

Copper Catalysts for Alcohol Oxidation

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Academic Dissertation

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This dissertation is dedicated to:
My wife, Nurjahan Begum
My beloved sons, Navid Ahmad and Nubaid Ahmad.

Abstract

The oxidation of alcohols to the corresponding carbonyl compounds is a key reaction in the synthesis of organic chemicals. Consequently, a vast number of diverse methods based on copper that accomplish this functional group transformation are reviewed in this work. A successful development from pressurized oxygen to open air and from organic to environmentally friendly water solvent in oxidation of alcohols to the corresponding carbonyl compounds catalyzed by copper is presented. The first direct organocatalytic oxidation of alcohols to aldehydes with O₂ in alkaline water was developed. One of the effects metal ions on the reaction was that the Cu ion is the most beneficial recipient of quantitative oxidation. Thus aerobic oxidation of alcohols to the corresponding carbonyl compounds catalyzed by TEMPO/Cu-2-*N*-arylpyrrolecarbaldimine in alkaline water was discovered.

The solid and solution structures of sterically hindered salicylaldehyde and *cis-trans* isomers of the corresponding Cu(II) complexes are discussed. High yield synthetic routes for mixed ligand Cu(II)-complexes derived from salicylaldehyde and the corresponding salicylaldehyde were developed. New crystal structures of the above compounds were determined by X-ray crystallography. The catalytic property of homo and heteroligated bis(phenoxidoimino)Cu(II) complexes toward oxidation reactions were investigated. Accordingly, facile base free aerobic oxidations of alcohols to aldehydes and ketones in toluene using low loading of both TEMPO and catalysts under mild conditions were introduced.

In addition to the aerobic catalytic methods, oxidation of alcohols to the corresponding carbonyl compounds with H₂O₂ as an end oxidant in pure water using simple CuSO₄ as a catalyst is presented. The effect of various additives, such as acids or bases, radical scavengers and N-containing ligands, on the efficiency/selectivity of the catalyst system was studied as well. Finally, highly efficient open air oxidation of alcohols in water catalyzed by *in situ* made Cu(II)-phenoximine complexes without additional auxiliaries such as base or co-solvent are described.

Preface

The work for this thesis was carried out at the Laboratory of Inorganic Chemistry in the University of Helsinki. I have many people to thank for their support and encouragement throughout the years. So many people contributed to my success in completing this scientific work and in keeping my sanity while doing it. First of all I have much pleasure to express my deepest sense of gratitude to my supervisors, Professors Markku Leskelä and Timo Repo for their indispensable guidance, advice and inexhaustible cooperation throughout the progress of my research work. Thank you for allowing me this opportunity to work under your guidance.

Besides my advisors, I am most indebted to my honorable teacher Markku R. Sundberg for giving me an opportunity to study in the top most educational institution like Helsinki University and also for help with theoretical and computational aspects of the project.

I want to express thanks to my classmate, co-author and closest friend Dr. Minna T. Räsänen who encouraged me in various ways during the course of my studies. I would like to discern many valuable contributions from Dr. Martin Nieger especially for help with X-ray diffraction measurements. I am also grateful to Drs. Pawel J. Figiel and Petro Lahtinen for their contributions to this work. Many thanks also to my ex-colleagues Drs. Antti Pärssinen, Erkki Aitola, Markku Talja and Pertti Elo for their advices in laboratory and meaningful conversations outside of work. Thanks to the Catlab Group (former and present members) for creating a pleasant working environment. I am delighted I had the great opportunity to work with a group of people that are able to get along so well with one another. It really made the days go by faster. I wish you all success and happiness in whatever you pursue in life.

I would like to give thanks to BAFFU (Bangladesh Academic Forum of Finnish Universities) for allowing spends time with the Bangladeshi students and their families in Finland. I love all of you.

Above all, I want to thank my dearest parents, Samas Uddin Ahmad and Jayeda Begum, for their immeasurable sacrifices, blessings and constant inspiration that are great assets to my study and life.

I would like to thank my wife, Nurjahan Begum, for her enduring support, love and encouragement. Thank you for believing in me and making this journey with me. Thank you for your willingness to leave a comfort zone in order to allow me to accomplish this goal. I sincerely could not have done this without you. Thank you for your patience and for lending your ear on those days when nothing seemed to go right. I love you more than words can ever express.

Finally, my warmest thanks go to my lovely sons Navid Ahmad and Nubaid Ahmad for the gleaming moments which you have brought to my life.

List of Original Publications

The thesis is based on the following original publications and they are referred to the text by their respective Roman numerals **I–IX**.

I P. J. Figiel, A. Sibaouih, J. U. Ahmad, M. Nieger, M. T. Räisänen, M. Leskelä, T. Repo
Aerobic Oxidation of Benzylic Alcohols in Water by 2,2,6,6–Tetramethylpiperidine–1–oxyl (TEMPO)/Copper(II) 2–N–Arylpyrrolocarbaldimino Complexes
Adv. Synth. Catal. 351 (2009) 2625.

II J. U. Ahmad, P. J. Figiel, M. T. Räisänen, M. Leskelä, T. Repo
Aerobic oxidation of benzylic alcohols with bis(3,5–di–tert–butylsalicylaldehyde) copper(II) complexes
Appl. Catal. A 371 (2009) 17.

III P. Lahtinen, J. U. Ahmad, E. Lankinen, P. Pihko, M. Leskelä, T. Repo
Organocatalyzed oxidation of alcohols to aldehydes with molecular oxygen
J. Mol. Catal. 275 (2007) 228.

IV J. U. Ahmad, M. Nieger, M. R. Sundberg, M. Leskelä, T. Repo
Solid and solution structures of bulky tert–butyl substituted salicylaldehydes
J. Mol. Struct. 995 (2010) 9.

V J. U. Ahmad, M. T. Räisänen, M. Leskelä, T. Repo
Copper catalyzed oxidation of benzylic alcohols in water with H₂O₂
Appl. Catal. A 411–412 (2012) 180.

VI J. U. Ahmad, M. T. Räisänen, M. Nieger, M. Leskelä, T. Repo
A facile synthesis of mixed ligand Cu(II) complexes with salicylaldehyde and salicylaldehyde ligands and their X–ray structural characterization
Inorg. Chim. Acta 384 (2012) 275.

VII J. U. Ahmad, M. T. Räisänen, M. Nieger, P. J. Figiel, M. Leskelä, T. Repo
Synthesis and X–ray structural characterization of sterically hindered bis(3,5–di–tert–butylsalicylaldehyde)Cu(II) complexes
Polyhedron XXX (2012) XXX.

VIII J. U. Ahmad, M. T. Räisänen, M. Kemell, M. J. Heikkilä, M. Leskelä, T. Repo
Facile Open Air Oxidation of Alcohols in Water by *in situ* made Copper(II) complexes
Submitted for publication in Green Chemistry.

IX J. U. Ahmad, M. T. Räisänen, M. Nieger, A. Sibaouih, M. Leskelä, T. Repo.
Heteroligated Bis(phenoxyimino) Copper(II) Complexes in Aerobic Oxidation of Alcohols
Manuscript.

List of Abbreviations

Ac	Acetate
Atm	Atmospheric pressure
bipy	Bipyridine
BSB	2,2'-Bis(salicylideneamino)-1,1'-binaphthyl
CHP	Cumyl hydroperoxide
EPR	Electron paramagnetic resonance
ESI	Electrospray ionization
DABCO	1,4-Diazabicyclo[2.2.2]octane
DAPHEN	9,10-Diaminophenanthrene
DBAD	di- <i>tert</i> -Butylazodicarboxylate
DBADH ₂	di- <i>tert</i> -Butylazohydrazine
DFT	Density functional theory
DMG	Dimethyl glyoxime
DMF	Dimethylformamide
EtOAc	Ethylacetate
FESEM	Field emission scanning electron microscopy
GO	Galactose oxidase
GC	Gas chromatography
HSB	Salicylaldehyde
KOH	Potassium hydroxide
L	Ligand
L. S.	Least squares
MeCN	Acetonitrile
MeOH	Methanol
MS	Mass spectrometry
NEt ₃	Triethylamine
NHPI	<i>N</i> -Hydroxyphthalimide
PC	Photochromism
PINO	Phthalimide- <i>N</i> -oxyl
phen	1,10-Phenanthroline
RDS	Rate determining step
r.t.	Room temperature
SINO	Saccharin <i>N</i> -oxyl
SP	Square pyramidal
TBP	Trigonal bipyramidal
TC	Thermochromism
TEMPO	2,2,6,6-Tetramethylpiperidine <i>N</i> -Oxyl(radical scavenger)
THF	Tetrahydrofuran
TMEDA	<i>N,N,N',N'</i> -Tetramethyl ethylenediamine
TOF	Turnover frequency (catalytic cycles/moles of catalyst)
TON	Turnover number
TPA	Tris(4-bromophenyl)ammonium
UV	Ultraviolet
XRD	X-ray diffraction

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1 Introduction

For economical and environmental reasons, the development of efficient and selective catalyst for oxidation of alcohols into their corresponding carbonyl compounds is a vital prerequisite in the chemical industry.^[1] Transition metal-catalyzed oxidation of organic substrates is of current interest.^[2] Various catalytic methods based on transition metals have been developed.^[3] However, catalytic oxidation was first inspired by the necessity to understand the function of natural enzymes and later by its significance in the chemical industry.^[4] Consequently, elegant transition metal complexes have been synthesized and their catalytic properties in oxidation, epoxidation, carboxylation, hydrogenation and other functional group transformations have been reported.^[5]

Copper is an important metal, available in the earth's crust. It exists in various metalloproteins particularly in enzymes^[6] such as Galactose oxidase (GO), laccases, hemocyanin, cytochrome c oxidase and superoxide dismutase. These enzymes play an important role in different bio-oxidation reactions. Thus copper has drawn particular attention in catalyst design and exciting research activities in the realm of coordination chemistry with small molecular model complexes have been reported.^[7] These model complexes offer a valuable platform for the development of Cu based homogeneous catalysts. They are able to oxidize a variety of organic substrates. However, from the industrial viewpoint, simple and inexpensive copper catalysts, which can activate molecular oxygen or hydrogen peroxide with high catalytic activity and selectivity, are attractive alternatives for conventional stoichiometric oxidation methods.

Molecular oxygen is a nonpoisonous and inexpensive oxidant for the oxidative transformation of alcohols. Currently it is used in several large-scale oxidation reactions, catalyzed by stoichiometric amounts of heterogeneous catalyst mostly chromium (VI) reagents.^[8] These reagents are toxic or hazardous and produce heavy metal waste. In addition, these oxidation reactions are carried out at elevated temperatures and pressures, even in the gas phase. The heterogeneous oxidation methods, however, are inexpedient for the reactions required in the fine chemical industry, where selective and highly efficient oxidation systems under mild reaction conditions required because of economical and environmental considerations. The insufficiency of alcohol transformation processes that simply use open air or atmospheric O₂ as the end-oxidant in water solution is particularly important and challenging.^[9]

The conjugated nitroxyl radicals, for example the diphenylnitroxyl radical have been known for a century.^[10] Stable nonconjugated free radicals especially TEMPO (2,2,6,6-tetramethyl-piperidinyloxy) reported^[11] in the 1960s have found important applications as powerful inhibitors of free radical chain processes such as autooxidations and polymerizations.^[12] Furthermore TEMPO and its derivatives are well known as some of the most effective mediators in oxidation reactions and they have a wide-range of applications in organic synthesis.^[13] Particularly they can be used to catalyze conveniently the oxidation of alcohols to their corresponding aldehydes and ketones by a variety of oxidants and catalysts;^[14] including ruthenium^[15] and copper^[16]. Although various catalytic methods based on Cu and TEMPO using O₂ or H₂O as an end oxidant have been developed; new catalysts, especially those which

require low catalyst loadings and possess more accessible oxidation potentials in aqueous media without additional auxiliaries such as base or co-solvent remain important synthetic goals.

2 Literature Review

2.1 Copper

Copper is a natural element essential to all forms of life and is the third most abundant trace element found in the human body, after iron and zinc. It is not only found in its metallic form but as a wide variety of Cu compounds, where Cu is either found as Cu(I) or Cu(II). Generally, simple Cu(I) compounds are not stable in water and they are readily oxidized to Cu(II) compounds. Only highly insoluble Cu(I) compounds such as CuCl and CuCN are stable in water. In addition, Cu(I) can form complexes with chelating ligands. Normally Cu(I) complexes form four coordinated tetrahedral or trigonal-pyramidal (TBP) geometries. There are also three and two coordinated Cu(I) complexes but five coordinated Cu(I) are unusual and have at least one significantly elongated Cu-ligand bond.^[17]

A large number of Cu(II) compounds exist in the literature; many of them are water soluble. Cu(II) complexes have been extensively studied in recent years. Due to their flexibility, facility of preparation and capability of stabilizing unusual oxidation states and successful performance in mimicking particular geometries around metal centers, they have very interesting spectroscopic properties and varied catalytic activities.^[18] However, the Cu(II) ion can form a variety of complexes with coordination numbers from 4–6.^[19] The geometry around the Cu ion dominates primarily with the combination of various ligands and ligand backbone as well as electronic and steric constraints of its ligand. For example, typically the five-coordinated Cu(II) ion exists in either a square-pyramidal (SP) or a TBP geometry (or any of the distorted intermediate geometries). The degree of distortion from TBP to SP can be estimated by measuring the distortion index τ proposed by Addison *et al.* [$\tau = (\theta - \phi)/60$; θ and ϕ are the two largest angles between the bonds formed by the coordinated metal]; where $\tau = 0$ for SP and 1 for TBP.^[20]

As with many other metals, the chemistry of hypervalent Cu complexes has been explored to a very limited extent. Cu(IV) compounds have not been recognized in a systematic manner, while their Cu(III) counterparts have been the subject of only a handful of reports.^[21] The preparation and properties of tetrapeptide complexes of trivalent Cu have been reported.^[22] Tetravalent hypervalent Cu(III) complexes exist in a square planar geometry and they are usually stabilized by strong basic anionic ligands.^[23]

2.2 Nitroxyl radicals

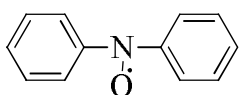
Nitroxyl radicals are known to act as radical scavenging antioxidants. They are extremely popular in various fields of science and technology. A great number of scientific papers as well as patents present their application as inhibitors in free radical processes such as polymerization reactions.^[24] Nitroxyl radical and their diamagnetic precursors are employed to improve the quality of sealants, alcohols, fats, oils, lubricants, detergents and other polymeric materials.^[25]

They have been drawn particular attention and have gained wide popularity in biology and medical science as their use for spin labels, spin–immunology probes and enzyme inhibitors.^[26] More recently they have found wide applications as oxidation catalysts.

Based on their properties and applications, two types of nitroxyl radicals have been reported.^[27]

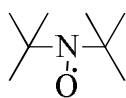
Stable (persistent) radicals: inhibitors

(a) Conjugated

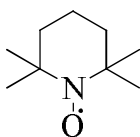


Di-phenylnitroxyl radical

(b) Nonconjugated

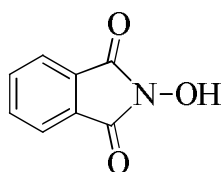


Di-*tert*-butylnitroxyl radical

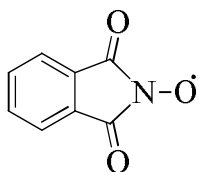


TEMPO

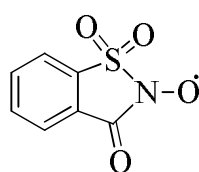
Reactive (non–persistent) radicals: catalysts



NHIPI



PINO



SINO

2.3 Catalytic oxidation of alcohols

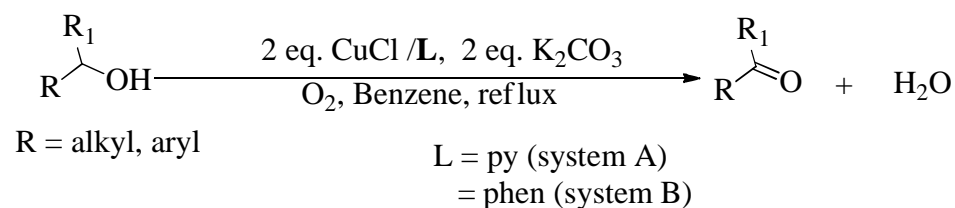
The development of highly active catalyst for the selective oxidation of alcohols with air in aqueous media is a tremendously important topic in chemistry today. Despite the improvement of transition metal catalyzed aerobic alcohol oxidations, various challenges exist in the progress of the systems. These include mild reaction temperature, low O₂ pressure especially inflammable organic solvents, low catalyst loads and the avoidance of costly or toxic auxiliary substances. While acknowledging the pioneering work based on copper that has been done in this area, we believe that the design and development of novel catalyst system that exhibits a wide range of

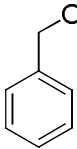
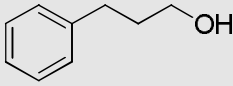
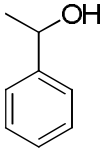
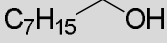
substrate tolerance under mild and open air conditions in pure water still remains a major challenge.

2.3.1 Ligand-assisted copper systems

A ligand-assisted Cu system for oxidation of alcohols into their corresponding carbonyl compounds was first reported in 1977.^[28] The simple Cu complex of pyridine (py) and 1,10-phenanthroline (phen) catalyzes the selective oxidation of alcohols to aldehydes using O₂ as an end-oxidant (Table 1).

Table 1 The oxidation of selected alcohols catalyzed by Cu-py and Cu-phen.^[28]



Substrate	Method	Time (h)	Yield (GC)%
	A	2	35
	B	2	86
	A	2	56
	B	2	83
	A	2	5
	B	2	65
	B	4	93
	A	4	10
	B	2	22

Method A: CuCl (5 mol), py 20 mL, alcohol (2.5 mol), K₂CO₃ (5 mol), 112 °C, 1 atm O₂

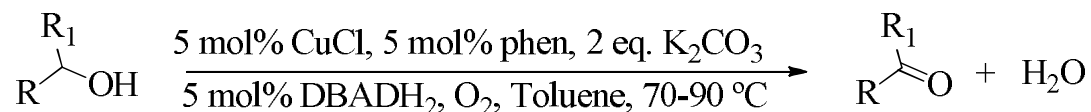
Method B: CuCl (5 mol), phen (5 mol), alcohol (2.5 mol), K₂CO₃ (5 mol), benzene 12 mL, 112 °C, atm O₂

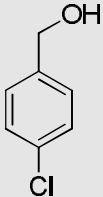
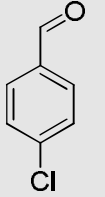
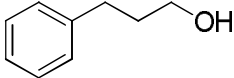
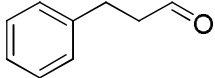
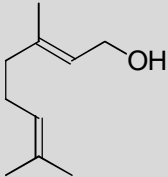
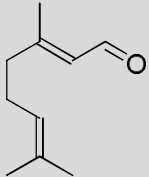
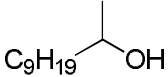
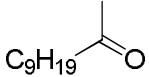
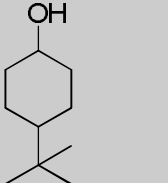
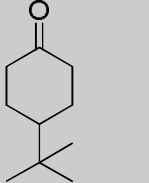
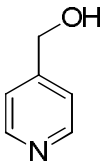
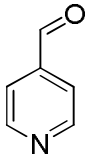
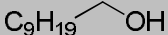
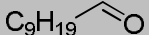
Oxidation of benzylic alcohols with CuCl/py (Table 1, system A, 2 h) gave 35–56% corresponding aldehydes, whereas with CuCl/phen (Table 1, system B, 2 h) 83–86% aldehyde was obtained. Therefore, the Cu-phen complex is a more efficient catalyst than the py one. Benzylic and allylic alcohols are oxidized faster than aliphatic alcohols. Unfortunately, two equivalents of Cu complex have to be used to achieve good conversions. Elevated temperature

(112 °C) and high basic condition e.g. 2 eq. of K₂CO₃ are required. In addition, the system is severely limited to benzylic substrates and aliphatic alcohols have proved to be either unreactive or undergo competing C–C bond cleavage.

After two decades, phen–assisted Cu system was reinvestigated ^[29] and modified. Additives such as di-*tert*-butylazohydrazine (DBADH₂) were introduced and they enhanced the rate and total turnover numbers (TON) of the reactions (Table 2).

Table 2 The oxidation of selected alcohols catalyzed by Cu–phen/DBADH₂. ^[29]



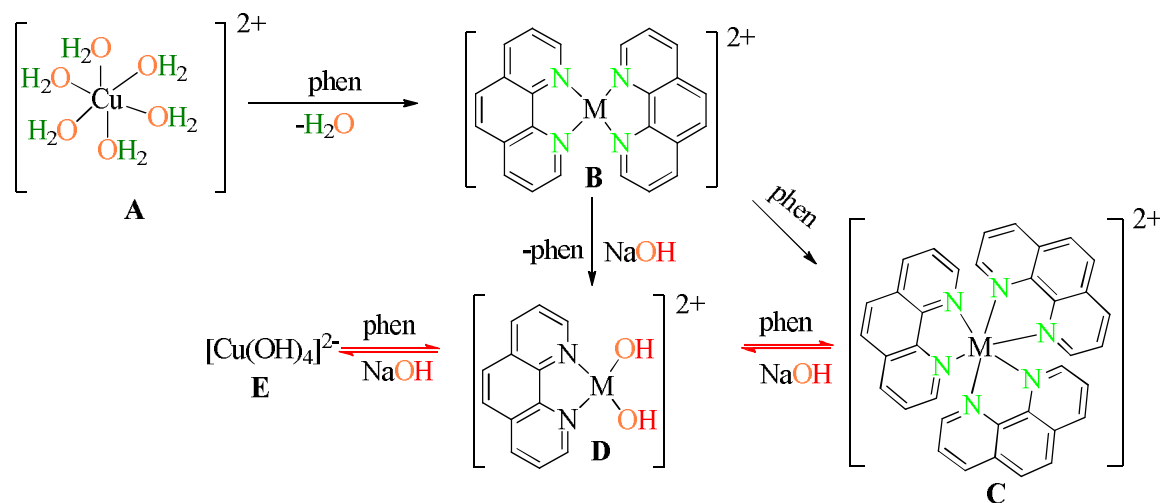
Substrate	Product	Yield (conv.)%	Time (min)
		83 (100)	90
		89 (100)	60
		71(75)	60
		88 (90)	120 ^a
		84 (87)	120 ^b
		81 (92)	60
		73 (87)	45 ^c

^a) 5 mol% DBAD used instead of DBADH₂.

^b) 10 mol% CuCl/phen and DBAD used.

^c) 10 mol% CuCl/phen and DBADH₂ used.

This method (see Table 2) is universal for the oxidation of benzylic, allylic, primary and secondary alcohols but it requires high catalyst loading (5–10 mol%) as well as base and additives. The base K_2CO_3 is insoluble in toluene and the active catalyst absorbed on solid base. So the system is considered as being heterogeneous. Previously, the phen–assisted Cu system has also been investigated in various solvents [30] other than toluene such as MeCN [31], DMF, pyridine and alcohols [32]. In most of the systems, the Cu–phen complexes were made *in situ*. The characterization of active catalyst is difficult due to the variation of the reaction conditions used. Recently, one of our groups has shown how different species from Cu and phen can be formed by changing the pH and ligand used to metal molar ratios (Scheme 1). [33] Similar studies with Cu–bipyridine (bipy) in aqueous solution have also been investigated. [34]



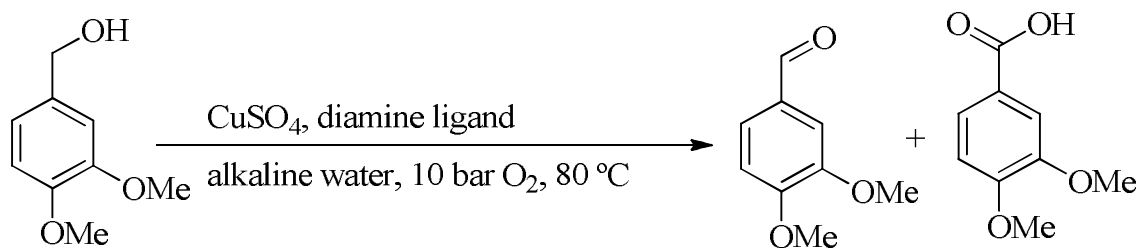
Scheme 1 Formation of the catalytically active species in aqueous alkaline solution in the presence of phen. [33]

The catalytic activity of other N containing ligands such as bipy and TMEDA with Cu are also known. [35] In 1993 bipy–assisted Cu system was developed [36] and two equivalents of base in an O_2 saturated MeCN solution is required to achieve efficient transformation of alcohols to corresponding carbonyl compounds. With benzyl alcohol, the reaction reached 80% completion in 1 hour. However, for all conditions, the oxidation reaction essentially stops after 20–80 TON due to the formation of a red solid such as Cu_2O .

Another bipy–assisted Cu system for aerobic oxidation of alcohols has been reported. [37] This system without a strong base has been found to be a good improvement on the previously designed bipy based system. A dramatic ligand effect on the catalytic activity of Cu–complexes was found and bipy exhibits higher activity than other diamine ligands in the system. The oxidation reactions are carried out in MeCN solution at 60 °C.

In conclusion, the ligand–assisted Cu systems are found to be very efficient for a wide range of alcohols. In most cases, aliphatic alcohols are less efficient than benzylic ones and primary alcohols are more reactive than their secondary isomers. However, the most common drawback of the ligand–assisted Cu–systems mentioned above is the use of organic solvents.

In our laboratory the catalytic activity of diamine ligands have also been studied with CuSO_4 for oxidation of veratryl alcohol in alkaline water under 10 bars of O_2 (Scheme 2).^[38]

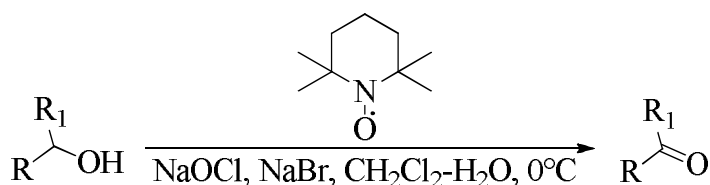


Scheme 2 Oxidation of veratryl alcohol catalyzed by CuSO_4 /diamine in alkaline water.^[38]

By combinatorial screening, the most active catalysts were found to incorporate TMEDA, 1,2-diaminocyclohexane (DACH) or 9,10-diaminophenanthrene (DAPHEN). Unfortunately, the systems (Scheme 2) are efficient only for oxidation of veratryl alcohol to veratraldehyde.

2.3.2 Organocatalytic oxidation of alcohols

The metals free NaOCl (household bleach) oxidant system using 1 mol% TEMPO in combination with NaBr as co-catalyst in dichloromethane/water (pH 9) at 0°C has been widely employed in organic synthesis.^[39]

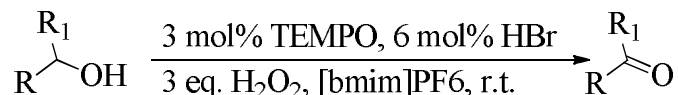


Scheme 3 Bleach oxidant system for oxidation of alcohols.^[40]

Although the stable free radical TEMPO may oxidize a number of functionalities, most of the studies reported have been for the transformation of alcohols to the corresponding carbonyl compounds. TEMPO with variant oxidants is considered as a selective, efficient and convenient catalyst for the oxidation of alcohols. Nevertheless, the inexpensive and readily available NaOCl is commonly used as the primary oxidant. In most cases $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ is used as the solvent (Scheme 3).^[40]

The bleach oxidation method was first introduced in 1989.^[41] 4-methoxy-TEMPO instead of TEMPO as catalyst was utilized for the oxidation of diols in $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (pH 8.9) at 0°C . The bleach oxidations are highly selective and the reactions were carried out at or below room temperature (r.t.). The drawbacks of the methods are that at least one equivalent of NaCl is produced per mole of alcohol oxidized and the use of hypochloride as oxidant can also produce chlorinated by-products. Other limitations are the use of 10 mol% Br^- as a co-catalyst. However, a major issue with these systems is the use of highly volatile CH_2Cl_2 as a solvent, which is subject to increasingly stringent regulations because of health and environmental

hazards. Accordingly, several greener alternatives to CH_2Cl_2 that can be successfully used as a solvent in oxidation of alcohols catalyzed by TEMPO were developed.^[42] For instance, the first efficient use of TEMPO as an organocatalyst for the oxidation of alcohols with H_2O_2 in ionic liquid such as [bmim][PF₆] ([bmim]⁺ = 1-butyl-3-methylimidazolium) was introduced in 2005 (Scheme 4).^[42a]

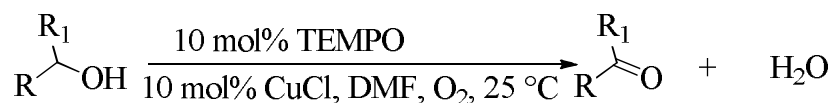


Scheme 4 Oxidation of alcohols with H_2O_2 catalyzed by TEMPO.

This system (Scheme 4) is efficient for the oxidation of π -activated benzylic alcohols into the corresponding carbonyl compounds. Both electron-deficient and neutral benzylic alcohols afforded good to excellent isolated yields. However, electron-rich benzylic alcohols only gave a trace amount of aldehyde. No activity is achieved for primary aliphatic and secondary alcohols. Presumably, the actual oxidant in this system is HOBr. In that sense, the system is not halogen free and may produce halogenated byproducts. On the other hand, the direct organocatalytic oxidations of alcohols to aldehydes are really sparse.^[43] A first metal-free aerobic oxidation protocol, which uses *N*-hydroxyphthalimide (NHPI) as a catalyst, was reported.^[44] Later on the efficient use of TEMPO and 5-Fluoro-2-azaadamantane *N*-oxyl as organocatalysts in aerobic oxidation of alcohol has been developed.^[43d-e] However, in most cases the use of $\text{NaNO}_2/\text{Br}_2$ as co-oxidants makes the system less attractive for industrial applications.

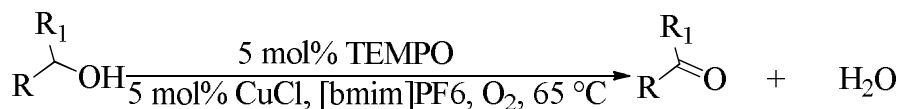
2.3.3 TEMPO-mediated copper systems

The TEMPO-mediated Cu system for aerobic oxidation of MeOH to formaldehyde was first developed in 1966.^[44] Almost two decades later the ligand free TEMPO mediated Cu system for the aerobic oxidation of alcohols was introduced (Scheme 5). 10 mol% CuCl and 10 mol% TEMPO were used to oxidize benzylic, allylic and aliphatic alcohols into the corresponding carbonyl compounds in DMF under an O_2 atmosphere at 25 °C.^[45]



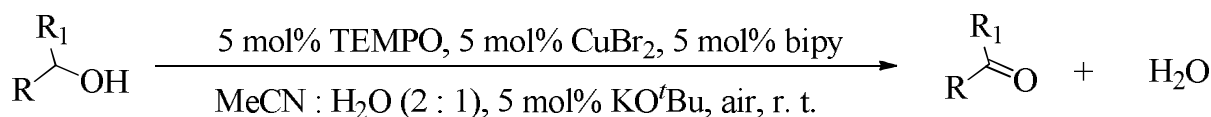
Scheme 5 Aerobic oxidation of alcohols catalyzed by CuCl-TEMPO.^[45]

After optimal reaction conditions for the system (Scheme 5) secondary alcohols were oxidized with significantly lower rates compare to primary alcohols. Later, several studies based on TEMPO and Cu for aerobic oxidation of alcohols to aldehydes have also been reported. For instance, in 2002 a CuCl-TEMPO catalyst aerobic oxidation of alcohols that succeeded in the ionic liquid rather than of the use of traditional organic solvent was developed (Scheme 6).^[46] The method (Scheme 6) was successfully utilized to the oxidation of benzylic, allylic and aliphatic alcohols to carbonyl compounds using 5 mol% CuCl and 5 mol% TEMPO at 65 °C.



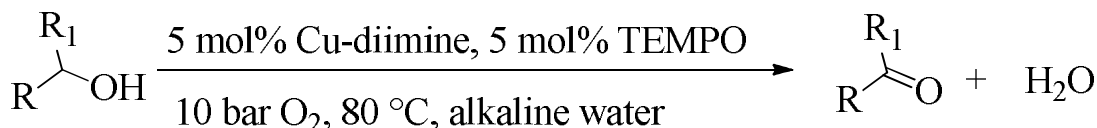
Scheme 6 Aerobic oxidation of alcohols in ionic liquid catalyzed by CuCl–TEMPO. ^[46]

After screening for a variety of Cu sources, it was found that bipy as a ligand and CuBr₂ as a metal source in combination with a catalytic amount of TEMPO results in the oxidation of primary alcohols to the corresponding aldehydes. ^[47] Overoxidation to the acids has never been observed while reactions were carried out in MeCN/H₂O (1 : 2) under air (Scheme 7). No oxidative transformation of secondary alcohols is observed due to steric hindrance associated with the methyl groups of TEMPO and secondary alcohol which is also observed in other TEMPO mediated systems. ^[42a, 62, 63–64, 125, 127]



Scheme 7 Aerobic oxidation of alcohols catalyzed by TEMPO/Cu–bipy. ^[47]

In addition to the TEMPO mediated Cu–bipy systems, a method for the selective oxidation of alcohols to carbonyl compounds by Cu and the perfluoroalkylated bipy ligand in the presence of catalytic amount of TEMPO has been developed. ^[48] The reactions were successful at 90 °C in a biphasic solvent for the oxidation of a broad range of primary, secondary, benzylic, allylic and aliphatic alcohols into the corresponding carbonyl compounds (Table 3).

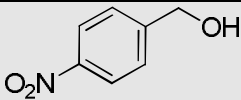
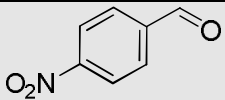
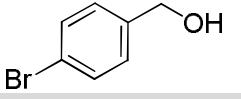
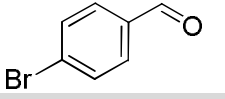
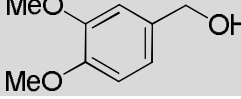
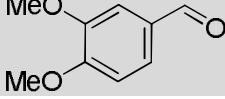
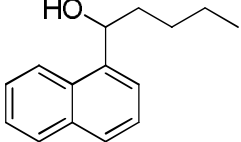
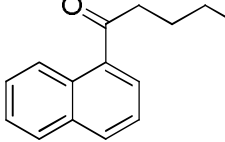
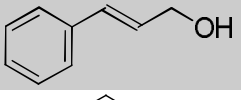
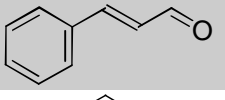
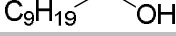
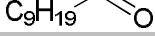
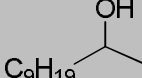
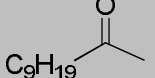
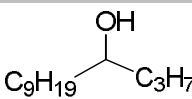
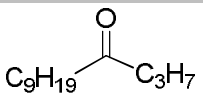


Scheme 8 Oxidation of alcohols in alkaline water catalyzed by TEMPO/Cu–diimine. ^[49]

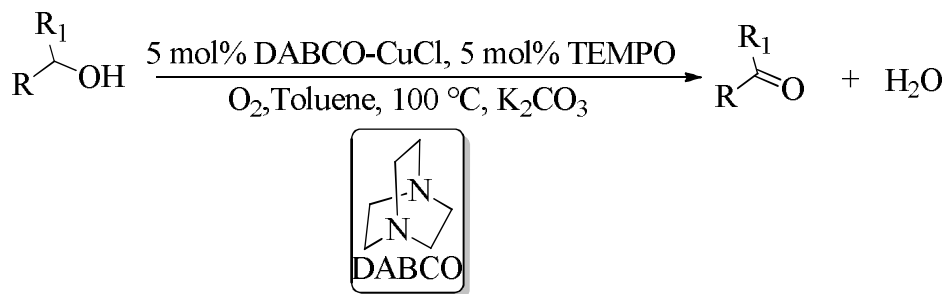
While this biphasic solvent system (see Table 3) provides the benefit of being able to reuse the catalyst up to eight times although with some loss of catalytic activity, high catalyst (3.5–10 mol% TEMPO) load, O₂ instead of air, highly volatile and flammable Me₂S as solvent and a long reaction time (17 h) are needed.

In our laboratory, the TEMPO mediated Cu/diimine system was reinvestigated and we first succeeded in the catalytic oxidation of benzylic alcohols to the corresponding carbonyl compounds in alkaline water under 10 bars of O₂ at 80 °C temperature. ^[49] Only the using of catalytic amount of TEMPO in alkaline water, the oxidation capability of the catalyst based on CuSO₄/phen (Scheme 8) is significantly improved in comparison to our previously developed Cu–DAPHEN system (Scheme 2). ^[38]

Table 3 The oxidation of alcohols catalyzed by TEMPO/Cu–perfluoroalkylated bipy. ^[48]

$ \begin{array}{c} \text{R}_1 \\ \\ \text{R}-\text{CH}-\text{OH} \end{array} \xrightarrow[\text{3.5 mol\% TEMPO, PhCl, O}_2]{\text{2 mol\% CuBr}\cdot\text{Me}_2\text{S, 2 mol\% L, 90 }^\circ\text{C, 17 h}} \begin{array}{c} \text{R}_1 \\ \\ \text{R}-\text{C}=\text{O} \end{array} + \text{H}_2\text{O} $		
$ \text{L} = \begin{array}{c} \text{C}_8\text{F}_{17}(\text{CH}_2)_4 \end{array} \begin{array}{c} \text{N} \\ \diagup \quad \diagdown \\ \text{---} \quad \text{---} \\ \text{N} \end{array} \begin{array}{c} \text{N} \\ \diagdown \quad \diagup \\ \text{---} \quad \text{---} \\ \text{N} \end{array} \begin{array}{c} (\text{H}_2\text{C})_4\text{C}_8\text{F}_{17} \end{array} $		
Substrate	Product	Yield (%)
		93
		96
		93
		91
		79
		73
		71
		31

Recently, a TEMPO mediated CuCl–DABCO (1,4-diazabicyclo[2.2.2]octane) catalytic system for the oxidation of alcohols to aldehydes in toluene at 100 °C have been reported (Scheme 9). ^[50] Interestingly, the developed system can work efficiently for the oxidation of various benzylic alcohols to the corresponding benzylic aldehydes with high loading of catalyst (5 mol%) at r.t. when the potentially explosive and highly polar CH₃NO₂ as an alternative of toluene is used as a solvent.



Scheme 9 Aerobic oxidation of alcohols catalyzed by TEMPO/CuCl–DABCO. ^[50]

The efficiency of the reaction (Scheme 9) is nearly the same with and without base in toluene similar to the more recently reported TEMPO/Cu–*N*–benzylidene–*N,N*–dimethylthane–1,2–diamine system ^[51]. Apparently, the applied ligand has adequate basicity for deprotonating the alcohol and hence the oxidation occurs without a base.

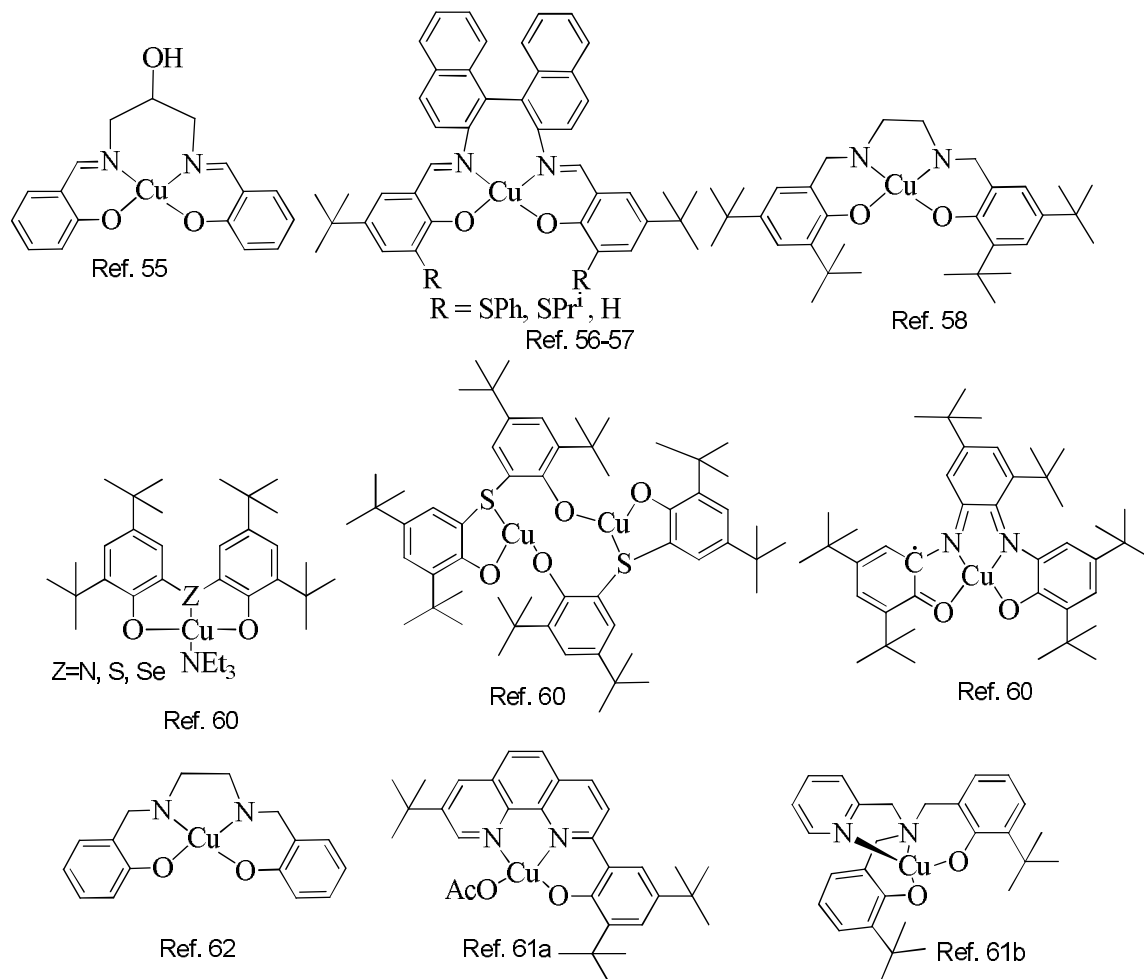
Early reports on TEMPO/Cu catalyzed transformation of alcohols to aldehydes assisted by bipy as a ligand and NMI as an additive in MeCN is also encouraging. ^[52] However, in all cases, oxidation requires additional auxiliaries such as base and/or co–solvent and the use of at least 5 mol% catalyst materials.

2.3.4 System based on isolated copper complexes

The catalytic oxidation of alcohols to aldehydes based on isolated Cu complexes (see Scheme 10) has been reported by several groups ^[53–62]. While the active form of the natural enzyme GO has been successfully accumulated in numerous model complexes, only a few functional models have been published. ^[53] The first synthesized Cu complex system, ^[54] which may be regarded as functional model of GO efficiently catalyzes the oxidation of alcohols to aldehydes under O₂ pressure (30 p.s.i) at 25 °C. Under identical reaction conditions, all the Cu (bipy)LX complexes where L= PPh₃, PMePh₂, PBuⁿ₃, PEt₃ and X= I, Br, Cl, revealed identical catalytic activity for the formation of acetaldehyde from ethanol. After evaluating a variety of isolated Cu complexes, only *N,N'*–(2–hydroxypropane–1, 3–diyl) bis(salicylaldiminato) Cu(II) ^[55] was found to be an effective catalyst for the oxidation of ethanol to ethanal used the substrate as a solvent. The oxidation experiments were carried out under atmospheric O₂ at 40 °C. The base KOH as an additive is obviously required to perform catalytic activity. Under comparable conditions propanol and hydroxyacetone can be oxidized to their corresponding carbonyl compounds as well. However, no evidence for the oxidation of other alcohols has been shown.

One decade later, functional models of GO based on Cu complexes were devised and their catalytic activities toward alcohols oxidation were discovered. ^[56] The Cu complexes with binaphthyl backbone catalyzed the oxidation of benzyl alcohol into benzaldehyde with [TBA] [SbCl₆] as oxidant in the presence of base (*n*–BuLi) under anaerobic conditions at –25 °C in MeCN. The highest TON measured in the reaction was 9.2. Further studies based on these isolated complexes corroborated the capability of these catalysts to oxidize benzyl alcohol, 1–phenyl ethanol and cinamyl alcohol to their corresponding carbonyl compounds in the presence of catalytic amounts of the base KOH with 1 atmosphere O₂ at 22 °C in MeCN. ^[57] The highest

TON altered to 9.2 from 1300 for 20 hours in the modified systems. Unfortunately, unactivated aliphatic alcohols such as 1-octanol or cyclohexanol are not oxidized.



Scheme 10 Schematic structures of isolated Cu complexes used as catalysts in the oxidation of alcohols.

At the same time, the Cu(II) complex of *N,N*-bis(2-hydroxy-3,5-di-*tert*-butylbenzyl)-1,2-ethylenediamine catalyzing the electrochemically one-electron oxidation of lower aliphatic alcohols into the corresponding aldehydes in the presence of KOH at r.t. in MeCN has been described.^[58] The highest TON of 30 was achieved in the reaction and moreover secondary alcohols were not oxidized.

In 2003, the first example of an isolated Cu catalyst for oxidation of alcohols to carbonyl compounds with H₂O₂ as the source of oxygen was reported.^[59] However, with this catalyst alcohols are oxidized to acids and the reactions are carried out in organic solvent (MeCN) at 80 °C in the presence of a high excess of H₂O₂ (10 equivalent to substrate). Interestingly, while primary alcohols are overoxidized to carboxylic acids, secondary alcohols are selectively and more efficiently oxidized into their corresponding ketones.

Table 4 The oxidation of selected alcohols catalyzed by TEMPO/di(*N,N'*-2-hydroxidobenzyl)ethylenediamineCu(II) complex. ^[62]

$$\text{R}-\text{CH}(\text{OH})-\text{R}_1 \xrightarrow[5 \text{ mol\% TEMPO, Toluene, O}_2]{5 \text{ mol\% catalyst, 100 } ^\circ\text{C}} \text{R}-\text{C}(=\text{O})-\text{R}_1 + \text{H}_2\text{O}$$

catalyst =

Substrate	Product	Yield (%) ^a	Time (h)
		99	10
		98	14
		70	19
		98	9
		98	11
		84 ^b	25
		75	22 ^c
		92	26
		2	12

^a) Isolated yield. ^b) GC yield. ^c) 7 mol% catalyst and TEMPO used.

The catalytic performance of isolated complexes can often be tuned by slight changes in the ligand framework or by utilizing different coordination environment surrounding the metal center, which induces steric and electronic effects. Thus a series of Cu complexes with different donor atoms were synthesized and employed as catalyst toward oxidation of alcohols. ^[60] The simple model phenoxyl radical complexes are dinuclear and mononuclear Cu centers consist of S, N and Se donor atoms. These complexes are capable of efficiently catalyzing the aerial oxidation of alcohols including methanol and ethanol to the corresponding aldehydes at ambient

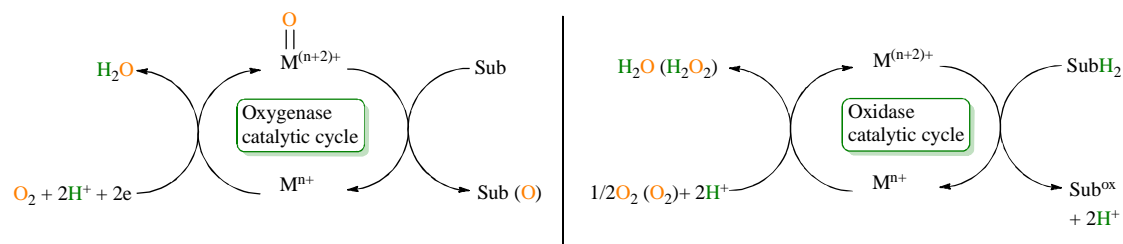
conditions in certain organic solvents such as THF and MeCN or in pure substrate solutions with high TON (about 5000 in the best case).^[60]

Obviously, Cu complexes bearing simple phenoxyl radicals are to date the best catalyst based on synthesized complexes. Other approaches^[61], however, are effective for the catalytic alcohol oxidations and they may be visualized. In particular, the process with the di(*N,N'*-2-hydroxidobenzyl)ethylenediamineCu(II) complex^[62] is an efficient catalyst for the oxidation of a variety of benzylic alcohols to the corresponding carbonyl compounds in toluene under atmospheric oxygen instead of H₂O₂^[59], where the alcohols have never been overoxidized to carboxylic acid due to the utilizing of TEMPO (Table 4).

The TEMPO/ di(*N,N'*-2-hydroxidobenzyl)ethylenediamineCu(II) system (see Table 4) has a similar scope to others TEMPO mediated Cu based systems.^[42a, 62, 63–64, 125, 127] However, it required high catalyst loading (5–7 mol %) and long reaction times (9–25 h) as well as elevated temperature (100 °C). Additionally, the catalyst can be recycled up to three times with freshly TEMPO addition each time. Overall, the effectiveness of these methods based on isolated Cu complexes rivals or surpasses that of traditional oxidation of alcohols to carbonyl compounds by using an additional base in an organic solvent.

2.4 Mechanism of alcohol oxidation

In nature metalloenzymes that catalyze selective aerobic oxidation of organic molecules, have been classified as oxygenases and oxidases (Scheme 11).^[63] In the oxygenase catalytic cycle, the oxidation of substrate involves O transfer from O₂ (as found in air), often through a high valent metal oxyl intermediate. The other O atom is obviously reduced to H₂O. Therefore this can be useful with metal ion having high oxidation state.

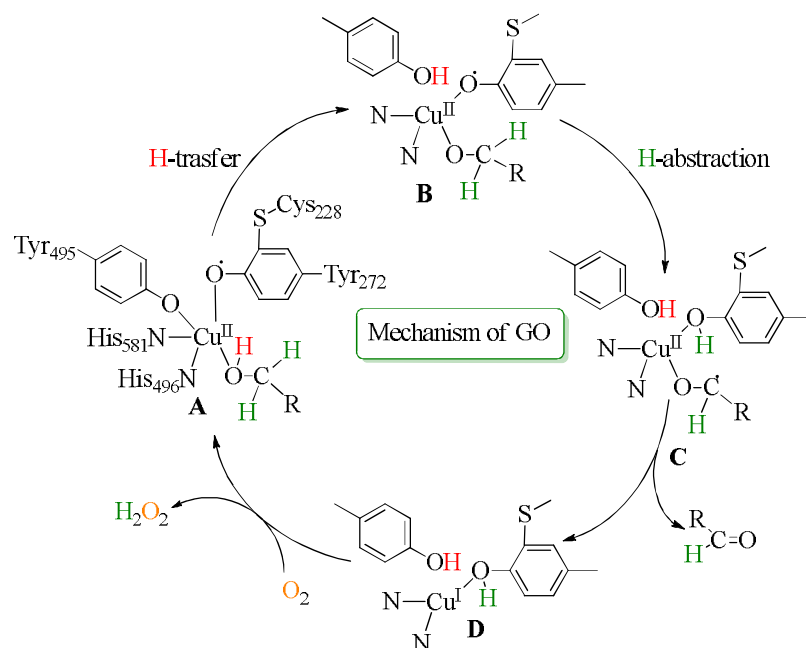


Scheme 11 Simple catalytic cycles for aerobic oxidation of organic substrate.^[63]

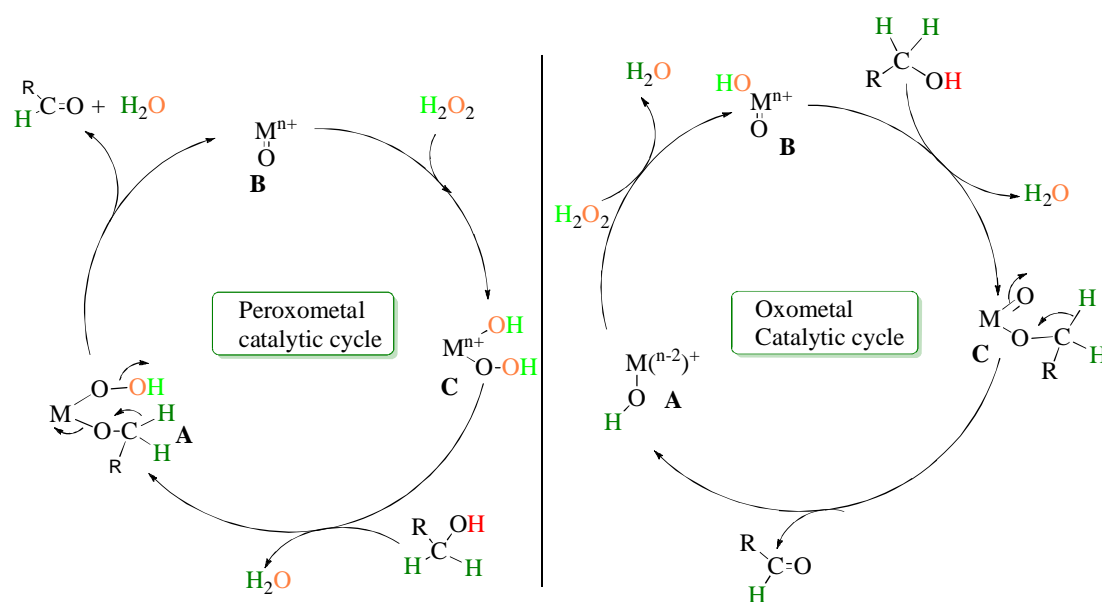
The oxidase catalytic cycle simply utilizes O₂ as a two-electron or two-proton acceptor in the catalytic oxidation of organic molecules. In the reaction, O atoms are eventually reduced to either H₂O or H₂O₂. Thus the transfer of O atoms to the substrate is not observed.

The most frequently exemplified oxidase catalytic cycle is the GO enzymatic reaction. The GO catalytic cycle has been widely studied and the reaction steps are well understood (Scheme 12).^[63–64] Initially, the alcohol binds to the active Cu center (**A**) and is deprotonated by phenolic tyr-495. The phenoxyl radical abstracts a β-H from the coordinated alcohol (**B**) to form a bound ketyl radical (**C**) which is converted to the aldehyde by a single electron transfer with

simultaneous formation of a Cu(I) species (**D**). In the presence of O₂, Cu(I) is reoxidized back to the original **A** and O₂ is reduced to H₂O₂.



Scheme 12 Proposed reaction mechanism of GO. ^[63–64]



Scheme 13 Simple catalytic cycles for alcohol oxidation with H₂O₂. ^[65]

Based on applied reaction conditions, oxidation of alcohol substrates with H₂O₂ catalyzed by metal complexes can follow free radical or ionic mechanisms. Ionic mechanisms can be classified as the peroxometal and oxometal catalytic cycles (Scheme 13). ^[65] The oxidation state of the metal ion does not change during reaction in the peroxometal catalytic cycle. In addition,

stoichiometric oxidation of alcohols is not observed. On the other hand, the oxometal catalytic cycle initiates a 2 electron transfer from the oxidant and thus the oxidation state of the metal ion changes to a higher valency. A stoichiometric alcohol oxidation is likely in the absence of H₂O₂.

3 Experimental Remarks

All the chemicals were purchased from commercial suppliers and used as received. The ligands used in this thesis were synthesized by literature procedures found elsewhere. The Cu complexes were prepared with slight modifications to the published procedure and newly developed synthetic routes. The purities of the compounds were confirmed by ¹H-NMR (if possible), melting point measurements and elemental analysis. NMR spectra (¹H and ¹³C) were obtained from a Varian Mercury 300 MHz spectrometer. Chemical shifts for ¹H NMR and ¹³C NMR were referenced with respect to CHCl₃ and TMS, respectively. EI-mass spectra were collected with a JEOL JMS-SX 102 mass spectrometer (ionization voltage 70 eV) from solid samples. IR spectra were recorded with a Perkin Elmer Spectrum GX spectrometer and a Perkin Elmer Spectrum one spectrometer for solution and solid samples, respectively. UV-vis spectra were run with a Hewlett Packard 8453 spectrophotometer. Melting points were determined in an electrothermal melting point apparatus. Elemental analyses were made using an EA 1110 CHNS-OCE instrument. Typically, the samples were obtained by EtOAc extraction from aqueous solution after oxidation.^{I, III, V, VIII} The samples were quantitatively analyzed with an GC (Agilent 6890 chromatograph, Agilent 19091J-413 capillary column 0.32mm×30m×0.25μm, FID detector) using internal standards. The GC-MS method was used for identification of the products (Agilent 6890N equipped with Agilent 5973 mass selective detector, HP 19091 L-102 capillary columns, 200mm×24m×0.31μm).^{I, II, III, V, VIII, IX}

4 Results and Discussion

4.1 Ligand precursors

4.1.1 Synthesis

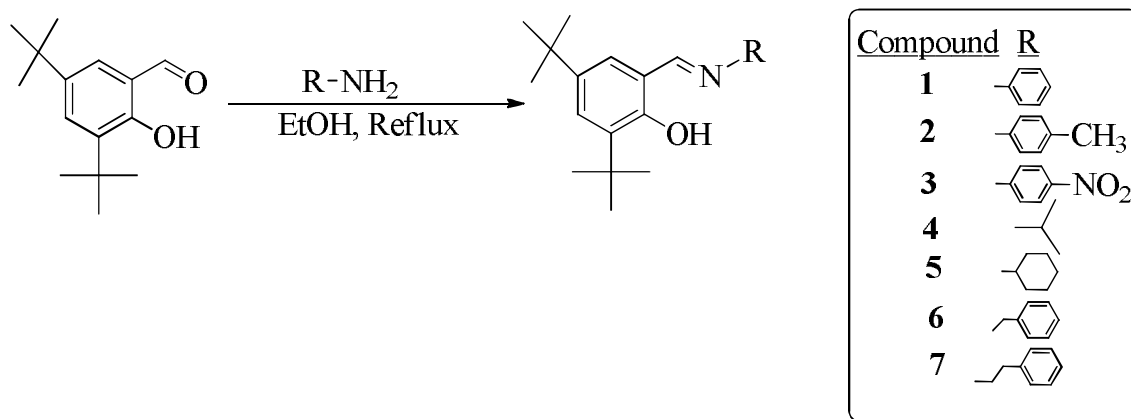
There are two types of imine: (a) imidates and (b) aldimines and ketimines. Imidates are compounds where azomethine carbon is attached to oxygen. An imine in which the azomethine carbon is connected with one hydrocarbyl group is called an aldimine. On the other hand, an imine in which azomethine carbon is attached to two hydrocarbyl groups is known as a ketimine. On the basis of their azomethine N, imines are classified into primary and secondary imines. In a primary imine the azomethine N is connected with H whereas in a secondary imine the azomethine N is connected with a hydrocarbyl group. Secondary imines are known as Schiff bases.

In 1864 the German chemist Hugo Josef Schiff discovered the immensely useful organic compounds by the condensation reaction between an aldehyde and amine. The compounds are known as Schiff bases, having a general formula RR₁C=NR₂ where R₂ is either an alkyl or aryl group but not for H. In general, they are characterized by the anil linkage -CH=N-. A Schiff base derived from aniline or substituted aniline can be called an anil. A Schiff base which is

derived from salicylaldehyde is known as salicylaldimine. In this study, special attention was paid to the synthesis of sterically hindered salicylaldimine and their structural properties in solid and solution states were examined.^{IV}

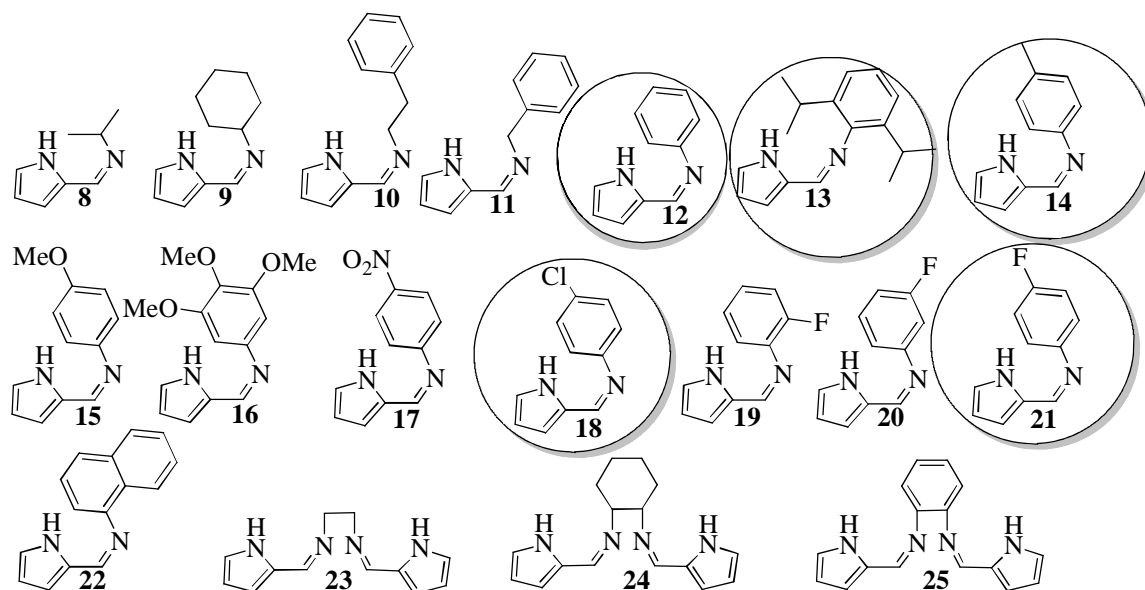
The formation of imines is a very important chemical reaction because of its significance in biological processes.^[66] Many biological systems involve the initial binding of carbonyl compound to an enzyme through imine formation.^[67] There are several reaction pathways to synthesize imine in the laboratory.^[68] The most common is the condensation reaction between a carbonyl compound and a primary amine. In the carbonyl group the carbon–oxygen double is strongly polarized by the electronegative O atom. Consequently, an attack of a nucleophilic N atom on the carbonyl C easily forms an unstable dipolar intermediate. Intramolecular H–transfer from the amine N to the oxide ion yields the aminoalcohol, which is then protonated in the presence of catalytic amounts of acid. The last step in this reaction is imine formation by elimination of water via the iminium ion.^[69]

The condensation of primary amine with salicylaldehyde in the presence of catalytic amounts of formic acid (2–3 drops) is the convenient way to synthesize salicylaldimines (Scheme 14).^{IV} Normally the reaction is carried out in protic solvents such as methanol and ethanol in refluxing conditions.^[70] Ambient conditions could be useful for the synthesis. In the process, water is formed as a byproduct and the reverse reaction can be taken place. To maximize the yield, dehydrating agents such as molecular sieves or anhydrous Na₂SO₄ are used in some cases.^[71] The synthesis of Schiff bases is performed by directly heating the reaction mixture in solvent free conditions.^[72] Recently, a novel and highly efficient synthesis protocol for salicylaldimine formation catalyzed by P₂O₅/Al₂O₃ under solvent free conditions has also been reported.^[63]



Scheme 14 Synthesis of sterically hindered salicylaldimine ligand precursors (1–7).^{IV}

In this work, both bidentate (8–22) and tetradentate (23–25) 2-*N*-pyrrolecaldimine ligands were also prepared by a condensation reaction in ethanol in ambient conditions (Scheme 15).^{I, V} Interestingly water has been found to be an ideal solvent for the remarkable high yield synthesis of easily hydrolysable 2-pyrrolecaldimines.^[74] The reaction in only water is very fast for the more basic alkylamine in comparison to the less basic arylamine.



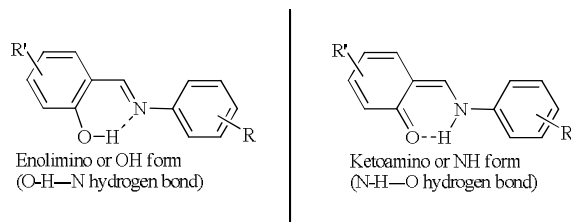
Scheme 15 Schematic presentation of a series of 2-*N*-pyrrolecaldimine ligand precursors (8–25). The circled ligands (12–14, 18 and 21) were used as preligand for the oxidation of alcohols.
I, V

4.1.2 Properties

The design and synthesis of organic molecules with targeted physical properties are of current interest. The Light-induced reversible color change of a molecule is known as photochromism (PC). The phenomenon of PC is derived from the reversible transformation of a chemical species between two forms by the absorption of electromagnetic radiation, where the two forms have different absorption spectra.^[75] The reversible or irreversible color change of molecule under the stimulus of heat is known as thermochromism (TC). A large variety of substrates, such as organic, inorganic, organometallic, and macromolecular systems (e.g., polythiophenes) or supramolecular systems (such as liquid crystals) display the phenomenon of TC. When the TC of molecular systems results from association with another chemical species such as a metal ion or proton or from variation of the medium by heat induced, the phenomenon is called thermosolvatochromism.^[76] The reversible variation of the electronic spectroscopic properties (absorption/emission) of a chemical species, induced by solvents is referred to as solvatochromism (SC).^[78] Schiff bases, especially salicylaldimines are distinctive organic molecules that exhibit either PC or TC depending on the substitution patterns of the aromatic ring.^[79] Both intramolecular proton transfer of the hydroxyl proton by photoexcitation with UV light or by the stimulus of heat and consequence of *cis*–*trans* isomerization are the characteristic feature of chromic salicylaldimines. The shift of equilibrium between enol and *trans*–*keto* forms of salicylaldimines results in the PC whereas the shift of equilibrium between enol and *cis*–*keto* isomers results in the TC.^[80]

Tautomerization of salicylaldimine derivatives represents a very important feature for studying H-bonding properties. Two types of strong intramolecular H-bonding mode formed by

O–H···N (enol–imino or benzenoid tautomer) or N–H···O (keto–imino or quinoid tautomer) exist in the six membered chelate rings of salicylaldimines (Scheme 16).

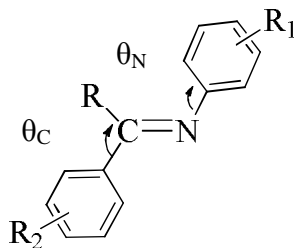


Scheme 16 Tautomeric forms of salicylaldimine. ^[80]

Schiff bases, which are the condensation product of salicylaldehyde and amine, always form the O–H···N type of hydrogen bonding despite N–substituent (alkyl or aryl). ^[81] However, the existence of either enol–imino (benzenoid) or keto–imino (quinoid) tautomer entirely depends on the position and the nature of the substituent on phenyl rings. ^[82] One aim of the thesis was to investigate the enol–keto tautomerization of sterically hindered salicylaldimine derivatives in solid and solution state by spectroscopic techniques such as IR, ¹H NMR, ¹³C NMR, UV–vis and X–ray diffraction. ^{IV} In the solid state, the studied salicylaldimine possesses a strong intramolecular hydrogen bond as enol tautomeric form. According to NMR, IR and UV–vis studies the enol form is also present in solutions. Computational results also reveal that in each keto–enol pair the enol form is more stable than the corresponding keto form.

4.1.3 Structures and applications

Numerous previous investigations of the molecular structures of imine have shown that *N*–aryl Schiff bases energetically favor a non–planar conformation that is largely influenced by steric and electronic effects. ^[83] The twisting of an *N*–aryl substituent along the C–N axis is determined by the twist angle θ_N , whereas the other phenyl ring is virtually co–planar with the C=N bond if the angle θ_C is nearly zero (Scheme 17). ^[84] Typically, the angle θ_N increases when electron withdrawing substituents are in the *p*–position of *N*–phenyl moiety or when alkyl and aryl substituents are in the azomethine C, while it decreases due to the electron releasing substituents in the *p*–position of the *N*–phenyl moiety. ^[85]



Scheme 17 Schematic presentation of non–planar conformation of Schiff base. ^[84]

According to the crystal structures of **1–3** the θ_N angles, are 24.1°, 40.4 and 31.8° and 38.5° respectively, these contrast to the twist angle θ_N of the corresponding compounds without *tert*–butyl group (e. g. θ_N = 55.2° in *N*–phenylsalicylaldimine and θ_N = 50.2° in *N*–*p*–

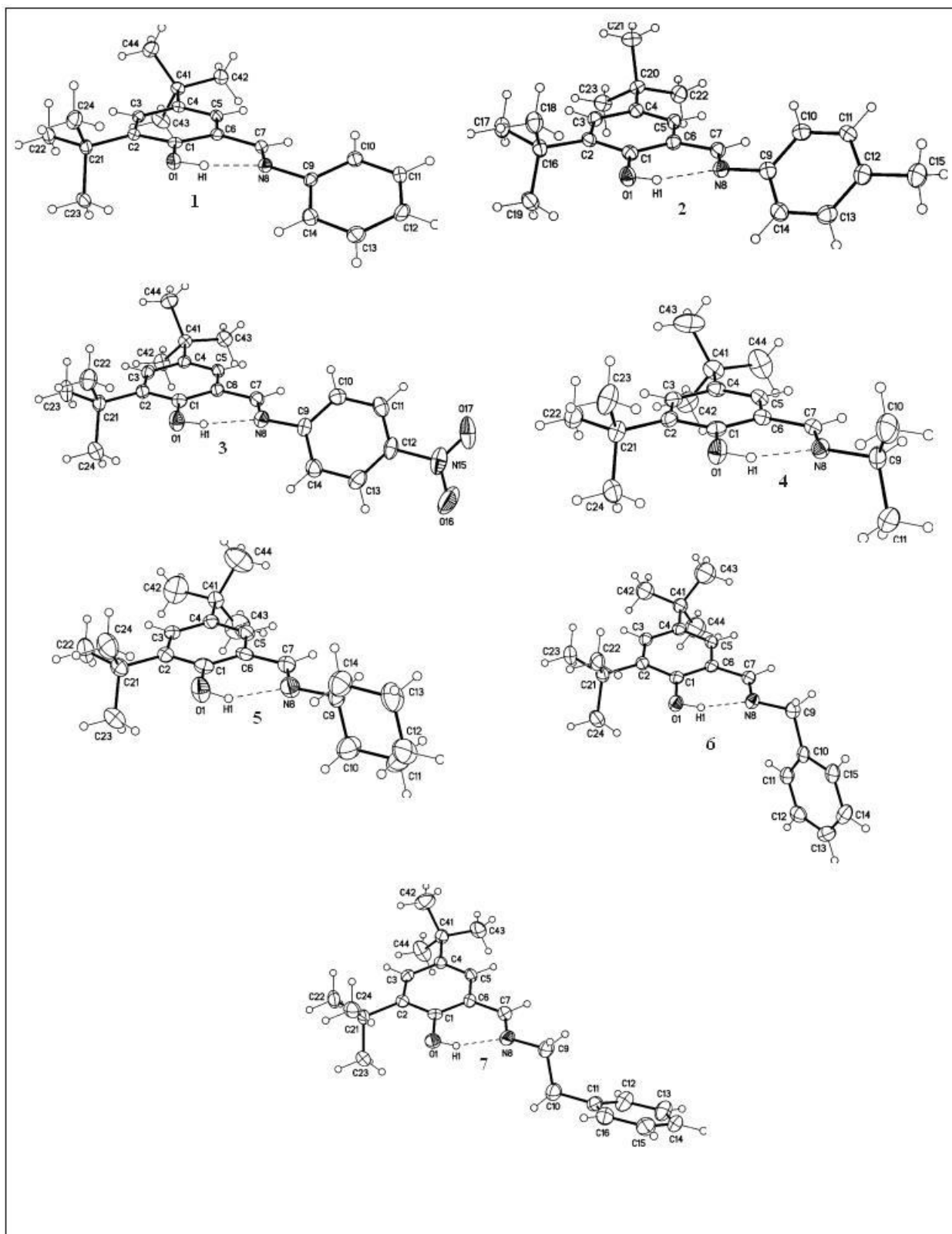


Figure 1 Solid state XRD molecular structures of **1–7** (displacement parameters are drawn the 50% probability level).^{IV}

nitrophenylsalicylaldimine).^[86] Conversely, the angle, θ_C is 3.0° for **1**, 11.5 and 3.0° for two conformers in **2**, 1.1° for **3**, 5.3 , 1 and 2.3° for three conformers in **4**, 2.6° for **5**, 7.3° for **6** and 2.1° for **7**. Accordingly, there is no large difference between all ligand structures.

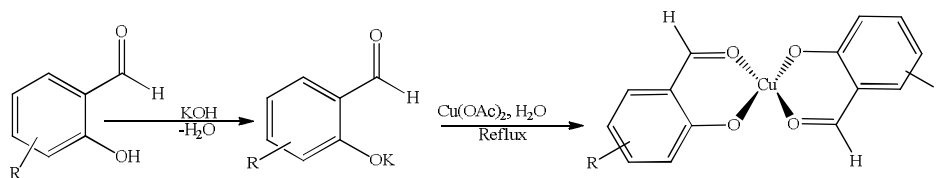
For torsion angles the energy/torsion is quite small. The Least squares (L. S.) plane fit of all the ligand structures (**1–7**); show that the C–connected aromatic rings are always coplanar due to the intramolecular H bond, forcing the aromatic ring into the plane. For the *tert*–butyl substituted salicylaldimines solvatochromism does not appear in polar H–bonding solvents. Apparently, the steric bulkiness of the *tert*–butyl groups in **1–7** in the proximity of N···H–O hampers the formation of intermolecular H–bonding between the imine and a solvent molecule.^{IV} However, all compounds (**1–7**) crystallize in the solid state into the enol tautomeric form and the observed hydrogen bond N···O distances are in the range from $2.550(2)\text{\AA}$ – $2.647(2)\text{\AA}$ (Figure 1).^{IV}

Schiff bases derived from aromatic amines and aldehydes have a wide variety of applications varying from biological to analytical chemistry.^[87] A lone pair electron in a sp^2 hybridized orbital of N atom of the imine group is of considerable chemical and biological importance. The relative synthetic flexibility, high yields, effortless purification and the special properties of C=N group enable them to be used in the design of suitable structural properties.^[88] The versatility of Schiff base ligands, structural similarities with natural biological substances and biological, analytical and industrial applications of their complexes have made further investigations in this area highly desirable.

4.2 Complex precursors

4.2.1 Bis(salicylaldehydato)Cu(II) complex precursors

Salicylaldehydes, which are versatile precursor of Schiff bases, themselves can act as ligand and form adducts or chelates with transition metals depending on the reaction condition used.^[89] A large number of metal complexes of bis–salicylaldehydato were synthesized by Tyson and Adams^[90] and more recently by I. Castillo *et al.*^[91] In the Tyson method, bis–Cu and –Ni–complexes were prepared by treating alcoholic solution of metal acetates with stoichiometric amounts of salicylaldehyde (metal : ligand= 1 : 2) at room temperature. The Castillo method is analogous to that of Tyson and it involves an aqueous solution of $\text{Cu}(\text{OAc})_2$ and ethanolic solution of salicylaldehyde in refluxing condition (Scheme 18). They used equimolar amounts of KOH as a base to deprotonate the ligand. Recently, a sterically hindered Cu complex of salicylaldehyde namely bis(3,5–di–*tert*–butylsalicylaldehydato)Cu(II), **26** has been synthesized and characterized.^[92]

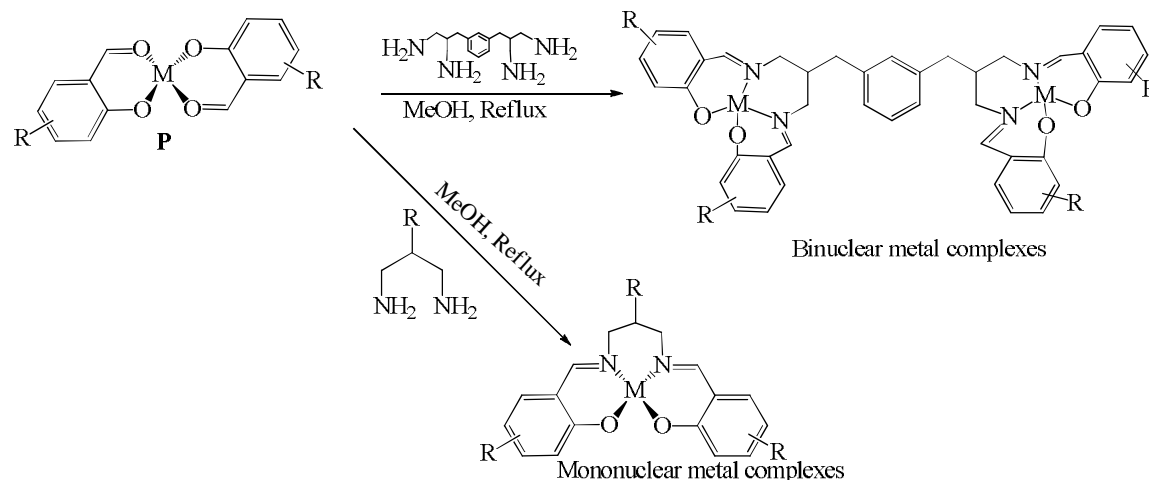


Scheme 18 Synthesis of bis–salicylaldehydato complex of copper(II).^[87]

This method ^[92] consists of warming of methanol solution in a 2.2 : 1 molar ratio of salicylaldehyde and $\text{Cu}(\text{ClO}_4)_2$ in the presence of 1.5 eq. of NEt_3 . In contrast to this method ^[92], where a potentially explosive perchlorate salt is used as metal source, even **26** was synthesized in higher yield at ambient temperature by treating salicylaldehyde with $\text{Cu}(\text{OAc})_2$ (2 : 1) in the presence of 2 eq. of Et_3N in MeOH (see Scheme 23, Section 4.2.2). ^{vi, vii} Interestingly, hydrolysis of (2-hydroxy-4,6-di-*tert*-butylbenzyl-2-pyridylmethyl)imine with hydrated $\text{Cu}(\text{ClO}_4)_2$ in methanol produced **26** as a main product identified by ESI mass spectroscopy. ^[92]

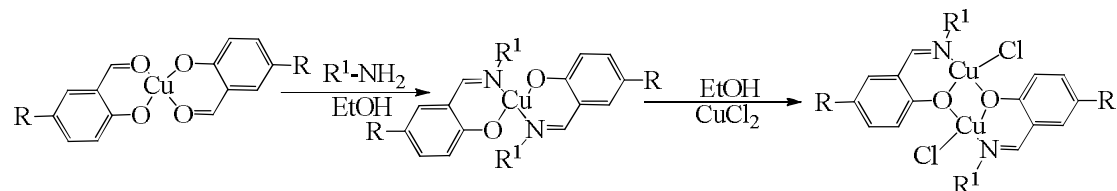
In this study, crystals suitable for X-ray diffraction studies were grown by slow layer diffusion of CH_2Cl_2 into a DMSO solution of **26**. The structure is a monoclinic polymorph of the published orthorhombic structure. ^[92] Crystallographic analysis reveals that in **26** two deprotonated salicylaldehydes are coordinated to Cu(II) ion which adapts in a monomeric square planar geometry where the O–Cu–O angles deviate slightly from the ideal value of 90° .

The main application of bis-salicylaldehydato complexes of transition metals is the synthetic precursor of mononuclear and binuclear metal complexes of Schiff bases. A large number of mono- and binuclear metal complexes using the bis-salicylaldehydato complexes, in which a transition metal is found in the quadricovalent state, have been synthesized and characterized (Scheme 19). ^[93]



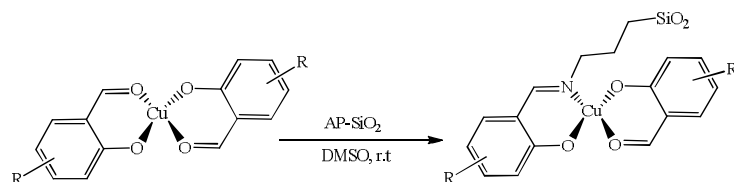
Scheme 19. Synthesis of mono- and binuclear metal complexes of Schiff bases. ^[93]

Recently the bis-salicylaldehydato complexes have been used as precursors in the synthesis of mononuclear Schiff base complexes of Cu(II) that were converted into their



Scheme 20 Synthesis of mono- and binuclear copper(II) complexes of Schiff bases. ^[94]

corresponding binuclear complexes by treating them with Cu(II) halides (Scheme 20).^[94] The binuclear dihalocopper(II) complexes together with their monomeric precursor complexes exhibit mesomorphic (liquid crystal) properties.^[94] An interesting application of Cu(II)–salicylaldehyde complexes is their use as synthetic precursors in the self-assembly of catalysts (Scheme 21)^[95] as well as in self-assembled monolayer (SAM)–modified electrode.^[96]



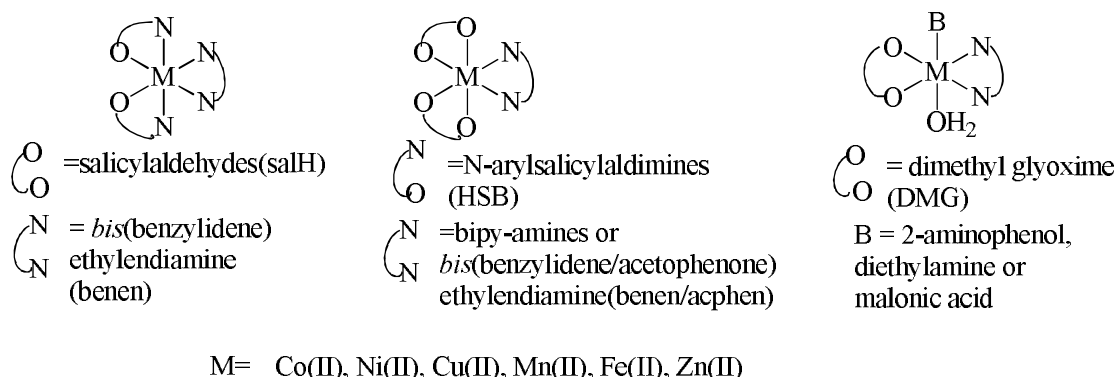
Scheme 21 Synthesis of immobilized copper(II) complexes of salicylaldehyde.^[95]

In this thesis, sterically hindered bis(3,5-di-*tert*-butylsalicylaldehydato)Cu(II), **26** was applied as a precursor for the synthesis of mixed ligand complexes (**27–32** and **58**)^{VI} precursors as well as heteroligated bis-salicylaldiminato of Cu(II) complexes (**33–39**).^{IX}

4.2.2 Mixed ligand complex precursors

The main focus of this work was to synthesize heteroligated bis(phenoxidoimino)Cu(II) complexes (**33–39**) by using the mixed ligand Cu(II) complexes (**27–32** and **58**) for instance **32** as a precursor and their application in the aerobic oxidation of alcohols.^{IX}

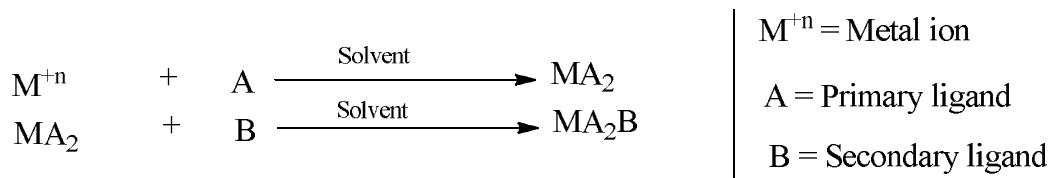
Mixed ligand complexes are well-known to play a significant role in biological systems and have received considerable attention.^[97] A large number of studies based on mixed ligand complexes of metals have been undertaken, because of their wide application in various fields of chemical activity and more particularly because of their existence in biological, analytical, environmental and other systems.^[98] In fact, naturally occurring metal complexes are mixed ligand complexes, which contain two or more different ligand moieties or if even where the ligand is a single macromolecule that consists of two or more different kinds of donor sets of atoms. Inspired by nature, various mixed ligand complexes of transition metals type of MA₂B and MAB have been reported. Traditional ligands such as phen and bipy type of ligands are



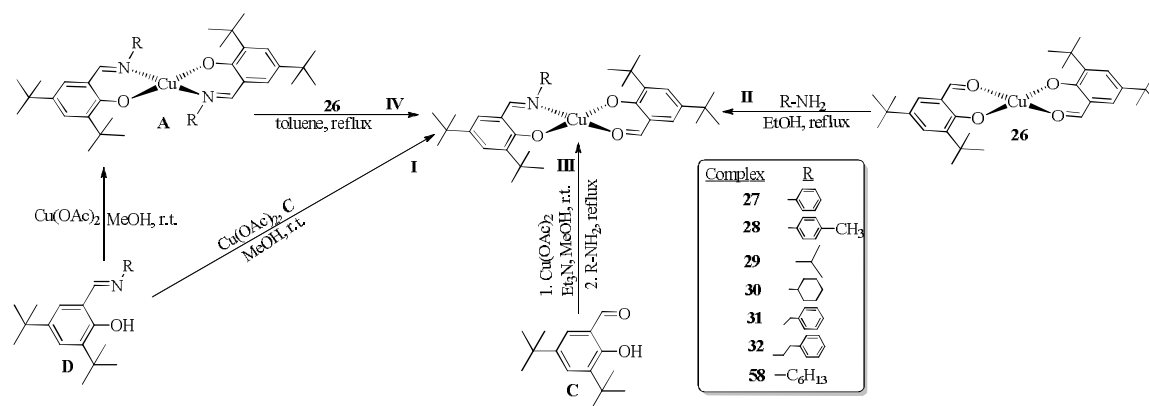
Scheme 22 Schematic presentation of some mixed ligand complexes.^[98]

common in mixed ligand complexes due to their metal chelates having enhanced activities varying from biological to catalysis. A large number of MA₂B complexes have been synthesized and their antimicrobial activities against bacteria, yeast and fungi have been investigated (Scheme 22). These complexes show higher antimicrobial activities compare to the corresponding ligand, metal salts or bis-complexes. Therefore it is established that mixed ligand complexes are more active biologically than the ligand itself as well as its bis-complexes.

The synthesis of MA₂B complexes is very simple and straightforward. A solution of pre-made bis-complex of primary ligand is refluxed with a solution of secondary ligand to obtain the mixed ligand complex. Interestingly, the MA₂B complexes can be formed by stirring (with or without heat) a solution of primary ligand with a metal salt followed by the addition of a solution of secondary ligand in a one-pot synthesis. DMF, EtOH and H₂O/EtOH were used as a solvent and base is use sometime to facilitate the reaction. The synthetic route of the complexes is outlined in the following simple equations:



Recently, various mixed ligand complexes of the types MAB have been synthesized and characterized.^[99] In 1940 Pfeiffer *et al.*^[100] first introduced the mixed ligand complex (CuAB) derived from salicylaldimine and the corresponding aldehyde which was obtained by heating Cu(sal)₂ with amine in the absence of solvent. Later on the CuAB was reproduced by Balundgi and coworker^[101] by refluxing a 1 : 1 molar ratio of (sal)₂Cu and amine in toluene. The CuAB could also be synthesized when a 1 : 1 mixture of CuA₂ and CuB₂ was heated in toluene. In this work, the mixed ligand Cu(II) complexes (**27–32** and **58**) of the type CuAB were synthesized by using the methods above including two newly developed synthetic routes (Scheme 23).^{VI}



Scheme 23 Different synthetic routes for the preparation of mixed ligand Cu(II) complexes (**27–32** and **58**). Methods **I** and **II** proceed through salicylaldimine preligand and a bis(salicylaldehydato)Cu(II) complex, respectively. Method **III** is a one-pot synthesis whereas in

method **IV** the mixed ligand complex is obtained via successive formations of imine preligand and a bis(salicylaldiminato)Cu(II) complex and by final addition of bis(salicylaldehydato)Cu(II).

The mixed ligand Cu(II)–complexes (**27–32** and **58**) have been fully characterized by means of elemental analysis, UV–Vis and IR spectroscopy. Crystal structures obtained for **27**, **29**, **31** and **32** complexes show that three of them are *cis*–isomers and one is a *trans*–isomer with

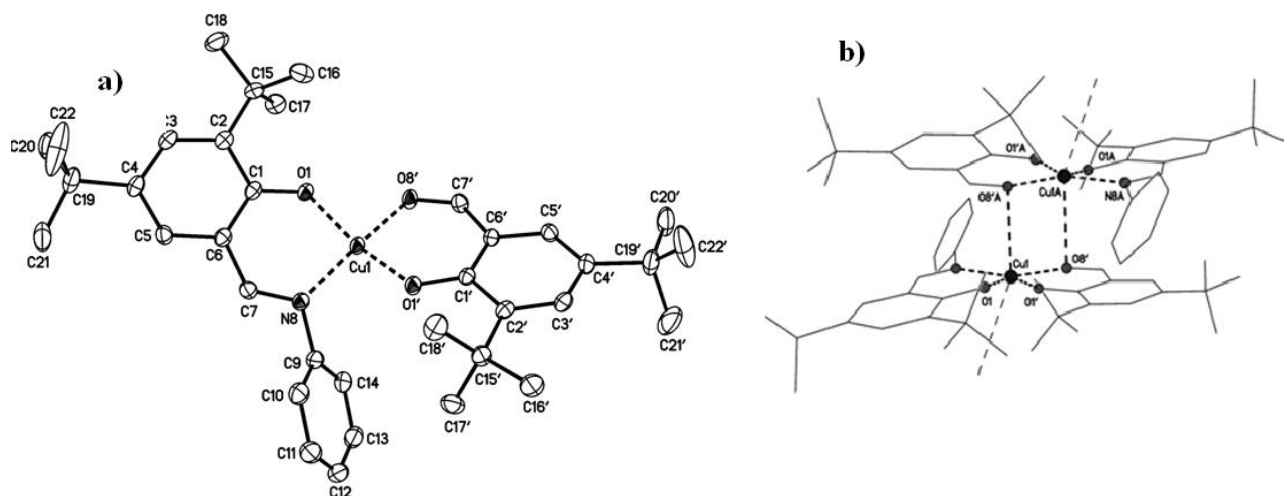


Figure 2 a) Molecular structure of the monomeric unit of **27** with the atom numbering scheme (displacement parameters are drawn at the 50% probability level). Hydrogen atoms are omitted for clarity. b) Dimeric structure of **27** showing the intermolecular Cu...O and Cu...H contacts with dashed lines. Selected bond lengths (Å) and angles (°): Cu1–O1 1.8868(15); Cu1–O1' 1.8963(15); Cu1–O8' 1.9556(16); Cu1–N8 1.9637(19); O1–C1 1.310(3); C7'–O8' 1.255(3); C7–N8 1.301(3); N8–C9 1.448(3); Cu1–H (symmetry operator: $-x+1, y-\frac{1}{2}, -z+\frac{1}{2}$) 3.12; Cu1–O8' (symmetry operator: $-x+1, -y+1, -z+1$) 2.8181(16); O1–Cu1–O1' 159.29(7); O1–Cu1–O8' 86.99(7); O1'–Cu1–O8' 92.70(6); O1–Cu1–N8 92.79(7); O1'–Cu1–N8 92.84(7); O8'–Cu1–N8 164.75(7).^{VI}

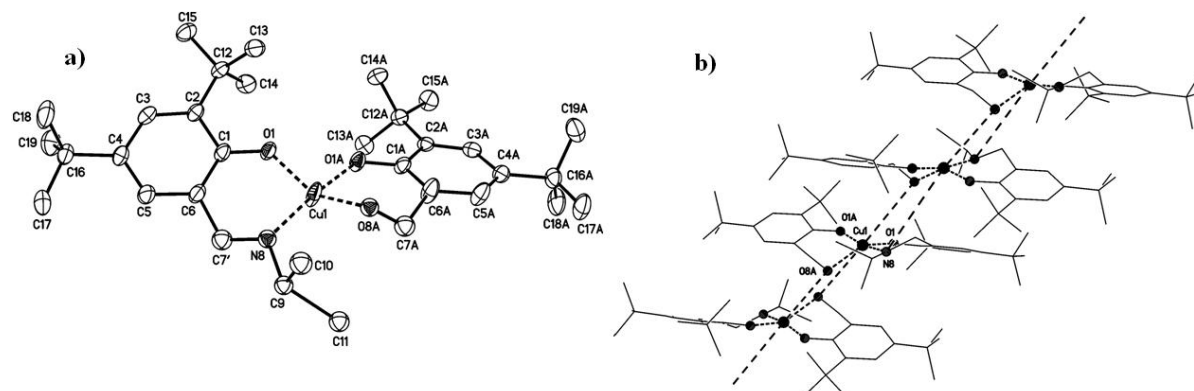


Figure 3 a) Molecular structure of the monomeric unit of **29** with the atom numbering scheme (displacement parameters are drawn at the 50% probability level). Hydrogen atoms and the disorder about the twofold axis of **29** are omitted for clarity. b) Polymeric structure of **29** showing the Cu...O, Cu...N and Cu...O...Cu...N contacts with dashed lines.^{VI}

respect to the phenolic O-atoms (Figure 2–5). **27**, **31** and **32** preferably form loose dimers in a crystal. In the dimers the geometry around the Cu ions is a distorted octahedron where the H atom occupies the sixth coordination place. **29** on the other hand favors an existence in a loose polymeric structure with a distorted octahedral geometry around the Cu(II) center.^{VI}

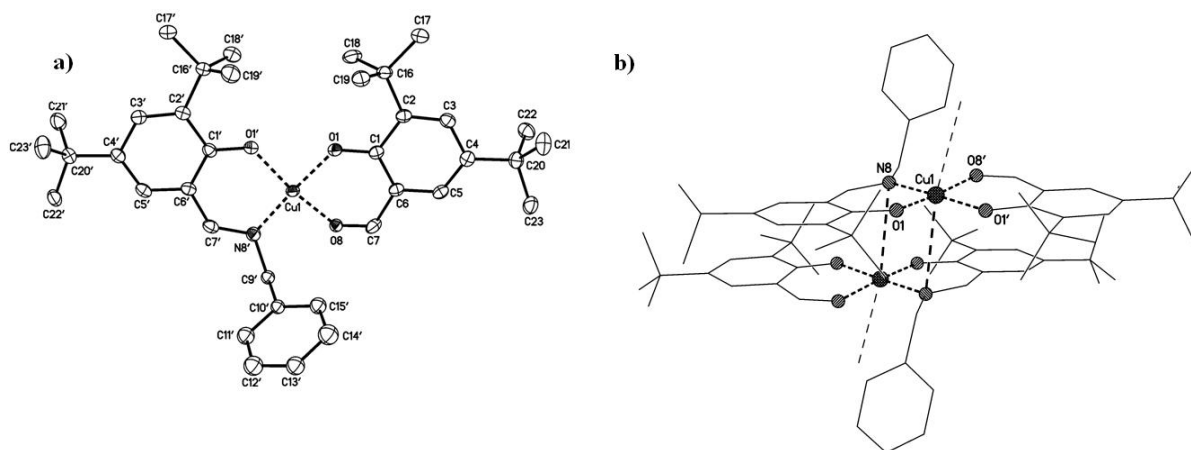


Figure 4 a) Molecular structure of the monomeric unit of **31** with the atom numbering scheme (displacement parameters are drawn at the 50% probability level). Hydrogen atoms and the minor disordered part of **31** are omitted for clarity. b) Dimeric structure of **31** with dashed lines indicating the intermolecular Cu...N and Cu...H contacts.^{VI}

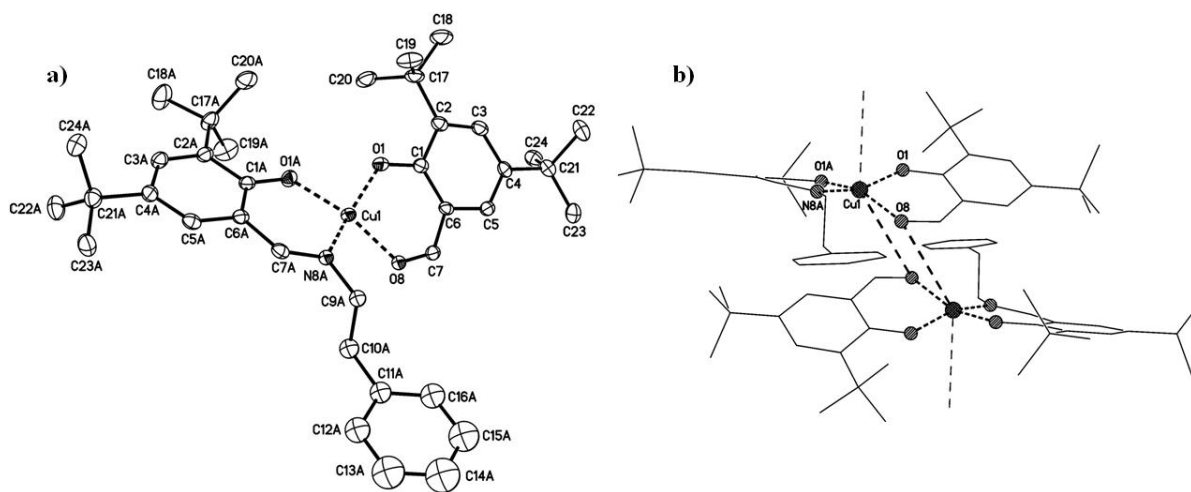
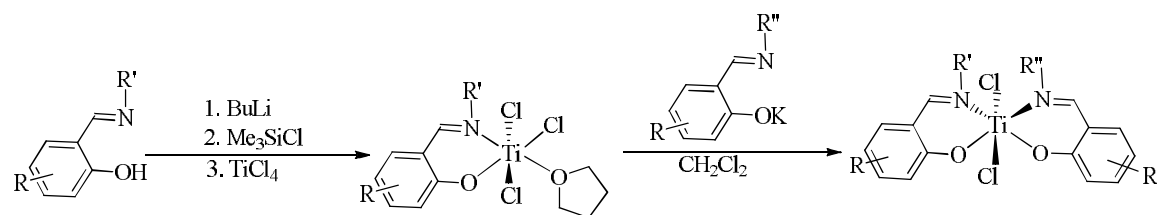


Figure 5 a) Molecular structure of the monomeric unit of **32** with the atom numbering scheme (displacement parameters are drawn at the 50% probability level). Hydrogen atoms and the disorder about the twofold axis of **32** are omitted for clarity. b) Dimeric structure of **32** where the dashed lines indicate the intermolecular Cu...O and Cu...H contacts.^{VI}

4.3 Heteroligated copper(II) complexes

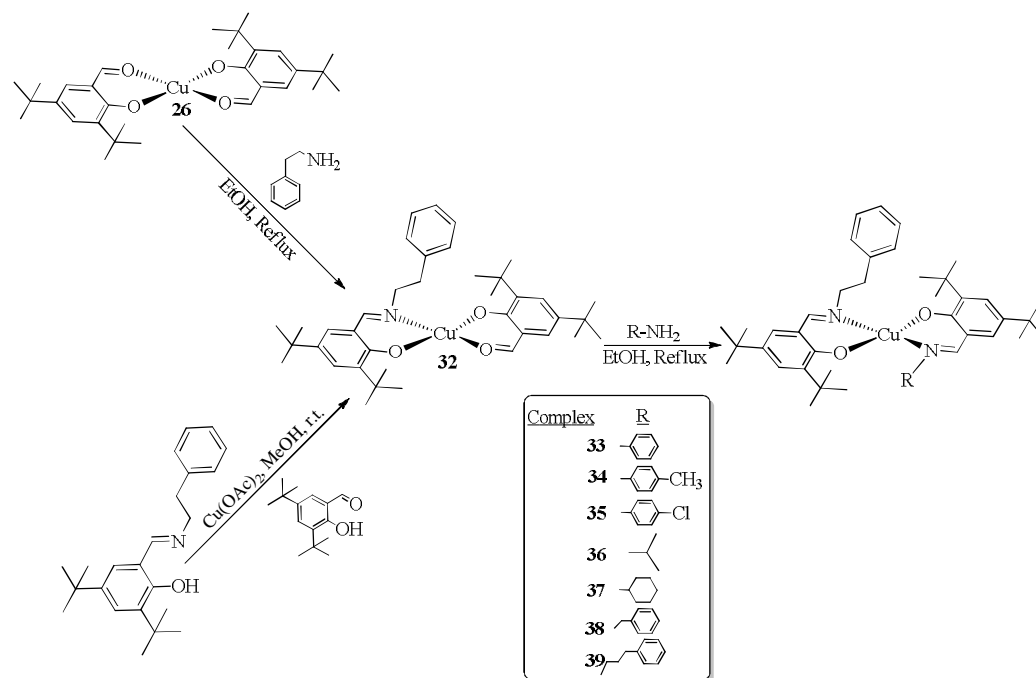
Transition metal complexes with non-bridged bis(phenoxidoimino) heteroligands, are much scarcer and so far only Ti complexes have been presented in the literature.^[102] These

heteroligated bis(phenoxidoimino) complexes have been successfully used as olefin polymerization catalysts. The systematic synthesis of heteroligated Ti-complexes requires a stepwise approach through a stable monoligated Ti-intermediate complex (Scheme 24).



Scheme 24 Synthesis of heteroligated bis(salicylaldiminato)Ti-Complexes. ^[102]

Thus, like in the case of Ti a stable intermediate Cu(II) complex containing one phenoxidoimino ligand was looked for. It was discovered that such an intermediate (see Scheme 23, Section 4.2.2), namely [(3,5-di-*tert*-butylsalicylaldehydato)(*N*-(2-phenylethyl)-3,5-di-*tert*-butylsalicylaldiminato)]Cu(II) (**32**), can be used as a precursor for the synthesis of heteroligated bis(phenoxidoimino)Cu(II) complexes (**33–39**).^{IX}



Scheme 25 Synthesis of heteroligated bis(salicylaldiminato)Cu(II) complexes (**33–39**).^{IX}

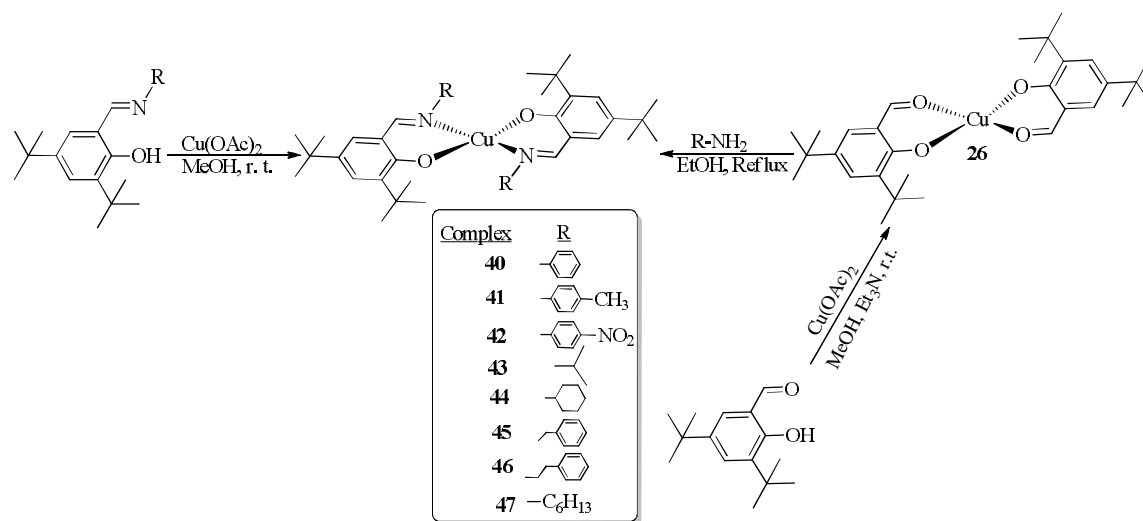
Therefore, a series of unprecedented heteroligated bis(phenoxidoimino)Cu(II) complexes (**33–39**) are prepared in excellent 80–90% yields simply by the addition of an appropriate second amine to a solution of **32** and refluxing the resulting mixture for 2 h (Scheme 25). The facile synthesis of the complexes in one-pot synthesis with sequential amine additions produces the heteroligated bis(phenoxidoimino) complexes in high yields. The characterization

of heteroligated complexes is facilitated by the fact that the C=O band at 1602 cm^{-1} in the IR spectrum of **32** disappears upon the bis(phenoxidoimino)Cu(II) complex formation^{IX} and a new band assignable^[103] to C=N appears at $1620\text{--}1621\text{ cm}^{-1}$.

The heteroligated Cu(II) complexes (**33–39**)^{IX} in general exhibit higher catalytic activities than their corresponding homoligated Cu(II) complexes (**40–47**)^{VII} in oxidation of benzyl alcohol under identical reaction conditions. They can be efficiently used for aerobic oxidation of a variety of alcohols to the corresponding carbonyl compounds. Significantly, the catalysts also work efficiently for aliphatic primary and secondary alcohols; this is rare case in TEMPO mediated Cu systems.^[42a, 62, 63–64, 125, 127]

4.4 Homoligated Copper(II) complexes

Copper proteins contain a distorted metal ion environment of low symmetry with a diverse donor set of atoms. Thus Cu(II) complexes with different donor atoms as structural models for the active site of copper proteins are of current interest. This may also be attributed to their stability and potential applications in many fields varying from catalysis to pharmaceutical applications including molecular materials having nonlinear optical properties.^[104] The object of the studies presented in this report includes the synthesis of Cu(II) complexes with two different donor atoms incorporating through N and O as ligands donor. Salicylaldimine as an example of N–O donor atoms has been well-known to enhance metal ion chelation and provide additional stability to the metal center.^[55] Consequently, homoligated bis(salicylaldiminato)Cu(II) complexes bearing bulky *tert*-butyl groups at the 3rd and 5th positions of the phenyl moiety of salicylaldimine have a variety of applications in material chemistry.^[105–106]



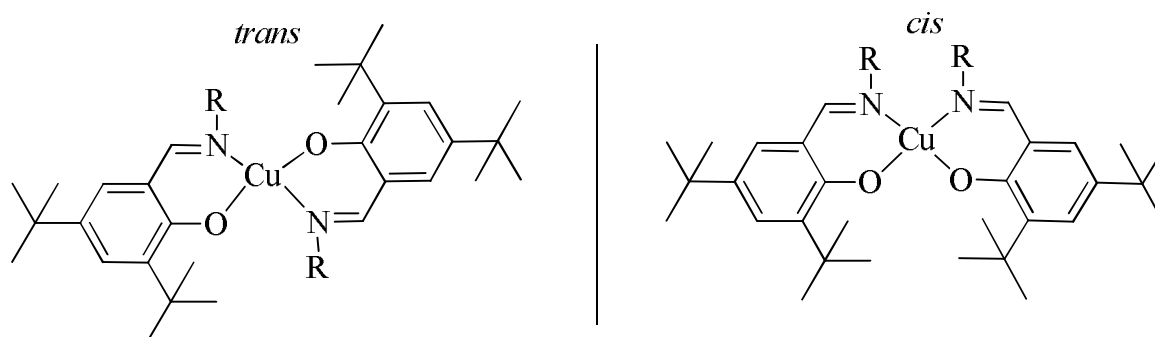
Scheme 26 Synthesis of bis(3,5-di-*tert*-butylsalicylaldiminato)Cu(II) complexes (**40–47**).^{VII}

The most widely used method for obtaining these homoligated complexes is based on the interaction of salicylaldimine with the metal salts (a method of direct interaction between the reactants). In some cases the ligand precursor is deprotonated by a base such as Et_3N .^[107]

Cu(OAc)₂ is mainly used as a metal source because it is soluble in alcohols and is a salt of a weak acid. A sophisticated way to synthesize the complexes is first to prepare the bis(aldehydo) Cu(II) complex then convert it to bis(imino)Cu(II) complex via its amine (the Pfeiffer method).^[108] In order to simplify the experimental procedure, the homoligated Cu(II) complexes can also be prepared in one step reaction making the aldehyde, amine and Cu-salt (2 : 2 : 1) in methanol (the Charles method).^[109]

However, the sterically hindered bis(phenoxidoimino)Cu complexes (**40–47**) of this study were prepared by slightly modified methods (Scheme 26).^{vii} The complexes were fully characterized by various spectroscopic methods (UV-Vis, IR, electron paramagnetic resonance (EPR) and EI-MS). In addition, the crystal structures of complexes **40–45** and **47** were determined by X-ray crystallography (Figure 6).^{vii} In spite of all efforts, single crystals suitable for X-ray structure determination were not obtained for **46**. Two different structures symbolized by **45** and **45T** (with toluene solvent molecule in the asymmetric unit) were obtained for **45**.

The Cu ion has a N₂O₂ coordination environment with a tetrahedrally distorted square-planar geometry in the solid state of all the complexes just as in solution as confirmed by UV-Vis and EPR results. In two complexes, **40** and **42**, the ligands are in an unusual *cis*-configuration whereas the rest of the complexes (**41**, **43–45**, **45T**, **47**) are typical *trans*-isomers with respect to each other.^{vii} However, it is not obvious why **41** crystallized as a *trans*-isomer although it has *p*-MePh substituted at imine N. Apparently, interaction between the Cu(II) and H atom of toluene molecule in **41** could affect the geometric arrangement of the corresponding ligand and hence the ligands eventually oriented in a *trans*-configuration.^{vii} It is noteworthy that suitable crystals of **41** for X-ray measurement could only be obtained in toluene under refrigerated conditions. Accordingly, the solvent might have an important role in crystallizing and forming the preferred isomer.^[110] Computational studies verify that in the case of complex with *N*-alkyl fragment the preferred isomer is *trans*, while the opposite behavior is observed for the complex with the *N*-phenyl substituent (Scheme 27).^{vii}



Scheme 27 *Cis-trans* isomeric pattern of bis(salicylaldiminato)Cu(II) complex. For complexes with *N*-alkyl and *N*-aryl fragment the preferred isomers are *trans* and *cis*, respectively.^{vii}

A literature survey of the crystal structures of bis(salicylaldiminato)Cu(II) complexes show that most of these types of complexes are *trans* isomers in the solid state.^[111] Nevertheless,

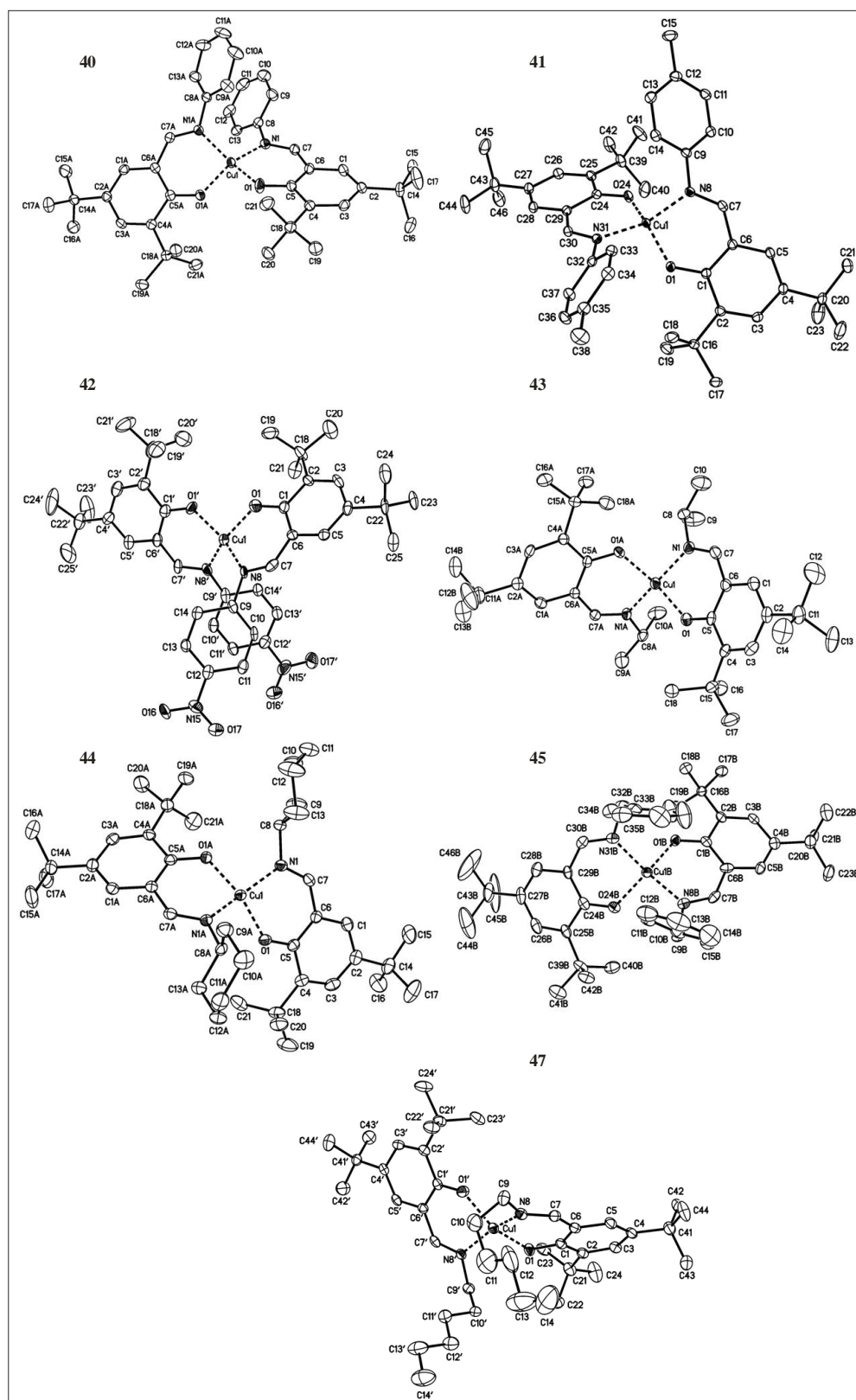


Figure 6 Molecular structures of complexes **40–45** and **47** with the atom numbering schemes. Displacement parameters are drawn at the 50% probability level^{VII}.

cis isomers have been reported for example bis[*N*-(phenyl)-5-chloro-salicylaldiminato]Cu(II), bis[*N*-(3,5-di-*tert*-butylphenyl)salicylaldiminato]Cu(II) and bis[*N*-(phenyl)-3,5-di-*tert*-butylsalicylaldiminato]Cu(II).^[111b-1] Excluding one structure, the complexes crystallizing as a *cis* isomer have *N*-aryl substituents.

4.5 Aerobic oxidation of alcohols

Catalytic transformation of organic substrates is sometimes referred to as a “foundational pillar” of green chemistry.^[112] Catalysis often reduces energy required in the system and decreases separations due to increased selectivity; it permits the use of renewable feed stocks or minimizes the quantities of reagents needed.^[113] In addition catalysis often allows the use of less toxic reagents, as in the case of alcohol oxidation using molecular oxygen^[114] or hydrogen peroxide^[115] in place of traditionally the use of stoichiometric inorganic oxidants (e.g. CrO₃, KMnO₄, MnO₂, SeO₂, Br₂).

Green chemistry principles have a great influence on the research of catalytic oxidation of alcohols to their corresponding carbonyl compounds. The search for a good oxidation catalyst also involves investigating green chemistry concepts. The new catalyst should be very robust, with high turnover frequency (TOF) and selective. Thus numerous methods have been developed for efficient and selective oxidation of alcohols to aldehydes so far (see the literature review, Section 2). However, most of the catalysts reported in the literature are expensive, a high loading of catalysts are required to obtain efficient systems, some of them may lead to environmental pollution, some noxious reagents are required as solvents and the reaction times are often long. The aim of the thesis was to (i) minimize reagents required in oxidation recipes, (ii) catalyze in short reaction times, (iii) avoid the use of auxiliaries (iv) substitute the traditional heavy metal catalysts and (v) replace the use of stoichiometric inorganic oxidants and organic solvents with the most environmentally friendly oxidants and solvents for instance open air and pure water, respectively.

4.5.1 Open air oxidation of alcohols^{VIII}

The synthesis of organic compounds in water is attractive and of great current interest since water is safe and it is the most accessible solvent. However, in spite of these undeniable benefits, their synthesis in water is rather scarce due to many difficulties associated with the use of water. The reagents might have limited water-solubility, most catalytic active species are very sensitive even to trace amounts of moisture, and reactions are not kinetically favorable in water when the reagents are hydrophobic. For all these reasons, catalytic oxidations of alcohols to aldehydes in water are challenging and only a limited number of studies where an efficient catalytic aerobic oxidation of alcohol has been achieved in aqueous media exist. The systems include synthesized transition metal complexes,^[116] Fe,^[117] Ru,^[118] Au^[119] and Pd^[120] nanoparticles, polymer-stabilized Au nanoclusters^[121] and bimetallic^[122] clusters. In addition, recent studies reporting Cu and TEMPO based systems are encouraging.^[44a, 123] The system of Sheldon and co-workers is based on Cu, bipyridine and TEMPO and it efficiently converts primary benzylic alcohols into aldehydes in air.^[42a] Two other reported systems convert primary alcohols into aldehydes in air with the use of bifunctional^[124] and multinuclear, water-soluble^[125] Cu(II)-complexes. A completely different approach to the catalytic functional group

transformation of alcohols in water involved gas/liquid phase reactions using air–microbubbles under Sheldon's conditions.^[126]

A common drawback of the above mentioned catalytic systems including our developed systems described later herein^{I, III} is that auxiliary substances such as base and/or co–solvent were required for an efficient oxidation of alcohols. Thus the aim of this project was to develop a new catalytic method based on Cu–complexes which can be efficient for open air oxidation in pure water without additional auxiliary substances like a base or co–solvent. However, the initial set of experiments (Table 5) demonstrate the capability of *in situ* made **43** and **46** complexes to catalyze the oxidation of benzyl alcohol to benzaldehyde in water without a base in the open air.

Table 5 Copper catalyzed open air oxidation of benzyl alcohol in water.^{VIII}

$$\text{Ph-CH}_2\text{OH} \xrightarrow[1.5 \text{ h, } 80^\circ\text{C, open air, 5 mL of pure water}]{1 \text{ mol\% catalyst, 2 mol\% L, 5 mol\% TEMPO}} \text{Ph-CHO}$$

run	catalyst	Ligand(L)	Conversion (%)
1	none	7	0
2	CuSO ₄	None	7
3	CuSO ₄	7	34
4	Cu(OAc) ₂	7	37
5	Cu(NO ₃) ₂	7	25
6	CuCl ₂	7	28
7 ^a	CuBr ₂	7	21
8 ^a	CuBr ₂	7	5
9 ^b	CuBr ₂	4	0
10 ^b	Cu(L 3) ₂	none	0
11	CuBr ₂	7	41/98 ^c
12	CuBr ₂	1	25
13	CuBr ₂	4	72/100 ^d
14	43	none	97 ^d

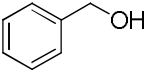
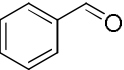
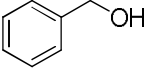
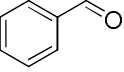
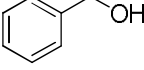
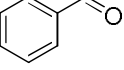
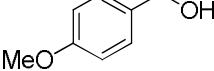
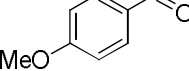
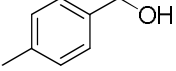
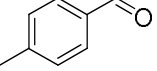
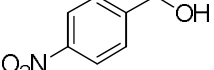
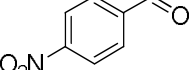
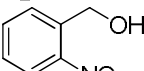
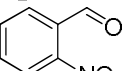
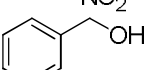
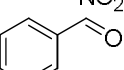
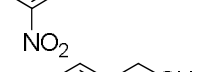
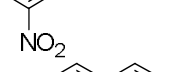
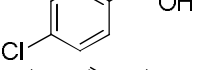
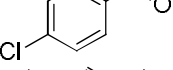
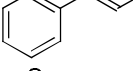
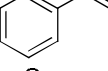
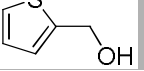
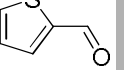
^a 5 mL 0.1 M base solution instead of pure water. ^b reaction without TEMPO. ^c 5 h reaction. ^d 2.5 h reaction.

After extensive experiments, it was discovered that 0.3 mol% CuBr₂, 2 mol% **4**, 3 mol% TEMPO in distilled water (5 mL) at 80 °C in the open air were the optimal conditions. In optimized reaction conditions, various benzylic and allylic aldehydes were synthesized from

their corresponding, readily available, alcohols in water at 80 °C. These results collected in Table 6 show that the oxidation reaction in aqueous media has a high degree of functional-group tolerance.

Table 6 Open air oxidation of selected alcohols in water catalyzed by Cu/**4**/TEMPO system.^{VIII}

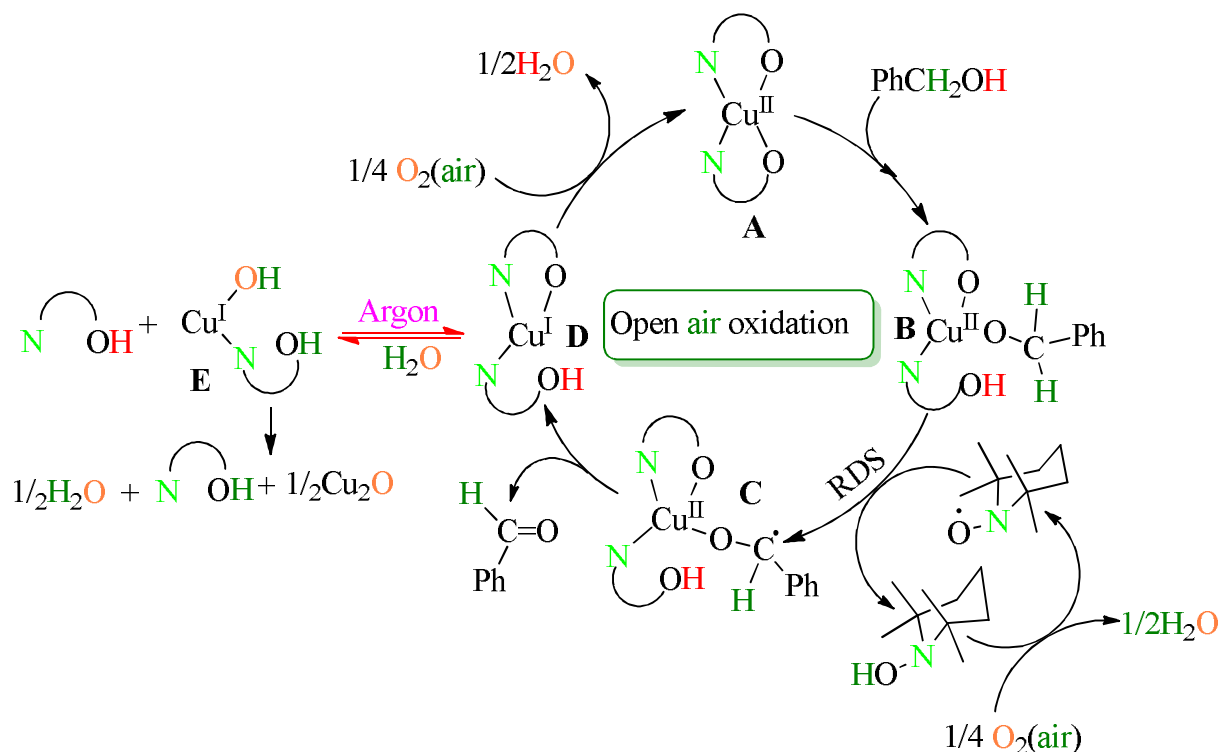
$$\text{R-CH}_2\text{OH} \xrightarrow[3.5 \text{ h, } 80^\circ\text{C, open air, 5 mL of pure water}]{0.3 \text{ mol\% CuBr}_2, 2 \text{ mol\% } \mathbf{4}, 3 \text{ mol\% TEMPO}} \text{R-CHO}$$

Run	Substrate	Product	Conv. (%) ^a
1			100 (87)
2			80 ^b
3			98 ^c
4			66 (56) / 92 ^d
5			88(83)
6			91 (86)
7			87 (81)
8			100 (95)
9			91 (90)
10			63 (57) / 100 ^d
11			27/71(56) ^e
12			47 (43) / 94 ^f

^a Conversion determined by ¹H NMR. Isolated yield in parenthesis. ^b 7 h reaction at r.t. ^c Oxidation with 0.3 mol % of isolated **43** and excess of ligand **4** (1.4 mol%). ^d 5 h reaction. ^e 8 h reaction. ^f 12 h reaction. Selectivity in all runs >99.9%.

In various TEMPO/Cu systems, alcohol is deprotonated to alkoxide by a base^[42a, 125] or the coordinated ligand^[62, 63–64, 127] (Cu^{II} species **B** in Scheme 28)^{VIII} resulting in a formation of

species **C**. In the open air, the reaction proceeds further by the β -H abstraction and completes the proposed catalytic cycle.^[16a, 62, 128]



Scheme 28 Proposed mechanism for the Cu/ligand/TEMPO catalyzed open air oxidation of alcohols in water.^{VIII}

However, in the absence of air, **C** is unable to initiate the alcohol oxidation due to its rapid hydrolysis, which eventually results in a formation red precipitate. The red solid was characterized by XRD and FESEM techniques. XRD showed the indexed reflections for a cubic Cu_2O (Figure 7).^{VIII}

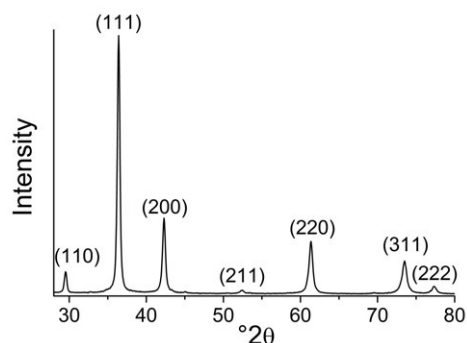


Figure 7 The XRD pattern of red solid obtained from reaction mixture during oxidation under argon. Reaction conditions: 1 mol% CuBr_2 , 2 mol% **4**, 5 mol% TEMPO, 1.5 h, 80 °C, open air, 5 mL of water.^{VIII}

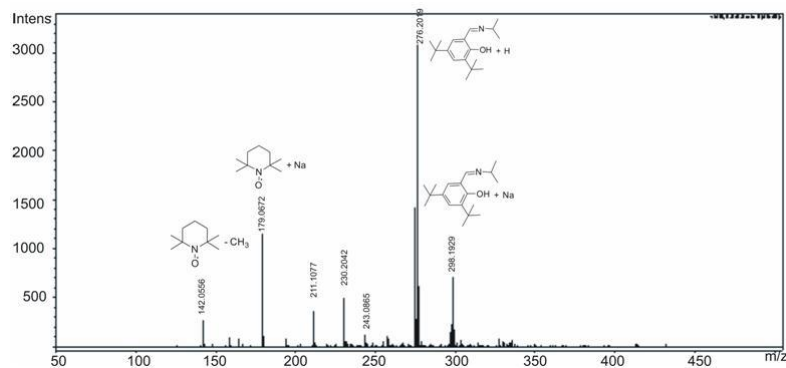


Figure 8 ESI-MS spectrum of solution obtained after oxidation reaction under argon. Reaction conditions: 1 mol% **43**, 5 mol% TEMPO, 1.5 h, 80 °C, open air, 5 mL of water.^{VIII}

FESEM imaging revealed that the solid consists mostly of small particles (diameter below 50 nm) even though particles with a >1 μm diameter were observed (Figure 9).^{VIII} A similar reaction was carried out with isolated **43** instead of *in situ* made complex analyzed by GC-MS and ESI-MS. The data suggested that the resulting solution contained mainly free ligand **4** and TEMPO (Figure 8).^{VIII} UV-vis studies also reveal that after addition of TEMPO under argon, Cu^{II} species **B** reduces to Cu^{I} species **D**.

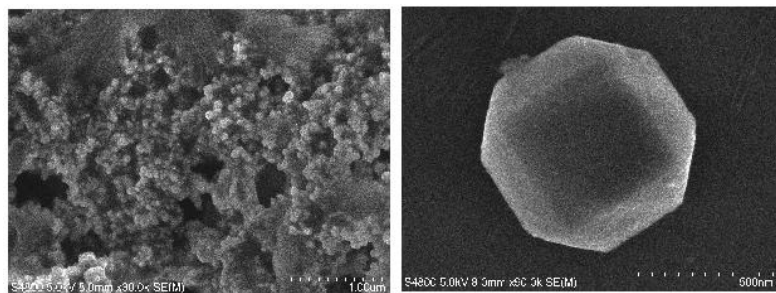


Figure 9 FESEM images of red solid obtained from the reaction mixture during oxidation under argon. The reaction conditions were the same as for Figure 7.^{VIII}

4.5.2 Organocatalyzed aerobic oxidation of alcohols^{III}

Reports on oxidation of alcohols to carbonyl compounds with organocatalyst are scarce. Only persistent nitroxyl radicals such as TEMPO or its derivatives are known to catalyze the oxidation of alcohols to the corresponding carbonyl compounds with various oxidants rather than oxygen. The direct oxidation of alcohols to aldehydes with an organocatalyst and molecular oxygen is possible only with non-persistent nitroxyl radicals derived from NHPI (see the literature review, Section 2.3.2). However, with this catalyst primary alcohols were overoxidized to acids and the reactions were carried out at elevated temperatures in organic solvent (PhCN). In addition, a high loading of catalyst (10 mol%) and longer reaction times (5–75 h) are required to achieve good conversions.

Copper complexes with bipyridine type ligands are well-known as catalysts in the oxidation of primary alcohols to aldehydes since the 1970s.^[129] Consequently, various catalytic

systems based on Cu and N-donor ligands have been developed as already mentioned in the literature review (Section 2). With this in mind, the catalytic activity of *in situ* prepared Cu-DAPHEN complex has been introduced for the oxidation of benzylic alcohols to benzylic aldehydes in basic aqueous media by our group.^[38]

The catalyst exhibited moderate activity toward the oxidation of veratryl alcohol to veratraldehyde due to extensive dimerization of DAPHEN in applied conditions.^[130] In further studies with DAPHEN-based oxidation catalysts, it was found that DAPHEN possesses redox-activity and is fully capable of aqueous oxidation catalysis even in the absence of a metal cofactor. Thus the first direct oxidation of benzylic alcohols to aldehydes with DAPHEN as an organocatalyst was developed using molecular oxygen as the terminal oxidant.^{III} The effect of various metal ions on catalytic activity of DAPHEN was also investigated. Addition of metal ion increased the catalytic activity of the reaction significantly (Figure 10).^{III} Up to 80% conversion of alcohol was obtained with DAPHEN whereas for complete conversion, Cu ion was required as a cofactor.

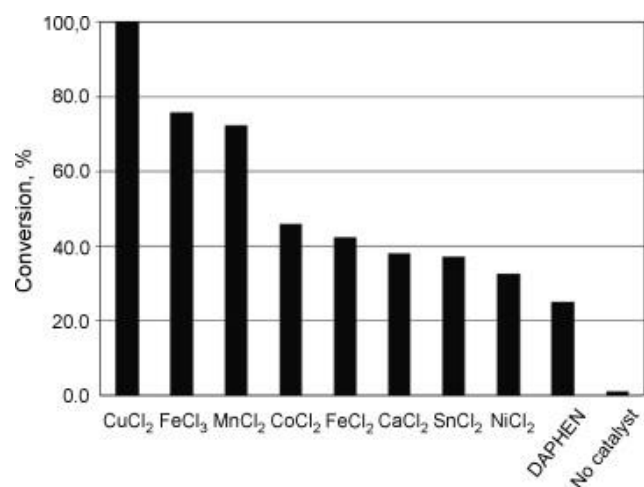
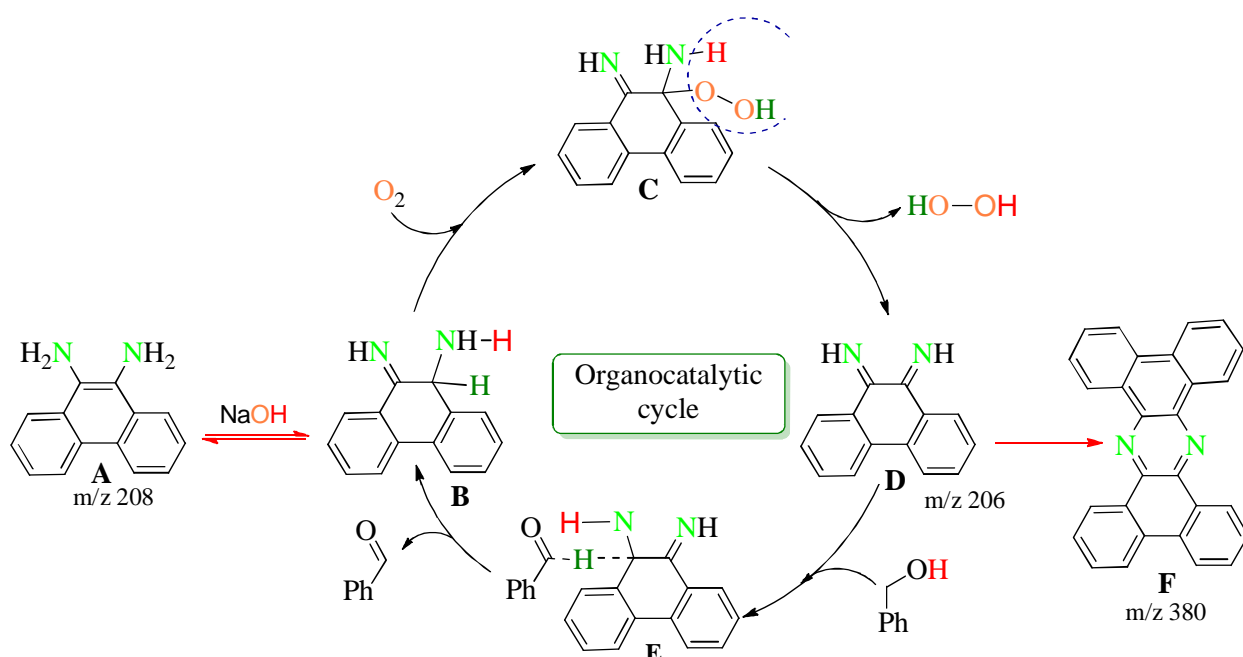


Figure 10 Oxidation of veratryl alcohol to veratraldehyde catalyzed by selected metal-DAPHEN catalysts. Reaction conditions: 10 bar O₂, 0.25 M NaOH, 1 mol% DAPHEN/metal (48 mmol/L DAPHEN and metal), 100 °C and 3 h.^{III}

Based on the literature and our experimental data, we proposed the following catalytic cycle for organocatalyzed oxidation of alcohols (Scheme 29).^{III} In alkaline aqueous solution, an imine resonance isomer of DAPHEN is expected which provides a reactive H-C bond (**B**). In the presence of O₂, it forms a hydroperoxo semi-iminoquinone (**C**) which reacts further to give hydrogen peroxide and an iminoquinone (**D**, *m/z* 206). The formation of H₂O₂ is confirmed by iodometric titration from the reaction mixture. Iminoquinone is then reduced back to DAPHEN with the help of alcohol in a two-step radical pathway. In this respect, the deactivation of the catalyst by combination of two **D**, which eventually resulted in a precipitation of a yellow solid as dimer of DAPHEN is unambiguous. The proposed mechanism uncovers its similarities with previously reported catalytic cycle based on flavin-organocatalysts.^[131]

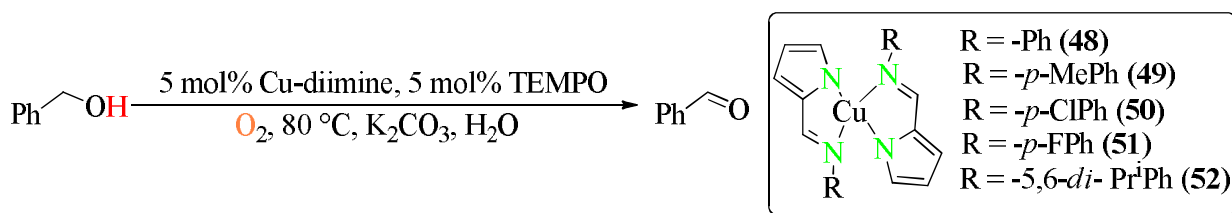


Scheme 29 Proposed catalytic cycle for DAPHEN catalyzed alcohol oxidation.^{III}

4.5.3 Copper catalyzed aerobic oxidation of alcohols^I

The main focus of this project was to find new N based ligand candidates which could substitute classical bipy and phen with improved catalytic activity for the oxidation of benzylic alcohols. Thus we paid attention to the synthesis of 2-*N*-pyrrolocarbaldimine (**8–25**) ligands (see Scheme 15, Section 4.1.1). These monoanionic ligands have been known since the 1929s^[132] and exhibit common features with porphyrins although their catalytic properties have not been extensively studied.

A series of 2-*N*-arylpyrrolocarbaldimine ligands (**12–14**, **18** and **21**) and their corresponding Cu(II) complexes were selected in order to investigate their catalytic properties toward the oxidation of benzyl alcohol in alkaline water (Scheme 30).^I The results indicated that the *in situ* made complexes had similar catalytic oxidation properties as the isolated complexes. Evaluated by oxygen uptake measurements, it was found that the *in situ* made complexes (**48–51**) exhibited analogous catalytic activity (see Figure 11b)^I under identical reaction conditions except **52** which has two bulky isopropyl groups at 2nd and 6th positions of the phenyl moiety.



Scheme 30 A series of Cu(II) complexes (**48–52**) and reaction conditions applied in the catalytic oxidation of benzyl alcohol.^I

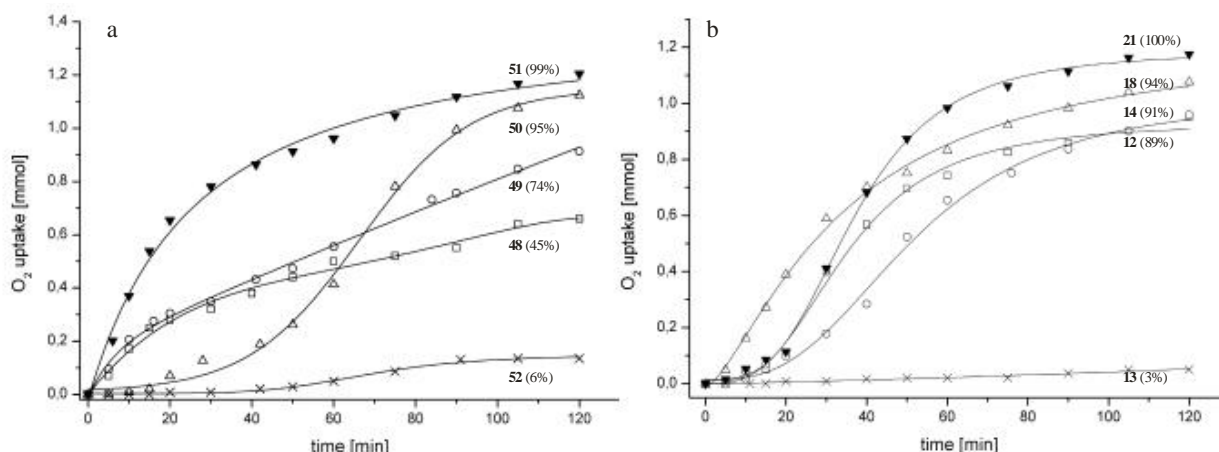


Figure 11 The catalytic activity of a) pre-made and b) *in situ* made complexes (**48–52**) in the aerobic oxidation of benzyl alcohol. Reaction conditions: 3 mmol of benzyl alcohol, 5 mol% TEMPO, 80 °C, 1 atm O₂, 2 h, 0.1 M K₂CO₃, a) 1 mol% catalyst b) 1 mol% CuSO₄ and 2 mol% ligand. Conversion values at the end points for the corresponding complexes (**48–52**) and preligands (**12–14**, **18** and **21**) are shown in parenthesis.¹

The lower catalytic activity of **52** may result from the steric interactions caused by the ligand around the catalytically active Cu(II) center. However, in the series of the studied complexes, **51** was beneficial for quantitative conversion of benzyl alcohol to benzaldehyde. Interestingly, these catalysts can also work with other oxidants than oxygen (Table 7).¹

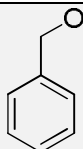
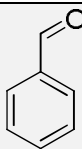
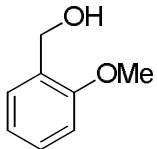
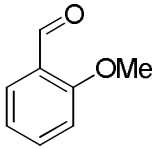
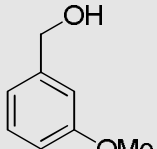
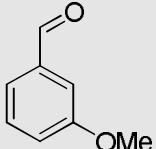
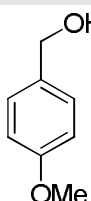
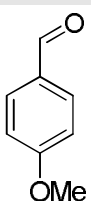
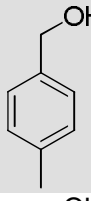
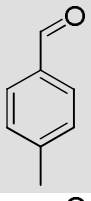
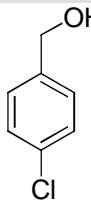
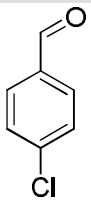
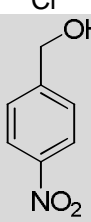
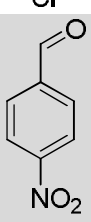
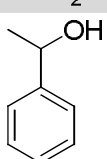
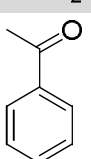
Table 7 The effect of different oxidants on the oxidation of benzyl alcohol with TEMPO (5 mol%), CuSO₄ (1 mol%) and **21** (2 mol%) in 0.1 M K₂CO₃.¹

Run	Oxidant	Amount of oxidant/ eq. ^d	Conv. (%)	Select. (%)	Time (h)
1	O ₂	1 atm	100	99	2
2	air	1 atm	17	99	2
3	air	1 atm	99	99	18
4 ^a	H ₂ O ₂	0.5 mL/1.9 eq.	62	99	2
5	H ₂ O ₂	1 mL/3.8 eq. 100	99	2	
6 ^a	<i>t</i> -BuOOH	0.55 mL/2 eq.	19	99	2
7 ^a	CHP ^b	1 mL/1.8 eq.	25	99	2
8 ^a	Oxone ^{®c}	3.7 g/2 eq.	28		

^a Reactions carried out under an argon atmosphere, ^b CHP=cumyl hydroperoxide,

^c The active oxidant of Oxone[®] is KHSO₅, ^d Equivalent vs substrate.

Table 8 The oxidation of selected alcohols catalyzed by CuSO₄/**21** 1:2 in an *in situ* system^{a, 1}

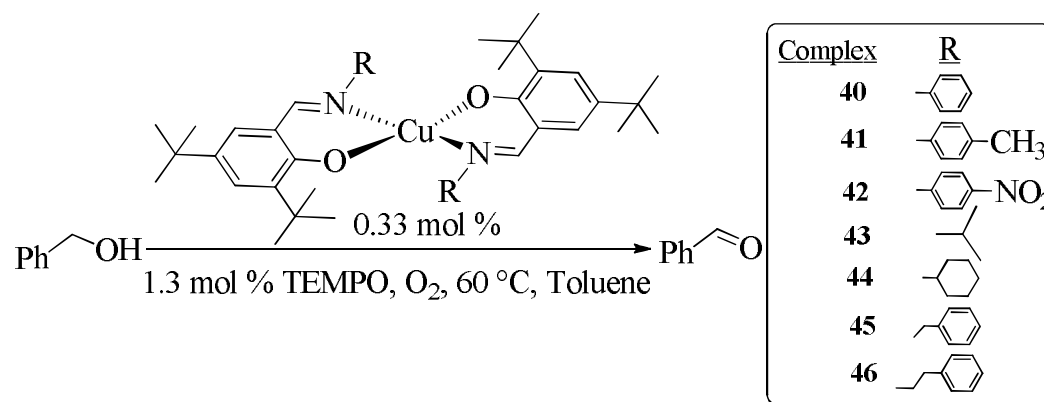
Run	Substrate	Product	Time (h)	Conv. (%)	Select. (%)
1			2	100	>99
2			2	94	>99
3			2	99	>99
4			2	81	>99
5			2	88	>99
6			2	92	>99
7			2	89	>99
8			20	68	100

^a Conditions: 3 mmol of substrate, 5 mol% of TEMPO, 1 mol% of CuSO₄ and 2 mol% of **21** in 0.1 M K₂CO₃, 1 atm of O₂.

The utility of the newly developed system based on CuSO₄ and 2-*N*-*p*-fluorophenylpyrrolecarbaldehyde (**21**) was examined with oxidation of other alcohols (Table 8).¹ As can be seen unsubstituted benzylic alcohol is oxidized more efficiently than substituted ones (Table 8, runs 1–7). These results suggest that the influence of the remote *para* substituent appears to be more related to steric than electronic effects. Secondary benzylic alcohols such as 1-phenylethanol are also oxidized with good efficiency (Table 8, run 8). While primary and secondary benzylic alcohols are oxidized with good to excellent conversion aliphatic alcohols are barely reactive like other reported Cu/TEMPO systems.^[42a, 62, 63–64, 125, 127]

4.5.4 Base-free aerobic oxidation of alcohols^{II, IX}

As stated in the literature review (Section 2.3.4), various isolated Cu complexes can be utilized as efficient oxidation catalysts.^[53–62] Indeed, most of these catalysts are bridged Cu(II) complexes with two different O and N donor atoms but the variation is associated mostly with the type of N atom in the ligand structure. In Wieghardt's system^[60d] amine type N is coordinated to the metal but in Stack's work the ligand is BSB (2,2'-bis(salicylideneamino)-1,1'-binaphthyl)^[61a], which is an imine type. In Gellon's catalyst^[61b] amine type N is also coordinated with Cu and the Fabbrini system^[13a] which uses multi-copper oxidase – laccase and TEMPO as a mediator. In a more recent report on the Cu catalyst, the coordinated ligand is also restricted in a bridged type amine.^[62]



Scheme 31 A series of Cu(II) complexes (**40–46**) and reaction conditions applied in the catalytic oxidation of benzyl alcohol.^{II}

However, it has been established that salicylaldehydes having bulky *tert*-butyl groups find it easy to form peripherally-bound, stable phenoxyl radical complexes.^[105] In addition, the complexes, which are considered as a simple model of GO, have shown high catalytic activities for alcohol oxidation.^[60] Encouraged by these results a series of bis(3,5-di-*tert*-butylsalicylaldehyde)Cu(II) complexes (**40–46**) were synthesized and employed in the catalytic oxidation of alcohols using molecular oxygen as a terminal oxidant (Scheme 31).^{II}

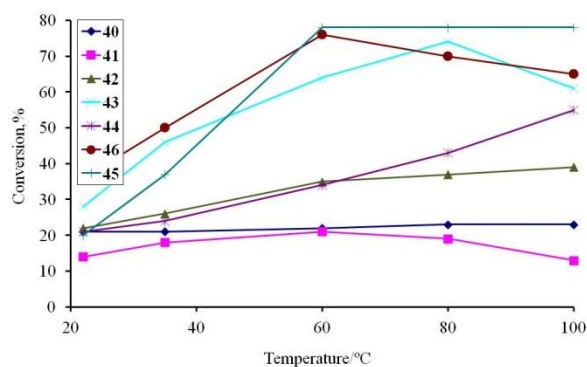


Figure 12 Effect of reaction temperature on the catalytic activities of Cu(II) complexes (**40–46**) in aerobic oxidation of benzyl alcohol. Reaction Conditions: 3 h, 0.96 mmol benzyl alcohol, 1.3 mol% TEMPO, 0.33 mol% complex, 1 mL solvent, 1 atm O₂.^{II}

All the synthesized complexes (**40–46**) are inactive in aerobic oxidation of alcohols under applied conditions. However, the combination of these complexes with TEMPO gives a high

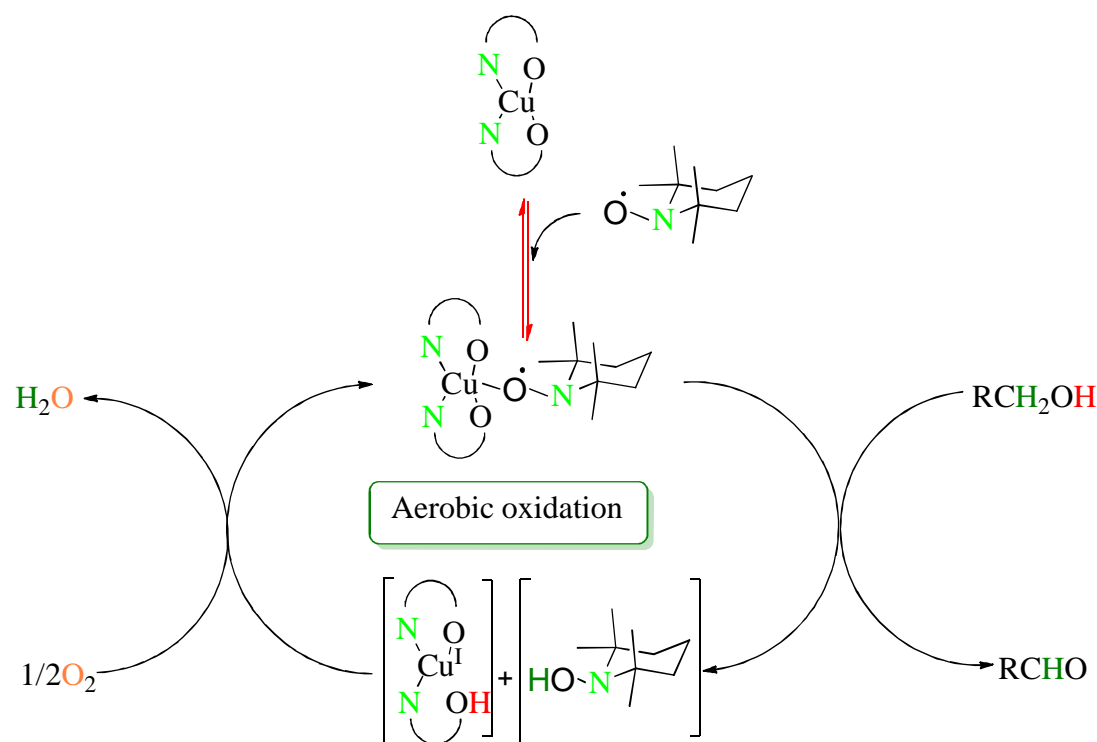
Table 9 Aerobic oxidation of selected alcohols catalyzed by **46**/TEMPO system.^{II}

	Substrate	Product	Conv.(%) after 1 h / 2 h
1	C ₆ H ₅ CH ₂ OH	C ₆ H ₅ CHO	85 / 100
2	<i>o</i> -MeOC ₆ H ₄ CH ₂ OH	<i>o</i> -MeOC ₆ H ₄ CHO	67 / 100
3	<i>m</i> -MeOC ₆ H ₄ CH ₂ OH	<i>m</i> -MeOC ₆ H ₄ CHO	70 / 100
4	<i>p</i> -MeOC ₆ H ₄ CH ₂ OH	<i>p</i> -MeOC ₆ H ₄ CHO	57 / 100
5	2,4-diMeOC ₆ H ₃ CH ₂ OH	2,4-diMeOC ₆ H ₃ CHO	61 / 100
6	2,3-diMeOC ₆ H ₃ CH ₂ OH	2,3-diMeOC ₆ H ₃ CHO	46 / 100
7	3,4-diMeOC ₆ H ₃ CH ₂ OH	3,4-diMeOC ₆ H ₃ CHO	71 / 100
8	2,4,5-triMeOC ₆ H ₂ CH ₂ OH	2,4,5-triMeOC ₆ H ₂ CHO	62 / 100
9	3,4,5-triMeOC ₆ H ₂ CH ₂ OH	3,4,5-triMeOC ₆ H ₂ CHO	55 / 100
10	<i>o</i> -MeC ₆ H ₄ CH ₂ OH	<i>o</i> -MeC ₆ H ₄ CHO	21 / 53
11	<i>m</i> -MeC ₆ H ₄ CH ₂ OH	<i>m</i> -MeC ₆ H ₄ CHO	55 / 79
12	<i>p</i> -MeC ₆ H ₄ CH ₂ OH	<i>p</i> -MeC ₆ H ₄ CHO	62 / 90
13	<i>o</i> -NO ₂ C ₆ H ₄ CH ₂ OH	<i>o</i> -NO ₂ C ₆ H ₄ CHO	n.d. / 26
14	<i>m</i> -NO ₂ C ₆ H ₄ CH ₂ OH	<i>m</i> -NO ₂ C ₆ H ₄ CHO	n.d. / 60
15	<i>p</i> -NO ₂ C ₆ H ₄ CH ₂ OH	<i>p</i> -NO ₂ C ₆ H ₄ CHO	n.d. / 82
16	PhCH=CHCH ₂ OH	PhCH=CHCHO	45 / 100
17	CH ₃ (CH ₃)C=CHCH ₂ OH	CH ₃ (CH ₃)C=CHCHO	n.d. / 100
20	C ₄ H ₄ O-2-CH ₂ OH	C ₄ H ₄ O-2-CHO	n.d. / 60
21	C ₄ H ₄ S-2-CH ₂ OH	C ₄ H ₄ S-2-CHO	n.d. / 51

Reaction Conditions: 0.96 mmol substrate, 2 mol% TEMPO, 0.66 mol% **46**, 1 atm of O₂, 60 °C, 1 mL toluene. Conversions were determined by GC. Selectivity of the transformation in all runs was above 99%. n.d. = not determined.

conversion of alcohol whereas no oxidation was observed with TEMPO itself. The effect of various organic solvents such as CH₃CN, THF, and DMF etc was studied and toluene appears to be the most favorable solvent. The electron donating or electron withdrawing substituent at imine N provides different electron densities on the Cu center in these complexes and should affect their catalytic activity. Therefore *N*-alkylphenyl substituted Cu(II) complexes (**45–46**) are more efficient than their *N*-alkyl (**43–44**) or *N*-phenyl (**40–42**) counterparts. The effect of reaction temperature on catalytic activity of the complexes (**40–46**) was also studied and 60 °C was the optimized temperature for the systems (Figure 12).^{II}

Of the studied catalysts, complex **46**, which has the ethylphenyl group at imine N was the best. With this catalyst at optimized reaction conditions most of primary benzylic, allylic and heterocyclic alcohols are quantitatively converted to the corresponding aldehydes in 2 hours. However, the developed catalyst is highly selective toward benzylic and allylic alcohols as primary aliphatic alcohols are poorly oxidized whereas secondary aliphatic alcohols are totally inactive (Table 9).^{II}



Scheme 32 Proposed mechanism for the Cu/TEMPO-catalyzed aerobic oxidation of alcohols.^{II}

The proposed reaction mechanism for the system is shown in scheme 32.^{II} As the catalysts are effective in the absence of additional base, the removal of an alcoholic proton by the ligand is expected. This produces an alkoxide complex where one of the phenoxide groups is converted to phenol.^[62, 64b, 128] Intramolecular abstraction of β -hydrogen with TEMPO leads to the formation of the aldehyde and Cu(I) species. In the presence of oxygen TEMPOH is regenerated to TEMPO which reoxidizes the Cu(I) species back to the original Cu(II) complex.^[13a, 56, 127]

4.6 Copper catalyzed oxidation of alcohols with H₂O₂^V

The development of an efficient and selective catalyst for oxidation of alcohols with molecular oxygen or hydrogen peroxide is considered as an essential requirement in the chemical industry. Using oxygen is sometime complicated to control and may result in combustion especially when the oxidation is carried out in organic solvent at high pressures.^[133] In this respect, H₂O₂ and water solve this problem as a liquid reagent and an inflammable solvent, respectively.

Indeed, H₂O₂ is a safe, effective, flexible and “green” oxidant. It creates only water as a byproduct. It is an ecologically ‘clean’ and non-toxic chemical that must, however, be a preferable oxidant from the environmental viewpoint.^[134] In addition, H₂O₂ is much easier to handle after oxidation, especially for batch reactions.^[135]

Thus our aim for this work was to use H₂O₂ as an end oxidant for the Cu catalyzed oxidation of alcohols to the corresponding carbonyl compounds in water. In this context, various Cu-salts were used as oxidation catalysts with H₂O₂ and simple CuSO₄ was found to be most efficient catalyst for the oxidation of a variety of alcohols to carbonyl compounds at optimized reaction conditions (Table 10).^V

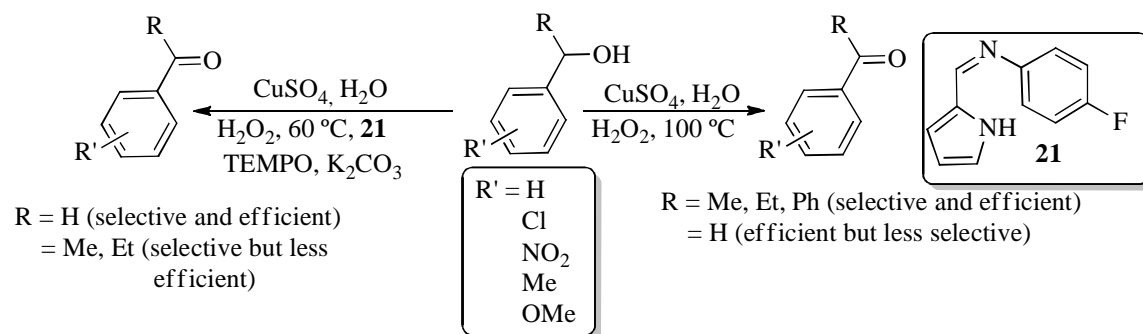
Table 10 Oxidation of alcohols to carbonyl compounds catalyzed by CuSO₄/H₂O₂^{a, V}

Entry	Substrate	Major Product (%) ^b	Time (min)	Conv. (%)	Select ^c . (%)
1	C ₆ H ₅ CH ₂ OH	C ₆ H ₅ CHO (69)	15	98	71
2	<i>p</i> -MeOC ₆ H ₅ CH ₂ OH	<i>p</i> -MeOC ₆ H ₅ CHO (84)	15	>99	84
3	<i>p</i> -MeC ₆ H ₅ CH ₂ OH	<i>p</i> -MeC ₆ H ₅ CHO (82)	120	92	90
4 ^{run1}	<i>p</i> -ClC ₆ H ₅ CH ₂ OH	<i>p</i> -ClC ₆ H ₅ CHO (84)	120	90	94
4 ^{run2}	<i>p</i> -ClC ₆ H ₅ CH ₂ OH	<i>p</i> -ClC ₆ H ₅ CHO (73)	120	80	95
4 ^{run3}	<i>p</i> -ClC ₆ H ₅ CH ₂ OH	<i>p</i> -ClC ₆ H ₅ CHO (65)	120	71	94
5	<i>p</i> -NO ₂ C ₆ H ₅ CH ₂ OH	<i>p</i> -NO ₂ C ₆ H ₅ COOH (73)	15	94/78 ^d	80
6	C ₆ H ₅ CH=CHCHOH	C ₆ H ₅ CHO (60)	180	100	60
7	C ₆ H ₅ CHOHCH ₂ OH	C ₆ H ₅ CHO (50)	30	100	50
8	OHCH ₂ C ₆ H ₅ CH ₂ OH	OHCH ₂ C ₆ H ₅ CHO (70)	120	100	70
9	C ₆ H ₅ CHOHCH ₃	C ₆ H ₅ COCH ₃ (89)	180	98	92
10	C ₆ H ₅ CHOHCH ₂ CH ₃	C ₆ H ₅ COCH ₂ CH ₃ (84)	180	90	95
11	C ₆ H ₅ CHOHC ₆ H ₅	C ₆ H ₅ COC ₆ H ₅ (89)	30	100	98
12	1-naphthylmethanol	1-naphthaldehyde (47)	180	48	99

^aReaction conditions: 3 mmol benzyl alcohol, 1 mol% CuSO₄, 5 mL H₂O, 1 mL 30% H₂O₂, 100 °C. ^bConversion (mol%) of the major product is given in parenthesis. ^cSelectivity is obtained from the conversion of the major product. ^dIsolated yield.

CuSO₄ alone is highly efficient but oxidation of primary alcohols proceeds with unsatisfactory selectivity (Table 10, Entries 1–8). Only secondary alcohols are oxidized with high selectivity and activity (Table 10, Entries 9–11). Interestingly, by applying 2-*N*-(*p*-fluorophenyl)-pyrrolocarbalimine (**21**) as a ligand in combination with TEMPO and K₂CO₃

high oxidation selectivities are obtained for both primary and secondary benzylic alcohols at 60 °C but the conversions are high only for primary alcohols (Scheme 33).^v



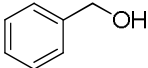
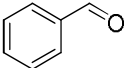
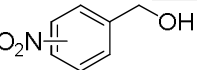
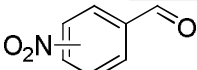
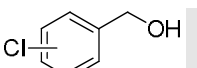
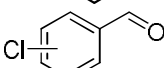
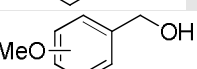
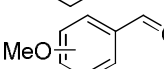
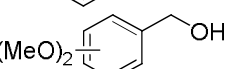
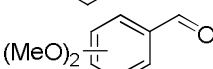
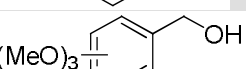
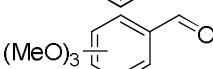
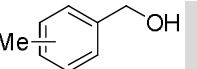
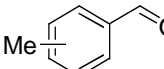
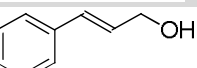
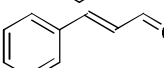
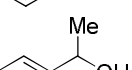
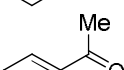
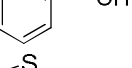
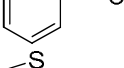
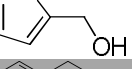
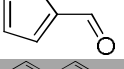
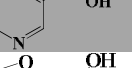
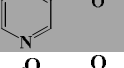
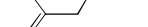
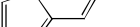


Scheme 33 Oxidation of alcohols with H_2O_2 .^v

Thus the ligand mediated system was optimized with respect to temperature, pH and TEMPO concentration for the oxidation of benzyl alcohol to benzaldehyde with H_2O_2 in K_2CO_3 solution. Subsequently, a series of other alcohols are studied under optimized reaction conditions (1 mol% CuSO_4 , 2 mol% **21**, 5 mol% TEMPO, 5 mL of 0.1 M K_2CO_3 , 60 °C). Surprisingly, no catalytic activity is observed under the optimized reaction conditions when *p*-nitrobenzyl alcohol is used as a substrate. Presumably, the inactivity of the catalyst causes from the low solubility of *p*-nitrobenzyl alcohol in alkaline water. Interestingly, the conversion of *p*-nitrobenzyl alcohol can be increased from 0 to 82% by increasing the volume of the reaction mixture up to 20 mL of the solvent. Accordingly, the ligand assisted catalyst system was individually optimized for a wide range of benzylic and allylic alcohols.

As can be seen in Table 11, the selected benzylic alcohols are nearly quantitatively converted to the aldehydes without overoxidation regardless of the type, position and number of the substituents (Table 11, Entries 2–7).^v Allylic alcohols such as cinamyl alcohol is oxidized to the corresponding α,β -unsaturated aldehyde without affecting the double bond (Table 11, Entry 8). Heterocyclic alcohols such as 2-thiophene methyl and furfuryl alcohols are smoothly converted into the corresponding aldehydes in good to moderate conversions (Table 11, Entries 10 and 12). In contrast, with 2-pyridine methanol only a very low conversion of alcohol is detected (Table 11, Entry 11) due to the formation of a new complex with overoxidized product such as picolinic acid. After oxidation blue crystals suitable for X-ray crystallography measurement were isolated and identified as a Cu-complex (m/z 307 for $\text{C}_{12}\text{H}_8\text{CuN}_2\text{O}_4$). It is important to notice that the ligand assisted system is highly selective towards primary benzylic and allylic alcohols as secondary benzylic alcohols are oxidized in poor conversions and primary and secondary aliphatic alcohols are barely active or totally inactive (Table 11, Entries 13–14).

In most cases the oxidation of organic molecules with H_2O_2 follows the free radical catalytic cycle.^[136] The negative influence of radical scavengers TEMPO and hydroquinone (in quantitative amounts with respect to the oxidant) on reaction rate of the CuSO_4 catalyzed system strongly suggest that the reaction proceeds through ionic rather than free radical pathways. UV-vis studies reveal that the catalytic reaction proceeds via the peroxocopper pathway as the oxidation state of Cu does not change during the oxidation.^[117a]

Table 11 Selective oxidation of benzylic and allylic alcohols catalyzed by the CuSO₄/TEMPO/**21** system^{a, v}

Entry	Substrate	Product	Conversion, % (mL) ^b		
			<i>o</i> -/2,3-di/2,4,5-tri	<i>m</i> -/2,4-di/3,4,5-tri	<i>p</i> -/3,4-di
1			100 (5)		
2			100 (10)	100 (10)	82 (20)
3			100 (10)	100 (10)	100 (20)
4			100 (15)	100 (10)	100 (15)
5			60 (10)	100 ((20)	82 (5)
6			99 (5)	98 (10)	
7			97 (20)	100 (5)	100 (10)
8			89 (10)		
9			10 (10)		
10			62 (5)		
11			8 (5)		
12			41 (10)		
13			3 (5)		
14			0		

^a Optimized reaction conditions: 1 h, 1 mL 30% H₂O₂, 5 mol% TEMPO, 1 mol% CuSO₄, 2 mol% **21**, 60 °C. Samples were directly analyzed by GC–MS. Selectivities were >99% according to GC–MS analysis. ^bOptimized volume of 0.1 M K₂CO₃ for the corresponding substrate is shown in parenthesis.

In order to gain further insight into the mechanism a 1 mM Cu^{II} salt water solution containing benzyl alcohol (2 µL) was treated with 30% H₂O₂. As shown in Figure 13 gradual 5

μL additions of 30% H_2O_2 into the solution resulted in the spectral changes that suggest the interaction between Cu^{II} and H_2O_2 .^V

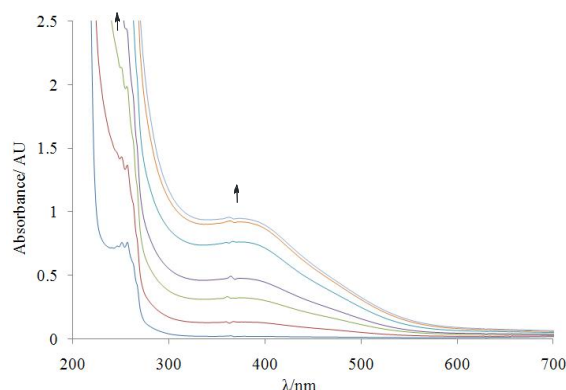
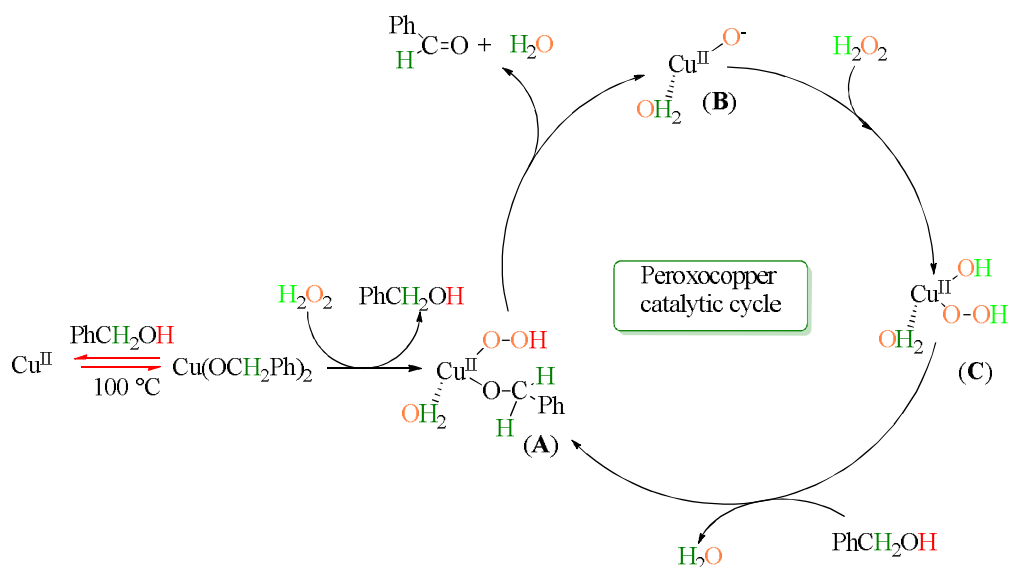


Figure 13 Spectral changes during gradual addition of 30% H_2O_2 into Cu^{II} and benzyl alcohol water solution. Reaction conditions: 2 mL 1 mM $\text{Cu}(\text{OAc})_2$, 2 μL benzyl alcohol, 5 \times 7 μL 30% H_2O_2 , room temperature.^V

Based on our experimental data and the existing literature, we propose the following reaction mechanism (Scheme 34)^V for exclusively CuSO_4 catalyzed oxidation of alcohols with H_2O_2 in pure water.^[136, 137] The Cu^{2+} ion interacts with the catalytic cycle by the formation of perhydroxy Cu^{2+} complex (**A**) in the presence of benzyl alcohol and H_2O_2 . After an intramolecular abstraction of β -hydrogen with perhydroxy moiety, the corresponding aldehyde and $\text{Cu}(\text{II})$ species (**B**) is formed. The species **B** changes to $\text{Cu}(\text{II})$ perhydroxide (**C**) with H_2O_2 which is regenerated back to **A** in the presence of benzyl alcohol.



Scheme 34 Proposed reaction mechanism for the CuSO_4 catalyzed oxidation of benzylic alcohols in water with H_2O_2 .^V

5 Summary and Conclusions

In this study, a successful development from pressurized oxygen to open air and from organic to environmentally friendly water solvent in oxidation of alcohols catalyzed by copper is presented. The first organocatalytic oxidation of alcohols to aldehydes was developed by using commercially available 9,10-diaminophenanthrene (DAPHEN) in alkaline water with 10 bar O₂ as an end oxidant.^{III} The effect of metal cofactors was also investigated and Cu ion was found to have significant influence on catalytic activity of DAPHEN. In order to substitute commonly used bipyridine or phenanthroline type ligands as catalyst precursor in oxidation of alcohols, a series of monoanionic ligand precatalysts such as 2-*N*-arylpyrrolecarbaldehyde was synthesized. The *in situ* and isolated Cu-2-*N*-arylpyrrolecarbaldehyde complex in combination with TEMPO demonstrated highly efficient catalytic activity on aerobic oxidation of benzylic alcohols into the corresponding carbonyl compounds in alkaline water.^I Open air could be utilized instead of atmospheric O₂ without affecting the efficiency of the process but this required a longer reaction time (18 h). The most significant benefit of this system is that water is used as a solvent under mild reaction conditions (80 °C temperature, pH >11). The drawback of the system is that an additional auxiliary substance such as K₂CO₃ is required for efficient oxidations. Other shortcoming is the use of 5 mol% TEMPO as a cocatalyst.

Additionally, a series of *tert*-butyl substituted salicylaldehydes was synthesized and characterized by IR, ¹H NMR, ¹³C NMR, UV-vis and X-ray diffraction.^{IV} The effect of two bulky *tert*-butyl groups on the keto-enol tautomerization in solution and the solid state was thoroughly investigated and only the enol form of the ligands was identified experimentally and theoretically. These salicylaldehyde ligands were used in complexation with copper to obtain homoligated bis(phenoxidoimino)Cu(II) complexes.^{VII} The complexes were thoroughly characterized by various spectroscopic methods (UV-Vis, IR, EPR and EI-MS). The crystal structures of the complexes were determined by X-ray crystallography. In two solid state structures, the ligands have an unusual *cis*-orientation whereas the rest of the complexes are *trans*-isomers. Computational studies suggested that in the case of the complex with the *N*-alkyl fragment the preferred isomer is *trans*, while the opposite behavior is observed for the complex having the *N*-phenyl substituent.

The homoligated bis(phenoxidoimino)Cu(II) complexes, when combined with TEMPO form a highly efficient catalytic system for the aerobic oxidation of primary benzylic, allylic and heterocyclic alcohols to the corresponding aldehydes under mild reaction conditions.^{II} Attractive features of this catalytic system include the efficient use of molecular oxygen, high selectivity, low loading of both TEMPO (2 mol%) and the copper catalyst (0.66 mol%) under mild reaction conditions (atmospheric O₂ and 60 °C temperature). The disadvantage of the system is that aliphatic primary and secondary alcohols are barely active.

Subsequently, the mixed ligand Cu(II) complexes derived from the salicylaldehyde ligands and corresponding aldehyde were synthesized and characterized by IR, UV-vis and X-ray diffraction.^{VI} Three of them are *cis*-isomers and one is a *trans*-isomer with respect to the phenolic O-atoms. These types of complexes can be successfully used as a complex precursor for the synthesis of novel heteroligated bis(phenoxidoimino)Cu complexes. For instance, a mixed ligand complex, namely [(3,5-di-*tert*-butylsalicylaldehydato)(*N*-(2-phenylethyl)-3,5-

di-*tert*-butylsalicylaldiminato)]Cu(II), can be used as a precursor for the synthesis of heteroligated bis(phenoxidoimino)Cu(II) complexes.

The synthesized heteroligated Cu(II) complexes catalyzed more efficiently the aerobic oxidation of benzyl alcohol into benzaldehyde than the corresponding homoligated Cu(II) complexes. The catalytic system was active also towards oxidation of secondary benzylic, primary and secondary aliphatic alcohols which is rarely the case with TEMPO-mediated Cu-based systems.^{IX} The drawback of the method is when it is used in traditional alcohol oxidation carried out in organic solvent e.g., toluene.

Hence a simple, efficient and sustainable copper catalyzed method has been introduced for oxidation of benzylic alcohols to the corresponding carbonyl compounds in pure water using H₂O₂ as the end oxidant.^V A variety of alcohols can be oxidized efficiently with 1 mol% CuSO₄ as a catalyst at 100 °C without base and ligand. Unfortunately, the system is selective only for secondary benzylic alcohols. By introducing 2-*N*-(*p*-fluorophenyl)-pyrrolecarbalimine as a ligand in combination with TEMPO and K₂CO₃ the oxidation selectivities turned to primary benzylic alcohols. The ligand modified system is also optimized separately for a wide range of benzylic and allylic alcohols. After optimization for each substrate, they were quantitatively and selectively converted into the corresponding aldehydes under very mild reaction conditions (60 °C, 3 eq. of H₂O₂, 1 h).

Finally, open air oxidation of benzylic alcohols using *in situ* made Cu-phenoximine complexes in water under mild reaction conditions was developed.^{VIII} Notably, this is the first example of facile alcohol oxidation with a homogeneous catalyst in the open air in pure water without additional auxiliaries.

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