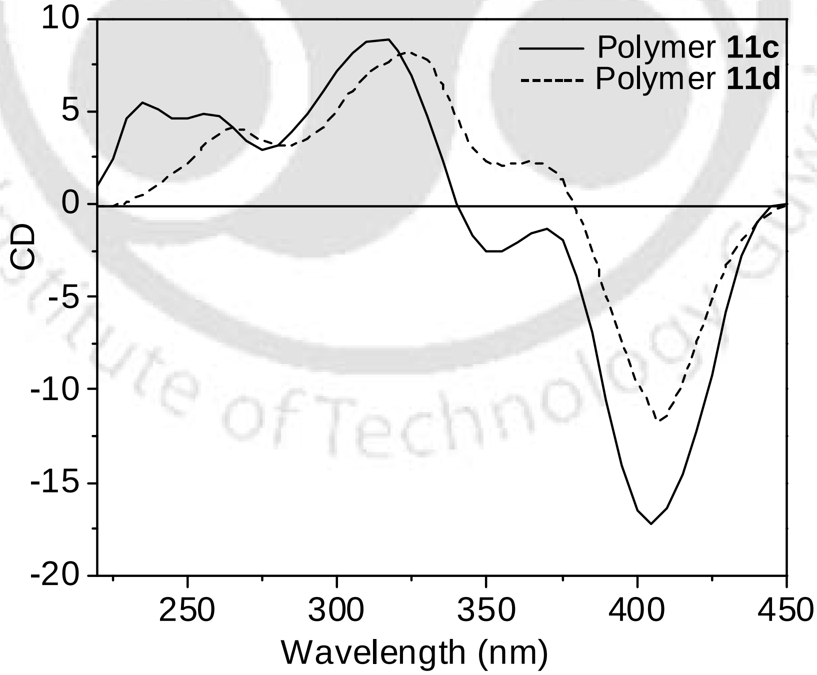


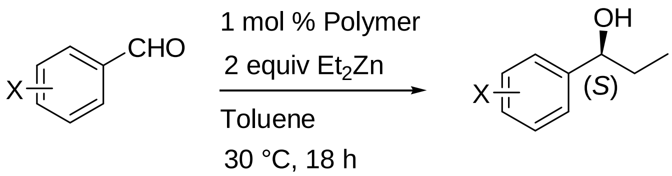
Figure 6. CD Spectra of the Polymers in $CHCl_3$ [C = 5.16 x 10^{-6} M for **11c** and C = 3.52 x 10^{-5} M for **11d**].

The absorption, emission and circular dichroism properties of the polymers **11a-d** were studied. The UV-vis spectra of THF solutions of **11a-b** exhibited absorption λ_{max} at 302 and 333 nm (Figure 1) and **11c-d** exhibited λ_{max} at 320 and 382 nm (Figure 2). The fluorescence spectra of THF solutions of **11a-b** showed emissions (λ_{max}) at 408 and 563 nm ($\lambda_{excitation}$ = 340 nm) (Figure 3) and **11c-d** showed emissions (λ_{max}) at 432 and 499 nm ($\lambda_{excitation}$ = 380 nm) (Figure 4). These solutions emitted strong green light under UV irradiation. The CD spectra of $CHCl_3$ solutions of **11a-b** exhibited weak positive cotton effect with splitting at 271, 291, 331, 355, 387 nm, and a negative cotton effect at 238 nm showing a positive chirality (Figure 5). The CD spectra of $CHCl_3$ solutions of **11c-d** exhibited strong negative Cotton effect at 406 nm and weak positive Cotton effects at 276 and 304 nm showing a negative chirality (Figure 6). The purpose of the alkyl chain in the polymer is to enhance their solubility in organic solvents.

Polymers **11a-b** were then studied for Et_2Zn addition to 3-nitrobenzaldehyde (Table 1). We were pleased to find that the reaction occurred to afford the corresponding alcohol with 50 % ee when the reaction was stirred in the presence of 1 mol % of **11a** (with respect to monomeric unit) and 2 equiv of Et_2Zn in toluene at ambient temperature.[15] The enantioselectivity was further increased to 70 % ee when the polymer **11b** was employed in the place of polymer **11a**. These reactions did not involve any additive. Benzaldehyde and 4-methoxybenzaldehyde were next reacted with Et_2Zn to provide the corresponding alcohols with 50 % and 60 % ee, respectively. A similar result has been reported with the monomeric salen ligand for Et_2Zn addition to aldehydes.[15d] The advantage of the present system is that polymer **11b** can be recovered from the reaction mixture by adding MeOH and then recycled. The recovered **11b** was used for the fresh reaction of 3-nitrobenzaldehyde with Et_2Zn. As above, the reaction occurred to give the respective alcohol with 70 % ee. This study clearly suggests that the polymer is recyclable without loss of selectivity.

The proposed catalytic cycle is shown in scheme 15. The reaction of **11b** with Et_2Zn may provide complex ***a***, which may transform to intermediate ***b*** by reaction with Et_2Zn and aldehyde. The transfer of the ethyl group from the coordinated Et_2Zn to the coordinated aldehyde in ***b*** may give intermediate ***c*** which on reaction with new Et_2Zn and aldehyde may complete the catalytic cycle.

Table 1. Polymer **11a-b** Catalyzed Et_2Zn Addition to Aldehydes



Entry	X	Polymer	Yield[a,b] (%)	ee (%)
1	3-NO_2	10a	72	50
2	3-NO_2	10b	74	70
3	3-NO_2	10b	73	70[c,d]
4	H	10b	83	50[e]
5	4-OMe	10b	70	60[e]

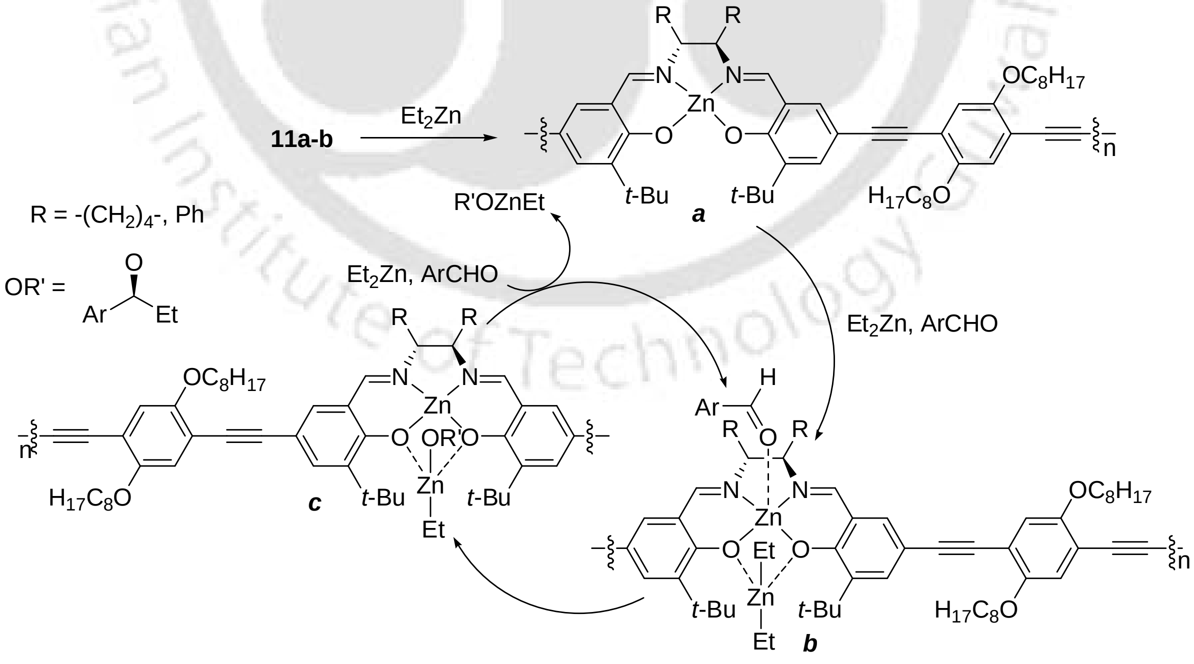
[a] Aldehyde (1 mmol), Et_2Zn (2 mmol) and polymer **11a-b** (1 mol % with respect to monomeric unit) were stirred at 30 °C in toluene under N_2 atmosphere.

[b] Isolated yield.

[c] Recovered **11b** used.

[d] Determined by HPLC with chiralcel AD-H column using hexane/isopropanol (90:10).

[e] Determined by HPLC with chiralcel OD-H column using hexane/isopropanol (97:3).

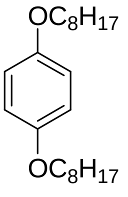


Scheme 15. Proposed Catalytic Cycle

In summary, the synthesis of π-conjugated chiral main chain polymers **11** was accomplished. These polymers are rigid, stereoregular, soluble in common organic solvents and exhibit high specific optical rotation. The polymers **11a-b** catalyze the Et_2Zn addition to aldehydes with good enantioselectivity as recyclable ligands without loss of activity and selectivity.

Experimental Section

General. All experiments were carried out under nitrogen atmosphere. 2-*tert*-Butylphenol (99 %), trimethylsilylacetylene (99 %), (1*R*,2*R*)-1,2-diaminocyclohexane (99 %), (1*R*,2*R*)-1,2-diphenylethylenediamine (99 %), CuI (99.99 %), $Pd(PPh_3)_2Cl_2$ (99.99 %), PPh_3 and octylbromide (99 %) were obtained from Aldrich and used without further purification. FT-IR spectra were recorded using Nicolet impact-410 spectrometer. Optical rotations were measured using Perkin Elmer Model-343 Polarimeter. Elemental analysis was obtained from Perkin Elmer 2400 series II CHNS analyzer. Flash column chromatography was performed using 230-400 mesh silica gel. UV-vis spectra were recorded from Perkin Elmer Lambda-25 spectrometer. The GPC analysis was performed on Waters 2410 instrument with ultrastyragel 100 Å 7.8 x 300 mm Waters column employing polystyrene as internal standard and THF as eluent. CD spectra were recorded on JASCO J-500 instrument. A cylindrical quartz cell with optical path length of 0.05 mm was used for solutions. The fluorescence spectra were recorded on Varian Cary Eclipse fluorescence spectrophotometer using a 1 cm quartz cuvette. NMR spectra were recorded on Mercury plus Varian-400 spectrophotometer with Me_4Si as an internal standard.



16

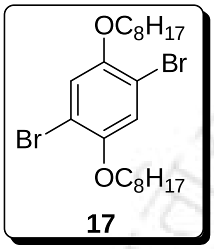
1,4-Dioctyloxybenzene 16. A mixture of 1-bromooctane (27.95 g, 144 mmol), 1,4-hydroquinone (5.31 g, 48.2 mmol) and KOH (5.409 g, 144 mmol) were stirred in ethanol (75 mL) for 24 h at ambient temperature. The solvent was then evaporated and the residue was dissolved in ethyl acetate (100 mL). The solution was washed with water (2 x 10 mL), dried (Na_2SO_4) and evaporated under reduced pressure to afford a residue which was crystallized in ethanol to provide **16** as a colorless solid in 80 % (12.9 g) yield.

Mp: 54-55 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.84 (s, 4H), 3.89 (t, *J* = 3.1 Hz, 4H), 1.70-1.79 (m, 4H), 1.20-1.57 (m, 20H), 0.88 (t, *J* = 3.0 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5, 140.3, 131.3, 112.4, 53.0, 24.1, 11.0.

Anal. Calcd for $C_{22}H_{38}O_2$: C, 78.99; H, 11.45. Found: C, 79.07; H, 11.43.



17

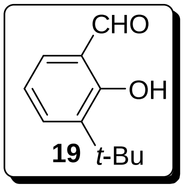
1,4-Dibromo-2,5-dioctyloxybenzene 17. To a stirred solution of 1,4-dioctyloxybenzene **16** (21 g, 63 mmol) in $CHCl_3$ (200 mL) at 0 °C, Br_2 (10.5 mL, 134 mmol) in $CHCl_3$ (100 mL) was added. After allowing the reaction mixture at ambient temperature for 8 h, it was cooled to 0 °C and aqueous KOH (1 N) was added until the excess Br_2 completely consumed. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic solution was washed with water (2 x 50 mL), dried (Na_2SO_4) and evaporated under reduced pressure to provide a residue which was crystallized in ethanol to afford **17** as a colorless solid in 95 % (29.1 g) yield.

Mp: 64-65 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (s, 2H), 3.95 (t, *J* = 3.1 Hz, 4H), 1.70-1.79 (m, 4H), 1.20-1.57 (m, 20H), 0.88 (t, *J* = 3.0 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.1, 118.5, 111.1, 70.3, 31.8, 29.3, 29.1, 26.0, 22.7, 14.1.

Anal. Calcd for $C_{22}H_{36}Br_2O_2$: C, 53.67; H, 7.37. Found: C, 53.74; H, 7.41.



19

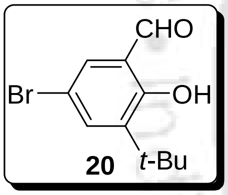
3-*tert*-Butylsalicylaldehyde 19. To a stirred solution of 2-*tert*-butylphenol (5 g, 3.33 mmol) and 2,6-dimethylpyridine (2.5 g, 13.33 mmol) in toluene (30 mL) at ambient temperature, $SnCl_4$ (0.4 mL, 3.33 mmol) was added. After 0.2 h, the reaction mixture was treated with paraformaldehyde (2.2 g, 33.3 mmol) and the resultant yellow solution was heated at 100 ^{o}C for 10 h. The reaction mixture was then cooled to ambient temperature and transferred into a 250 mL flask having 100 mL water. The *p*H of the solution was adjusted to 2 using 2 M HCL and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic solution was washed with brine (1 x 30 mL) and water (1 x 20 mL). Drying (Na_2SO_4) and evaporation of the solvent provided a residue which was purified on column chromatography using hexane as eluent to afford **19** as yellow liquid in 85 % (5.1 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.75 (s, 1H), 9.83 (s, 1H), 7.50 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.35 (dd, *J* = 7.6, 1.6 Hz, 1H), 6.91 (m, 1H), 1.41 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 197.0, 161.2, 138.3, 134.1, 132.0, 120.8, 119.3, 35.1, 29.5.

FT-IR (neat): ν 3412, 2960, 2873, 2736, 1652, 1613, 1481, 1432, 1385, 1314, 1264, 1190 cm^{-1}.

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.21; H, 7.96.



5-Bromo-3-*tert*-butylsalicylaldehyde 20. To a stirred solution of 3-*tert*-butyl-2-hydroxybenzaldehyde **19** (5.21 g, 29.31 mmol) in CH_3COOH (15 mL), Br_2 (2.3 mL, 30.67 mmol) in CH_3COOH (2 mL) was added at ambient temperature. After 1 h, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and washed successively with saturated $Na_2S_2O_5$ (1 x 10 mL), saturated $NaHCO_3$ (1 x 10 mL), brine (1 x 10 mL) and water (1 x 10 mL). Drying (Na_2SO_4) and evaporation of the solvent afforded yellow solid which was crystallized in methanol to give **20** in 95 % (6.77g) yield.

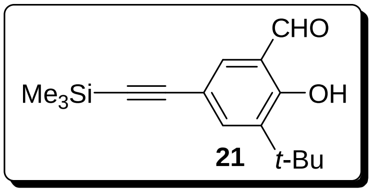
Mp: 62-63 $^{\circ}$C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.68 (s, 1H), 9.77 (s, 1H), 7.55 (d, *J* = 2.4 Hz, 1H), 7.49 (d, *J* = 2 Hz, 1H),1.39 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.9, 160.2, 141.2, 137.1, 133.6, 121.8, 111.2, 35.4, 29.2.

FT-IR (KBr): ν 3087, 2956, 2868, 2719, 1654, 1603, 1430, 1303, 1272, 1197, 1166, 931, 867, 738, 713 cm^{-1}.

Anal. Calcd for $C_{11}H_{13}BrO_2$: C, 51.88; H, 5.10. Found: C, 51.94; H, 5.14.


21

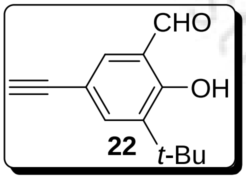
3-*tert*-Butyl-2-hydroxy-5-trimethylsilyl-ethynylbenzaldehyde 21. To a stirred solution of the aldehyde **20** (1.4 g, 5.45 mmol), Pd $(PPh_3)_2Cl_2$ (115 mg, 3 mol %) and PPh_3 (21 mg, 2 mol %) in THF (20 mL) at ambient temperature, Et_3N (1.45 mL, 10.9 mmol) and trimethylsilylacetylene (0.85 mL, 6 mmol) were added. After 0.2 h, the reaction mixture was treated with CuI (40 mg, 4 mol %) and the resultant dark brown solution stirred overnight. The solvent was then evaporated and the residue was dissolved in Et_2O. The solution was passed through a short pad of celite and the filtrate was evaporated under reduced pressure to give a yellow oil which was purified on flash column chromatography using hexane and ethyl acetate (19:1) as eluent to give **21** in 85 % (1.5 g) yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.90 (s, 1H), 9.83 (s, 1H) ,7.59 (d, *J* = 2.2 Hz, 1H), 7.56 (d, *J* = 2.2 Hz , 1H), 1.40 (s, 9H), 0.26 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.6, 161.4, 138.8, 137.4, 135.7, 120.3, 114.2, 104.0, 93.0, 34.9, 29.1, 29.0.

FT-IR (neat): ν 3007, 2965, 2151, 1653, 1605, 1442, 1414, 1320, 1268, 1153, 1030, 981, 930, 888, 857 cm^{-1}.

Anal. Calcd for $C_{16}H_{22}O_2Si$: C, 70.03; H, 8.08. Found: C, 70.14; H, 8.06.


22

3-*tert*-Butyl-5-ethynyl-2-hydroxybenzaldehyde 22. To a stirred solution of the aldehyde **21** (1 g, 5.65 mmol) in MeOH (10 mL) at ambient temperature, K_2CO_3 (0.755 g, 5.48 mmol) was added. After 6 h, the salt was filtered and the filtrate was evaporated under reduced pressure to afford a residue which was treated with water (5 mL) and CH_2Cl_2 (25 mL). The organic layer was separated and the aqueous solution was further extracted with CH_2Cl_2 (3 x 5 mL). The combined organic solution was dried (Na_2SO_4) and evaporated to give a residue which was purified on flash column chromatography using hexane and ethyl acetate (19:1) as eluent to provide **22** in 60 % (0.442 gm) yield.

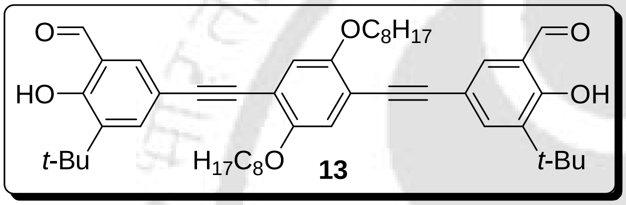
Mp: 57-58 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.89 (s, 1H), 9.80 (s, 1H), 7.59 (d, *J* = 1.9 Hz, 1H), 7.55 (d, *J* = 2.2 Hz, 1H), 3.0 (s, 1H), 1.40 (s, 9H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.5, 161.6, 139.0, 137.5, 135.8, 120.5, 113.3, 82.9, 76.4, 35.3, 29.4.

FT-IR (KBr): ν 3434, 2961, 1645, 1608, 1443, 1410, 1394, 1382, 1364, 1324, 1264, 1148, 1029, 970, 889 cm^{-1}.

Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.26; H, 6.70.



13

Dialdehyde 13. To a stirred solution of the aldehyde **22** (0.230 g, 1.138 mmol), 1,4-dibromo-2,5-dioctyloxybenzene **17** (0.279 g, 0.569 mmol), $Pd(PPh_3)_2Cl_2$ (0.0239 g, 3 mol %) and PPh_3 (5.9 mg, 2 mol%) in THF (10 mL) at ambient temperature, $(^iPr)_2NH$ (2.5 mL, 17.83 mmol) was added. After 0.2 h, the orange colored solution was treated with CuI (8.64 mg, 4 mol %) and the resultant dark brown solution was heated to reflux overnight. After cooling to ambient temperature, the solvent was evaporated and the residue was dissolved in $CHCl_3$ (50 mL). The solution was passed through a short pad of silica gel and the filtrate was concentrated under reduced pressure to give a residue which was purified on flash column chromatography using hexane and ethyl acetate (19:1) as eluent to give **13** in 20 % (0.167 g) yield.

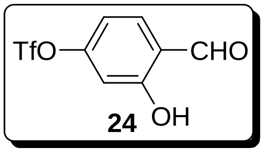
Mp: 123-125 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.88 (s, 2H), 9.83 (s, 2H), 7.66-7.57 (m, 4H), 6.99 (s, 2H), 4.02 (t, *J* = 6.4 Hz, 4H), 1.85 (m, 4H), 1.58-1.46 (m, 4H), 1.43 (s, 18H), 1.31-1.25 (m, 12H), 0.86-0.83 (t, *J* = 6.8, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.6, 161.3, 153.7, 139.0, 137.2, 136.4, 135.1, 124.3, 120.6, 117.0, 94.0, 85.0, 69.9, 35.3, 32.2, 29.7, 29.4, 29.4, 26.4, 23.0, 14.4, 29.1.

FT-IR (KBr): ν 3428, 2929, 2857, 2142, 1646, 1444, 1411, 1212, 1146, 1031, 969, 782 cm^{-1}.

Anal. Calcd for $C_{48}H_{62}O_6$: C, 78.44; H, 8.50. Found: C, 78.55; H, 8.53.



24

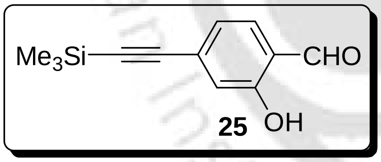
2-Hydroxy-4-trifluoromethanesulfonylbenzaldehyde 24. To a stirred solution of the aldehyde **23** (2 g, 14.49 mmol) and pyridine (1.16 ml, 14.49 mmol) in CH_2Cl_2 (15 ml) at 0 ^{o}C, trifluoromethanesulfonic anhydride (2.436 mL, 14.49 mmol) was added. After 0.5 h, the reaction mixture was allowed to warm to ambient temperature and the stirring continued for an additional 25 h. The organic layer was separated and the residue was extracted with CH_2Cl_2 (2 x 15 mL). The combined solution was then washed with water (2 x 10 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give a residue which was purified on flash column chromatography using hexane and ethyl acetate (9:1) as eluent to afford **24** in 60 % (2.3 g) yield as a colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.27 (s, 1H), 9.90 (s, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 6.94-6.89 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.2, 163.2, 154.7, 135.9, 120.4, 113.2, 111.0.

FT-IR (neat): ν 3406, 3109, 2873, 1706, 1688, 1602, 1432, 1216, 1133, 969, 879, 608 cm^{-1}.

Anal. Calcd for $C_8H_5F_3O_5S$: C, 35.56; H, 1.87; S, 11.87. Found. C, 35.62; H, 1.89; S, 11.88.



25

2-Hydroxy-4-trimethylsilylethynylbenzaldehyde 25. To a stirred solution of the aldehyde **24** (0.270 g, 1 mmol), $Pd(PPh_3)_2Cl_2$ (21.03 mg, 3 mol %) and PPh_3 (5.7 mg, 2 mol %) in THF (10 mL) at ambient temperature, Et_3N (0.25 mL, 2 mmol) and trimethylsilylacetylene (0.108 g, 1.1 mmol) were added. After 1 h, the reaction mixture was treated with CuI (5.7 mg, 4 mol %) and the resultant dark brown solution was allowed to stir overnight. The solvent was then evaporated and the residue was dissolved in Et_2O (5 mL) and passed through celite. The filtrate was concentrated and the residue was purified on flash column chromatography using hexane and ethyl acetate (19:1) as eluent to afford **25** as yellow solid in 80 % (0.218 g) yield.

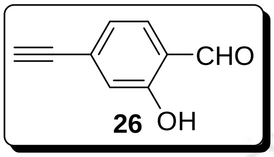
Mp: 79-80 $^{\circ}$C.

^{1}H NMR (400 MHz, CDCl$_3$): δ 10.97 (s, 1H), 9.83 (s, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.05 (d, *J* = 9.2 Hz, 2H), 0.24 (s, 9H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 195.9, 161.4, 133.5, 131.8, 123.5, 120.9, 120.4, 103.7, 99.9.

FT-IR (KBr): ν 3223, 2960, 2926, 2854, 2160, 1655, 1622, 1555, 1494, 1297,1220, 1193, 1163, 1120, 974, 845, 814, 760, 664 cm^{-1}.

Anal. Calcd for $C_{12}H_{14}O_2Si$: C, 66.02; H, 6.46. Found. C, 66.09; H, 6.48.



26

4-Ethynyl-2-hydroxybenzaldehyde 26. A mixture of aldehyde **25** (0.98 g, 4.495 mmol) and K_2CO_3 (0.930 g, 6.74 mmol) was stirred in MeOH (10 mL) for 6 h at ambient temperature. The solid was filtered and the filtrate was evaporated to afford a residue which was treated with 1:3 mixture of H_2O and CH_2Cl_2 (15 mL). The organic layer was separated and the aqueous solution was further extracted with CH_2Cl_2 (2 x 5 mL). Drying (Na_2SO_4) and evaporation of the organic layer afforded a residue which was purified by flash column chromatography using hexane and ethyl acetate (19:1) to afford **26** as a yellow solid in 60 % (0.393 g) yield.

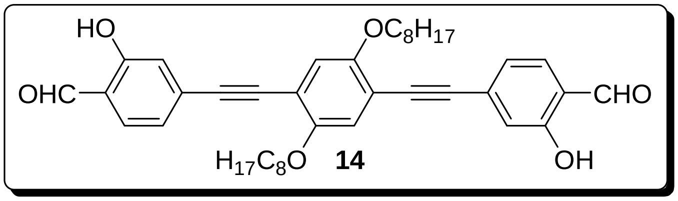
Mp: 54-55 °C.

^{1}H NMR (400 MHz, CDCl$_3$): δ 10.98 (s, 1H), 9.86 (s, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.09-7.07 (m, 2H), 3.27 (s, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 196.0, 161.4, 133.6, 130.8, 123.6, 121.3, 120.7, 82.5, 81.7.

FT-IR (KBr): ν 3439, 3275, 2961, 2923, 2851, 2098, 1655, 1624, 1555, 1493, 1436, 1364, 1273, 1224, 1195, 1125, 966, 885, 803, 680 cm^{-1}.

Anal. Calcd for $C_9H_6O_2$: C, 73.97; H, 4.14. Found. C, 74.04; H, 4.17.



14

Dialdehyde 14. To a stirred solution of the aldehyde **26** (0.230 g, 1.5 mmol), 1,4-dibromo-2,5-dioctyloxybenzene **17** (0.492 g, 0.785 mmol), $Pd(PPh_3)_2Cl_2$ (33 mg, 3 mol %) and PPh_3 (8.4 mg, 2 mol %) in THF (12 mL) at ambient temperature, $(^{i}Pr)_2NH$ (2.5 mL) was added. After 0.2 h, the reaction mixture was treated with CuI (11.9 mg, 4 mol %) and the resultant brown colored solution was heated to reflux overnight. The solvent was then evaporated under reduced pressure and the residue was dissolved in $CHCl_3$ (20 mL). The solution was passed through a short pad of silica gel and concentrated under reduced pressure and purified by flash chromatography using hexane and ethyl acetate (19:1) as eluent to afford **14** as orange solid in 23 % (122.2 mg) yield.

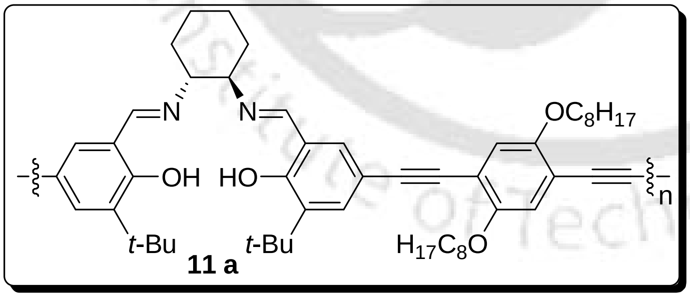
Mp: 130-132 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 11.06 (s, 2H), 9.88 (s, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.15-7.13 (m, 4H), 7.01 (s, 2H), 4.03 (t, *J* = 6.4 Hz, 4H), 1.88-1.81 (m, 4H), 1.57-1.53 (m, 4H), 1.38-1.25 (m, 16 H), 0.87-0.84 (m, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.9, 161.5, 154.2, 133.6, 132.2, 123.2, 120.4, 117.1, 94.3, 90.7, 69.8, 32.0, 29.9, 29.6, 26.3, 22.8, 14.2.

FT-IR (KBr): ν 3435, 2923, 2853, 2211, 1648, 1622, 1491, 1323, 1261, 1215, 1106, 973, 804, 744, 542 cm^{-1}.

Anal. Calcd for $C_{40}C_{46}O_6$: C, 77.14; H, 7.44; Found. C, 77.22; H, 7.47.



11 a

Polymer 11a. To a stirred solution of dialdehyde **13** (200 mg, 0.272 mmol) in $CHCl_3$ (3 mL), (1*R*,2*R*)-1,2-diaminocyclohexane **12a** (31.8 mg, 0.272 mmol) was added. The resulting solution was stirred at 40 °C for 3 h and cooled to ambient temperature. The solution was treated with MeOH (2 mL) and the precipitate **11a** was collected as yellow powder with 76 % (176.1 mg) yield.

$[\alpha]_D^{25}$ = +376 (*c* = 0.1, $CHCl_3$).

GPC: M_w = 18512, M_n = 15242 (PDI = 1.2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 14.00-14.30 (m, 2H), 8.23 (br s, 2H), 7.39 (s, 2H), 7.18 (s, 2H), 6.94 (s, 2H), 3.95 (t, J = 6.4 Hz, 4H), 3.33 (br s, 2H), 1.20-1.99 (m, 50H), 0.83-1.0 (m, 6H).

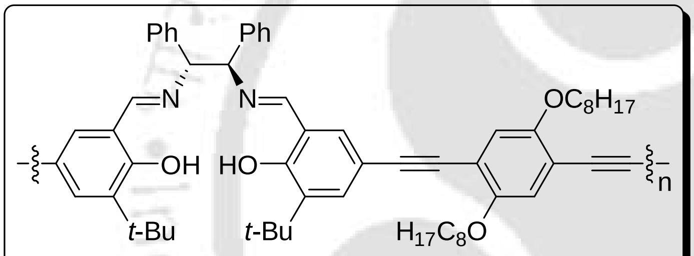
^{13}C NMR (100 MHz, $CDCl_3$): δ 164.9, 161.0, 154.0, 149.5, 137.8, 134.2, 133.1, 132.9, 118.3, 118.3, 117.6, 117.1, 113.4, 112.9, 112.7, 94.4, 83.5, 72.5, 70.2, 69.9, 35.2, 33.3, 32.2, 30.0, 29.6, 29.6, 26.4, 26.4, 24.5, 23.0, 14.5.

FT-IR (KBr): ν 3450, 2928, 2857, 1630, 1495, 1467, 1441 cm^{-1}.

UV-vis (THF): λ_{max} (ε) 301 (22222), 333 nm (28985 $mol^{-1}dm^3cm^{-1}$).

Fluorescence (λ_{exc} = 345 nm, THF): 408, 563 nm.

Anal. Calcd for $(C_{54}H_{70}O_4N_2)_n$: C, 79.76; H, 8.92; N, 3.44. Found: C, 79.87; H, 8.97; N, 3.49.



11 b

Polymer 11b. To a stirred solution of dialdehyde **14** (150 mg, 0.204 mmol) in $CHCl_3$ (3 mL), (1*R*,2*R*)-1,2-diphenylethylenediamine **12b** (43.2 mg, 0.204 mmol) was added. The resulting solution was stirred at 40 °C for 3 h and cooled to ambient temperature. The solution was then treated with MeOH (2 mL) and the resultant precipitate **11b** was collected as a yellow powder in 70 % (135.2 mg) yield.

$[\alpha]_D^{25}$ = +166 (c = 0.1, $CHCl_3$).

GPC: M_w = 4864, M_n = 3441 (PDI = 1.4).

^{1}H NMR (400 MHz, $CDCl_3$): δ 14.00-14.30 (m, 2H), 8.27 (m, 2H), 7.45 (m, 2H), 7.25-7.21 (m, 10H), 7.01 (s, 2H), 6.99 (s, 2H), 4.70 (bs, 2H), 3.99 (t, J = 6.4 Hz, 4H), 1.90-1.20 (m, 42H),1.00-0.80 (m, 6H).

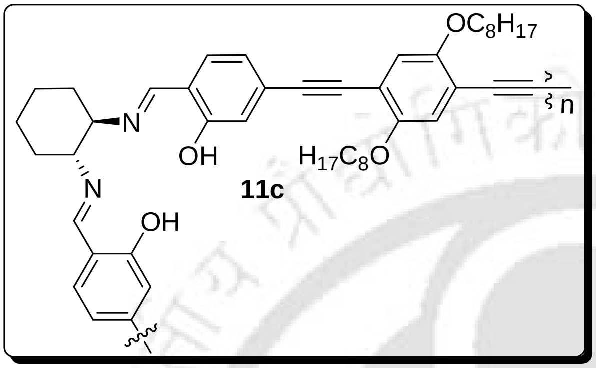
^{13}C NMR (100 MHz, $CDCl_3$): δ 166.3, 166.1, 160.8, 154.0, 149.5, 139.1, 139.0, 137.9, 134.4, 133.9, 133.3, 133.2, 128.6, 128.0, 127.9, 118.5, 118.2, 117.6, 113.3, 112.9, 112.8, 94.3, 83.5, 80.2, 70.3, 70.1, 35.2, 32.1, 29.6, 29.5, 26.3, 23.0, 14.5.

FT-IR (KBr): ν 3446, 2928, 2857, 1629, 1456, 1415, 1382, 1262, 1212, 1097, 1028 cm^{-1}.

UV-vis (THF): λ_{max} (ε) 301 (31658), 333 nm (43216 $mol^{-1}dm^{3}cm^{-1}$).

Fluorescence (λ_{exc} = 345 nm,THF): 411, 560 nm

Anal. Calcd for $C_{62}H_{70}N_2O_4$: C, 82.09; H, 7.22; N, 3.08. Found: C, 82.18; H, 7.27; N, 3.15.



11c

Polymer 11c. To a stirred solution of aldehyde **14** (0.08 mmol, 50 mg) in $CHCl_3$ (3 ml), (1*R*,2*R*)-1,2-diamino-cyclohexane **12a** (0.080 mmol, 9.12 mg) was added and the resulting solution was heated at 40 °C for 3 h. The reaction mixture was then cooled to room temperature and treated with MeOH. The precipitate **11c** was collected by filtration as yellow powder in 78 % (43.80 mg) yield.

$[\alpha]_D^{20}$ = -797 (*c* = 0.1, $CHCl_3$).

GPC: M_w = 12102, M_n = 9513 (PDI = 1.27).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (s, 2H), 7.09 (d, *J* = 7.6, 2H), 7.02 (s, 2H), 6.97-6.92 (m, 4H), 3.96 (t, *J* = 6.4 Hz, 4H), 3.28 (br s, 2H), 1.91-1.60 (m, 16H), 1.47-1.45 (m, 6H), 1.31-1.22 (m, 10H), 0.80 (m, 6H).

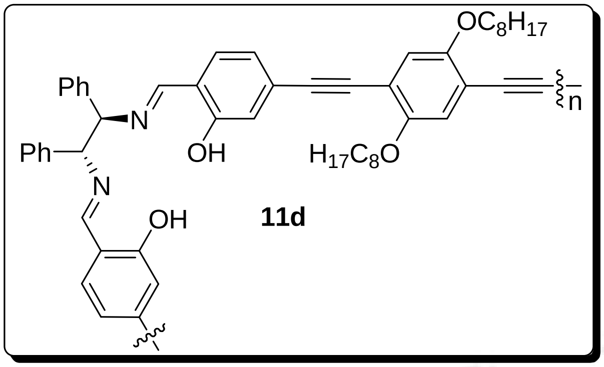
^{13}C NMR (100 MHz, $CDCl_3$): δ 164.4, 160.9, 153.9, 131.4, 127.3, 122.2, 119.7, 118.7, 117.1, 114.1, 94.9, 88.0, 72.7, 69.8, 33.2, 31.9, 29.5, 26.2, 24.3, 22.8, 14.3.

FT-IR (KBr): ν 3463, 2961, 2928, 2862, 2373, 2071, 1629, 1462, 1262, 1215, 1091, 1028, 801, 697 cm^{-1}.

UV-vis (THF): λ_{max} (ε) = 320 (24501), 382 (35000) nm ($mol^{-1}dm^{3}cm^{-1}$).

Fluorescence (λ_{exc} = 380 nm, THF): 432, 499 nm.

Anal. Calcd for $C_{46}H_{56}N_2O_4$: C, 78.82; H, 8.05; N, 4.00. Found: C, 78.88; H, 8.07; N, 4.05.



11d

Polymer 11d. To a stirred solution of the dialdehyde **14** (0.08 mmol, 50 mg) in $CHCl_3$ (3 ml), (1*R*,2*R*)-1,2-diphenylethylenediamine **12b** (0.080 mmol, 16.90 mg) was added and the resulting solution was heated at 40 °C for 3 h. The reaction mixture was then cooled to room temperature and treated with MeOH. The precipitate **11d** was collected by filtration in 76 % (48.76 mg) yield.

$[\alpha]_D^{20}$ = -244 (*c* = 0.1, $CHCl_3$).

GPC: M_w = 22157, M_n = 14853 (PDI = 1.49).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (s, 2H), 7.18-6.93 (m, 18H), 4.71 (s, 2H), 3.97 (t, *J* = 6.4 Hz, 4H), 1.80 (t, *J* = 6.8 Hz, 4H), 1.59-1.47 (m, 8H), 1.23 (br s, 12H), 0.81 (br s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.8, 160.8, 153.9, 139.3, 131.7, 128.6, 128.0, 127.7, 122.3, 119.8, 118.6, 117.1, 114.1, 94.8, 88.3, 80.4, 69.8, 31.9, 29.5, 29.4, 26.2, 22.8, 14.3.

FT-IR (KBr): ν 3452, 2961, 2923, 2857, 2362, 2093, 1627, 1377, 1262, 1212, 1102, 1023, 973, 697 cm^{-1}.

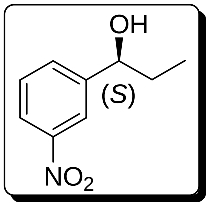
UV-vis (THF): λ_{max} (ε) = 321 (27600), 381 (38000) nm ($mol^{-1}dm^3cm^{-1}$).

Fluorescence (λ_{exc}=380 nm, THF): 434, 499 nm.

Anal. Calcd for $C_{54}H_{58}N_2O_4$: C, 81.17; H, 7.32; N, 3.51. Found: C, 81.25; H, 7.33; N, 3.58.

General Procedure for Et_2Zn Addition to Aldehydes

To a solution of polymer **11a** or **11b** (1 mol %) in dry toluene was added Et_2Zn (1 mol %) and the resulting mixture was stirred for 1 h at ambient temperature. This solution was cooled to – 40 °C and Et_2Zn (2 mmol) was added. After 5 min, the aldehyde (1 mmol) was added and the stirring was continued for 1 h at - 40 °C. The resulting solution was warmed to room temperature and then allowed to stir for an additional 18 h. After the aldehyde was consumed, the reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with Et_2O. The combined organic layer was concentrated to 1 mL and treated with MeOH to precipitate polymer **11a** or **11b**. The filtrate was evaporated on a rotary evaporator and the residue was passed through a short pad of silica gel (60–120 mesh) using ethyl acetate and hexane (1:19) to afford analytically pure alcohols.



(*S*)-(-)-1-(3-Nitro-phenyl)-propan-1-ol (Table 1, entry 3).[15p] Polymer **11b** (9 mg, 1 mol %), Et_2Zn (10 μL of 1 M in hexane solution, 1 mol %), Et_2Zn (2 mL of 1 M in hexane solution, 2 mmol) and 3-nitrobenzaldehyde (151 mg, 1 mmol) were subjected to the reaction conditions described in the general procedure to afford the title compound as color less oil in 73 % (132 mg) yield.

$[\alpha]_D^{20}$ = - 23 (c = 1.2, EtOH).

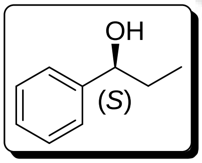
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (s, 1H), 8.12-8.09 (d, *J* = 8.4 Hz, 1H) 7.52-7.46 (m, 2H), 4.80-4.73 (t, *J* = 6.4 Hz, 1H), 1.85-1.75 (m, 2H), 0.97 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.3, 146.6, 132.0, 129.2, 122.3, 120.9, 74.7, 32.1, 9.7.

FT-IR (neat): ν 3394, 3092, 3070, 2967, 2927, 2873, 1529, 1351, 1095, 736, 691 cm^{-1}.

Anal. Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.75; H, 6.15; N, 7.79.

HPLC: Chiralpak AD-H column, n-hexane/isopropanol (90:10), wavelength: 254 nm, flow rate: 0.5 mL/min, retention time: 15.44 min, 19.10 min; 73 % ee.



(*S*)-(-)-1-phenylpropan-1-ol (Table 1, entry 4).[15f] Polymer **11b** (9 mg, 1 mol %), Et_2Zn (10 μL of 1 M in hexane solution, 1 mol %), Et_2Zn (2 mL of 1 M in hexane solution, 2 mmol) and benzaldehyde (106 mg, 1 mmol) were subjected to the reaction conditions reported in the general procedure to give the title compound as color less oil in 83 % (112 mg) yield.

$[\alpha]_D^{20}$ = - 13 (c = 1, CH_2Cl_2).

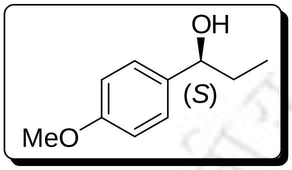
^{1}H NMR (400 MHz, CDCl$_3$): δ 7.38–7.26 (m, 5H), 4.57 (m, 1H), 1.86–1.71 (m, 3H), 0.92 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 144.8, 128.3, 127.4, 126.6, 75.7, 31.6, 10.4.

FT-IR (neat): ν 3390, 3089, 3075, 2992, 2940, 2875, 1430, 1370, 1005, 720, 699 cm^{-1}.

Anal. Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.44; H, 8.92.

HPLC: Chiralcel OD-H column, n-hexane/isopropanol (97:3), wavelength: 254 nm, flow rate: 0.5 mL/min, retention time: 20.21 min, 22.72 min; 50 % ee.



(*S*)-(-)-1-(4-Methoxyphenyl)-propan-1-ol (Table 1, entry 5).[15f]

Polymer **11b** (9 mg, 1 mol %), Et$_2$Zn (10 μL of 1M in hexane solution, 1 mol %), Et$_2$Zn (2 mL of 1 M in hexane solution, 2 mmol) and 4-methoxybenzaldehyde were subjected to the reaction conditions shown in the general procedure to afford the title compound as color less oil in 70 % (116 mg) yield.

$[\alpha]_D^{20}$ = - 22 (c = 1.1, Benzene).

^{1}H NMR (400 MHz, CDCl$_3$): δ 7.29–7.25 (m, 2H), 6.90–6.87 (m, 2H), 4.56–4.53 (m, 1H), 3.81 (s, 3H), 1.85–1.69 (m, 3H), 0.92 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 158.8, 136.7, 127.1, 113.4, 75.4, 55.1, 31.1, 10.1.

FT-IR (neat): ν 3380, 3082, 3073, 2965, 2933, 2869, 1445, 1366, 1003, 725, 695 cm^{-1}.

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.37; H, 8.53.

HPLC: Chiralcel OD-H column, n-hexane/isopropanol (97:3), wavelength: 274 nm, flow rate: 0.5 mL/min, retention time: 28.42 min, 39.80 min; 60 % ee.

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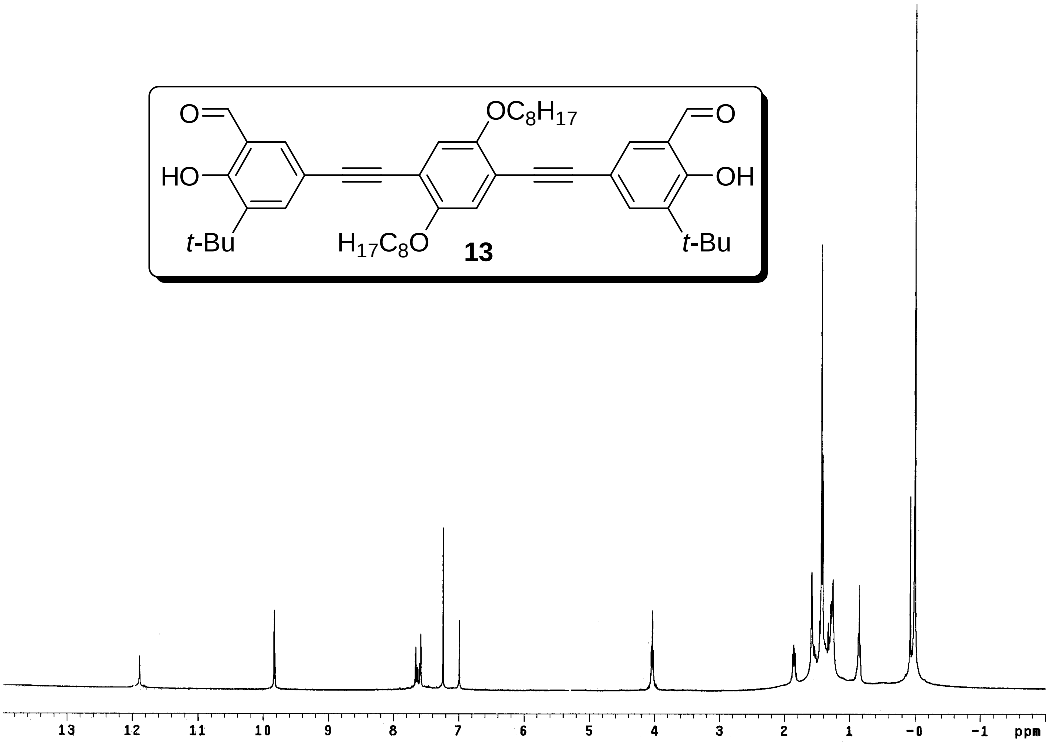
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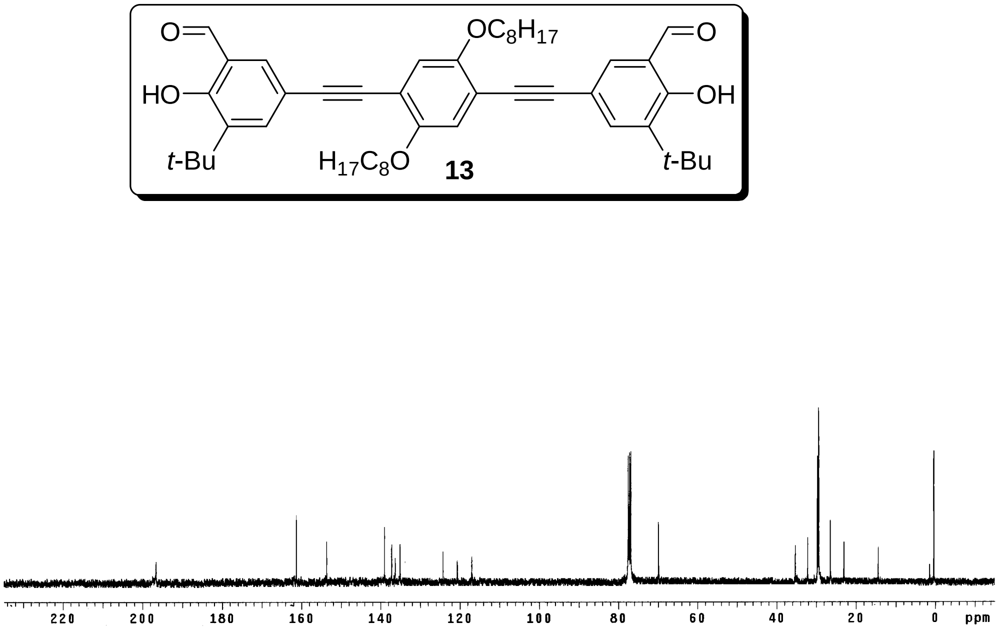
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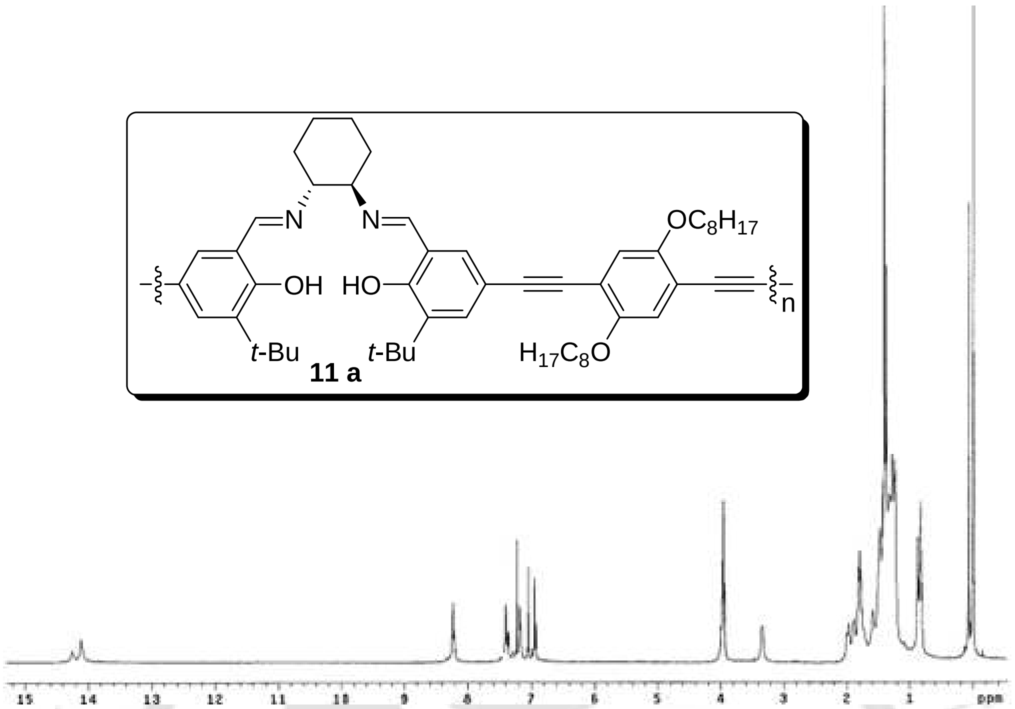
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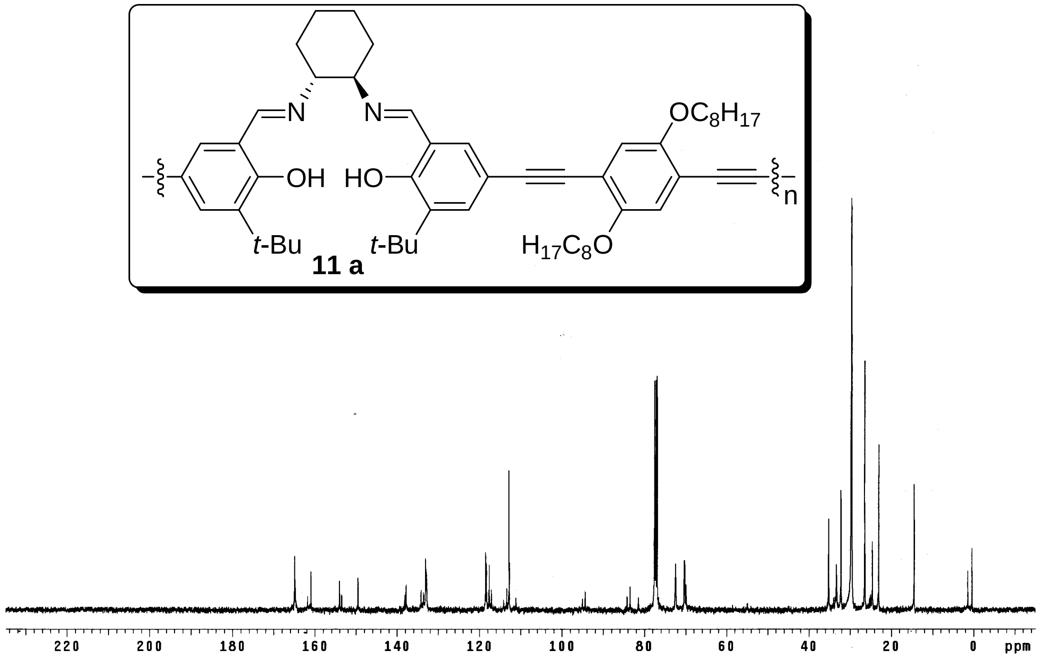
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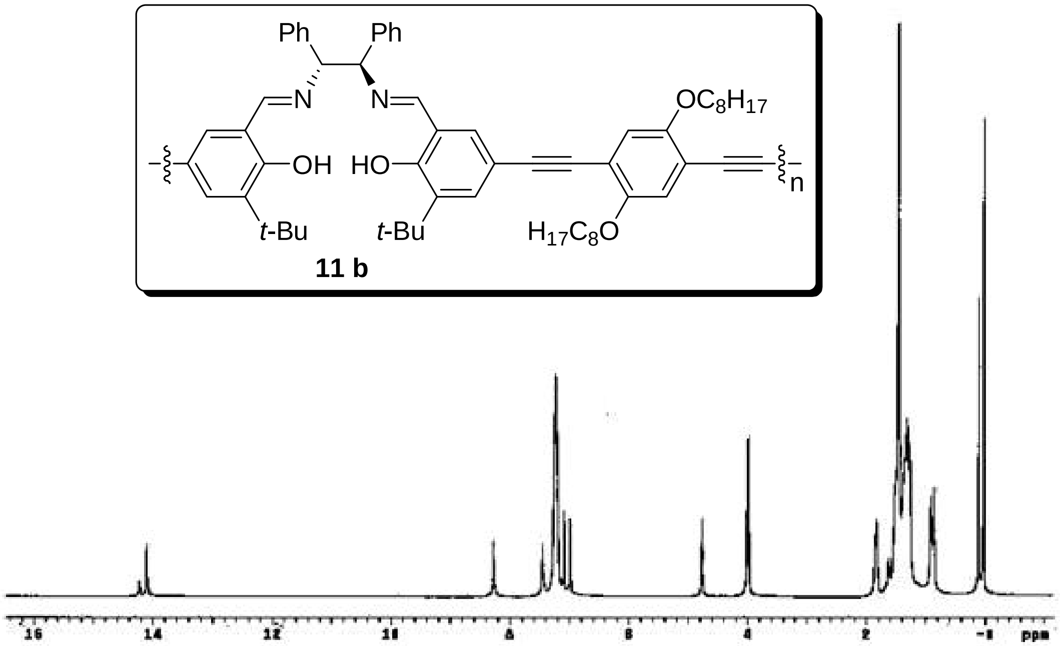
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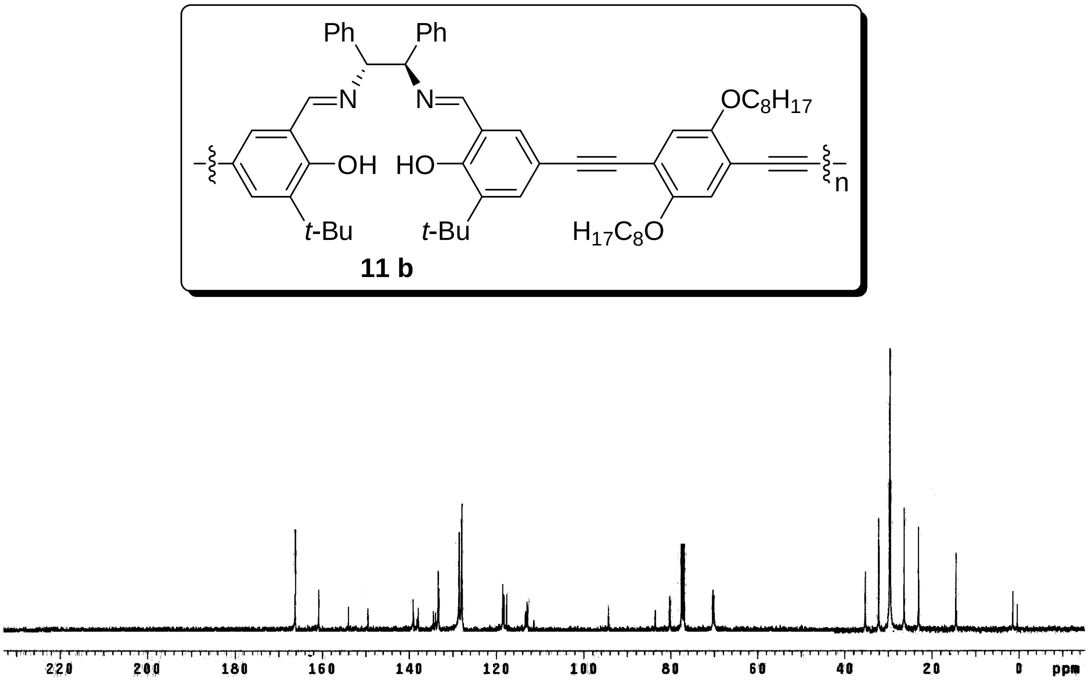
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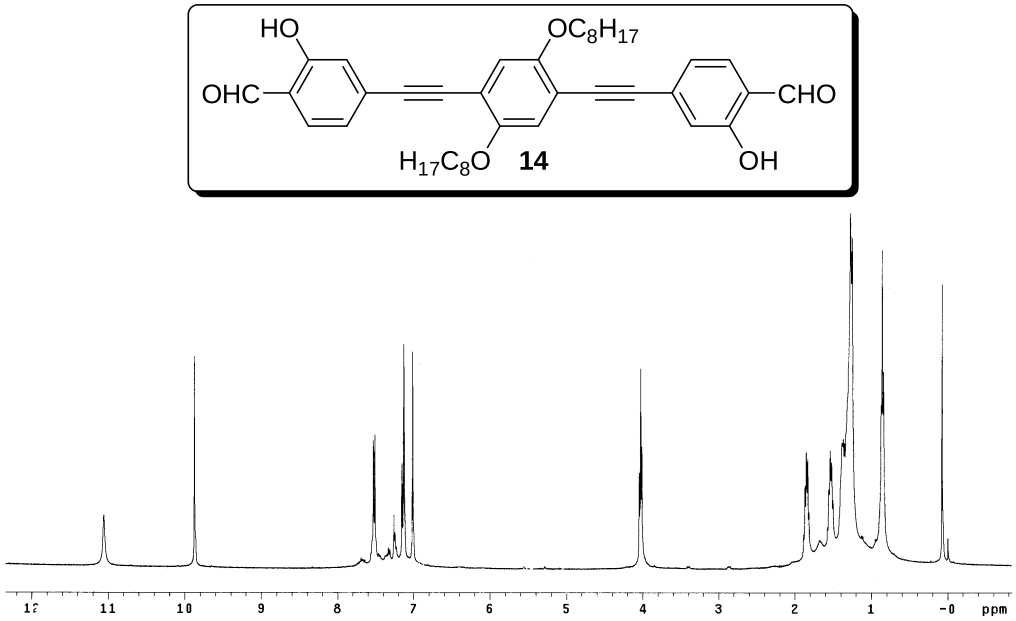
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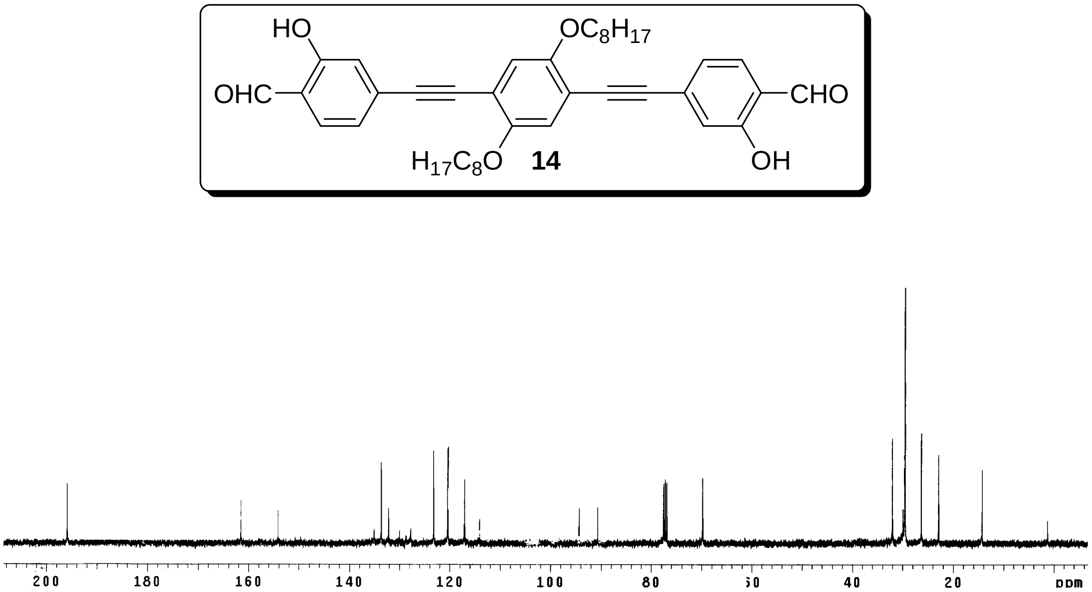
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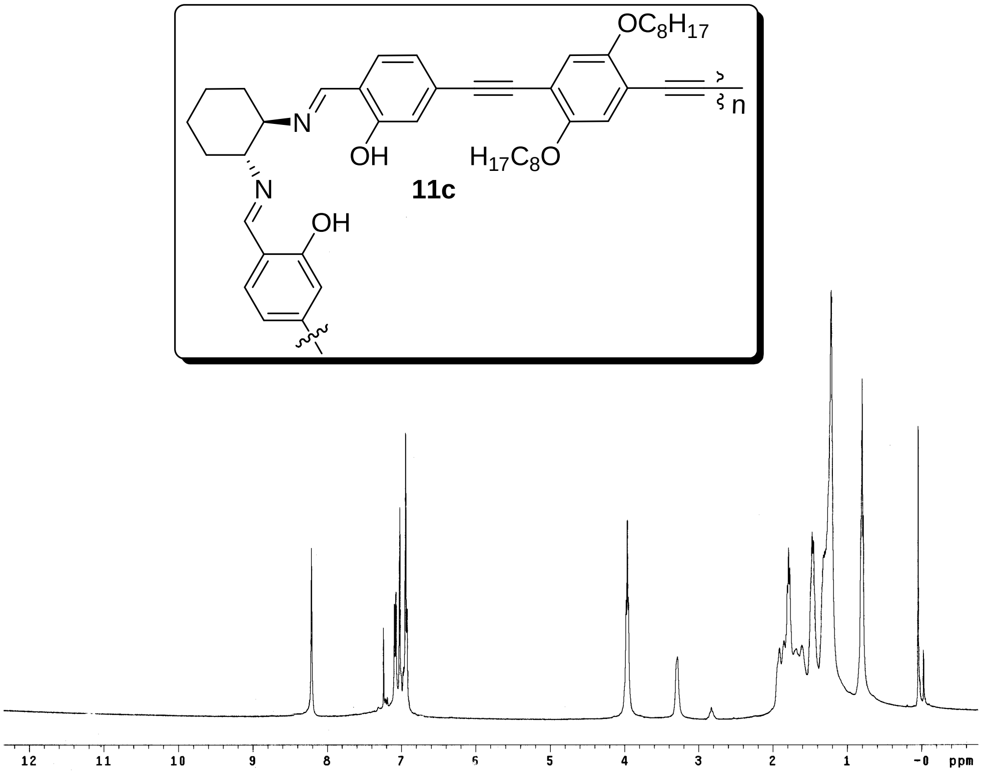
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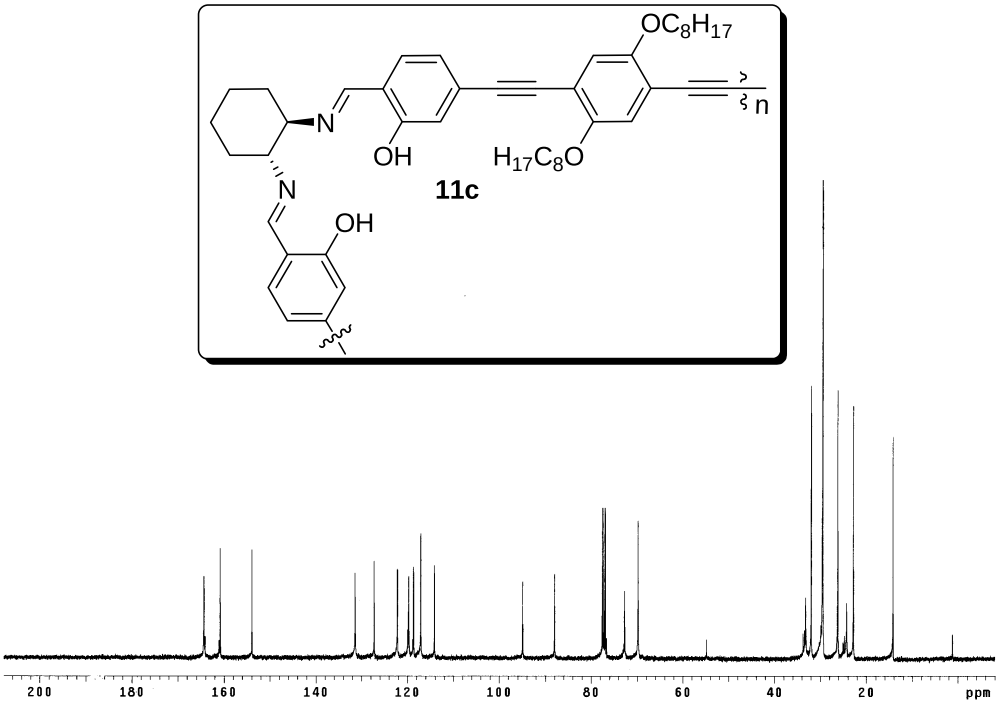
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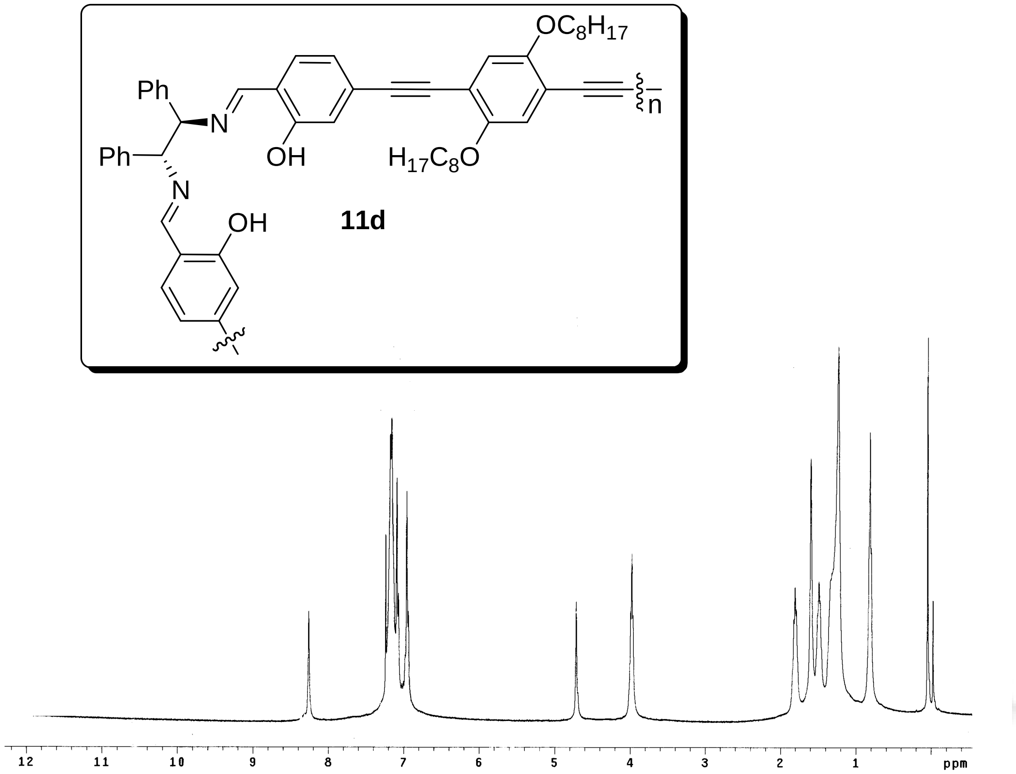
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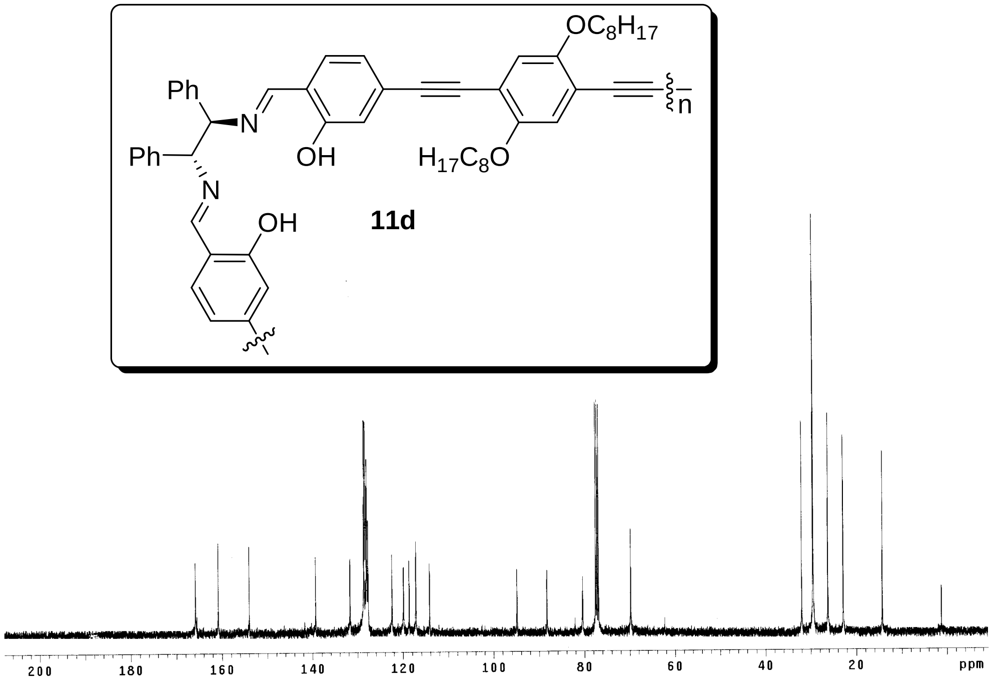
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List of Publications

1 Chiral Linear Polymers Bonded Alternatively with Salen and 1,4-Dialkoxy-2,5-diethynylbenzene: Synthesis and Application to Diethylzinc Addition to Aldehydes.
Jammi, S.; Rout, L.; Punniyamurthy, T. *Tetrahedron: Asymmetry* **2007**, *18*, 2016.

2 Novel CuO Nanoparticle Catalyzed *C-N* Cross-Coupling of Amines with Iodobenzene.
Rout, L.; Jammi, S.; Punniyamurthy, T. *Org. Lett.* **2007**, *9*, 3397.

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10 Synthesis, Structure and Catalysis of Tetranuclear Copper(II) Open Cubane for Henry Reaction on Water
Jammi, S.; Punniyamurthy, T. *Eur. J. Inorg. Chem.* **2009**, 2508.

11 Synthesis of Chiral Main Chain Polymers Bonded Alternatively with 1,4-Diethynyl-2,5-dioctyloxybenzene and Salen.
Jammi, S.; Saha, P.; Punniyamurthy, T. *Tetrahedron: Asymmetry* Communicated

12 Cu_2O Nanoparticles Catalyzed *N*-Arylation of Amides and Imidazoles and *S*-Arylation of Thiols with Aryl Iodides.
Jammi, S.; Krishnamurthy, S.; Saha, P.; Kundu, D. S.; Sakthivel, S.; Ali, Md. A.; Paul, R.; Punniyamurthy, T. *Manuscript under Preparation*.

Conferences

1. Stereoregular Chiral Polymers for Asymmetric Synthesis.
Jammi, S.; Punniyamurthy, T ICOB-5 & ISCNP-25 *IUPAC International Conference on Biodiversity and Natural Products*, Kyoto, Japan, July 23-28, **2006**.

2. Stereoregular Chiral (*1R,2R*)-Diamine Based Co-Polymers: Synthesis and Application to Enantioselective Et_2Zn Addition to Aldehydes.
Jammi, S.; Punniyamurthy, T. INDO-US CCNP-2006, Indian Institute of Chemical Technology, Hyderabad, Nov. 13-14, **2006**.