COPPER COORDINATION CHEMISTRY WITH PYRIDYL-IMINE LIGANDS AND THEIR APPLICATION IN AEROBIC OXIDATION REACTIONS

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Copper Coordination Chemistry with Pyridyl-Imine Ligands and their Application in Aerobic Oxidation Reactions

by

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Abstract

Recyclable catalysts and oxidation chemistry are two important areas in the field of Green Chemistry. In this thesis, research efforts towards the development of a re-usable aerobic oxidation catalyst are described. The background to this field and a review of relevant literature are presented in Chapter 1.

In Chapter 2, the preparation and characterization of a series of six potentially tetradentate di(pyridyl-imine) ligands presented. In each case the pyridyl-imine groups were separated by a different linking unit (in **L1**, $CH_2CH_2CH_2(SiMe_2O)_{20}SiMe_2CH_2CH_2CH_2$; in **L2**, $CH_2CH_2CH_2SiMe_2OSiMe_2CH_2CH_2CH_2$; in **L3**, CH_2CH_2; in **L4**, $CH_2(CH_2)_4CH_2$; in **L5**, $CH_2(CH_2)_7CH_2$; in **L6**, $CH_2CH_2CH_2OCH_2CH_2OCH_2CH_2OCH_2CH_2CH_2$). The solubilities of **L1** and **L2** in supercritical carbon dioxide were determined. The coordination chemistry of **L1**-**L2** with Cu(I) was studied by UV-Vis, multinuclear NMR and IR spectroscopies, MALDI-TOF and ESI mass spectrometries and elemental analysis. Dicopper complexes of **L3**-**L6** were prepared for comparison. PGSE (pulsed-gradient spin-echo) NMR spectroscopy was used to determine the hydrodynamic radii of the species in solution and comparison of these data with computational models for the complexes was made. There is no evidence to support linear metallopolymer formation but data suggest that [2+2] and [1+1] metallomacrocyles were formed, with siloxane linking groups encouraging the formation of [1+1] species. Solid-state NMR data on [Cu(**L1**)](PF_6) indicate the presence of two different environments for the PF_6^- anions and this could be due to the location of PF_6^- anions both inside and outside the metallomacrocyclic species.

In Chapter 3, an investigation into the ability of **L1-L6** in catalytic oxidations of alcohols when combined with copper bromide ($CuBr_2$) and 2,2,6,6-tetramethylpiperidyl-1-oxy (TEMPO) is described. Analogous bidentate ligand (**L7**) showed poorer catalytic activity than **L1-L6**. Also, the ratio of Cu:ligand was of crucial importance in maintaining high yields. The polydimethylsiloxane (PDMS) derived pyridyl-imine terminated ligand **L1** combined with copper (II) ions afforded an effective and selective catalyst for aerobic oxidations of primary and secondary alcohols under aqueous conditions. Preliminary mechanistic studies suggested that bimetallic complexes may be playing a role in the catalytic transformation.

In Chapter 4, oxidation of amines using a copper-containing catalytic system is described. $CuBr_2$ with TEMPO was successfully employed for the aerobic oxidation of primary and secondary benzyl amines in aqueous acetonitrile. The same catalyst system was also used for oxidative cross-couplings of benzylamines with anilines. The electronic and steric properties of the aniline partner were found to be of crucial importance in determining reactivity or lack thereof. A mechanism for these reactions is proposed based on the data obtained to date. In the absence of benzyl amines, electron-rich anilines were found to undergo dehydrogenative coupling and yields of the resulting azo products could be increased by replacing $CuBr_2$ with CuBr. No ligand (e.g. pyridine) is required for either reaction to proceed and presumably water and acetonitrile solvate the copper-containing intermediates.

Chapter 5 contains a summary of the thesis and suggestions for future research in this area.

Dedication

To my wife, **Zhuoyu Sun**, for all her support and understanding during my Ph.D study.
&
To my parents and sister for all their unconditional support in whole my life.

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This research project would not have been possible without the support of many people. First, I would like to express my gratitude to my supervisor, Prof. Francesca M. Kerton, who was very helpful and offered invaluable assistance, support and guidance throughout the duration of my studies. I appreciate her vast knowledge and skill in many areas, and her helpful revisions and comments while writing my thesis. I want to thank Prof. Christopher Kozak for sharing his experience with me during 4 years of intensive work. I was graced by his lab skills and wisdom. I would like to thank my superivisory committee members, Prof. Paris E. Georghiou and Prof. Robert J. Helleur, for their helpful suggestions in my annual progress meetings and their kind comments on my thesis.

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List of Abbreviations

AE: Atom Economy

ATRP: Atom transfer radical polymerization

[BMIm]PF_6: 1-butyl-3-methylimidazolium hexafluorophosphate

[BMIm]OSO_3Oc: 1-butyl-3-methylimidazolium octylsulfate

[BMIm]BF_4: 1-butyl-3-methylimidazolium tetrafluoroborate

[BMPy]PF_6: 1-butyl-4-methylpyridinium hexafluorophosphate

BARF: tetrakis-(3,5-bis(trifluoromethyl)phenyl)borate

C-C: Carbon-carbon

CFCs: Chlorofluorocarbons

CM: Cross-metathesis

$DBADH_2$: di-tert-butyl hydrazine-1,2-dicarboxylate

DMA: 2-(dimethylamino)ethyl methacrylate

DMF: Dimethylformamide

DMSO: Dimethylsulfoxide

E-factor: Environmental factor

ESI: Electrospray ionization

FT-IR: Fourier transform infrared

GOase: Galactose oxidase

GPC: Gel permeation chromatography

HRMS: High- resolution mass spectrometry

IL: Ionic liquid

LCA: Life Cycle Assessment

MALDI-TOF: Matrix-assisted laser desorption/ionization-Time of Flight

M_w: Weight-average molecular weight

M_n: Number-average molecular weight

NHC: N-heterocyclic carbene

NMR: Nuclear magnetic resonance

P_c : Critical pressure

PDMS: Polydimethylsiloxane

PEG: Polyethylene glycol

PGSE: Pulse Gradient Spin-Echo

RCM : Ring-closing metathesis

ROMP: Ring-opening metathesis polymerization

$ScCO_2$: Supercritical carbon dioxide

SCFs: Supercritical fluids

SILP: Supported ionic liquid phase

TBTA: tris-(benzyltriazolylmethyl)amine

T_c: Critical temperature

TEMPO: 2,2,6,6-tetramethyl-1-piperidinyloxyl

Tg: Glass transition temperature

TGA: Thermal gravimetric analysis

THF: Tetrahydrofuran

TOF: Turnover of frequency

TON: Turnover number

UV: Ultraviolet

VOCs: Volatile organic compounds

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Chapter 1

Introduction

1-1 Historic background of Green Chemistry and the importance of greener methods of oxidation

Over the past decade, significant progress has been made in developing new chemical methodologies that reduce risk to human health and the environment. This new approach is associated with many names including Atomic Economic and Benign By Design Chemistry, Clean Chemistry, Sustainable Chemistry, Environmentally Benign Chemistry and Green Chemistry.[1] Green Chemistry can be simply defined as the utilization of principles that reduce or eliminate the use or generation of hazardous substances in the design, manufacture and application of chemical products.[2-3] This definition of Green Chemistry was first introduced at the beginning of the 1990s, almost 20 years ago.[4] Since then, widespread interest in Green Chemistry has been demonstrated all over the world. In particular, many leading research programs and government initiatives have been established in the U.S.A. and Europe. In 1991, the U.S. Environmental Protection Agency (EPA) started the first research project of its Green Chemistry Program.[5] In 1993, the name "U.S. Green Chemistry Program" was officially employed by the EPA. The U.S. Presidential Green Chemistry Challenge Awards and the annual Green Chemistry and Engineering Conference were established in 1995. The ACS (American Chemistry Society) Green Chemistry Institute (GCI) was founded following this in 1997, and has grown to include 25 international chapters up to the present.[6] In the U.K., several initial research and education programs in Green Chemistry were launched in the early 1990s. The Green Chemistry Network (GCN) was started in 1998 with funding from the Royal Society of Chemistry which aimed to spread Green Chemistry in industry, government, to the public and in schools through education and training. The first volume of the Green Chemistry journal was published by the Royal Society of Chemistry in 1999.[7] In Italy, a multi-university consortium (INCA) highlighted Green Chemistry research as its central theme. Meanwhile, Japan organized and officially launched the Green and Sustainable Chemistry Network (GSCN) in March 2000, with an emphasis on promoting research and development on green and sustainable chemistry.

One of the important reasons for the rapid development of Green Chemistry was due to the awareness that environmentally benign products and processes would be more practical and economical in the long term. Green Chemistry focuses on pollution prevention, rather than waste treatment. Green Chemistry has demonstrated how fundamental methodologies can protect the environment and human health in an economical manner. It should be mentioned that the development of green processes and products requires benign design based on the principles of Green Chemistry. The twelve principles of Green Chemistry (Figure 1-1) have played an important role in promoting the subject and in explaining its aims since they were introduced by Paul Anastas and John Warner in 1998.[3] These principles have been broadly applied to all aspects of the process life-cycle. However, the 12 principles are difficult to memorize, especially for those audiences who are non-native English speakers. Tang et al. summarized a simpler statement and more convenient acronym of the 12 principles: "PRODUCTIVELY" (Figure 1-2).[8]

1. **Prevention**
   It is better to prevent waste than to treat or clean up waste after it has been created.
2. **Atom Economy**
   Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.
3. **Less Hazardous Chemical Syntheses**
   Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment.
4. **Designing Safer Chemicals**
   Chemical products should be designed to effect their desired function while minimizing their toxicity.
5. **Safer Solvents and Auxiliaries**
   The use of auxiliary substances (e.g., solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.
6. **Design for Energy Efficiency**
   Energy requirements of chemical processes should be recognized for their environmental and economic impacts and should be minimized. If possible, synthetic methods should be conducted at ambient temperature and pressure.
7. **Use of Renewable Feedstocks**
   A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.
8. **Reduce Derivatives**
   Unnecessary derivatization (use of blocking groups, protection/ deprotection, temporary modification of physical/chemical processes) should be minimized or avoided if possible, because such steps require additional reagents and can generate waste.
9. **Catalysis**
   Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.
10. **Design for Degradation**
    Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.
11. **Real-time analysis for Pollution Prevention**
    Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.
12. **Inherently Safer Chemistry for Accident Prevention**
    Substances and the form of a substance used in a chemical process should be chosen to minimize the potential for chemical accidents, including releases, explosions, and fires.

Figure 1-1. The twelve principles of Green Chemistry.

Condensed Principles of Green Chemistry

P - Prevent Waste
R - Renewable materials
O - Omit derivatization steps
D - Degradable chemical products
U - Use safe synthetic methods
C - Catalytic reagents
T - Temperature, Pressure ambient
I - In-Process Monitoring
V - Very few auxiliary substances
E - E-factor, maximise feed in product
L - Low toxicity of chemical products
Y - Yes, it is safe

Figure 1-2. Simper twelve principles of Green Chemistry: PRODUCTIVELY.

The twelve principles of Green Chemistry are ''design rules'' to help chemists achieve the international goal of sustainable development. As a consequence, the 12 principles of Green Chemistry mainly focus on the following: a) the process design, maximizing the amount of reactant that converts into the desired product, and decreasing the amount of waste products; b) the use of environmentally benign materials including renewable feedstocks, catalysts and solvents; and c) energy savings by using efficient energy systems and designing suitable processes that minimize energy consumption.[9] Significant progress has been made in several research areas, such as catalysis, the development of renewable feedstocks, the design of safer chemicals and the use of environmentally benign solvents.

In addition to the principles, there are some other important concepts such as atom efficiency and Enviromental factors that must be understood in order to make progress in Green Chemistry. In 1990 Barry Trost introduced the concept of Atom Economy (AE) which is also called Atom Efficiency.[10-11] It describes the conversion efficiency of a chemical process in terms of all atoms involved (desired products produced). Atom economy can be written as Equation 1-1:

$$\%\ atom\ economy = \frac{Molecular\ \ Weight\ of\ desired\ \ products}{Molecular\ \ Weight\ of\ all\ reactants} \times 100 \text{ (Equation 1-1)}$$

In an ideal chemical process, the amount of starting materials or reactants equals the amount of all products generated and no atom is wasted. For example, the AE of Diels-Alder reaction is 100% (Scheme 1-1). Atom economy is a theoretical value used to quickly assess how efficient a reaction will be. However, the method for calculating atom economy is simplified by several assumptions. It ignores reaction yield and molar excesses of reactants, and does not account for solvents and co-reagents.[12] The Environmental (E) factor, in contrast, takes those into account and is another important concept of Green Chemistry. In 1992, Roger Sheldon defined the E factor as the mass ratio of waste to desired product.[13] It can be written as Equation 1-2:

$$E\text{-}factor = \frac{Total\ mass\ of\ waste\ (kg)}{Mass\ of\ desired\ \ product\ \ (kg)} \text{ (Equation 1-2)}$$

Scheme 1-1. Diels-Alder reaction as an example of an atom-economical reaction.

A theoretical E factor can be obtained from the atom economy, e.g., an atom economy of 50% corresponds to an E factor of 1 (50/50). However, the E factor will generally be much higher in practice since it takes the chemical yield into account and includes reagents, solvent losses and process aids used in the work-up.[14] Roger Sheldon summarized the different magnitudes of the waste problem in the various segments of the chemical industry in 2007 (Table 1-1).[15]

Table 1-1. E factors in the chemical industry.

Industry segment	Annual Production (t)	E factor	Waste Produced (t)
Oil Refining	10^6-10^8	Ca. 0.1	10^5-10^7
Bulk chemicals	10^4–10^6	<1–5	10^4-5×10^6
Fine chemical industry	10^2–10^4	5–50	5×10^2-5×10^5
Pharmaceutical industry	10–10^3	25–100	2.5×10^2-10^5

The E factor is a good metric to quickly assess the waste produced in a process. However, it may be difficult for an industry such as the pharmaceutical industry to routinely use this metric in its operations. As shown in Table 1-1, despite the high E-factor of the high profit pharmaceutical industry, it generates a much lower tonnage of waste than any other sector because of its lower production levels. Also, the specific hazard posed by different waste types is not taken into account. However, the E-factor concept draws some attention to the fine chemicals and pharmaceutical industries to commence more green processes.[16] Beyond these approaches, life cycle assessment can be used as a powerful evaluation tool in assessing the "greenness" of a chemical reaction or process.

Life cycle assessment (LCA) was first defined by the Society of Environmental Toxicology and Chemistry in 1993 as: "An objective process to evaluate the environmental burdens associated with a product, process or activity by identifying and quantifying energy and materials used and wastes released to the environment, and to evaluate and implement opportunities to effect environmental improvements. The assessment includes the entire life cycle of the product, process or activity, encompassing extracting and processing raw materials; manufacturing, transportation and distribution; use; re-use, maintenance; recycling and final disposal".[17] There are a series of ISO standards for life cycle assessment to promote sustainable development. According to the ISO14044:2006 standard, LCA includes 4 main stages: the goal and scope of the study, inventory analysis, impact assessment and interpretation (Figure 1-3).[18]

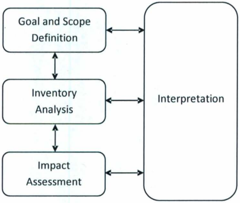


Figure 1-3. Basic stages in a Life Cycle Assessment.

The main goal of LCA is to provide a quantitative assessment of the environmental impact of products and services by guiding the decision-making process. For a chemical reaction, LCA can be used as a tool to evaluate and compare the different routes from an environmental point of view. Total inputs and emissions for production, distribution, use and disposal will be taken into account in the method. LCA has been greatly involved in the development and promotion of Green Chemistry.[9, 19-22] Furthermore, the combined use of LCA with economic evaluations is an important tool for the evaluation of industrial processes.

Oxidation reactions are very important for converting petroleum-based feedstocks to a wide range of useful oxygen-containing molecules such as epoxides, alcohols, ketones and carboxylic acids. Millions of tons of these compounds are annually produced worldwide and find applications in all areas of the chemical industries, ranging from pharmaceutical to large-scale commodities such as plastics and synthetic fiber materials. However, from a Green Chemistry perspective, oxidation is among the most problematic of processes. For economic and environmental reasons, the development of benign oxidation processes for bulk chemical industries must satisfy the following issues: (1) high atom economy; (2) low E-factor and (3) low environmental load. Traditionally, oxidation is accomplished by addition of stoichiometric amounts of inorganic oxidants (e.g. $KMnO_4$, CrO_3, SeO_2, and HNO_3), which often generate environmentally hazardous or toxic by-products.[23] Such reactions have a low atom economy and high E-factor. Large amounts of organic solvents are often used as the reaction medium and in extractions during traditional oxidation processes. From LCA analysis, conventional oxidation processes will bring a lot of side-effects to the chemical table such as huge energy consumption and potential climate change.[24] Potential pollution and waste disposal issues are not the only concerns. Therefore, from both economic and environmental points of view, it is important to develop more atom efficient and greener oxidation methods that employ clean oxidants and use a high efficiency (preferably recyclable) catalyst to replace conventional ones.

Oxidation reactions employing inexpensive and non-toxic air and molecular oxygen as the sole terminal oxidant are ideal methods and this field has gained much interest in recent years.[25-26] The high atom efficiency of the reaction and non-toxic by-products make aerobic oxidation a promising and attractive synthetic method. One drawback for aerobic oxidation is that it is often difficult to control and sometimes results in combustion or over-oxidation. Hydrogen peroxide is also an ideal oxidant and produces water as a by-product. An advantage of H_2O_2 oxidation is the high tunability of the reaction parameters.[27] It should be noted that it is not desirable to carry out an oxidation reaction with an H_2O_2 concentration of more than 50% due to safety concerns. Generally, it is not possible to use these clean oxidants alone. Normally, this type of oxidation reaction is facilitated with some sort of metal catalyst. As one of the important Green Chemistry principles, the use of catalysts, rather than stoichiometric reagents, is often at the heart of new greener chemical processes. Furthermore, catalysts allow the reactions to be performed in a controlled manner and allow high conversions to be achieved whilst avoiding over-oxidation. Meanwhile, green solvents such as water and supercritical carbon dioxide ($scCO_2$), are important in the development of greener oxidation methods. Therefore, the ideal oxidation catalysts of the future should satisfy the following three criterion: high selectivity, environmentally benign and highly stable (Figure 1-4).[28]

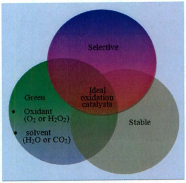
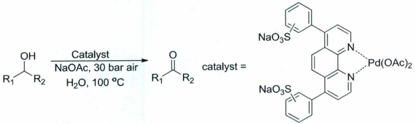


Figure 1-4. The ideal homogeneous oxidation catalyst system.[28]

Many highly efficient metal-catalyzed oxidation reactions using air, O_2 or H_2O_2 as the sole terminal oxidant have been developed in recent years. Notably, Sheldon et al. reported an efficient catalyst system for palladium catalyzed aerobic oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones (Scheme 1-2).[29] The palladium catalyst bearing a bathophenanthroline ligand was soluble and stable in water and could be reused several times. Furthermore, this oxidation reaction system used air as the oxidant and water as the solvent. It utilized at least four principles of Green Chemistry and proved to be an environmentally-friendly and economical green method.



Scheme 1-2. Palladium catalyzed aerobic oxidation of alcohols.

1-2 Polymeric ligands

In accordance with the principles of Green Chemistry, the use of catalysts rather than stoichiometric reagents is often at the heart of new greener chemical processes. In particular, homogeneous catalysts, which are in the same phase as the reactants, have some advantages for optimizing catalytic systems, because they can be easily prepared and modified by ligand design.[30] Moreover, their structures and reaction pathways can be characterized by various spectroscopic techniques, including NMR and IR. The major disadvantage of homogeneous catalysts is the difficulty of isolating and recovering them from the products. Homogeneous catalysts also decompose relatively easily. These drawbacks limit their broader application, especially for industrial scale reactions. Heterogeneous catalysts by contrast, may be separated from the product and therefore, can be easily recovered and recycled. Efficient recovery and reuse of catalysts has many environmental and economic benefits, including reduced solvent waste and reduced product purification costs. There are many different ways to recycle catalysts.[31] Liquid polymers are non-volatile and recyclable; this catalyst phase has shown much promise, especially when combined with $scCO_2$ as the solvent.[32] Another effective approach to promote recyclability is to heterogenize the catalyst by attaching it to an insoluble polymeric support (inorganic or organic).[31] Recent efforts in the development of environmentally benign synthesis have focused on the design and development of polymer-derived metal catalysts for organic synthesis.[33] Typically, polymer-supported metal complexes have several significant benefits for use in catalysis, including non-volatility, non-flammability, high activity and selectivity. Furthermore, they can be used and recycled in green solvents such as liquid polymers and $scCO_2$. Therefore they are easily separable from products and may be reused many times.

In polymer-supported transition metal catalysts (Figure 1-5), the desired metal complex is generally attached to the functionalised polymer by a coordinate bond. The first step in the design of the complex is the selection of an end-functionalized polymeric ligand. End-functionalized polymers are commercially available or they may be easily prepared. A polymeric ligand containing anchoring sites like N, O or P can be incorporated either by functionalization of a polymer having coordinating ability, or by the polymerization of a monomer possessing the coordinating site. The synthesis results in an organic polymer with inorganic functionalities.

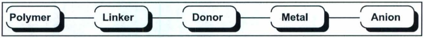


Figure 1-5. Modular approach to polymeric homogeneous catalysts.

By adjustment of the polymer properties, the metal catalyst's performance can also be tuned. The catalyst behaviour is influenced by the physical and chemical properties of the polymer support. For example, the polymer-supported catalyst can be designed to be water soluble or insoluble by using different polymer supports such as polyethylene glycol (PEG) or polystyrene (PS). In addition, the choice of different donor end-groups e.g. N, O, or P, can affect the activity and selectivity of the metal catalyst. The desired metal ion coordinates with the functionalized polymeric ligands to form the complex. Many synthetic, polymer-derived metal complexes have been found to possess high catalytic activity and selectivity.[34-36]

1-2-1 Types of polymeric ligands (PS, PEG, PDMS supported)

In 1963, Merrifield reported the first solid phase peptide synthesis using a rigid hydrophobic resin.[37] Since this time, polymer supports have been used extensively in other areas of chemistry. For example, versatile polymer supports, including those that are insoluble and soluble, have been used in organic chemistry for the synthesis of fine chemicals. Different types of polymers such as polyalkenes, polyethers and polysiloxanes can be used for the backbones of polymeric ligands.

Polyalkene polymers have been the most widely used class of macromolecules in organic synthesis. This is likely due to their ease of preparation, relative inertness, and low cost. In particular, PS and its analogues have been widely explored in this area. Many non-cross-linked and various heterogeneous divinylbenzene cross-linked PS are commercially available. Furthermore, strategies have been applied to modify them in order to improve their efficiencies in synthetic organic chemistry (Figure 1-6).[38] Several routes have been employed which include: using different heterogeneous cross-linked divinylbenzene polystyrene; modulating the physical and chemical properties of the PS resin by adding various cross-linkers other than divinylbenzene; functionalizing PS on the backbone in order to provide desired properties; and grafting polystyrene onto a heterogeneous support such as PEG. These structural modifications greatly improve the performance of PS in synthetic applications. For example, Lee et al. reported the synthesis of core-shell N-heterocyclic carbene (NHC)-functionalized heterogeneous polystyrene.[39] In this case, the ionic liquid monomer was immiscible in both the aqueous and styrene phases and was located between these two phases during the polymerization process. Therefore, the NHC

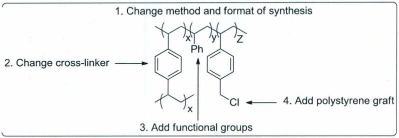
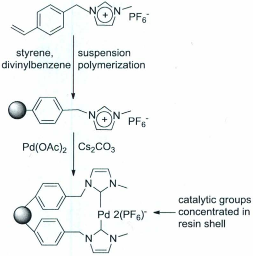


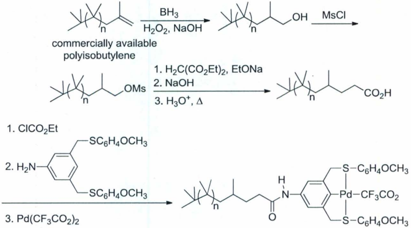
Figure 1-6. Routes to polystyrene modification.

groups were incorporated on the surface of the polymer resin as the beads formed. The polymeric (NHC) ligands were located in the shell of a resin bead, which reduced the need for resin swelling (Scheme 1-3). The polymer-supported NHC palladium complex was effective for heterogeneous Suzuki, Heck and Sonogashira cross-coupling reactions.[40-42]



Scheme 1-3. Synthesis of heterogeneous polystyrene supported palladium catalyst.

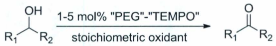
Some other types of polyalkenes, *viz*. polyisobutylene and polynorbornene have also been used as catalyst supports recently. Polyisobutylene, a non-polar hydrocarbon analogue of PEG supports, with an average molecular weight of 1000 or 2300 Da, is commercially available. Polyisobutylene is exclusively soluble in nonpolar solvents such as heptanes, and therefore, can be recycled based on solubility. The terminal C-C double bond can be transformed to other functional groups for further use. For example, Bergbreiter and Li reported the first synthesis and application of a polyisobutylene-supported Pd catalyst (Scheme 1-4).[43] The terminal alkene was first converted to the carboxylic acid by a series of transformations, then the polyisobutylene-supported S-C-S Pd(II) species was produced, which was highly efficient in catalyzing Heck reactions. More importantly, the catalyst could be recycled three times without any loss of activity, simply by separating the catalyst in the heptanes-rich phase from the polar phase containing the product.



Scheme 1-4. Synthesis of polyisobutylene-supported Pd(II) catalyst.

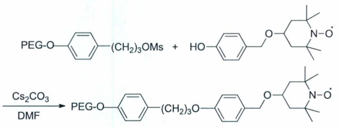
More recently, Bergbreiter et al. reported polyisobutylene-supported copper-catalyzed cyclopropanation reactions[44] and atom transfer radical polymerization (ATRP) reactions.[45] A polyisobutylene-supported ruthenium ring-closing metathesis (RCM) catalyst[46] and a chromium-based polycarbonate polymerization catalyst have also been reported by the same group.[47] All of these polyisobutylene supported catalysts were easily recovered and reused without detectable loss of activity.

Polyethers such as poly(ethylene glycol) (PEG) and polyglycerol have also been extensively used as inexpensive and easily functionalized supports to facilitate catalysis and synthesis.[48] Along with PS, PEG was one of the first soluble polymers used for the immobilization of reagents and catalysts. PEG is a linear polymer that is highly soluble in water and a variety of polar organic solvents (e.g., acetonitrile, DMF, DMSO) and insoluble in less polar solvents (e.g., hexane, diethyl ether). It was determined from its solubility properties that a PEG-supported catalyst can be used under homogeneous conditions and easily recovered and reused. Many PEG derivatives are commercially available and therefore, are easily accessible supports for ligands and catalysts. Bayer et al. first reported the use of a PEG support for liquid-phase peptide synthesis.[49-50] The rapid solid-phase peptide synthesis using graft copolymers of weakly cross-linked PS and linear PEG has also been reported by the same group.[51] Polymer-bound organocatalysts have played an important role in the field of catalysis due to their advantages of performing catalytic reactions under metal-free conditions and the facile recovery of the catalyst. PEG-supported TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxyl) proved to be an effective catalyst for the oxidation of alcohols with other stoichiometric oxidants such as sodium hypochlorite (Scheme 1-5).



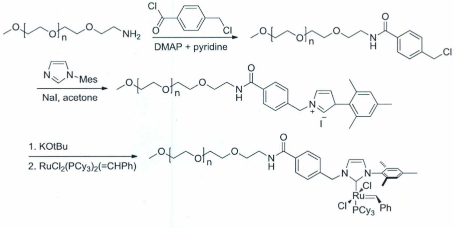
Scheme 1-5. Polymer-supported catalytic model for oxidation of alcohols.

Benaglia et al. investigated the effect of PEG-bound TEMPO with a trimethyleneoxy benzyl ether linker for oxidation of primary and secondary alcohols to aldehydes and ketones with stoichiometric quantities of oxidants (Scheme 1-6).[52] The PEG supported TEMPO organocatalyst proved to be highly effective and was easily recovered by precipitation with diethyl ether.



Scheme 1-6. Example of PEG-bound TEMPO catalyst.

PEG and its derivatives have also been widely used to immobilize transition-metal catalysts. One notable example is the PEG-bound Grubbs-type catalyst. Grubbs et al. reported a water-soluble ruthenium-based olefin metathesis catalyst supported by a PEG-conjugated N-heterocyclic carbene ligand in 2005 (Scheme 1-7).[53] The desired PEG-supported catalyst was highly active for aqueous ring-opening metathesis polymerization (ROMP) reactions. The second-generation of PEG-bound Grubbs catalyst was developed by the same group in 2006.[54] The modified water-soluble catalyst showed excellent activity in ROMP, RCM, and CM (Cross-metathesis) reactions carried out in aqueous media.



Scheme 1-7. PEG-Supported Grubbs-Type Catalyst.

PEG can also be grafted onto a PS backbone to form a heterogeneous resin for peptide synthesis. *TentaGel* and *ArgoGel* are two commercially available examples (Figure 1-7).[55] The incorporation of the PEG chains into the PS backbones significantly increases resin compatibility with polar solvents. Compared to the traditional Merrifield resin, this heterogeneous polymer support can overcome the drawback of the need for resin swelling.

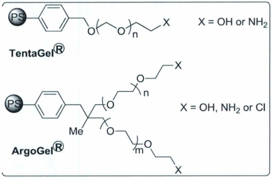
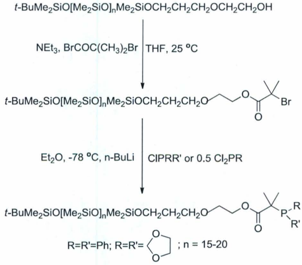


Figure 1-7. TentaGel and ArgoGel supports.

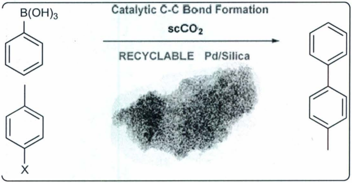
Polydimethylsiloxanes (PDMS) are the most widely used, commercially available, silicon-based organic polymers. They have found use in a wide range of commercial applications from contact lenses and medical devices to elastomers due to their attractive features. PDMS has an extremely low glass transition (Tg) temperature (-123 °C), high flexibility, gas permeability, and thermal and oxidative stability, and low surface energy. In addition to these desirable physical properties, PDMS is considered to be inert, low-toxic and non-flammable. Furthermore, PDMS is inexpensive and simple to modify, allowing for its widespread application. With these features at hand, PDMS and its derivatives have been widely used as membranes in catalytic reactions, as they enable homogeneous catalysts to be used in a heterogeneous fashion.[56] In this respect, the reagents dissolve in an aqueous solvent and diffuse into hydrophobic PDMS slabs to react with catalysts. The water-insoluble occluded catalysts do not diffuse out of the hydrophobic PDMS slab. The PDMS slab can act as an "active membrane" to exclude polar reagents to alter the reactivity of occluded catalysts. Notable examples are the incorporation of Jacobs' catalysts in a PDMS membrane for a wide range of oxidation reactions.[57-60] Also, occluded Grubbs- and Schrock-type catalysts in PDMS have been reported.[61-63]

Despite their use in membranes, the catalytic application of functionalized PDMS derivatives has only been reported recently by Kerton and co-workers.[34] They described the synthesis, characterization and application of phosphine and phosphinite ligands containing PDMS tags (Scheme 1-8). Generally, low molecular weight siloxane-based polymers are soluble in supercritical carbon dioxide ($scCO_2$).[64] The PDMS-supported phosphine ligands and Pd complexes proved to be soluble in $scCO_2$ and were effective for the Heck, Stille and Suzuki cross-coupling reactions in this green reaction medium. Also,

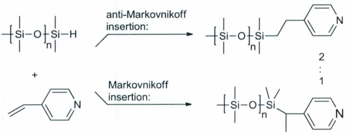


Scheme 1-8. Synthetic route to PDMS-tagged phosphine ligands.

PDMS and its metal complexes could be adsorbed onto silica to form heterogeneous catalysts and could potentially be recovered and reused several times in catalysis.[65] The Pd complexes of polydimethylsiloxane derived ligands were adsorbed onto silica and subsequently reduced *in situ* in $scCO_2$ to generate palladium nanoparticles.[35] Pd nanoparticles on silica, generated during C–C coupling reactions in $scCO_2$, could be recycled several times without any loss in activity (Scheme 1-9). Montilla, Galindo and co-workers have also done some outstanding work on this area recently. In 2007, they reported the syntheses and use of pyridine-functionalised polydimethylsiloxane polymers as a supercritical carbon dioxide solubilising support for copper compounds (Scheme 1-10).[66] The PDMS derived pyridine ligands have been used for olefin epoxidation and alcohol oxidation reactions.[36, 67-69]



Scheme 1-9. Silica supported Pd catalyzed C-C bond formation.

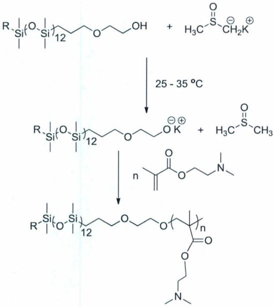


Scheme 1-10. Synthesis of the pyridine-functionalised polydimethylsiloxane.

1-2-2 Preparation and functionalization of polymeric ligands and metal complexes

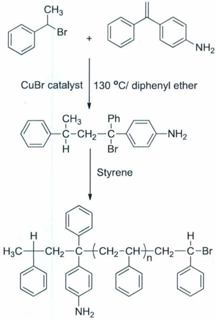
Despite their broad range of applications in agriculture, medicine, industry and sports, many commercially available polymers are limited for chemical catalysis due to a lack of functional groups. The polymer support must be functionalised with an N, O or phosphine group before exploiting them in chemical processes such as catalysis and metal ion separation. Functionalization involves the incorporation of a functional group to the polymer support. Functionalized polymers, especially end-functionalized polymers, may be prepared by two general different methods including polymerisation of monomers with functional groups and post-polymerization polymer modification. The polymerisation methods include step-growth polymerization, atom transfer radical polymerization or ring-opening metathesis polymerization. Polymer modification is generally achieved by functional group transformation. Typically, a combination of these two methods is used to make functionalised polymers.

Many naturally occurring and some synthetic functional polymers, including polyesters and polyamides are produced *via* step-growth polymerization. Armes et al. synthesized a series of novel, well-defined dimethylsiloxane-2-(dimethylamino)ethyl methacrylate diblock and triblock copolymers.[70] This was achieved by the oxyanion-initiated polymerization of 2-(dimethylamino)ethyl methacrylate (DMA) using either monofunctional or bifunctional low molecular weight poly(dimethylsiloxane) (PDMS) as macroinitiators (Scheme 1-11).

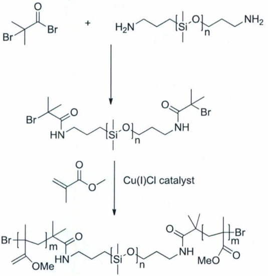


Scheme 1-11. Reaction scheme for the oxyanionic polymerization of 2-(dimethylamino)ethyl methacrylate (DMA) using the monocarbinol PDMS macroinitiator.

Atom transfer radical polymerization (ATRP) is a controlled free radical process that provides an efficient method for the synthesis of polymers with well-defined compositions, architectures, and functionalities.[71] Summers et al. prepared primary amine functionalized polystyrenes in quantitative yields by ATRP using the adduct of 1-(bromoethyl)benzene and 1-(4-aminophenyl)-1-phenylethylene as the initiator for styrene polymerization in the presence of a copper(I) bromide/ pentamethyldiethylenetriamine catalyst system (Scheme 1-12).[72] Haddleton et al. reported the synthesis of a triblock polymer of methyl methacrylate and PDMS with high molecular weight (29600 Dalton) and narrow molecular weight distribution (1.27).[73] The difunctional bromo-2-methylpropionamide poly(dimethylsiloxane) initiator could be easily prepared from the reaction of commercially available diaminopropyl-terminated PDMS with 2-bromoisobutyryl bromide (Scheme 1-13).



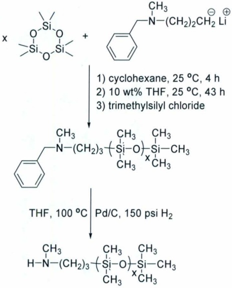
Scheme 1-12. Synthetic pathway for the ATRP polymerization of styrene in the presence of CuBr/PMDETA catalyst.



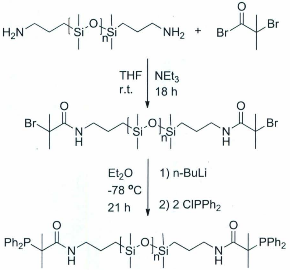
Scheme 1-13. Synthesis of a triblock polymer of methyl methacrylate and PDMS period.

The ring-opening polymerization (ROP) of cyclic oligomers is the primary route to the majority of silicon-based polymers and copolymers.[74] This route includes anionic, cationic and emulsion polymerization. Long and Elkins reported the living anionic polymerization of hexamethylcyclotrisiloxane using functionalized initiation.[75] A series of PDMS homopolymers were synthesized via living anionic polymerization using a protected amine functionalized initiator. The secondary amine functionalized PDMS could be subsequently obtained by removing the protection group which was suitable for further functionalization (Scheme 1-14).

Polymer modification can be considered the most common and easiest way to prepare the desired functionalized polymers. First, the commercially available functional polymer with desired support can be chosen. A series of functional group transformations enables the initial polymer to be transformed as desired. For example, commercially available diaminopropyl-terminated PDMS can be transformed to the PDMS-tagged phosphine ligand by amidation and subsequent nucleophilic substitution (Scheme 1-15).[76]

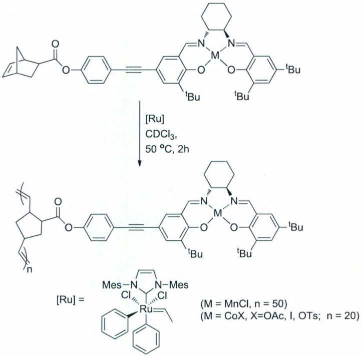


Scheme 1-14. Synthetic pathway for secondary amine-functionalized PDMS.



Scheme 1-15. Preparation of PDMS-tagged phosphine ligand by polymer modification.

The synthesis of polymer-supported metal complexes serves to provide an organic polymer with inorganic functionalities. The properties of the inorganic moiety are greatly controlled by the polymer support. When a functionalized polymeric ligand is mixed with a metal salt or metal complex under suitable reaction conditions, a polymeric metal complex is formed. Complex formation is typically achieved by mixing polymer-containing ligands such as amine, phosphine, carboxylic acid and Schiff bases with a solution of the metal complex. This results in the formation of various types of coordination complexes with pendant, inter- or intramolecular bridged structures. Moreover, a polymeric metal complex can also be obtained by polymerising a low molecular weight metal complex.[77] For example, Holbach and Weck reported a modular approach toward polymer-supported, metalated, salen catalysts.[78] The polymer-supported salen complexes were prepared by ROMP of the synthesized monofunctionalized Mn- and Co-salen complexes (Scheme 1-16). The obtained polymeric manganese and cobalt complexes were successfully employed as catalysts for the asymmetric epoxidation of olefins and the hydrolytic kinetic resolution of epoxides.

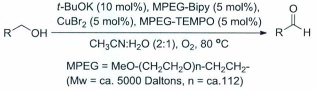


Scheme 1-16. ROMP of norbornene-functionalized salen complexes.

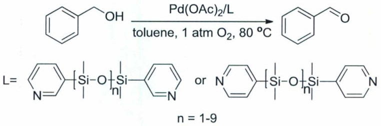
1-3 Selective polymer-supported catalysis in synthetic organic chemistry

Polymer–metal complexes have captured the interest of researchers in light of their potential applications in various fields, which include: waste water treatment,[79-80] electroluminescent devices[81] and transition metal-catalyzed reactions.[82] The use of polymer-supported catalysts, in general, offers several potential advantages. The main characteristics of the catalyst resulting from the polymer structure are the insolubility, increased activity, stability and selectivity since the polymeric catalyst combines the advantages of both heterogeneous and homogeneous catalysts. Polymer-supported metal complexes have been broadly used in oxidation, cycloaddition and C-C cross-coupling reactions.

Many polymer-bound oxidation catalysts have been developed in the last decade.[83] Toy et al. developed a multipolymer reaction system for the selective aerobic oxidation of primary alcohols.[84] A water-soluble polymer-supported 2,2′-bipyridine group and a similarly immobilized TEMPO derivative were used as ligands to coordinate with copper. It was the first reported example of using two different polymer-supported ligands together to form an organometallic species capable of catalyzing aerobic oxidation (Scheme 1-17). Very recently, Kung and co-workers reported bis(pyridyl)siloxane–Pd(II) complex catalyzed oxidations of benzyl alcohol to benzaldehyde (Scheme 1-18).[85] The steric bulk of the siloxane chain had a pronounced effect on the catalytic activity. It was proposed that the longer chain of the ligand with the siloxane backbone could improve the stability of the Pd catalyst and prevent agglomeration more effectively. Polymer-supported triphenylphosphine ligands have also been widely utilized as the ligands in transition-metal based oxidation reactions.[86-87] Polymer-supported Schiff base complexes of metal ions have also demonstrated high catalytic activity in oxidation reactions. For example, Ram and co-workers reported the epoxidation of cis-cyclooctene to cyclooctene oxide in the presence of a series of supported Ru Schiff base catalysts (Figure 1-8).[88] Benzene and styrene have also been oxidized to phenol and benzaldehyde respectively by polymer-supported Schiff base complexes of various metal ions.[89]



Scheme 1-17. Multipolymer reaction system for selective aerobic alcohol oxidation.



Scheme 1-18. Poly(pyridyl)siloxane Pd(II)-catalyzed oxidation of benzyl alcohol .

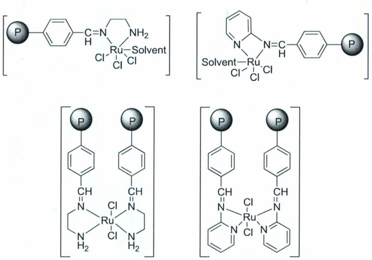
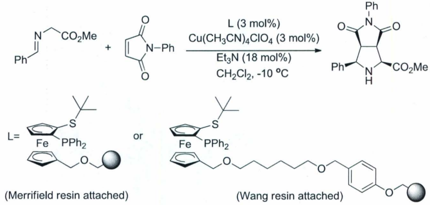


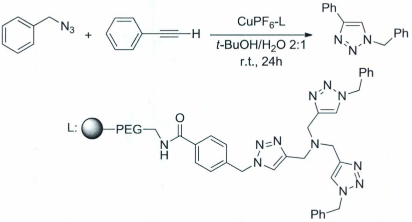
Figure 1-8. A series of polymer supported Ru(II) Schiff base catalysts.

Polymer-supported transition-metal complexes have also been developed for the catalysis of cycloaddition reactions.[82] Recently, Carretero et al. prepared two Fesulphos-based chiral ligands and immobilized them on a polystyrene backbone.[90] These supported chiral ligands with Cu(I) salt were very efficient catalysts in 1,3-dipolar cycloaddition with excellent activities and enantioselectivities (Scheme 1-19). The polymer-supported Cu complex could be recycled several times without loss of catalytic activity. Furthermore, the Fesulphos-based chiral ligand attached to Merrifield resin was also used in palladium-catalyzed asymmetric allylic substitution reactions with good results. Chan et al. developed a Cu(I)-stabilized tristriazole ligand which was effective for "click" reactions (azide-alkyne cycloaddition).[91] Recently, the tris-(benzyltriazolylmethyl)amine (TBTA) ligand has been immobilized on a TentaGel resin by the same research group.[92] The supported ligand was also very efficient for the copper-catalyzed "click" reaction

(Scheme 1-20); leaching of copper was minimal, and the polymer-bound TBTA ligand could be recycled up to ten times with only a small decrease in efficiency.

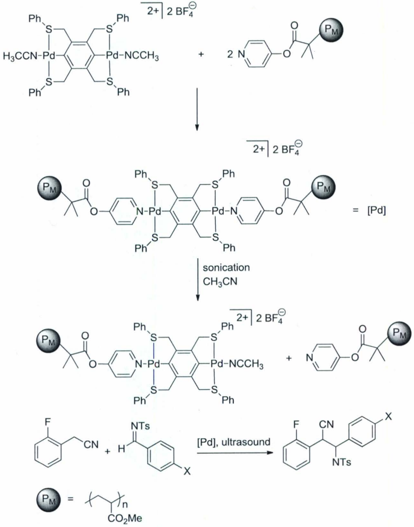


Scheme 1-19. Application of polymer-bound Fesulphos ligands in the cycloaddition.



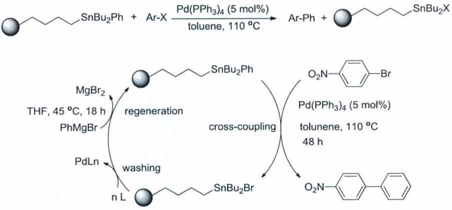
Scheme 1-20. A polymer-supported copper-tris(triazolyl) complex as a catalyst for the cycloaddition of an azide to an alkyne.

Carbon-carbon (C-C) cross coupling is a fundamental reaction in organic chemistry. It has proven synthetic utility in materials chemistry and the fine chemicals industry. Notably, the Pd-catalyzed Heck, Stille, Suzuki, Negishi, Hiyama, Kumada and Sonogashira type reactions have enabled C-C bond formation under mild conditions.[93] The significance of these reactions was acknowledged by the awarding of the 2010 Nobel Prize in Chemistry to R. F. Heck, E. Negishi, and A. Suzuki.[94] However, due to the high price and high toxicity of noble metals, it would be desirable to develop methods to perform these widely applicable and important transformations in more simple, atom-economical, and clean ways. Thus, it is not surprising that extensive efforts have been made to carry out cleaner and greener cross-coupling reactions through the use of polymers as supports. Polymers have served to make C-C cross-coupling reactions cleaner by acting as supports for reagents or catalysts, allowing for improved separations and catalyst recycling.[95] Very recently, Bielawski et al. reported a mechanical activation of catalysts for C-C bond formation and anionic polymerization reactions from a single macromolecular reagent.[96] First, they developed a cyclometalated dipalladium complex which they combined with a pyridine-functionalized poly(methyl methacrylate) support (Scheme 1-21). A chain cleavage occurred selectively at the metal-pyridine bond upon application of ultrasound. The scission cleavage process created active Pd species that could be effective for C-C coupling reactions.



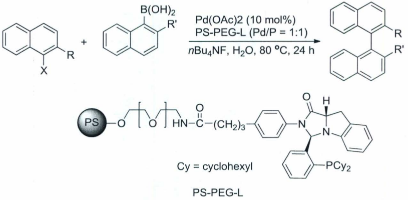
Scheme 1-21. Ultrasound activation of a polymer-supported Pd catalyst.

Compared to other types of cross-coupling reactions, the Stille reaction is an easier manipulation and there is no need for added base. The reaction has been extensively employed in the formation of natural products, especially in the generation of cyclic structures.[93] The main drawback of the Stille reaction is the toxicity of the organotin derivatives employed.[97] This has limited the use of the Stille reaction for pharmaceutical applications, which require the complete separation of the tin by-product from the target coupling product. The utilisation of polymer-supported tin reagents has greatly improved this problem. For example, Quintard and co-workers recently reported the use of polymer-supported dibutylphenyltin for Stille cross-coupling reactions.[98] The biaryl products were isolated in good to high yields with very low contamination by tin and palladium residues after removal of the residual supported organotin halide. The regeneration and recyclability of the supported dibutylphenyltin reagent was possible by treatment of the used polymer with 2,4,6-trimercaptos-triazine before the next cycle (Scheme 1-22).



Scheme 1-22. Stille cross-coupling reaction using polymeric dibutylphenyltin.

Polymer-supported Pd-catalyzed cross-coupling reactions can also be performed in green reaction media. As previously reported, Kerton and co-workers developed PDMS-derived Pd complexes which were efficient for Heck and Suzuki reactions in $scCO_2$.[34-35] There is also a growing interest in developing supported palladium catalysts to perform cross-coupling reactions in water. Uozumi et al. reported the Suzuki and Cu-free Sonogashira cross-coupling reactions in water using an amphiphilic resin-supported palladium catalyst.[99-101] The same group also reported an asymmetric Suzuki–Miyaura coupling for the synthesis of a variety of axially-chiral biaryl compounds with high stereoselectivity.[102] The cross-coupling reactions were carried out in water with a novel recyclable palladium complex of a PS-PEG-supported chiral phosphine ligand (Scheme 1-23). In addition, the recovered catalyst beads could be used for the next asymmetric coupling without further purification or additional charging with palladium salts.



Scheme 1-23. Polymer supported Pd-catalyzed Suzuki–Miyaura coupling in water.

Given their advantages, the use of polymer-supported catalysts for future applications is foreseeable. Research involving the design, synthesis and recovery of effective polymer-supported catalysts will undoubtedly continue to attract much interest.

1-4 Brief introduction to reactions in supercritical carbon dioxide

According to the 12 principles of Green Chemistry, the design of green chemical processes includes selection of feedstocks, solvents, catalysts and reaction route. Organic solvents are a major source of waste if not recycled, and their efficient control can produce a substantial improvement in the environmental impact of a process.[103] Ideally, the best solvent is no solvent at all. If a solvent is needed, green solvents or relatively green alternatives should be considered for the process. One important aspect of Green Chemistry is the scientific evaluation of potential replacements for volatile organic compounds (VOCs) as solvents and reaction media.[104] The design of environmentally benign solvents systems has been one of the most active areas of Green Chemistry over the past 20 years. Jessop recently presented four criteria for searching for green solvents: finding a sufficient range of green solvents; recognizing an actual green solvent; finding an easily-removable polar aprotic solvent and eliminating solvent distillation.[105] Supercritical fluids (SCFs) are gases that are nearly as dense as liquids, and can act as good alternative solvents. The cheapest supercritical fluid, $scCO_2$, which has solvent properties similar to those of light hydrocarbons, apart from an unusually high affinity for fluorocarbons, has been considered as one of the greenest solvents in the twenty-first century.[106] The first commercial decaffeination process utilizing $scCO_2$ as the solvent can be tracked to the 1960s.[107] As the phase diagram shows (Figure 1-9),[108] $scCO_2$ has easily accessible critical points (P_c: 72.9 atm, ρ: 0.47 g mL^{-1}, T_c: 31.1 °C).[106] It possesses hybrid properties of both liquid and gas. Its gas-like viscosity and high diffusion is advantageous to organic reactions, especially those involving gaseous reagents. Its solvency is tuneable through control of its density by variation of temperature and pressure leading to unusual chemical effects not easily achieved in conventional solvents. Also, the addition of small amounts of modifier is very useful in extending $scCO_2$ use in synthesis/extraction. In addition, CO_2 is abundant, inexpensive, non-flammable, non-toxic and chemically inert under many conditions. For example, the carbon atom of CO_2 has the highest oxidation state for carbon and therefore, cannot be oxidized. Furthermore, separation of $scCO_2$ from the reaction mixture is simple and energy efficient. Due to these significant features, $scCO_2$ has been successfully used as an environmentally friendly solvent for extraction and reaction.

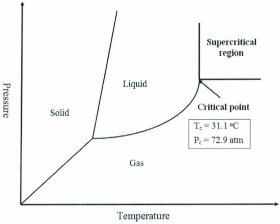
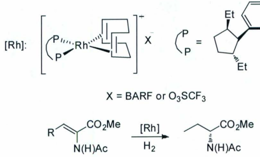


Figure 1-9. Phase diagram of CO_2.

1-4-1 Development of $scCO_2$-soluble catalysts

Although metal-catalyzed homogeneous reactions in $scCO_2$ would be attractive, the commonly used organometallic complexes usually have poor solubilities in $scCO_2$, which limits their catalysis applications using $scCO_2$ as a reaction medium. Therefore, enhancing the solubility of such catalysts in $scCO_2$ has been an important research target in recent years. The solubility of a solute in $scCO_2$ is extremely dependent on its structure. Normally, low polarity and high vapour pressure compounds are more soluble than highly polar substances or salts. However, a more efficient and practical method to improve solubility of metal complexes in $scCO_2$ is to introduce "CO_2-philic" groups into metal complexes including the use of "CO_2-philic" ligands. $ScCO_2$-philic functional groups, like perfluoroalkyl, polysiloxane substituents or polyether/polycarbonate copolymers give enhanced CO_2 solubility.[109] Burk, Tumas and co-workers employed the lipophilic, fluorinated tetrakis-(3,5-bis(trifluoromethyl)phenyl)borate (BARF) and trifluoromethane-sulfonate counteranions to enhance the solubility of cationic rhodium complexes (Scheme 1-24).[110] The corresponding Rh complexes proved to be effective for asymmetric hydrogenation in $scCO_2$ medium with high enantioselectivities. At the same time, different kinds of CO_2-philic ligands have been employed as solubilisers of metal complexes in $scCO_2$. The most successful and broadly used approach is to insert perfluorinated chains into aryl phosphines (Figure 1-10). Leitner and co-workers introduced perfluoroalkyl-substituted arylphosphanes as ligands for homogeneous catalysis in $scCO_2$.[111] Erkey et al. reported a series of homogeneous catalytic hydroformylations using Rh and fluorinated arylphosphine ligands in $scCO_2$.[112-115]



Scheme 1-24. Rh-catalyzed hydrogenation reaction in $scCO_2$.

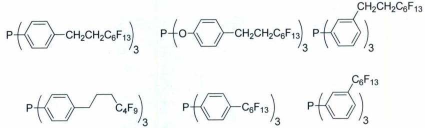


Figure 1-10. CO_2-philic fluorinated phosphines.

Fluorinated materials have been found to be highly CO_2-soluble and have been applied in the design of highly CO_2-soluble ligands in the last decade. However, from a sustainability and economy point of view, it is not desirable to utilize these fluorinated compounds in modern catalytic reactions. First, it is difficult and expensive to prepare ligands of this sort. In addition, the strongly electron-withdrawing fluorine can have an effect on the activity of the catalyst. Furthermore, certain fluorinated compounds can persist in the environment and therefore, are harmful to the environment and public health over a long period. For these reasons, the design of new, easily prepared and environmentally friendly solubilisers, that do not alter the chemical properties of the catalyst, is highly desirable. A few nonfluorinated CO_2-philes have been developed by different groups (Figure 1-11). Jessop and co-workers prepared analogues of triphenylphosphine with peracetylated sugar groups to enhance the solubility.[116] Kerton[34-35] and Montilla[66, 117] reported the use of PDMS and trimethylsilyl groups as $scCO_2$ solubilisers. Tan and Copper prepared functional oligo(vinyl acetate) CO_2-philes for solubilization and emulsification.[118]

Although the corresponding metal complexes of CO_2-philic ligands are not always soluble in $scCO_2$, it is still a promising method to develop CO_2-soluble, especially nonfluorinated ligands and surfactants in the future. It will greatly decrease the temperature and pressure of the reaction process in $scCO_2$ and therefore, will decrease energy consumption and safety concerns.

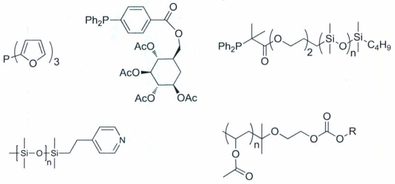
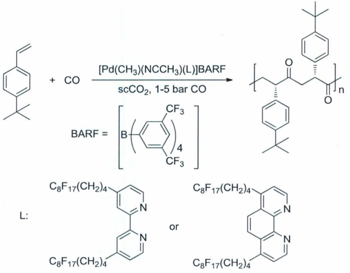


Figure 1-11. Nonfluorinated CO_2-philes.

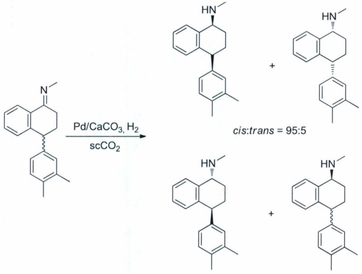
1-4-2 Select catalytic reactions in $scCO_2$

As mentioned above, $scCO_2$ has some significant features and can be utilized as a reaction medium for many catalytic reactions. Several reviews have reported on catalytic reactions in $scCO_2$.[108-109, 119-125] $ScCO_2$ has been used as a green reaction medium for polymerization, hydrogenation, hydroformylation and alcohol oxidation reactions. Recently, Schubert et al. reported a review about recent developments in the utilization of green solvents like $scCO_2$ in polymer chemistry.[125] Masdeu-Bultó, Leitner and co-workers reported CO/*tert*-butylstyrene copolymerisation in $scCO_2$ using soluble palladium complexes with perfluorinated bipyridine and phenanthroline ligands (Scheme 1-25).[126] Compared with conventional solvents, the polyketones obtained in $scCO_2$ are more syndiotactic with narrower polydispersities.



Scheme 1-25. Pd-catalyzed copolymerization in $scCO_2$.

$ScCO_2$ has been shown to be an excellent solvent for the replacement of conventional ones in hydrogenation reactions.[125] The enhanced solubility of hydrogen gas in $scCO_2$ offers good process control in terms of both selectivity and overall efficiency. It is possible to reduce the mass transport limitations which affect some conventional hydrogenation processes. In addition, hydrogenation is usually a highly exothermic reaction. The use of organic solvents with highly flammable hydrogen gas is often a safety concern, and in such situations the substitution of organic solvents by $scCO_2$ is desirable. $ScCO_2$ can act as both reactant and solvent in hydrogenation. Notable examples have been reported by Jessop and Noyori.[127-131] Hydrogenation of olefins is an important aspect in synthetic chemistry. Significant work has been done in the Clean Technology Group at the University of Nottingham.[132-137] Since 1995, led by Dr. Poliakoff, this group has worked with Thomas Swan & Co. Ltd. to develop continuous flow hydrogenation in $scCO_2$. As a successful collaboration result, the world's first, multi-reaction, supercritical flow reactor, capable of producing 1000 tons per annum, was commissioned in 2002.[138] Hydrogenation in $scCO_2$ has also been used in the pharmaceutical chemistry. Recently, Poliakoff et al. reported the hydrogenation of a pharmaceutical intermediate, [4-(3,4-dichlorophenyl)-3,4-dihydro-*2H*-naphthalenyidene]-methylamine using $scCO_2$ as a reaction medium.[137] As shown in Scheme 1-26, the continuous flow hydrogenation of *rac*-sertraline imine has been performed utilizing a $Pd/CaCO_3$ catalyst and hydrogen in $scCO_2$ with superior levels of selectivity. It was proposed that high diastereoselectivity obtained in the flow system was possibly due to the efficient heat transfer properties of $scCO_2$ which assisted removing excess heat from the catalyst surface. Even though various types of hydrogenations (e.g. heterogeneously catalyzed hydrogenations, homogeneous hydrogenations and asymmetric hydrogenations) have been extensively studied recently, it should be mentioned that the reaction conditions need to be carefully optimized. The reaction pressure and temperature of $scCO_2$ can greatly impact the activity and selectivity. In addition, the reduction of CO_2 should be avoided because the reduction products, CO and H_2O, may poison the catalyst.



Scheme 1-26. Hydrogenation of pharmaceutical intermediate imine in $scCO_2$.

Selective aerobic oxidation reactions using green solvents have been an important goal in Green Chemistry. Due to the properties of miscibility with molecular oxygen and excellent heat capacity, $scCO_2$ has attracted particular interest for utilization in oxidation reactions. Seki and Baiker have published a comprehensive review of these reactions recently.[124] Aerobic oxidation reactions in $scCO_2$ have been reported by numerous groups. Baiker[139-147] and Leitner[148-152] have done a lot of pioneering work in the field of heterogeneous catalytic oxidation using $scCO_2$ as a reaction medium. The employment of Pd nanoparticles stabilised on PEG-modified silica as catalysts for continuous-flow fixed-bed alcohol oxidation in $scCO_2$ has been reported by Leitner and co-workers recently (Figure 1-12).[150] The covalently bound PEG chains led to excellent activity and prevented agglomeration of the Pd nanoparticles on the surface during the catalytic oxidation process. Also, it was found that singlet oxygen can be efficiently sensitized in $scCO_2$ with an extended lifetime compared to many conventional solvents.[153] Because of this feature, $scCO_2$ proved to be a good solvent in which to carry out synthetic photosensitized oxidations.[154-156] Very recently, Herbert, Montilla and Galindo reported the first copper-TEMPO catalyzed aerobic alcohol oxidation system in $scCO_2$ (Scheme 1-27).[68] Although solubilisation of the metal catalyst in $scCO_2$ was not necessary in their system, $scCO_2$ proved to be a green replacement for the conventional solvents used in aerobic alcohol oxidations. Without a doubt $scCO_2$ will continue to be used as a green oxidation reaction medium in the future. The reaction conditions should be carefully optimized to avoid over-oxidation because of the high concentrations of O_2 in $scCO_2$.

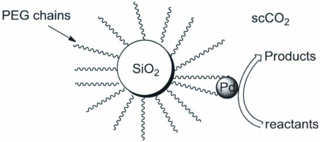
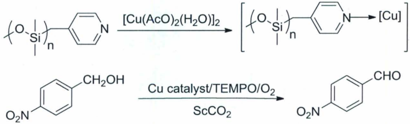


Figure 1-12. Palladium nanoparticles stabilised on PEG-modified silica for alcohol oxidation using scCO$_2$ as mobile phase for reactants and products.



Scheme 1-27. Cu-TEMPO catalyzed aerobic oxidation in scCO$_2$.

As an ambient gas, CO$_2$ can be easily recycled to reduce any possible new contributions to the greenhouse effect. Furthermore, it will not generate new CO$_2$ when using scCO$_2$ as a solvent, as the CO$_2$ used is a waste material from industrial processes including fermentation and combustion. The design, immobilization or recycling of environmentally friendly scCO$_2$-philic catalysts will still be a trend in the future. Furthermore, it is important to develop more general catalytic reactions using scCO$_2$ as the reaction medium by the introduction of co-solvents, liquid polymers or ionic liquids to the system.

1-5 Copper-catalyzed reactions

1-5-1 Copper-catalyzed reactions of alcohols

Catalysis can significantly improve the efficiency of a reaction by avoiding the use of stoichiometric amounts of reagents, lowering the energy input required and increasing the selectivity.[157] This leads to less feedstock, less energy consumption and less waste. Transition metals have been broadly used as efficient catalysts in various reactions e.g. polymerization, oxidation and cross-coupling reactions.[158-160] Noble metal catalysts are particularly well known for their high catalytic activities.[93] A notable example is Pd catalysts in cross-coupling reactions, a topic which has been recognized with the Nobel Prize for Chemistry 2010.[94] Moreover, catalysis makes some chemical reactions possible which cannot be accessed by traditional methods. However, the limited availability and high price of noble metals make their broad applications unaffordable and unsustainable. If the same catalytic activity can be achieved, it is desirable to use cheap and readily available alternatives. By comparing the prices and abundances of Cu, Ru, Rh and Pd in the Earth's crust obtained from the Sigma-Aldrich website in 2011, one can see that Cu is much cheaper and more easily available (Figure 1-13). Replacement of noble metals with Cu in some catalytic reaction is desireable. Cu catalysts have been broadly used in cross-coupling, addition and oxidation reactions.[161-164] Cu-catalyzed aerobic oxidations of alcohols have been extensively employed to replace traditional methods achieved by using stoichiometric amounts of toxic oxidants. Galactose oxidase (GOase), a natural mononuclear copper enzyme, is well known to oxidize benzylic and allylic alcohols to aldehydes with O_2 under mild reaction conditions and in aqueous solutions.[165-166] Semmelhack et al. reported the first practical CuCl-catalyzed aerobic oxidation of alcohols with TEMPO in 1984.[167] Since this pioneering work, Cu-catalyzed aerobic oxidation of alcohols has been greatly developed. Markó and co-workers developed three generations of alcohol oxidation catalysts with CuCl-Phenanthroline catalysts and di-*tert*-butyl hydrazine-1,2-dicarboxylate ($DBADH_2$).[168-173]

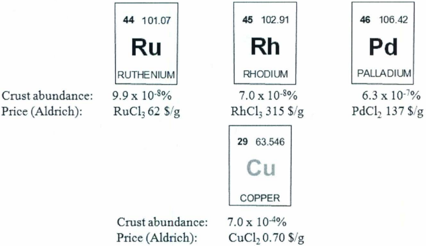


Figure 1-13. Crust abundance and price of select metal salts in 2011.

In addition, recent breakthroughs in Cu-catalyzed alcohol oxidation systems were also developed by Sheldon's,[174-177] Reedijk's[178-180] and Repo's groups.[181-186] For these catalytic systems, TEMPO is an essential co-catalyst. The main functionality of TEMPO is to abstract one hydrogen atom from the alcohol and facilitate the regeneration of the Cu catalytic cycle.[83, 187-192] Also, ligands play another important role for Cu-catalyzed oxidation reactions. Notably, various N-containing ligands (Figure 1-14) are used to pre- or *in situ* generate the copper complexes which are efficient for the selective aerobic alcohol oxidation reactions. Various reaction mechanisms of Cu-catalyzed aerobic alcohol oxidation have been proposed by different groups. The mechanism reported by Sheldon et al. for $CuBr_2$(bipyridine)-TEMPO catalyzed aerobic alcohol oxidation, based on galactose oxidase-catalyzed oxidation of alcohols, dominates this field (Figure 1-15).[175-176] Initially, the Cu^{II} species **I**, alcohol substrate and added strong base combine to give the coordinated alcoholate in intermediate complex **II**. Subsequent coordination of the H-acceptor TEMPO to Cu affords intermediate species **III** which is crucial to the catalytic cycle. The radical intermediate **IV** was formed *via* C-H abstraction from the alcoholate by the coordinated TEMPO molecule, which was stabilized by hydrogen bonding to the second β-hydrogen atom and the oxygen atom of TEMPOH. Then TEMPOH and the aldehyde dissociated from radical species **IV** and Cu(I) complex **V** was

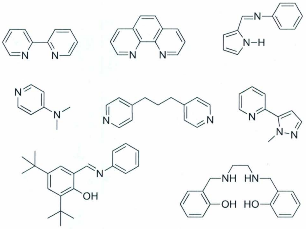


Figure 1-14. Commonly used N-containing ligands in Cu-catalyzed oxidation reactions.

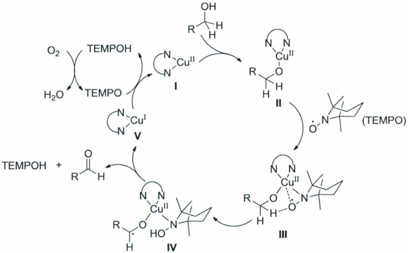
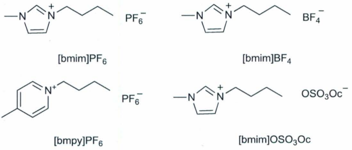


Figure 1-15. Dominated Cu-catalyzed oxidation mechanism proposed by Sheldon et al.

formed. Cu(II) complex **I** and TEMPO were regenerated by the oxidation of Cu(I) complex **V** and TEMPOH with oxygen and thus the catalytic cycle was completed. However, this mechanism is not appropriate for the oxidation of secondary alcohols.

Cu-catalyzed aerobic oxidation can also be performed in non-conventional solvents. As described before, Herbert et al. reported the first copper-TEMPO catalyzed aerobic alcohol oxidation system in $scCO_2$.[68] A few examples of Cu-catalyzed aerobic oxidations of alcohols in ionic liquids have also been reported.[193-197] Various commercially available ionic liquids such as $[bmim]PF_6$ and $[bmim]BF_4$ were efficiently used (Figure 1-16). In these cases, the ionic liquids can be recycled and reused several times. Recently, Chrobok et al. reported a supported ionic liquid phase catalysis for aerobic oxidations of primary alcohols.[197] A large amount of ionic liquid, which is necessary for use in a homogenous reaction system, is not needed in the new supported ionic liquid phase (SILP) catalysis system. The Cu-TEMPO catalyst system based on SILP can oxidize primary alcohols to the corresponding aldehydes with excellent yields. Furthermore, the catalysts can be recycled and reused over seven cycles without significant loss of activity. Water, the most environmentally benign and accessible solvent, can be also employed as the oxidation reaction medium. Repo et al. have developed different effective catalyst systems for Cu-catalyzed aerobic oxidation in water.[184, 186]



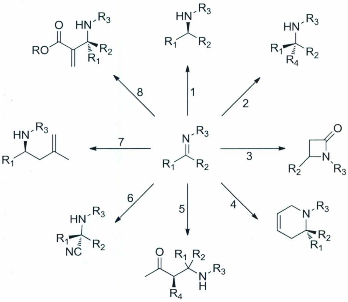
[bmim]PF_6 [bmim]BF_4

[bmpy]PF_6 [bmim]OSO_3Oc

Figure 1-16. Commercially available ionic liquids which have been used in Cu-catalyzed oxidation reactions. [OSO_3Oc^- = n-octylsulfate]

1-5-2 Copper catalyzed reactions of amines and anilines

Imines are important intermediates in organic synthesis which can serve as electrophilic reagents in many transformations such as condensations and additions (See Scheme 1-28 for selective examples).[198] Imines are also versatile starting materials for the synthesis and racemisation of chiral amines, which are important intermediates in the preparation of biologically-active compounds.[199-202] The traditional protocol for the synthesis of imines involves the condensation of an amine with a carbonyl compound such as an aldehyde or ketone. Owing to the unstable and reactive nature of carbonyl compounds, alternative routes for the synthesis of imines would be more desirable. For example, the direct oxidation of amines to imines has attracted much attention recently. Largeron and co-workers reported an environmentally friendly biomimetic electrocatalytic method for the oxidation of primary aliphatic amines to imines with high yields.[203] A few transition metal-catalyzed oxidations of amines with stoichiometric amounts of various oxidants have also been reported.[204-205] In addition, a few highly efficient catalysts for the aerobic

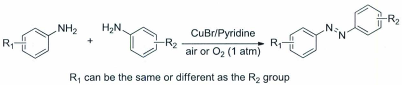


Scheme 1-28. Examples of imines as intermediates: 1) hydrogenation;[206] 2) addition;[207] 3) condensation;[208] 4) aza-Diels-Alder;[209] 5) Mannich addition;[210] 6) Strecker;[211] 7) imino—ene;[212] 8) aza-Baylis-Hillman.[213]

oxidation of amines have been developed recently using cobalt,[213] gold,[214-218] palladium[214], ruthenium[215-219] and vanadium[220] complexes. As described above, copper complexes can serve as efficient catalysts for the aerobic oxidation of alcohols. A few copper complexes have also been employed for the catalysis of aerobic dehydrogenation of amines to imines.[221-224] Very recently, Adimurthy and Patil reported a simple Cu-catalytic system for the aerobic oxidation of amines to imines (Scheme 1-29).[224] Notably, the catalytic reactions can be carried out under neat conditions with low catalyst loading.

Scheme 1-29. CuCl catalyzed oxidation of amines to imines under neat conditions.

Azo derivatives have been widely utilized in industry as organic dyes, indicators and radical reaction initiators.[225-227] Two examples of Cu-catalyzed aerobic oxidative dehydrogenative coupling of anilines to azo compounds have been reported by Xi's and Jiao's groups.[228-229] In the research by Zhang and Jiao, CuBr and pyridine were highly efficient in preparing symmetric and asymmetric aromatic azo compounds by aerobic oxidative dehydrogenative coupling of anilines (Scheme 1-30).[229] A wide range of functional groups, whether electron-donating or electron-withdrawing, could be tolerated and therefore, could be used for further transformations.



Scheme 1-30. CuBr catalyzed oxidative dehydrogenative coupling of anilines.

1-6 Summary and structure of thesis

A brief historic background of Green Chemistry has been presented in Chapter 1. From the principles of Green Chemistry, it is desirable to develop green synthetic routes including the utilization of environmentally benign reagents, catalysts and solvents. As one of the most important functional group transformations, the importance of greener oxidation methods was described. The preparation and application of polymeric ligands and metal complexes has also been presented followed by a description of their advantages. The development of catalysts and selective catalytic reactions in $scCO_2$, a green reaction medium in the 21st century, was discussed. At the end of this Chapter, oxidation reactions of alcohols and amines catalyzed by Cu, which is readily available and cheap, were presented.

Chapter 2 presents the synthesis and characterization of polydimethylsiloxane-supported ligands and copper complexes and their analogues. The solubility experiments of the PDMS derived ligands and copper complexes in $scCO_2$ are also presented.

Chapter 3 discusses the room temperature aerobic oxidation of alcohols using $CuBr_2$ with TEMPO and a tetradentate polymer-based pyridyl-imine ligand.

Chapter 4 presents Cu-TEMPO-catalyzed aerobic dehydrogenation of amines and anilines.

Finally, Chapter 5 contains the conclusion of this thesis and some proposed future research.

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Co-Authorship Statement

This PhD thesis includes results of joint research that have been submitted to peer reviewed journals in the form of three full papers, as follows:

Chapter 2: Preparation of α-ω-di(pyridyl-imine) ligands with flexible linkers and their coordination chemistry with copper

Authors: Zhenzhong Hu, Céline M. Schneider, Christina N. Price, Whitney M. Pye and Francesca M. Kerton

Journal: Submitted to *Dalton Transactions* in September 2011

The principal author (Zhenzhong Hu) contributed to all aspects of the project as the main researcher including: literature review, performing all the experiments, collecting and analyzing the data, designing new experiments, presenting and discussing the data with the corresponding authors, mentoring Christina N. Price and Whitney M. Pye who were both undergraduate summer students and writing the first draft of the submitted manuscript.

The co-author (Céline M. Schneider) ran around 20% of the NMR experiments and data analysis including all solid state NMR and 2D NMR. Through running solid-state NMR experiments, she also came up with the initial idea of the metallomacrocycle acting as a host for the PF_6^- anion. Also, she ran the PGSE experiments for the copper complexes and assisted analyzing the data.

The co-authors (Christina N. Price and *Whitney M. Pye)* performed the initial UV-Vis and IR spectroscopic experiments on **L1** and its complexes. This amounts to approximately 5% of the experiments. However, they did not contribute significantly to the data analysis.

The corresponding author (Dr. Francesca M. Kerton) suggested the initial research idea and contributed to different aspects of the project including: data analysis, design of new experiments, computational studies, revision of the prepared manuscript and submission to the journal as well as supervision of both the principal author (Z. H.) and co-authors (C. N. P. and W. M. P.).

Chapter 3: Room-Temperature Aerobic Oxidation of Alcohols Using $CuBr_2$ with TEMPO and a Tetradentate Polymer Based Pyridyl-Imine Ligand

Authors: Zhenzhong Hu and Francesca M. Kerton

Journal: Submitted to *Applied Catalysis A: General* in August 2011, accepted subject to revision

The principal author (Zhenzhong Hu) contributed to all aspects of the project as the main researcher including: literature review, performing all the experiments, collecting and analyzing the data, designing new experiments, presenting and discussing the data with the corresponding author and writing the first draft of the submitted manuscript.

The corresponding author (Dr. Francesca M. Kerton), supervision of the principal author (Z. H.), contributed to several aspects of the project including: data analysis, design of new experiments, revision of the prepared manuscript and submission to the journal.

Chapter 4: Simple copper/TEMPO catalyzed aerobic dehydrogenation of benzylic amines and anilines

Authors: Zhenzhong Hu and Francesca M. Kerton

Journal: Accepted by *Organic and Biomolecular Chemistry* in November 2011

The principal author (Zhenzhong Hu) contributed to all aspects of the project as the main researcher including: literature review, performing all the experiments, collecting and analyzing the data, designing new experiments, presenting and discussing the data with the corresponding author and writing the first draft of the submitted manuscript.

The corresponding author (Dr. Francesca M. Kerton), supervision of the principal author (Z. H.), contributed to several aspects of the project including: data analysis, design of new experiments, revision of the prepared manuscript and submission to the journal.

Chapter 2

Preparation of α-ω-di(pyridyl-imine) ligands with flexible linkers and their coordination chemistry with copper

A version of this chapter has been submitted to *Dalton Transactions* in September, 2011.

Some modifications were made to the original paper for inclusion as a chapter in this thesis.

2-1 Introduction

A number of research groups have previously used mono end-capped polydimethylsiloxane (PDMS) in green chemistry and other applications,[1-9] including the preparation of CO_2-philic molecules with potential uses in green catalysis.[1, 5-6] Difunctional PDMS, containing ligating groups at either end of a PDMS chain, has been explored to a lesser extent in the field of coordination chemistry and catalysis. In such a situation, the ligands could bind to metal centres in a number of ways (Figure 2-1). Tritopic ligands separated by short polydimethylsiloxane chains have been used by Lehn and co-workers to prepare metal-containing extended polymers that can be processed into films with potential sensor applications.[10] Pyridyl-imine based ligands have recently found applications in the field of catalytic water oxidation,[11] and have also been used extensively in olefin dimerization, oligomerization and polymerization catalysis.[12-15]

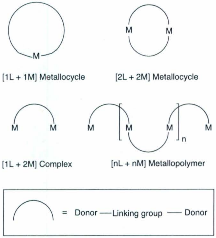
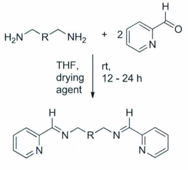


Figure 2-1. Schematic representation of possible binding modes for bridging/linked ligands.

In the course of studying PDMS-derived ligands, evidence has been obtained for a large-sized [1+1] metallocyclic species [Cu(**L1**)]PF_6 that is discussed herein, which although able to form crystalline domains, is not amenable to single-crystal X-ray crystallographic analysis. Therefore, other analytical methods were pursued and a series of other ligands and complexes prepared for comparison. Recently, Constable and co-workers have shown that PGSE NMR spectroscopy is a valuable technique to use in determining the size and, therefore, the major species in solution for $[Co_nL_n][PF_6]_{3n}$ metallomacrocyles.[16] Use of rigid linkers between two ligands has allowed chemists to isolate [2+2] metallocycles and other molecules with larger numbers of metal ions.[17-20] However, there are very few examples of [1+1] metallocycles,[21-24] and if the ligands are separated by flexible, long bridging groups, there is a tendency for mixtures to form. In the study presented here, the formation of [2+2] species cannot be ruled out, as common analytical methods are not able to easily distinguish between [1+1] and [2+2] complexes in solution (UV-Vis and NMR spectroscopy) or the gas-phase (mass spectrometry). A combination of methods is required to confirm their formation.

2-2 Results and Discussion



Scheme 2-1. General reaction route for the ligand preparation.

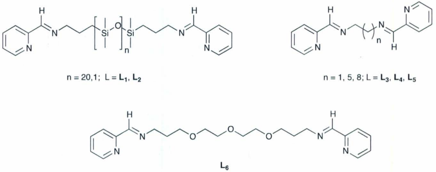


Figure 2-2. Ligands used in this study.

Amino terminated PDMS (PDMS-NH_2), 1,3-bis(aminopropyl)tetramethyldisiloxane, ethylenediamine, 1,6-diaminohexane, 1,9-diaminononane and 4,7,10-trioxa-1,13-tridecanediamine react readily via a Schiff-base condensation with two equiv. 2-pyridinecarboxaldehyde in the presence of drying agents to give **L1-L6** (Scheme 2-1, Figure 2-2). **L3** has been widely studied by others (see below) and was included in this work for comparative purposes. The polymeric starting material PDMS-NH_2 and ligands were characterized using ^{1}H NMR, ^{13}C NMR, FT-IR, MALDI-TOF mass spectrometric (MS) data and elemental analyses. GPC analysis confirmed that no polymer degradation or coupling occurred during the synthesis of **L1** as its retention volume was nearly identical to PDMS-NH_2. The number of dimethylsiloxane repeat units (n) was determined using end-group analysis of the ^{1}H NMR spectrum, elemental analysis and MS data. MS analysis revealed that **L1** had M_w 1567, M_n 1317 and a resulting polydispersity of 1.19. Overall, the spectrum had a similar appearance to that of its coordination complex in that the peak separations (74 mass units), their intensities and isotope patterns are typical for monodisperse PDMS chains.[25] In previous studies, monodentate PDMS-derived ligands and their Pd complexes were found to be soluble in supercritical carbon dioxide ($scCO_2$).[1] Therefore, the solubilities of **L1** and **L2** in $scCO_2$ were assessed. **L2** was miscible in liquid CO_2 at room temperature. Cloud point data for **L1** over the temperature range 60-100 °C were measured (Figure 2-3). Copper complexes of these ligands were prepared, see below, and their solubility in $scCO_2$ gauged. Significantly higher temperatures and pressures were needed to dissolve [Cu(**L2**)](PF_6) compared with the uncoordinated parent ligand **L2**, presumably due to the ionic nature of the metal complex. Unfortunately, [Cu(**L1**)](PF_6) was insoluble in CO_2 at all temperatures and pressures studied (25-120 °C, 4000-7500 psi).

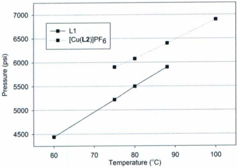


Figure 2-3. Cloud point data for **L1** and [Cu(**L2**)](PF_6), measurements made using using a SFT Phase Monitor II.

Initial investigations into the coordination chemistry of **L1** were performed via UV-Vis spectroscopy (Figure 2-4). The spectra of [Cu(CH_3CN)$_4$](PF_6) and **L1** show no absorbances in the visible region. However, a MLCT band was seen to grow in intensity

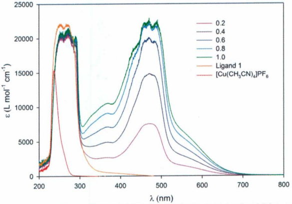


Figure 2-4. UV-Vis spectra for the titration of **L1** with [Cu(CH_3CN)$_4$](PF_6) in CH_2Cl_2; Cu = [Cu(CH_3CN)$_4$](PF_6) only, **L1** = **L1** only, molar equiv. of Cu with respect to **L1** from 0.2 to 1.0.

relative to an increase in concentration of copper(I) ions. This band reached a maximum intensity (λ = 465 nm, ε = 21 000 L mol^{-1}cm^{-1}) when there was one copper(I) ion per each **L1** corresponding to a [1+1] complex forming where each copper ion is surrounded by two chelating pyridyl-imine groups. This initial titration was performed in air but all further coordination chemistry experiments were performed under strictly air- and moisture-free conditions to avoid oxidation of the copper ion. The reaction was then performed on a synthetic scale and the resulting solid characterized using FT-IR, NMR, MALDI-TOF MS, GPC and elemental analyses. These data support the self-assembly of a [1+1] metallocyclopolymeric complex, [Cu(**L1**)](PF_6). The GPC chromatogram (using RI detection) contained a single peak at a retention volume nearly identical to **L1** and PDMS-NH_2. However, in contrast to previously characterized [1+1] metallocyclopolymers,[21] MS analyses show no evidence for larger [2+2] or other species. MALDI-TOF MS data revealed that the [Cu(**L1**)]$^+$ cations had M_w 1710, M_n 1382 and a polydispersity of 1.24 (Figure 2-5). Low molecular weight region m/z 500-2500 was shown for clarity in Figure 2-5, although a spectral window from 100-10,000 was analyzed. Modeling of ESI MS data also supported this formulation. On comparing the M_n values of the complex ion with **L1**, a difference of 65 mass units that is close to the molecular weight of Cu is obtained. Also, inspection of individual peaks within the mass spectrum showed an isotopic match corresponding to the presence of one copper atom and not two per polymer chain. However, at this stage, the possibility of either a gas-phase rearrangement/fragmentation within the mass

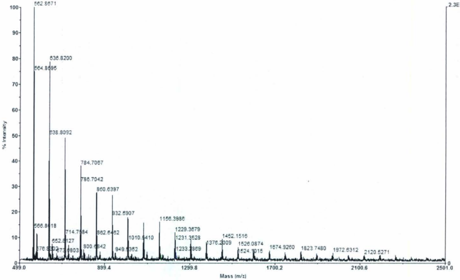


Figure 2-5. MALDI-TOF Mass spectrum of [Cu(**L1**)](PF_6).

spectrometer or the possibility of equilibration to yield the [1+1] complex from larger [n+n] species in solution during chromatographic analysis cannot be overlooked.

As very few well-characterized [1+1] complexes had been prepared to date,[21-24] the synthesis of a low molecular weight analog using L2 was undertaken. Spectral data for the resulting compound agreed with the formulation [Cu(L2)](PF_6). For example, the mass spectrum (positive mode) contained a single peak at an *m/z* and isotope match corresponding to [Cu + **L2**]$^+$ (Figure 2-6). Furthermore, UV-Vis analysis showed a MLCT band at 475 nm (ε = 16000 L mol^{-1}cm^{-1}). The frequency of this absorbance is similar to that reported for the known dicopper(I) helicate complexes of

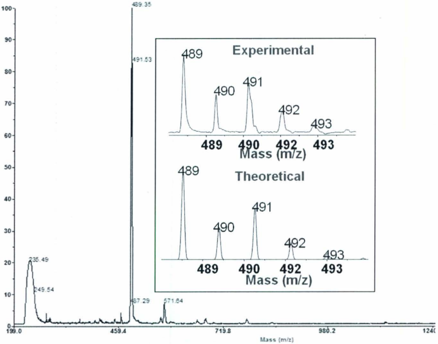


Figure 2-6. MALDI-TOF Mass spectrum of [Cu(**L2**)](PF_6), inset experimental and theoretical isotope pattern for $[Cu(\mathbf{L2})]^+$.

L3,[26] but the molar extinction coefficient for the MLCT of the **L1** and **L2** complexes is much greater. FT-IR data for these complexes are similar to structurally-verified copper(I) and nickel(II) complexes of bidentate and tetradentate pyridyl-imine ligands (Figure 2-7).[27-29] However, both the electronic and vibrational spectroscopic data would be alike for [1+1] and [2+2] species. ^1H and ^{13}C solution NMR data for [Cu(**L1**)](PF_6) and [Cu(**L2**)](PF_6) show the expected number of resonances, which are moderately shifted compared to the free ligands. ^1H-^1H coupling observable for the pyridyl protons in the free ligand was not observed in the complexes presumably due to the fluxionality of coordinate covalent bonds in solution leading to signal broadening. Through parallels with known copper(I) pyridyl-imine complexes,[30-32] processes including inter- and intramolecular ligand exchange through twisting at the metal or ligand dissociation are thought to occur.

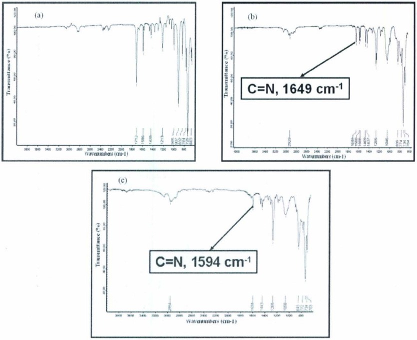


Figure 2-7. IR spectra of (a) PDMS-NH_2, (b) **L2** and (c) [Cu(**L2**)](PF_6).

Unfortunately to date, single crystals of the model complex, [Cu(**L2**)](PF_6), have not been obtained which could unambiguously confirm the cyclic [1+1] nature of the **L1** and **L2** complexes in the solid-state. However, over the course of these studies, it was noticed that during solvent evaporation from solutions of [Cu(**L1**)](PF_6) regions of dark intensity formed on the surface of the glassware. Upon further inspection under a microscope, crystalline domains were apparent which became more visible under cross-polarized light (Figure 2-8). At room temperature, powder X-ray diffraction analysis of [Cu(**L1**)](PF_6) showed two intense, sharp peaks at a constant Bragg angle 2θ of 0.42° and 1.44°. These correspond to d-spacings of 210.1 Å and 61.3 Å. Both are significantly longer than the predicted diameter of the metallocyclopolymer, which is calculated to be 24.6 Å for a [1+1] complex and 48.0 Å for a bimetallic [2+2] complex. Therefore, bimolecular (or greater) aggregration must exist within the layers of the crystalline phase (with one of these d-spacings corresponding to the distance between layers within the crystalline phase). Recently, Gloe and co-workers reported the remarkable self-assembly of three

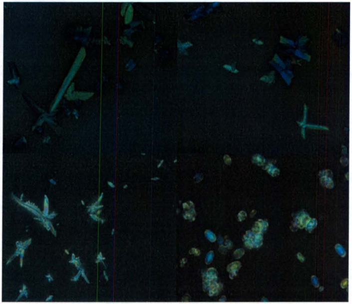


Figure 2-8. Photomicrographs of [Cu(**L1**)](PF_6) under cross-polarized light obtained using a Leica DM 2500 microscope (20× magnification), top left: 298 K, top right: 318 K, bottom left: 333 K, bottom right: 373 K.

hexametallic copper(II) meso-helicates, $[CuL(SO_4)]_6 \bullet 24H_2O$ (where L is a linked bis-pyridyl-imine ligand), that were circular in shape.[33] The self-assembly was controlled by the coordination of sulfate ions with the copper(II) centres. The diameter of these structures in the solid-state was determined to be 31-32 Å by single-crystal X-ray diffraction analysis. At this stage, a multimetallic structure similar to these cannot be ruled out for $[Cu(\mathbf{L1})]_n(PF_6)_n$ in the solid-state. However, the crystalline nature of the complex does rule out a supramolecular linear metallopolymer, as by analogy to Lehn and Chow's results an elastomeric polymer would be expected due to the flexible nature of the PDMS linking group.[10]

L3-**L6** were prepared and their reactions with $[Cu(CH_3CN)_4](PF_6)$ investigated in order to obtain greater insight into the chemistry of **L1** and **L2**. **L4** has been explored to some extent previously,[34] and **L3** studied extensively by other chemists.[28-30, 32, 35-41] $[Cu_2(\mathbf{L3})_2](PF_6)_2$ and $[Cu_2(\mathbf{L3})_2](ClO_4)_2$ have been structurally characterized (Figure 2-9).[30, 32] The central dicopper(I) helicate cation was determined to be 13.7 Å in diameter. A [1L +2Cu] complex, $[Cu_2(\mathbf{L3})(PPh_3)_2I_2]$, has also been structurally characterized.[39] An extensive study of copper complexes of **L3** and related ligands has been performed by Fabbrizzi and co-workers involving spectroelectrochemistry and mass spectrometric monitoring of the assembly and disassembly of the copper helicates.[26] They propose the formation of $[Cu^I(L)]^+$ complexes upon reduction of the analogous copper(II) ion and prior to the self-assembly of the typical copper(I) bimetallic bis(ligand) helicates. The lifetimes of the intermediate $[Cu^I(L)]^+$ species were assessed to be less than 20 ms, however, their presence in this cycle shows that the formation of such complexes is not thermodynamically barred rather that there is a kinetic preference for the helicate structures with these particular ligands.

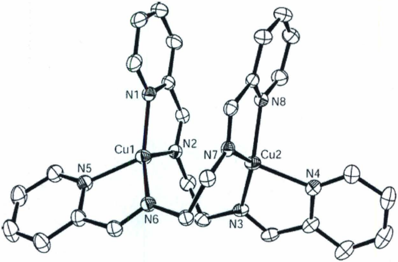


Figure 2-9. Molecular structure of the $[Cu_2(\mathbf{L3})_2]^{2+}$ cation prepared by Wild and co-workers.[32] Reprinted with permissions from Ref. 32. Copyright 2006 American Chemical Society.

In 1984, van Koten and co-workers reported extensive NMR studies on the dynamic behavior and solution-state structures of pyridyl-imine complexes of Ag(I) and Cu(I) including $[Cu_2(\mathbf{L3})_2](O_3SCF_3)_2$,[30-31] using ^1H, natural-abundance INEPT ^{15}N and INEPT ^{109}Ag NMR experiments. Where present, the nature of the bridging C_2 chain between the pyridyl-imine ligands was determined to be the major influence on intramolecular fluxional processes.[30] FD mass spectra for the complexes in that study confirmed the formation of dimetallic dications including $[Cu_2(\mathbf{L3})_2]^{2+}$. More recently, ESI mass spectra for $[\mathrm{Cu^{II}}(\mathbf{L3})](\mathrm{CF_3SO_3})_2$ showed a peak at *m/z* 450 corresponding to $\{[\mathrm{Cu}(\mathbf{L3})]\mathrm{CF_3SO_3}\}^+$ and for $[\mathrm{Cu^{I}}_2(\mathbf{L3})_2](\mathrm{ClO_4})_2$ showed a peak at *m/z* 701 corresponding to $\{[\mathrm{Cu_2}(\mathbf{L3})_2]\mathrm{ClO_4}\}^+$.[26] In ESI experiments, the mass spectrum for the copper(I) complex of **L3** contained a peak at *m/z* 747 corresponding to $\{[\mathrm{Cu_2}(\mathbf{L3})_2]\mathrm{PF_6}\}^+$. However, even with the fragmentor voltage set to low, all coordination compounds reported in this chapter afforded spectra containing 100% intensity peaks which could be assigned to $[\mathrm{Cu} + \mathbf{L}]^+$ on the basis of *m/z* and isotope patterns. It should be noted that $[\mathrm{Cu_2}(\mathbf{L})_2]^{2+}$ species would appear at the same *m/z* positions as $[\mathrm{Cu} + \mathbf{L}]^+$ ions but would possess significantly different isotope patterns. It should also be noted that care was taken to avoid oxidation of the copper(I) complexes in this study and therefore, the peaks in the mass spectra are not from copper(II) species. For **L2, L4-6**, ESI mass spectra showed no peaks that could be assigned to bimetallic species. Mass spectra for the polymeric ligand **L1** and its copper complex were discussed above. These data were obtained using a MALDI-TOF mass spectrometer. Therefore, we studied the complexes of **L2-L6** using this method. Using this type of ionization, bimetallic ions were observed for **L4-L6**. The molecular ion region of the mass spectra and theoretical isotope patterns for $\{[\mathrm{Cu_2}(\mathbf{L})_2]\mathrm{PF_6}\}^+$ (**L** = **L4**, **L5** or **L6**) are available in Appendix 1. Numerous MS spectra of **L1**-**L2** complexes were obtained but none showed evidence of bimetallic species. These results highlight that, if numerous related coordination complexes (monometallic, bimetallic, trimetallic etc.) could potentially be formed, it would be advisable to perform as broad a range of mass spectrometric experiments as possible to confirm initial results and data obtained using one technique.

Pulse-field gradient spin-echo (PGSE) diffusion NMR spectroscopy can be used to obtain diffusion coefficients of solution-state species and in turn this data can be used to obtain molecular sizes.[42-43] This method has been successfully applied to a range of coordination compounds including metallomacrocycles. In the absence of structural data, and for comparison with NMR data, MMFF- and semi-empirical PM3-calculations were performed using SPARTAN '08 software to obtain approximate radii for the compounds in their geometry optimized equilibrium [1+1] and [2+2] forms (Figure 2-10 and Table 2-1).

Table 2-1. Measured solution viscosity (n) and solution diffusion coefficients (*D*), calculated hydrodynamic radii from NMR data, r_H, calculated MMFF- and semi-empirical PM3-calculations, for copper coordination compounds and calculated or known radii for [1+1] and [2+2] species.

Complexes	$n/10^{-3}$ kg s^{-1} m^{-1}	$D/10^{-9}$ m^2 s^{-1}	r_H/Å	[1+1] /Å	[2+2] /Å
$[Cu(\mathbf{L1})](PF_6)$	0.70	0.54± 0.06	13.7± 0.1	12.3	24.0
$[Cu(\mathbf{L2})](PF_6)$	0.41	2.50 ± 0.12	4.1± 0.2	6.4	10.5
$[Cu_2(\mathbf{L2})_2](BF_4)_2$	0.29	3.44 ± 0.21	4.0 ± 0.5	6.4	10.5
$[Cu_2(\mathbf{L3})_2](PF_6)_2$	0.28	2.94 ± 0.06	7.9 ± 0.1	4.8	6.8[a]
$[Cu_2(\mathbf{L4})_2](PF_6)_2$	0.35	1.96 ± 0.07	9.6 ± 0.4	5.1	9.9
$[Cu_2(\mathbf{L5})_2](PF_6)_2$	0.38	1.18 ± 0.02	14.8 ± 0.3	5.6	10.5
$[Cu_2(\mathbf{L6})_2](PF_6)_2$	0.34	2.06 ± 0.25	9.7 ± 1.1	6.4	10.4

[a] The radius for $[Cu_2(\mathbf{L3})_2]^{2+}$ in the solid-state from crystallographic data reported in ref. 32

The hydrodynamic radii, r_H, of the $[Cu_nL_n]^{n+}$ species in solution were determined from the sample diffusion coefficients, Table 1, once a proper model (spherical model, ellipsoidal-prolate or ellipsoidal-oblate model) and equation had been chosen. Typically, the hydrodynamic radius (r_H) of the diffusing species can be estimated from the diffusion coefficient using the Stokes–Einstein equation (2-1).

$$D_t = \frac{kT}{6\pi\eta r_H} \quad (2\text{-}1)$$

For equation (1), k is the Boltzmann constant, T is the absolute temperature and η is the fluid viscosity. However, equation (1) has some limitations in deriving r_H from D_t for some species, especially for small or medium-sized particles.[43] Therefore, equation (1) is modified to allow radii to be determined for a broader range of particle size, equation (2-2).

$$D_t = \frac{kT}{B\eta r_H} \quad (2\text{-}2)$$

The numerical coefficient B can be in the range of 2 to 6π.[44,45] The B value depends on the sample size, shape and NMR methods used. Herein, pure chloroform-*d* and acetonitrile-d_3 were used as the internal standards to obtain the appropriate B value. The viscosity of deuterated chloroform or acetonitrile, η(25 °C) = 0.542 or 0.342 cp, was measured. The hydrodynamic radii of the solvents, $r_H(CDCl_3)$ = 2.65 Å and $r_H(CD_3CN)$ = 4.09 Å were used according to the literature.[46-47] The corresponding B value was determined to be 9.9 and 6.2. According to the modified numerical coefficient, the hydrodynamic radii of the copper coordination compounds were calculated and are presented in Table 2-1. Data from these diffusion studies, alongside computational studies, clearly suggest that **L1** and **L2** form [1+1] metallic complexes. The radius extracted from NMR data for the copper(I) complex with **L3** showed a good agreement with that derived from X-ray diffraction data for the [2+2] species. Similarly, hydrodynamic radii data and computational studies clearly suggest that **L4**, **L5** and **L6** form bimetallic dicationic complexes in solution. Furthermore, the NMR-derived radii for the copper complexes with all ligands showed good agreement with the formulation determined from mass spectrometric evidence.

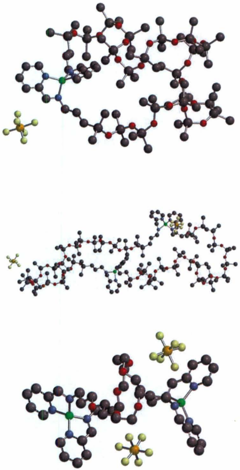


Figure 2-10. Molecular models of $[Cu_n(\mathbf{L1})_n](PF_6)_n$ (n = 1 and 2) and $[Cu_2(\mathbf{L6})_2](PF_6)_2$.

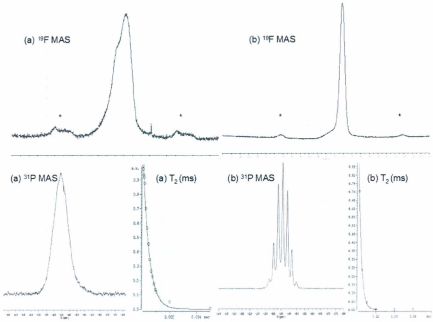


Figure 2-11. Solid-state NMR spectra for (a) $[Cu(L1)](PF_6)$, ^{19}F-NMR δ -65 (v.br) (deconvoluted as two environments δ -67 (F1 35%), –60 (F2 65%), ^{31}P-NMR δ -139 (v.br), $J_{F\text{-}P}$ = 685 Hz, T_2 = 0.46 ms, T_2^* = 0.34 ms; (b) $[Cu(L2)](PF_6)$, ^{19}F-NMR δ -70 (br), ^{31}P-NMR δ -141 (septet), $J_{F\text{-}P}$ = 711 Hz, T_2 = 2.81 ms, T_2^* = 1.26 ms. (* = spinning side bands).

In an attempt to confirm the presence of cyclic species in the solid-state, MAS NMR experiments were performed (Figure 2-11). For $[Cu(CH_3CN)_4](PF_6)$, the ^{19}F NMR spectrum in solution exhibits a doublet at –75 ppm, $J_{P\text{-}F}$ = 711 Hz with a relaxation time T_2^* of 72.0 ms. In the solid-state, the signal shifts to higher frequency, -67 ppm, $J_{P\text{-}F}$ remains unchanged and T_2^* decreases to 2.0 ms. The solid-state ^{31}P NMR spectrum of $[Cu(CH_3CN)_4](PF_6)$ exhibits a septet at -142 ppm, $J_{P\text{-}F}$ = 709 Hz and T_2^* of 5.2 ms. This frequency and coupling constant is typical for a non-constrained hexafluorophosphate anion.[48-49] ^{19}F NMR spectra of [Cu(**L1**)](PF$_6$) and [Cu(**L2**)](PF$_6$) in solution display the expected doublet resonance, but in the solid state [Cu(**L1**)](PF$_6$) is significantly different to the other species studied. The relaxation time for the ^{31}P environment is significantly shorter for the **L1** complex (0.34 ms) compared with the **L2** complex and [Cu(CH$_3$CN)$_4$](PF$_6$) (1.26 ms and 5.2 ms). This leads to significant broadening of the resonances for the **L1** species. The dramatically shorter T_2* and T_2 values suggest that the anions are held in a much more rigid environment in the cyclopolymer complex. Furthermore, for [Cu(**L1**)](PF$_6$) the broad ^{19}F resonance, –65 ppm, can be modelled as two ^{19}F environments, –67 and –60 ppm, with occupancies of 35% and 65% respectively. These unusual differences in NMR data could be interpreted in a number of ways. It is proposed that in [Cu(**L1**)](PF$_6$) some of the anions are held within the cyclic structures like a metal ion within a crown ether and therefore, have restricted motion compared with the small molecule **L2** analog where the anion cannot fit inside the macrocycle. Hydrolysis of the PF$_6^-$ anion or oxidation of the copper ion were ruled out as the reasons for the signal broadening and the presence of two environments in the ^{19}F MAS NMR spectrum, because (i) if the same sample is dissolved and solution NMR data is obtained a single environment is observed, and (ii) ESI MS showed no evidence of PF$_6^-$ hydrolysis or copper oxidation.

2-3 Experimental

2-3-1 General information

All reactions were carried out under dry nitrogen using standard Schlenk-line techniques. THF was dried and distilled over sodium benzophenone ketyl, whilst CH_2Cl_2 was dried and distilled over CaH_2. 2-Pyridinecarboxaldehyde, tetrakis(acetonitrile)copper(I) hexafluorophosphate and other reagents unless specified were purchased from Aldrich and used as received. PDMS-NH_2 ($H_2N(CH_2)_3(SiMe_2O)_{20}SiMe_2(CH_2)_3NH_2$) and 1,3-Bis(aminopropyl)tetramethyldisiloxane were purchased from Gelest. Elemental analyses were performed by Canadian Microanalytical Service Ltd. (Delta, BC). ^{1}H-NMR spectra were acquired on a Bruker AVANCE 500 MHz spectrometer. ^{13}C-, ^{19}F- and ^{31}P-NMR spectra were acquired on a Bruker AVANCE 300 MHz spectrometer. ^{19}F-NMR and ^{31}P-NMR solid-state (and some solution) spectra were acquired on a Bruker AVANCE II 600 MHz spectrometer. Chemical shifts were reported in ppm using the residual protons of the deuterated $CDCl_3$ or tetramethylsilane as an internal reference. Tetramethylsilane-free deuterated solvents were used in the collection of NMR spectra for all siloxane containing species. For polymeric samples in solution, delays were increased to allow complete relaxation of all protons and to obtain more accurate integration. For **L1**, **L2** and their copper complexes, MALDI-TOF mass spectral data were obtained using an Applied Biosystems Voyager mass spectrometer. Dithranol was used as the matrix. For copper complexes of **L2**, **L4**-**L6**, mass spectral data were obtained using an ABI QSTAR XL (Applied Biosystems/MDS Scies, Foster City, USA) hybrid quadrupole TOF MS/MS system equipped with an oMALDI 2 ion source. Dihydroxybenzoic acid (DHB) was used as the matrix. Also, for copper complexes of **L1-L6**, ESI-MS spectra were recorded using direct injection into an Agilent 1100 LC/MSD (G1946A) instrument in ESI mode (solvent: acetonitrile, concentration: 1 mg/mL). The capillary voltage of the instrument was 3000 V and the fragmentor voltage was varied through low, medium and high settings for all samples. X-Ray Powder Diffraction data were obtained on a Rigaku Ru-200 12KW Automated Powder Diffractometer. Polarized microphotographs were obtained using a Leica DM 2500 microscope. A Bruker TENSOR 27 spectrometer was used to record FT-IR spectra. Gel permeation chromatographs (GPC) were obtained using a Viscotek VE 2001 instrument equipped with RI detector using the following condition: column type: Poly[Analytik]n, PAS-106M-H, 8.0 mm (ID) × 300 mm (L); flow rate: 1.0 mL/min; solvent: chlorobenzene. UV-Vis spectra were recorded using an Ocean Optics UV-Vis spectrometer. TGA was performed on a Universal V4.5A TA instrument. The solubility of ligands and complexes in supercritical carbon dioxide was studied using a Supercritical Fluids Technologies Phase Monitor II (SFT PM II).

2-3-2 General procedure for Schiff Base condensation reactions to yield L1-L6

For **L1:** 2-Pyridinecarboxaldehyde (1.04 g, 9.71 mmol) was added to a mixture of PDMS-NH_2 (4.60 g, 3.00 mmol) and anhydrous sodium sulfate (5.02 g, 35.3 mmol) in 50 mL dry THF. The mixture was stirred at room temperature and the reaction was judged to be complete after 12 h by monitoring the disappearance of the C=O absorption band and the appearance of the newly formed C=N bond using infrared spectroscopy. The mixture was filtered *via* cannula. Solvent and unreacted starting materials were evaporated under vacuum. The product **L1** was isolated as an orange oil. Yield: 86%.

Ligands **L2** to **L7** were prepared in a similar way but reactions were complete after 6 h. **L2**, orange oil. Yield: 92%. **L3**, yellow powder. Yield: 94%. **L4**, yellow powder. Yield: 94%. **L5**, yellow powder. Yield: 92%. **L6**, orange oil. Yield: 91%. Yellow solids were recrystallized from hexane to yield colorless crystals.

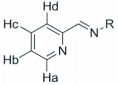


Figure 2-12. Lettering scheme used to distinguish ^{1}H-^{1}H coupling constants

L1. ^{1}H NMR (500 MHz, CDCl$_3$, 298 K): δ 8.61 (d, $J_{\text{Ha-Hb}}$ = 4.4 Hz, 2H), 8.35 (s, 2H), 7.97 (d, $J_{\text{Hc-Hd}}$ = 7.9 Hz, 2H), 7.70 (td, $J_{\text{Hb-Hc, Ha-Hc}}$ = 7.5, 1.5 Hz, 2H), 7.28 (ddd, $J_{\text{Hb-Hc, Ha-Hb, Hb-Hd}}$ = 7.5, 4.4, 1.1 Hz, 2H), 3.65 (td, J = 7.1, 1.1 Hz, 4H), 1.78–1.72 (m, 4H), 0.59–0.56 (m, 4H), 0.17 to -0.02 (br, 126H). ^{13}C{^{1}H} NMR (75 MHz, CDCl$_3$, 298 K): δ 161.8, 154.8, 149.5, 136.6, 124.6, 121.3, 64.8, 24.7, 16.0, 1.3, 1.1, 0.3. IR (KBr): ν/cm^{-1} 2962, 2360, 1650, 1588, 1469, 1437, 1258, 1013, 789, 703, 668. MS (MALDI-TOF, Matrix = Dithranol): *M*w: 1567, *M*n: 1317, polydispersity: 1.19. Found: C 39.78, H 7.79, N 3.29; $C_{60}H_{148}N_4O_{20}Si_{21}$ requires C 39.26, H 8.13, N 3.05%.

L2. ^{1}H NMR (500 MHz, CDCl$_3$, 298 K): δ 8.62 (ddd, $J_{\text{Ha-Hb, Ha-Hc, Ha-Hd}}$ = 4.8, 1.6, 0.9 Hz, 2H), 8.35 (s, 2H), 7.97 (d, $J_{\text{Hc-Hd}}$ = 7.9 Hz, 2H), 7.71 (td, $J_{\text{Hb-Hc, Ha-Hc}}$ = 7.5, 1.6 Hz, 2H), 7.28 (ddd, $J_{\text{Hb-Hc, Ha-Hb, Hb-Hd}}$ = 7.5, 4.8, 1.2 Hz, 2H), 3.64 (td, J = 7.1, 1.1 Hz, 4H), 1.77–1.70 (m, 4H), 0.59–0.54 (m, 4H), 0.05 (s, 12H). ^{13}C{^{1}H} NMR (75 MHz, CDCl$_3$, 298 K):

δ 161.6, 154.6, 149.3, 136.4, 124.5, 121.1, 64.6, 24.6, 15.9, 0.3. IR (KBr): ν/cm^{-1} 2929, 1649, 1588, 1568, 1469, 1437, 1265, 1045, 839, 774, 734, 704. Found: C 61.51, H 8.37, N 12.85; $C_{22}H_{34}N_4OSi_2$ requires C 61.92, H 8.03, N 13.13%.

L3. m.p. 66-67 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ 8.62 (ddd, $J_{\text{Ha-Hb, Ha-Hc, Ha-Hd}}$ = 4.8, 1.6, 0.9 Hz, 2H), 8.42 (s, 2H), 7. 98 (d, $J_{\text{Hc-Hd}}$ = 7.9 Hz, 2H), 7.71 (td, $J_{\text{Hb-Hc, Ha-Hc}}$ = 7.5, 1.6 Hz, 2H), 7.29 (ddd, $J_{\text{Hb-Hc, Ha-Hb, Hb-Hd}}$ = 7.5, 4.8, 1.2 Hz, 2H), 4.06 (s, 4 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 298 K): δ 163.4, 154.4, 149.4, 136.5, 124.8, 121.3, 61.3. IR (KBr): ν/cm^{-1} 2884, 1649, 1562, 1468, 1428, 1330, 1041, 969, 912, 863, 767. Found: C 70.22, H 5.74, N 23.43; $C_{14}H_{14}N_4$ requires C 70.57, H 5.92, N 23.51%.

L4. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ 8.63 (ddd, $J_{\text{Ha-Hb, Ha-Hc, Ha-Hd}}$ = 4.8, 1.6, 0.9 Hz, 2H), 8.36 (s, 2H), 7.97 (d, $J_{\text{Hc-Hd}}$ = 7.9 Hz, 2H), 7.72 (td, $J_{\text{Hb-Hc, Ha-Hc}}$ = 7.5, 1.6 Hz, 2H), 7.29 (ddd, $J_{\text{Hb-Hc, Ha-Hb, Hb-Hd}}$ = 7.5, 4.8, 1.2 Hz, 2H), 3.67 (td, J = 7.0, 1.1 Hz, 4H), 1.85–1.72 (m, 4H), 1.45–1.42 (m, 4H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 298 K): δ 161.6, 154.5, 149.3, 136.4, 124.4, 121.0, 61.3, 30.5, 27.0. IR (KBr): ν/cm^{-1} 2929, 2853, 1642, 1563, 1465, 1430, 1378, 1034, 988, 946, 768. Found: C 73.15, H 7.45, N 18.79; $C_{18}H_{22}N_4$ requires C 73.44, H 7.53, N 19.03%.

L5. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ 8.63 (ddd, $J_{\text{Ha-Hb, Ha-Hc, Ha-Hd}}$ = 4.8, 1.6, 0.9 Hz, 2H), 8.36 (s, 2H), 7.98 (d, $J_{\text{Hc-Hd}}$ = 7.9 Hz, 2H), 7.73 (td, $J_{\text{Hb-Hc, Ha-Hc}}$ = 7.5, 1.6 Hz, 2H), 7.30 (ddd, $J_{\text{Hb-Hc, Ha-Hb, Hb-Hd}}$ = 7.5, 4.8, 1.1 Hz, 2H), 3.66 (td, J = 7.0, 1.3 Hz, 4H), 1.76–1.68 (m, 4H), 1.37–1.32 (m, 10H). ^{13}C{^{1}H} NMR (75 MHz, Acetone-d$_6$, 298 K): δ 162.5, 156.0, 150.2, 137.2, 125.5, 121.2, 61.8, 31.6, 28.0. IR (KBr): ν/cm^{-1} 2921, 2849, 1646, 1563, 1464, 1434, 1345, 1046, 953, 946, 773. Found: C 74.82, H 8.36, N 16.64; $C_{21}H_{28}N_4$ requires C 74.96, H 8.39, N 16.65%.

L6. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ 8.64 (ddd, $J_{\mathrm{Ha\text{-}Hb,\ Ha\text{-}Hc,\ Ha\text{-}Hd}}$ = 4.9, 1.6, 0.9 Hz, 2H), 8.40 (s, 2H), 7.97 (d, $J_{\mathrm{Hc\text{-}Hd}}$ = 7.9 Hz, 2H), 7.73 (td, $J_{\mathrm{Hb\text{-}Hc,\ Ha\text{-}Hc}}$ = 7.5, 1.6 Hz, 2H), 7.30 (ddd, $J_{\mathrm{Hb\text{-}Hc,\ Ha\text{-}Hb,\ Hb\text{-}Hd}}$ = 7.5, 4.9, 1.2 Hz, 2H), 3.77 (td, J = 6.8, 1.2 Hz, 4H), 3.67-3.60 (m, 8H), 3.58 (t, J = 6.5 Hz, 4H), 2.03 (p, J = 6.5 Hz, 4H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 298 K): δ 162.1, 154.5, 149.4, 136.4, 124.6, 121.2, 58.0, 30.5. IR (KBr): ν/cm^{-1} 2860, 1647, 1465, 1436, 1355, 1102, 984, 877, 773. Found: C 65.96, H 7.48, N 13.87; $C_{22}H_{30}N_4O_3$ requires C 66.31, H 7.59, N 14.06%.

2-3-3 General procedure for preparation of Cu(I) complexes: [Cu(**L1**)](PF_6), [Cu(**L2**)](PF_6), [Cu(**L2**)](BF_4), [Cu_2(**L3**)$_2$](PF_6)$_2$, [Cu_2(**L4**)$_2$](PF_6)$_2$, [Cu_2(**L5**)$_2$](PF_6)$_2$, [Cu_2(**L6**)$_2$](PF_6)$_2$

For [Cu(**L1**)](PF_6): Tetrakis(acetonitrile)copper(I) hexafluorophosphate (0.744 g, 2.00 mmol) was added to a Schlenk flask containing THF (50 mL). This mixture was left to stir until all of the copper salt had dissolved. **L1** (3.64 g, 2.00 mmol) was dissolved in THF (5 mL) and transferred to the flask containing the copper salt *via* cannula. The solution was stirred at room temperature for 24 h. The solvent was removed under vacuum and the product was isolated as a dark brown sticky solid. Yield: 52%.

For the remaining complexes, reactions were performed in CH_2Cl_2 and stirred at room temperature for 12 h. [Cu(**L2**)](BF_4), [Cu_2(**L3**)$_2$](PF_6)$_2$, [Cu_2(**L4**)$_2$](PF_6)$_2$, [Cu_2(**L5**)$_2$](PF_6)$_2$ were isolated as dark brown powders. Yields: 83-88%. [Cu_2(**L6**)$_2$](PF_6)$_2$ was isolated as a black powder. Yield: 90%.

[Cu(**L1**)](PF_6). ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ 8.61 (s, 2H), 8.44 (s, 2H), 8.01 (s, 2H), 7.89 (s, 2H), 7.58 (s, 2H), 3.80 (s, 4H), 1.67 (s, 4H), 0.53 (s, 4H), -0.05 to +0.08 (br, 126H). ^{19}F NMR (565 MHz, solid state, 298 K): δ -61, -67. ^{31}P NMR (243 MHz, solid state, 298 K): δ -140 (v.br). IR (KBr): v/cm^{-1} 2963, 2359, 1592, 1437, 1301, 1258, 1017, 835, 793, 705, 668. MS (MALDI-TOF, Matrix = Dithranol): Mw = 1710, Mn = 1382, polydispersity 1.24. Found: C 35.10, H 7.01, N 2.91; $C_{60}H_{148}N_4O_{20}Si_{21}CuPF_6$ requires C 35.25, H 7.30, N 2.74%.

[Cu(**L2**)](PF_6). ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ 8.59 (s, 2H), 8.38 (s, 2H), 8.01 (s, 2H), 7.88 (s, 2H), 7.59 (s, 2H), 3.84 (s, 4H), 1.81 (s, 4H), 0.42 (s, 4H), 0.02 (s, 12H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$, 298 K): δ 161.3, 150.7, 148.7, 138.5, 128.0, 127.2, 63.6, 24.9, 15.3, 0.4. ^{19}F NMR (565 MHz, solid state, 298 K): δ -70 (br). ^{31}P NMR (243 MHz, solid state, 298 K): δ -141 (septet, $J_{F\text{-}P}$ = 711 Hz). IR (KBr): v/cm^{-1} 2954, 1594, 1443, 1265, 1058, 843, 772, 734, 703. MALDI-TOF MS (Matrix = Dithranol or Dihydroxybenzoic acid): m/z 489.3 [**L2**+Cu]$^+$. ESI MS (CH_3CN): m/z 489.2 (100) [**L2**+Cu]$^+$. Found: C 41.22, H 5.29, N 8.54; $C_{22}H_{34}N_4OSi_2CuPF_6$ requires C 41.60, H 5.40, N 8.82%.

[Cu(**L2**)](BF_4). ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): δ 8.59 (s, 2H), 8.39 (s, 2H), 8.01 (s, 2H), 7.87 (s, 2H), 7.58 (s, 2H), 3.84 (s, 4H), 1.81 (s, 4H), 0.41 (s, 4H), 0.03 (s, 12H). ^{13}C{^{1}H}-NMR (75 MHz, $CDCl_3$, 298 K): δ 161.3, 150.7, 148.7, 138.5, 128.0, 127.2, 77.6, 77.2, 76.7, 63.6, 24.9, 15.3, 0.4. MALDI-TOF MS (Matrix = Dihydroxybenzoic acid): *m/z* 489.3 [**L2**+Cu]$^+$. ESI MS (CH_3CN): *m/z* 489.2 (100) [**L2**+Cu]$^+$. Found: C 45.97, H 5.87, N 9.48; $C_{22}H_{34}N_4OSi_2CuBF_4$ requires C 45.79, H 5.94, N 9.71%.

[Cu_2(**L3**)$_2$](PF_6)$_2$. ^{1}H NMR (500 MHz, CD_3CN, 298 K): δ 8.48 (s, 2H), 8.24 (d, 2H), 7.93 (dd, 2H), 7.64 (dd, 2H), 7.46 (d, 2H), 4.20 (s, 4H). ^{13}C{^{1}H} NMR (75 MHz, CD_3CN, 298 K): δ 163.7, 151.0, 149.7, 139.4, 129.2, 127.5, 60.9. ^{19}F NMR (282 MHz, CD_3CN, 298 K): δ -72.66 (d, $J_{F\text{-}P}$ = 707 Hz). ^{31}P NMR (122 MHz, CD_3CN, 298 K): δ -144.5 (septet, $J_{F\text{-}P}$ = 707 Hz). IR (KBr): *v*/cm^{-1} 2913, 1593, 1471, 1436, 1306, 1260, 1155, 828, 773. ESI MS (CH_3CN): *m/z* 747.0 (40) [2**L3** + 2Cu + PF_6]$^+$, 301.1 (100) [**L3**+Cu]$^+$. Found: C 37.05, H 3.14, N 12.26; $C_{14}H_{14}N_4CuPF_6$ requires C 37.63, H 3.16, N 12.54%.

[Cu_2(**L4**)$_2$](PF_6)$_2$. ^{1}H-NMR (500 MHz, CD_3CN, 298 K): δ 8.58 (s, 2H), 8.37 (s, 2H), 8.07 (s, 2H), 7.81 (s, 2H), 7.62 (s, 2H), 3.73(s, 4H), 1.57 (s, 2H), 1.19 (s, 2H). ^{13}C{^{1}H} NMR (75 MHz, Acetone-d$_6$, 298 K): δ 162.6, 151.8, 150.0, 139.5, 129.1, 127.8, 60.4, 31.8, 27.4. ^{19}F NMR (282 MHz, Acetone-d$_6$, 298 K): δ - 73.00 (d, $J_{F\text{-}P}$ = 708 Hz). ^{31}P NMR (122 MHz, Acetone-d$_6$, 298 K): δ -144.1 (septet, $J_{F\text{-}P}$ = 708 Hz). IR (KBr): *v*/cm^{-1} 2928, 2857, 1592, 1441, 1302, 1254, 1157, 828, 770. MALDI-TOF MS (Matrix = Dihydroxybenzoic acid): *m/z* 859.2 [2**L4** + 2Cu + PF_6]$^+$. ESI MS (CH_3CN): *m/z* 357.4 (100) [**L4**+Cu]$^+$. Found: C 42.71, H 4.35, N 10.97; $C_{18}H_{22}N_4CuPF_6$ requires C 42.99, H 4.41, N 11.14%.

$[Cu_2(\mathbf{L5})_2](PF_6)_2$. ^1H NMR (500 MHz, Acetone-d_6, 298 K): δ 8.91 (s, 2H), 8.62 (s, 2H), 8.23 (s, 2H), 8.07 (s, 2H), 7.78 (s, 2H), 3.91 (s, 4H), 1.71 (s, 4H), 1.48 – 0.78 (m, 10H). $^{13}C\{^1H\}$ NMR (75 MHz, Acetone-d_6, 298 K): δ 162.5, 151.9, 150.1, 139.5, 129.2, 127.9, 60.7, 31.8, 27.7. ^{19}F NMR (282 MHz, Acetone-d_6, 298 K): δ -72.33 (d, $J_{F\text{-}P}$ = 708 Hz). ^{31}P NMR (122 MHz, Acetone-d_6, 298 K): δ -144.1 (septet, $J_{F\text{-}P}$ = 708 Hz). IR (KBr): v/cm^{-1} 2925, 2854, 1592, 1466, 1441, 1302, 1218, 1154, 830, 771. MALDI-TOF MS (Matrix = Dihydroxybenzoic acid): *m/z* 943.3 $[2\mathbf{L5} + 2Cu + PF_6]^+$. ESI MS ($CH_3CN$): *m/z* 399.5 (100) $[\mathbf{L5}+Cu]^+$. Found: C 45.84, H 5.07, N 10.59; $C_{21}H_{28}N_4CuPF_6$ requires C 46.28, H 5.18, N 10.28%.

$[Cu_2(\mathbf{L6})_2](PF_6)_2$. ^1H NMR (500 MHz, CD_3CN, 298 K): δ 8.66 (s, 2H), 8.46 (s, 2H), 8.09 (s, 2H), 7.88 (s, 2H), 7.66 (s, 2H), 3.89 (s, 4H), 3.43 (s, 8H), 3.37 (s, 4H), 1.85 (s, 4H) $^{13}C\{^1H\}$ NMR (75 MHz, CD_3CN, 298 K): δ 162.5, 151.9, 150.0, 139.3, 129.1, 127.7, 71.4, 70.5, 68.5, 57.6, 31.7. ^{19}F NMR (282 MHz, CD_3CN, 298 K): δ -72.71 (d, $J_{F\text{-}P}$ = 707 Hz). ^{31}P NMR (243 MHz, CD_3CN, 298 K): δ -144.5 (septet, $J_{F\text{-}P}$ = 707 Hz). IR (KBr): v/cm^{-1} 2862, 1592, 1466, 1444, 1301, 1260, 1099, 828, 771. MALDI-TOF MS (Matrix = Dihydroxybenzoic acid): *m/z* 1067.3 $[2\mathbf{L6} + 2Cu + PF_6]^+$. ESI-MS ($CH_3CN$): *m/z* 461.4 (100) $[\mathbf{L6}+Cu]^+$. Found: C 43.75, H 4.81, N 9.07; $C_{22}H_{30}N_4O_3CuPF_6$ requires C 43.53, H 4.98, N 9.23%.

2-3-4 PGSE NMR spectroscopy

Diffusion NMR measurements were performed on a Bruker Avance II 600 NMR spectrometer equipped with a 5 mm TXI probe and a z-gradient coil with a maximum strength of 5.35 G.cm^{-1} at 298 K. Samples were run in $CDCl_3$ and in CD_3CN. The 90° pulse lengths were determined for each sample. A standard 2D sequence with stimulated echo and spoil gradient (STEGP) was used. A gradient recovery delay of 2 ms was used and the relaxation delay was set at 10 s. The gradient strength was calibrated by using the self-diffusion coefficient of residual HOD in D_2O (1.9×10^{-9} m^2 s^{-1}). For each experiment, the gradient strength was increased from 2 – 95% in 32 equally spaced steps with 16 scans per increment. Values of δ (gradient pulse length) and Δ (diffusion time) were optimized on the sample HU-1 (coordination complex of **L1**) to give an intensity of between 5 and 10% of the initial intensity at 95% gradient strength and were set to 1.5 ms and 100 ms respectively for all subsequent samples.

The solvent peak was used as an internal standard to measure the viscosity of each sample. To that end, the diffusion coefficient of the pure solvent ($CDCl_3$ and CD_3CN) was first measured. This diffusion coefficient D_0 corresponds to the known viscosity η_0 of the pure solvent according to the Stokes-Einstein equation (2-3):

$$D_0 = \frac{kT}{Br\eta_0} \qquad (2\text{-}3)$$

Therefore for the solvent peak the diffusion coefficient in solution, D_{sol}, is afforded by (2-4):

$$D_{sol} = \frac{kT}{Br\eta_{sol}} \qquad (2\text{-}4)$$

Consequently the viscosity of each solution is obtained from (2-5):

$$\eta_{sol} = \frac{D_0}{D_{sol}}\eta_0 \qquad (2\text{-}5)$$

The numerical coefficient B has been shown to vary from 2 to 6π,[44] and can be calculated from the pure solvent diffusion coefficient too.

The data were plotted using MestReNova as Peak area vs. $Q=g^2\delta^2G^2(\Delta - \delta/3)$ and the diffusion coefficient (D) was extracted by fitting a mono exponential function ($I=I^0\exp(-D*Q)$) with the data analysis component of the software.

2-4 Conclusions

In summary, chelating pyridyl-imine ligands separated by a low molecular weight siloxane or polymeric siloxane group can form [1+1] metallocycles, although [2+2] metallocycles cannot be conclusively ruled out. Some of these compounds are soluble in $scCO_2$. PGSE NMR spectroscopy was useful in ascertaining the size of these and related complexes in solution and in confirming the formation of [1+1] or [2+2] species suggested from mass spectrometric data. Solid-state ^{19}F NMR data for the polymeric metallocycle suggests that the hexafluorophosphate anion resides both inside and outside the cycle, which is feasible given the size and resulting cavity in both [1+1] and [2+2] species. These observations confirm the importance of the linking groups in such self-assembly processes and it is likely that a serendipitous choice of ligand and metal led to the formation of the proposed metallocyclopolymer, [Cu(**L1**)](PF_6). Further experiments, such as preparing the analogous silver(I) complex, are required to rule out formation of larger metallocycles (2+2 or larger).

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Chapter 3

Room Temperature Aerobic Oxidation of Alcohols Using $CuBr_2$ with TEMPO and a Tetradentate Polymer Based Pyridyl-Imine Ligand

A version of this chapter has been accepted by *Applied Catalysis A: General* in November 2011.
Some modifications were made to the original paper for inclusion as a chapter in this thesis.

3-1 Introduction

The selective oxidation of primary and secondary alcohols to their corresponding aldehydes and ketones is an important functional group transformation in organic synthesis.[1-3] Traditionally, this is accomplished by addition of stoichiometric amounts of inorganic oxidants (e.g. $KMnO_4$, CrO_3, SeO_2, and Br_2), which often generate environmentally hazardous or toxic by-products.[4] There is a growing trend to develop safer and more environmentally friendly chemistry. From this perspective, it is not surprising that aerobic oxidation of alcohols using inexpensive and non-toxic air, O_2 or H_2O_2 as the sole terminal oxidant has continued to gain much interest in recent years.[5-7] The high atom efficiency of the reaction and non-toxic by-products make aerobic alcohol oxidations a promising and attractive synthetic method.

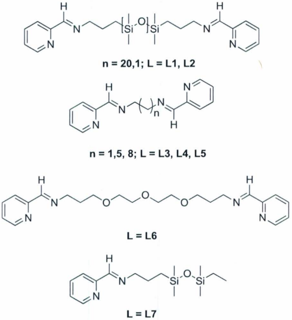
Many highly efficient catalysts for the aerobic oxidation of alcohols have been developed recently using palladium,[8-11] platinum,[12] ruthenium[13] and rhodium complexes.[14-17] In the interest of sustainability, there has been significant development in the use of more abundant and cheaper transition metals such as iron[18-19] and copper as active catalysts. Following the first reported aerobic oxidation of activated primary alcohols by Semmelhack et al. in 1984,[20] inexpensive and abundant copper has attracted much attention in the field of alcohol oxidations. Markó et al. have done pioneering work in this field and developed three generations of CuCl-phenanthroline catalytic systems, associated with di-*tert*-butyl hydrazine-1,2-dicarboxylate ($DBADH_2$) and strong base, for aerobic oxidation of alcohols.[21-25] Also, there has been significant interest in using the free radical TEMPO (2,2,6,6-tetramethyl-piperidinyl-1-oxy) or analogues as efficient co-catalysts in the aerobic oxidation of alcohols.[26-50] Sheldon and Reedijk et al. have reported the efficient use of copper-bipyridine and copper-pyrazole/TEMPO systems in oxidation reactions under air.[51-54] Velusamy et al. have reported a TEMPO/Copper-salen system that could efficiently oxidize a wide range of benzylic and heterocyclic alcohols (e.g. 2-furylmethanol) under an oxygen atmosphere.[55] Repo et al. recently reported a highly efficient catalytic system based on TEMPO/Copper-diimine (9.9 atm oxygen) and 2-*N*-arylpyrrolecarbaldimino (1 atm oxygen) systems for alcohol oxidation.[56-57] In recent studies, Koskinen et al. and Stahl et al. have described improved bipyridine-Cu-TEMPO catalytic systems for the effective oxidation of alcohols.[58-59] In both of these studies, trifluoromethanesulfonate copper salts were found to afford greater activity compared with copper halides, and use of N-methyl-imidazole as the base was advantageous. Furthermore, detailed kinetic studies performed by Koskinen and Kumpulainen indicate that bimetallic copper species play a crucial role in these transformations .[58]

Siloxane-derived ligands containing phosphorus donor atoms have been prepared previously and these ligands have been used in C-C coupling reactions.[60-61] More recently, pyridine terminated siloxane-derived ligands have been used in a variety of applications including oxidation catalysis.[62-67] This approach has been extended herein to prepare a bis(pyridyl-imine) terminated siloxane ligand and the first use of a series of tetradentate N-donor ligands in the aerobic oxidation of alcohols is reported.

3-2 Results and Discussion

3-2-1 Ligand effect

In order to further improve catalytic activity and strive towards a heterogeneous Cu/TEMPO based system, new chelating N-donor ligands were employed to substitute the classical bipyridine and salen-type ligands used in these homogeneous oxidation reactions. A series of α-ω pyridyl-imine terminated ligands were prepared (Figure 3-1). These ligands can be easily synthesized by the condensation reactions between pyridine-2-carboxylaldehyde and different diamines. This simple synthetic approach means that the ligand synthesis is amenable to forming heterogeneous solid-supported catalytic systems.[68] The resulting ligands contain backbones of differing chemical type and length attached to the donor groups. **L1-L6** are potentially tetradentate ligands whereas **L7** is bidentate.



n = 20,1; L = L1, L2

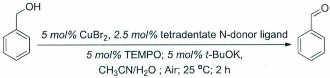
n = 1,5, 8; L = L3, L4, L5

L = L6

L = L7

Figure 3-1. Schematic structures of the ligands used in this catalytic study.

The oxidation of benzyl alcohol was chosen as a model reaction to investigate the utility of these ligands and any ligand effects (Scheme 3-1). As previously reported by Sheldon et al., TEMPO is crucial for the $CuBr_2$ catalyzed aerobic oxidation.[52] Furthermore, bases are used as co-catalysts to deprotonate the alcohol and increase the reaction rate. Catalysis using $CuBr_2$ with **L1-L7** also required TEMPO and base. Therefore, 5 mol% TEMPO and 5 mol% potassium *tert*-butoxide (*t*-BuOK) were chosen for screening ligand effects on the oxidation of benzyl alcohol to benzaldehyde (Table 3-1). The same results are obtained if potassium hydroxide is used as the base co-catalyst, however, *t*-BuOK was used as it can be more accurately weighed on a laboratory scale. Furthermore, it should be noted that in the absence of added base, the reaction still progresses albeit at a slower reaction rate. For entry 2, Table 3-1, a yield of 40% is obtained after 2 h reaction time in the absence of base and we presume that the organic basic groups within the ligand act as deprotonating co-catalysts. A quantitative yield of benzaldehyde was obtained after 8 h in the absence of added base. It should be noted that organic bases, e.g. N-methylimidazole, have been used in recent studies by other groups .[58-59]



Scheme 3-1. $CuBr_2$-catalyzed aerobic alcohol oxidation model reaction.

Encouraged by previous reports that some aerobic oxidation copper catalysts can be easily prepared *in situ* by mixing the copper salt and ligand in the reaction medium,[57, 69] an *in situ* approach to yield copper(II) complexes was used in this work. As revealed in Table 3-1, the yield of benzyl alcohol to benzaldehyde was very low in the absence of ligand (Table 3-1, entry 1). N-donor ligands are essential for the catalytic oxidation process. The PDMS derived tetradentate N-donor ligands (**L1** and **L2**) afforded very good yields when they were employed with $CuBr_2$ at 2:1 metal:L mole ratio (Table 3-1, entries 2 and 3). **L6** and the other tetradentate ligands employed also showed excellent activity (Table 3-1, entries 4-7). By comparing yields using these similar α-ω pyridyl-imine terminated ligands, the chain length of the ligand appeared to have some influence on the activity of the catalytic system. The ligands where donor groups were separated by a long chain led to greater catalytic activity than those containing short chains. These differences are possibly associated with freedom of movement and steric effects within the [Cu_2**L**] catalytic system. When provided with a long chain ligand, the copper coordination sphere has more space (less steric congestion). Therefore, it is easier for the substrate to enter the coordination sphere of the copper and become activated. These findings may be significant when designing heterogeneous tethered-Cu catalyst systems for aerobic oxidation processes, as two linked copper centres appear to be superior to copper centres that behave independently. It should be noted that replacement of tetradentate ligands (**L1**-**L6**) with a closely related pyridyl-imine bidentate ligand (**L7**) resulted in a much lower yield (Table 3-1, entry 9). Also, under the chosen reaction conditions, the employment of 1,10-phenanthroline (phen) and 2,2'-bipyridine ligands (Table 3-1, entries 10-11) gave lower yields than tetradentate ligands **L1-L6**. However, when TON are taken into account, commercially available ligands such as phen and 2,2'-bipyridine give very good results and would be more useful than tetradentate ligands **L1-L6** at the present time for practical chemistry applications.

The ratio of tetradentate ligand to copper was also important. When the amount of tetradentate ligand was increased to an equimolar amount with respect to $CuBr_2$, the yield dramatically dropped down to 12% (Table 3-1, entry 8). This can be explained by strong coordination of four N-donors to the copper centre and a difficulty in dissociating these to yield a vacant site. Cyclic coordination oligomers might be forming as previously reported for bis(pyridyl)siloxane ligands with palladium acetate.[66] Formation of such cyclic species would mean that coordination of the alcoholate group with the metal centre would be challenging.

Table 3-1. Influence of the ligand structure on the oxidation of benzyl alcohol to benzaldehyde.[a]

Entry	Catalytic System	Yield[b] (%)	TON (mols product/mol of Cu)
1	$CuBr_2$	4	1
2	$CuBr_2$ + **L1** (2:1)	91[c]	19
3	$CuBr_2$ + **L2** (2:1)	89	18
4	$CuBr_2$ + **L3** (2:1)	78	16
5	$CuBr_2$ + **L4** (2:1)	83	17
6	$CuBr_2$ + **L5** (2:1)	86	17
7	$CuBr_2$ + **L6** (2:1)	90	18
8	$CuBr_2$ + **L1** (1:1)	12	2
9	$CuBr_2$ + **L7** (1:1)	37	7
10	$CuBr_2$ + phen (1:1)	72	14
11	$CuBr_2$ + bipyridine (1:1)	85	17

[a] Reaction conditions: 5 mmol benzyl alcohol in the solvent mixture of 10 mL CH_3CN and 5 mL H_2O. *5 mol%* catalyst (Cu) loading, air, 2 h.

[b] GC yields (mols of benzaldehyde/100 mols of benzyl alcohol) using dodecane as an internal standard; in all cases selectivity was >99%. Yields were averaged for five runs under identical conditions, all values ± 2%.

[c] As per reaction conditions (a) but in the absence of t-BuOK, 40% yield obtained.

3-2-2 Solvent effect

Acetonitrile has been broadly used as a solvent in oxidation reactions. Gamez et al. has reported the great effect of acetonitrile on the Cu(II)-catalyzed oxidative coupling of 2,6-dimethylphenol.[69] The aerobic Cu(II)-catalyzed oxidation of primary alcohols has also been reported using a similar catalytic system.[52] In comparison with these results, the catalytic system reported here can tolerate a greater proportion of water in the solvent mixture and also achieved moderate yield levels in pure acetonitrile when the poly(dimethylsiloxane) derived **L1** was used, Table 3-2. Probably due to the insolubility of *t*-BuOK base in pure acetonitrile, water is essential to obtain catalytic activity when using 2,2′-bipyridine as the ligand. As shown in Table 2, using **L1** a moderate yield can be achieved in neat acetonitrile (Table 3-2, entry 1). Recently, Repo and co-workers reported the aerobic oxidation of alcohols using copper(II) 2-*N*-arylpyrrolecarbaldimino complexes under aqueous conditions (no added organic co-solvent), they achieved 100% yield in 2 hours under an O_2 atmosphere and 17% using air.[57] They also found that upon addition of co-solvents yields decreased. For the current catalytic system, 28% yield was obtained in water after 12 h using air (Table 3-2, entry 2). However, improved yields could be achieved when the amount of water was increased in acetonitrile/water solvent mixtures. 90% yield was obtained in 12 h with a 1:15 (v/v) acetonitrile/water solvent mixture (Table 3-2, entry 6). This reversal in activity trends compared with the results of other researchers may imply that catalytic system based on **L1** operates *via* a different mechanism to theirs. Also, at this stage, the presence of water assisted in solubilising *t*-BuOK and the presence of an organic solvent assisted in solubilising the substrates. Two other water-miscible co-solvents were also tested in place of acetonitrile for the oxidation of benzyl alcohol (Table 3-2, entry 7-8). A lower yield was obtained using acetone (Table 3-2, entry 7), but a good yield was achieved with a dioxane/water solvent mixture (Table 3-2, entry 8). An attempt at biphasic catalysis using a water/toluene system afforded a yield of 8% (TON 1.6) using conditions similar to those in Table 2 (Table 3-2, entries 7 and 8). The low TON in this case was likely due to the inefficient mixing of the reactants,[52] and the catalyst and co-catalyst residing in separate phases (TEMPO in the toluene phase and the copper-species in the aqueous phase). Furthermore, when two equiv. $CuBr_2$ were mixed with L1 in toluene, L1 formed a homogeneous solution but the $CuBr_2$ remained insoluble (black precipitate) and the organic phase remained colourless.

Even though **L1** is soluble in $scCO_2$ (a single continuous phase is observed at pressures exceeding 6000 psi between 50-90 °C), oxidation reactions were not studied in this reaction medium, as under the conditions studied (25-120 °C, 4000-7500 psi) homogeneity for a mixture of $CuBr_2$/**L1** (2:1) was not achieved. It should also be noted that due to the high pressures and moderate temperatures required to achieve a homogeneous supercritical phase, and that the reaction could be performed effectively in aqueous solution, studies using co-solvents and reagents to encourage solubilisation of the $CuBr_2$/**L1** catalyst system in $scCO_2$ were not performed. However, it should be noted that the alcohol substrates may be able to act as co-solvents and yield a homogeneous reaction system in the future.

Table 3-2. Optimization of the reaction medium for aerobic oxidation of benzyl alcohol.[a]

Entry	Solvent mixture (v/v)	Time (h)	Yield [b] (%)	TON (mols product/mol of Cu)
1	Acetonitrile	3	76	15
2	Water	12	28	6
3	Acetonitrile/Water (2/1)	2	91	18
4	Acetonitrile/Water (1/2)	2	93	19
5	Acetonitrile/Water (1/3)	2	82	16
6	Acetonitrile/Water (1/15)	12	90	18
7	Acetone/Water (1/2)	2	52	10
8	Dioxane/water (1/2)	2	84	17

[a] *Reaction conditions:* 5 mmol benzyl alcohol. 5 mol% $CuBr_2$, 2.5 mol% **L1**, 5 mol% TEMPO, 5 mol% *t*-BuOK, air, 2 h.

[b] GC yields (mols of benzaldehyde/100 mols of benzyl alcohol) using dodecane as an internal standard; in all cases selectivity was >99%.

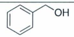
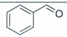
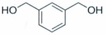
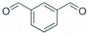
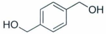
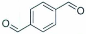
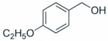
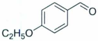
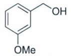
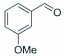
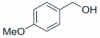
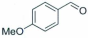
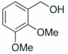
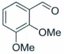
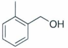
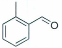
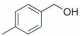
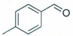
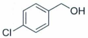
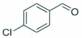
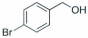
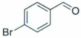
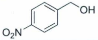
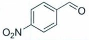
3-2-3 Aerobic oxidation of benzylic alcohols

Through the studies reported above and in order to compare results with a future heterogeneous catalyst system, the *in situ* $CuBr_2$/**L1** (2:1) complex in combination with TEMPO and base was chosen for an investigation of substrate scope. The oxidation reactions of a variety of benzylic alcohols were carried out in a 2:1 (v/v) water/acetonitrile solvent mixture (Table 3-3). As shown in Table 3-3, a range of benzylic primary alcohols was converted into the desired aldehydes with high yields and selectivities. The electronic property of the substituent on the benzene ring had no significant effect on the yields and selectivities. All the benzylic primary alcohols whether containing electron-donating or -withdrawing groups were smoothly oxidized to the corresponding aldehydes. Benzyl alcohols with electron-donating groups, e.g. entry 9 in Table 3-3, achieved slightly faster reaction rates compared with substrates bearing electron-withdrawing groups (Table 3-3, entries 10-12).

3-2-4 Aerobic oxidation of other primary and secondary alcohols into aldehydes and ketones

The **L1**-based catalytic system was also examined for aerobic oxidations of other alcohols (Table 3-4). 2-Furylmethanol, geraniol and citronellol were oxidized to their corresponding aldehydes with high yields (Table 3-4, entries 1-3). Also, aryl-aliphatic and aliphatic primary alcohols could also be converted to the aldehydes with moderate to good yields (Table 3-4, entries 4-6). However, the reaction rates were much slower in comparison with the oxidation of benzylic and allylic alcohols. This is most likely due to stronger C_α-H bond strengths in these species compared with those in benzylic and allylic alcohols.[70] Even when the reaction time was increased to 24 h, the yields did not improve significantly. Importantly, benzylic secondary alcohols could also be oxidized to ketones. However, in order to achieve high yields, longer times were essential (Table 3-4, entries 7-8). Also, the reactions of non-benzylic alcohols proceeded well in the presence of increased water content but longer reaction times were required (Table 3-4, entries 2, 3, 6-8).Unfortunately, the **L1**-based catalytic system was unable to oxidize secondary aliphatic alcohols (Table 3-4, entry 9).

Table 3-3. $CuBr_2$/L1/TEMPO-catalyzed aerobic oxidation of benzylic alcohols.[a]

Entry	Substrate	Product	Yield[b] (%)	Selectivity[b] (%)
1			100 (96[c])	>99
2			100	>99
3			100	>99
4			100	>99
5			100	>99
6			99	>99
7			98	>99
8			100	>99
9			100	>99
10			100[d]	>99
11			97[d]	>99
12			92[d]	>99

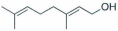
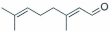
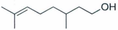
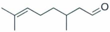
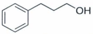
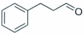
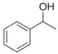
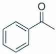
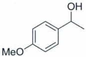
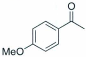
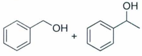
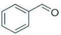
[a] *Reaction conditions:* 5 mmol benzyl alcohol in 5 mL CH_3CN and 10 mL H_2O. 5 mol% $CuBr_2$, 2.5 mol% **L1**, 5 mol% TEMPO, 5 mol% *t*-BuOK, air, 4 h.

[b] GC yields (mols of aldehyde/100 mols of alcohol) using dodecane as an internal standard; selectivities were also measured by GC-MS. TONs between 18 (entry 12, *p*-nitro benzyl alcohol) and 20 (entries 1-10).

[c] Isolated yield.

[d] 6 h.

Table 3-4. $CuBr_2$/**L1**/TEMPO-catalyzed aerobic oxidation of other selected alcohols.^{a}

Entry	Substrate	Product	Time (h)	Yield ^{b} (%)
1			4	100 (20)
2			4	91 (18) 95^c (19) 24 h
3			4	88 (18) 89^c (18) 36 h
4			6	75 (15)
5			8 24	59 (12) 61 (12)
6			8	64 (13) 60^c (12) 36 h
7			12	88 (18) 71^c (14) 36 h
8			12	87 ^{d} (17) 68^c (14) 36 h
9			24	3 (0.6)
10			4	100/0 ^{e} (20)

^{a} *Reaction conditions:* 5 mmol alcohol in 5 mL CH_3CN and 10 mL H_2O. 5 mol% $CuBr_2$, 2.5 mol% **L1**, 5 mol% TEMPO, 5 mol% *t*-BuOK, air.

[b] GC yields (mols of aldehyde/100 mols of alcohol) using dodecane as an internal standard; selectivities were also measured by GC-MS. TON values (mols product/mol of Cu) in parentheses.

[c] Reaction conditions same as other entries but 1 mL CH_3CN and 15 mL H_2O.

[d] Reaction conditions same as other entries but 4 mL CH_3CN and 12 mL H_2O.

[e] Competitive oxidation experiment, 100% selectivity for 1° benzyl alcohol oxidation shown in 4 h.

3-2-5 Comparison with known Cu-ligand-TEMPO catalyst systems for the oxidation of benzyl alcohol and some other alcohols

In order to more clearly present the activity of the Cu-**L1**/TEMPO system, Table 3-5 compares it with some other reported Cu-ligand/TEMPO catalytic systems. As shown in Table 3-5, entry 1, one of the early Cu-bipyridine/TEMPO systems oxidized benzyl alcohol to benzaldehyde smoothly at room temperature and under atmospheric air. However, this system was unable to oxidize secondary alcohols. For a Cu-pyrazole/TEMPO system (Table 3-5, entry 2), only the oxidation of benzyl alcohol to benzaldehyde was reported. For the Cu-DABCO/TEMPO system, oxidation of aliphatic alcohols was much less efficient compared with the oxidation of benzyl alcohol (Table 3-5, entry 3). Copper(II) 2-*N*-arylpyrrolecarbaldimino complexes combined with TEMPO have been shown to efficiently oxidize benzyl alcohol with low catalyst loadings in water (Table 3-5, entry 4). However, aliphatic alcohols could not be converted under these conditions. Compared to the selected literature catalytic systems described above, the **L1**-Cu/TEMPO system was more general for the aerobic oxidation of alcohols at room temperature and under atmospheric air (Table 3-5, entry 5), as moderate to good conversions for primary aliphatic and secondary benzylic alcohols could be obtained in shorter reaction times compared with those reported in the literature.

Table 3-5. Comparison of literature catalysts and our catalytic system for the aerobic oxidation of benzyl alcohol, 1-phenylethanol, 1-decanol and 1-hexanol.

Entry	Catalytic system	Reaction conditions for BnOH oxidation	Yield (%)	TON
1	Sheldon et al.[52]	5 mol% $CuBr_2$, 5 mol% *t*-BuOK, 5 mol% 2,2'-bipyridine, 5 mol% TEMPO, air, 25 °C, CH_3CN/H_2O (2:1), 2.5 h	100	20
			0[a]	0[a]
2	Reedijk et al.[53]	5 mol% $CuBr_2$, 5 mol% *t*-BuOK, 5 mol% 2-(1-methyl-1*H*-pyrazol-5-yl)pyridine, 5 mol% TEMPO, air, 25 °C, CH_3CN/H_2O (2:1), 24 h	89	19
3	Sekar et al.[37]	5 mol% CuCl, 5mol% TEMPO, 5 mol% 1,4-diazabicyclo[2.2.2]octane (DABCO), 5 mol% TEMPO, 1 atm O_2, 80 °C, toluene, 2 h	85	17
			20[b] (72 h)	4
4	Repo et al.[57]	1 mol% of $CuSO_4$, 2 mol% *N*-((1H-pyrrol-2-yl)methylene)-4-fluoroaniline, 0.1 M K_2CO_3, 5 mol% TEMPO, 1 atm O_2, 80 °C, water, 2 h	100	100
			6[c] (20 h)	6
5	*This work*	5 mol% $CuBr_2$, 5 mol% *t*-BuOK, 2.5 mol% **L1**, 5 mol% TEMPO, air, 25 °C, CH_3CN/H_2O (1:2), 4 h	100	20
			88[a] (12 h)	19
			64[b] (8 h)	13
			56[c] (8 h)	11

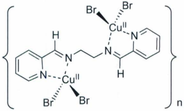
[a] Oxidation of 1-phenylethanol to acetophenone.

[b] Oxidation of 1-decanol to decan-1-al.

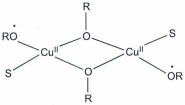
[c] Oxidation of 1-hexanol to hexan-1-al.

3-2-6 Preliminary mechanistic insights

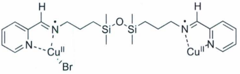
In order to investigate the selectivity of the catalytic system towards primary and secondary alcohols, a competitive oxidation experiment with equal amounts of benzyl alcohol and 1-phenylethanol was performed (Table 3-4, entry 10). The result shows the specificity of the $CuBr_2$/**L1**/TEMPO catalytic system towards the primary alcohol since 100% of the benzyl alcohol was converted into benzaldehyde, whereas 1-phenylethanol remained unreacted within 4 h. This chemoselectivity is consistent with one of the typical characteristics of the natural copper protein galactose oxidase (GOase) and can be used for the selective oxidation of different alcohols.[71-75] Also, this potentially offers some insight into the reaction mechanism in this system and the increased yields seen for **L1-L6** compared with **L7**. **L3** is known to form a di-copper complex[76] and it is proposed that the tetradentate ligands shown here are efficient in forming such species (Figure 3-2). Although density functional theory (DFT) calculations by Wu et al. show that monometallic mechanisms are favored,[77] there is some precedent for highly active bimetallic species.[75] Recently, a kinetic dependency for copper of 2.25 was identified for Cu-bipyridine/TEMPO complexes in aerobic alcohol oxidation reactions.[58] Also, it should be noted that given the differences in reactivity observed for the $CuBr_2$/**L1**/TEMPO catalyst system compared with those in the literature (Table 3-5), Cu-**L1** is likely to perform such oxidation reactions via a different mechanism compared with bipyridine-derived systems. The metal-centred reaction process was monitored by MALDI-TOF mass spectrometry using **L2** as an example. MALDI-TOF mass spectrometry is developing as a useful method for probing metal-centred reactions,



Cu_2(**L3**)$_2Br_4$, Harris and McKenzie, 1969



Chaudhuri, Wieghardt and co-workers, 1998



"Cu_2(**L2**)Br" observed by MALDI-TOF MS

Figure 3-2. Bimetallic Cu-species of relevance to this study.

especially when the paramagnetic nature of a metal centre thwarts NMR based methods of interrogation.[78-79] An aliquot of the reaction mixture was mixed with matrix (dithranol) and the solution was spotted onto the MALDI plate and allowed to evaporate. The resulting mass spectrum showed two main peaks at *m/z* = 493 and 633. By inspection of their isotope distribution and on the basis of their mass, they could be assigned to species containing one Cu atom and one equivalent of **L2** (*m/z* = 493) and two copper atoms, one equivalent of **L2** ($m/z = 493$) and two copper atoms, one ligand and one Br atom ($m/z = 633$) (see Appendix 2). This data provides some evidence to support the presence of a bimetallic species in the catalytic cycle but further experiments are needed in the future to confirm this possibility. Another option that cannot be overlooked at this stage is a mechanism that involves reaction of the imine ligand. However, similar imine ligands once coordinated to metals have been shown to be stable in water.[80] No evidence of ligand decomposition was seen in the mass spectra of reaction mixtures.

In order to understand the limitations of the catalyst system under investigation here, some catalyst deactivation studies were performed. For the model reaction studied, after benzyl alcohol oxidation was complete (same as table 3-3, entry 1), the acetonitrile solvent and benzaldehyde produced were removed under vacuum. Additional amounts of benzyl alcohol (5 mmol) and acetonitrile (10 mL) were added to the aqueous residue remaining from the initial reaction. If an additional 5 mol% of TEMPO was added at this time, 86% yield of benzaldehyde was obtained in 4 h (c.f. 100% in 4 h for initial reaction). For a similar Cu-L1 catalyst recycling study, only 7% yield was obtained when additional TEMPO was not used. Therefore, the activity of the copper complex is maintained after the reaction but the TEMPO has degraded and is the limiting reagent/factor with regards to catalyst re-use.

3-3 Experimental

3-3-1 Materials and methods

All functionalized silicon-containing chemicals were purchased from Gelest. Alcohols and other chemicals were purchased from Aldrich and Alfa Aesar and were used without further purification. The ^{1}H NMR spectra of the pyridyl-imine ligands were acquired on a Bruker AVANCE 500 MHz spectrometer. The ^{13}C NMR spectra were obtained on a Bruker AVANCE III 300 MHz spectrometer equipped with a BBFO probe. Chemical shifts are reported in ppm using the residual protons of the deuterated solvent as an internal reference. All solution-state spectra of **L1** and **L2** were obtained in tetramethylsilane-free $CDCl_3$ due to any overlap with $–OSiMe_2–$ resonances that might occur. Yield and selectivity for catalytic reactions were determined by GC-MS (Gas Chromatography Mass Spectrometry) analyses using an Agilent Technologies 7890 GC system coupled to an Agilent Technologies 5975C mass selective detector (MSD). Dodecane was used as an internal standard. The GC system was equipped with electronic pressure control, split/splitless and on-column injectors, and an HP5-MS column. MALDI-TOF MS spectra were recorded on an Applied Biosystems Voyager DE-PRO. Observations of cloud point data and reaction homogeneity in supercritical carbon dioxide ($scCO_2$) were performed using a Supercritical Fluid Technologies Phase Monitor II. (40 mg of **L1** was placed in the variable volume view cell and the mixture was allowed to equilibrate for approximately 15 minutes under each temperature/pressure condition prior to observations being made).

3-3-2 Ligand Synthesis

For **L1**: 2-Pyridinecarboxaldehyde (1.04 g, 9.71 mmol) was added to a mixture of diamino terminated PDMS (5.00 g, approx. 3.00 mmol) and anhydrous sodium sulfate (5.02 g, 35.3 mmol) in 50 mL dry THF. The mixture was stirred at room temperature. The reaction was judged to be complete after 12 h by monitoring the disappearance of the C=O absorption band and the formation of the newly formed C=N bond using infrared spectroscopy. The mixture was filtered *via* cannula. Solvent and unreacted starting materials were evaporated under vacuum. The product **L1** was isolated as an orange oil, 91% yield. The other ligands **L2-L6** were synthesized following the same method. Characterization data have been reported in Chapter 2.

For **L7**: 2-Pyridinecarboxaldehyde (0.70 g, 6.0 mmol) was added to a mixture of 3-aminopropylpentamethyldisiloxane (1.02 g, 5.00 mmol) and anhydrous sodium sulfate (5.02 g, 35.3 mmol) in 50ml dry THF. The mixture was stirred at room temperature. The reaction was judged to be complete after 6 h by reaction monitoring using infrared spectroscopy. The mixture was filtered *via* cannula. Solvent and unreacted starting materials were evaporated under vacuum. The product **L7** was isolated as an orange oil. Yield: 82%.^{1}H-NMR (500 MHz, $CDCl_3$, 25 °C): δ= 8.57 (dd, *J* = 3.5, 1.2 Hz, 1H), 8.31 (s, 1H), 8.00 – 7.88 (m, 1H), 7.66 (td, *J* = 7.7, 1.7 Hz, 1H), 7.27 – 7.19 (m, 1H), 3.67 – 3.54 (m, 2H), 1.86 – 1.57 (m, 2H), 0.51 (dt, *J* = 8.4, 6.2 Hz, 2H), 0.18 – -0.21 (m, 15H). ^{13}C-NMR (75 MHz, $CDCl_3$, 25 °C): δ=159.73, 152.76, 147.40, 134.52, 122.59, 119.36, 62.71, 22.93, 14.00, 0.39. Anal. Calcd for (%) for $C_{14}H_{26}N_2OSi_2$: C, 57.09; H, 8.90; N, 9.51. Found: C, 57.40; H, 8.77; N, 10.02.

3-3-3 Oxidation of alcohols

The oxidation reactions were carried out under air in a 25.0 mL three-necked round-bottom flask equipped with a magnetic stirrer. Typically, 5.00 mmol alcohol and 1.67 mmol dodecane (GC internal standard) were dissolved in 10 mL acetonitrile. 0.25 mmol (56 mg) of $CuBr_2$ (from a stock solution of 22.4 mg/mL in water) and 0.25 mmol (28 mg) of potassium *tert*-butoxide (from a stock solution of 11.2 mg/mL in water) were then added leading to the formation of a green suspension. 0.125 mmol (232 mg) **L1** was then added and the reaction mixture turned dark-blue. Finally, 0.25 mmol (39 mg) TEMPO was introduced and the reaction mixture immediately turned brown and ultimately a red solution formed. The progress of the oxidation reaction was monitored by GC analysis. Upon completion, the reaction mixture was extracted with diethyl ether. The organic layer was washed with water and brine. Prior to GC-MS analysis, the organic phase was dried with anhydrous magnesium sulfate and filtered through a short silica column. As an example, after concentrating under vacuum the product of the reaction from benzyl alcohol oxidation, benzaldehyde was obtained without further purification as a pale yellow liquid, 96% yield, ^1H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta = 10.02$ (s, 1H), 8.35 (s, 2H), 7.89-7.87 (m, 2 H), 7.64-7.61 (m, 1H), 7.54-7.51(m, 2H). The NMR spectroscopic data were in good agreement with those reported in the literature.[81] It should be noted that the isolated products were not contaminated with the PDMS-derived ligand, as evidenced by the absence of $-SiMe_2O-$ resonances. Also, all ^1H resonances of the product were sharp and well-defined indicating that the product was likely not contaminated with any paramagnetic Cu(II) residues.

3-4 Conclusions

In conclusion, a new catalyst system has been developed for room temperature $CuBr_2$-TEMPO catalyzed aerobic oxidation of alcohols based on known and novel tetradentate pyridyl-imine ligands. The polydimethylsiloxane (PDMS) derived pyridyl-imine ligand and other tetradentate ligands studied showed catalytic activity as good as 2,2'-bipyridine based systems. However, the bidentate pyridyl-imine ligands studied showed poor catalytic activity and for tetradentate ligands a ratio of 2Cu:L was crucial in maintaining good catalyst TON. A number of primary and some secondary alcohols could be oxidized to the corresponding aldehydes and ketones with high yields and selectivities. The exact mechanistic details are still under investigation, but likely involve a di-copper species. With these initial homogeneous catalyst based results as a starting point, in the future, pyridyl-imine ligands within heterogeneous or recyclable homogeneous catalyst systems will be studied for aerobic oxidation reactions.[82]A combination of PEG-modified Cu catalyst and PEG-modified TEMPO catalyst have previously been used to good effect,[83] and therefore, there is the potential to use Cu-L1 with a modified-TEMPO or other stable radical co-catalyst in future studies.

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Chapter 4

Simple copper/TEMPO catalyzed aerobic dehydrogenation of benzylic amines and anilines

A version of this chapter has been accepted by *Organic and Biomolecular Chemistry* in November 2011.
Some modifications were made to the original paper for inclusion as a chapter in this thesis.

4-1 Introduction

Imines are important intermediates which can be used as electrophilic reagents in many transformations such as alkylations, condensations and cycloadditions including aza-Diels-Alder reactions.[1] Imines also serve as versatile starting materials for the synthesis and racemisation of chiral amines, which are important intermediates in the preparation of biologically active compounds.[2-6] The traditional protocol for the synthesis of imines involves the condensation of an amine with a carbonyl compound such as an aldehyde or a ketone but alternative routes are desirable. For example, the syntheses of some imines through the reaction of alcohols and amines have been reported during the past decade.[7-11] Recently, direct oxidations of amines to imines have attracted much attention. Nicolaou et al. developed stoichiometric oxidations of secondary amines to imines using 2-iodoxybenzoic acid, and excellent yields were obtained.[12-13] Largeron at al. reported an environmentally-friendly biomimetic electrocatalytic method for the oxidation of primary aliphatic amines to imines.[14] A few transition metal-catalyzed oxidations of amines with PhIO,[15-16] $K_2S_2O_8$,[17] MnO_2[18] and ^{t}BuOOH[19-20] have also been reported. Significant progress has been made in the development of mild and green methods for the synthesis of imines including metal-catalyzed dehydrogenation of amines,[21-23] aerobic oxidation of amines using cobalt,[24] copper,[25-28] gold,[29-33] palladium[34], ruthenium[35-39] and vanadium[40] complexes. Very recently, Zhao et al. reported the selective aerobic photocatalytic oxidation of amines to imines on TiO_2.[41] However, many of these catalytic systems have limited substrate scope and are only active for secondary amines.

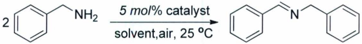
As an efficient hydrogen abstraction reagent, 2,2,6,6-tetramethylpiperidinyl-1-oxy

(TEMPO) has been broadly used in catalytic oxidation reactions of alcohols.[42-49] However, TEMPO has been used to a much lesser extent in oxidation reactions of amines. Semmelhack and Schmid reported TEMPO-assisted electro-oxidation of amines to nitriles and carbonyl compounds in 1983,[50] and this is the only example to date. In the study presented here, a simple $CuBr_2$-TEMPO catalytic system for aerobic oxidations of primary and secondary benzyl amines is reported. Also, CuBr-TEMPO catalyzed dehydrogenative coupling of electron-rich anilines, which yield azo compounds, is reported.

4-2 Results and discussion

4-2-1 Optimization of the reaction conditions

The oxidative self-coupling of benzylamine was chosen as a model reaction to optimize the reaction conditions (Scheme 4-1). Both copper salt and TEMPO were crucial for the oxidation of benzylamine (Table 4-1, entries 1 and 2). The ligands described in Chapter 3 were also used in these reactions. However, lower conversions were obtained when they were used and higher conversions were obtained without the addition of any ligands. Different copper salts were tested for catalytic oxidation activity. Copper (II) bromide gave the best activity with 86% conversion of benzylamine to *N*-benzylidene-benzylamine in 8 h (Table 4-1, entry 3).



Scheme 4-1. Catalyzed aerobic dehydrogenation model reaction.

Copper(II) chloride and copper(II) acetate led to only 58% and 62% conversion respectively under the same reaction conditions (Table 4-1, entries 4 and 5). These differences are possibly associated with a ligand dissociation step in the reaction mechanism, as the bromide anion would be weakly coordinated to the copper centre compared with chloride and acetate anions. This means that for the $CuBr_2$ system it is easier for the substrate to enter the coordination sphere of the copper and become activated. Good conversion was also achieved when copper(I) bromide was used. No conversion was obtained when $CuBr_2$ was replaced with $FeCl_3$. Acetonitrile has been broadly used as a solvent in Cu(II)-catalyzed oxidation reactions.[51-52] 86% conversion was obtained in 8 h with a 2:1 (v/v) acetonitrile/water solvent mixture (Table 4-1, entry 3). No conversion was achieved in neat CH_3CN due to the formation of a green precipitate (Table 4-1, entry 7) that is presumably a coordination polymer of copper. Conversion was decreased when the amount of CH_3CN was decreased in acetonitrile/water solvent mixtures, probably because of a decrease in the solubility of the organic substrate (Table 4-1, entry 8). Only 8% conversion was obtained when a biphasic solvent mixture was used (Table 4-1, entry 9). This may be explained by unsatisfactory mixing of the reactants, catalysts and co-catalysts.

Table 4-1. Optimization of the reaction conditions for aerobic dehydrogenation of benzylamine to imine.[a]

Entry	Catalyst	Solvent mixture (V/V)	Conversion[b] (%)
1	$CuBr_2$	CH_3CN/H_2O (2/1)	trace
2	TEMPO	CH_3CN/H_2O (2/1)	n.r.
3	$CuBr_2$ + TEMPO	CH_3CN/H_2O (2/1)	86(100[c])
4	$CuCl_2$ + TEMPO	CH_3CN/H_2O (2/1)	58
5	$Cu(CH_3COO)_2 .H_2O$ + TEMPO	CH_3CN/H_2O (2/1)	62
6	$FeCl_3$ + TEMPO	CH_3CN/H_2O (2/1)	n.r.
7	$CuBr_2$ + TEMPO	CH_3CN	n.r.
8	CuBr + TEMPO	CH_3CN/H_2O (1/2)	53
9	$CuBr_2$ + TEMPO	Toluene/H_2O (2/1)	8

[a] Reaction conditions: benzylamine (2 mmol), catalyst (0.05 mmol), solvent (9 ml), air (1 atm), 8 h.

[b] Selectivity in imine > 98%, determined by GC using dodecane as an internal standard. n.r. = no reaction.

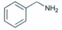
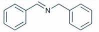
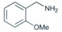
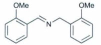
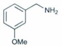
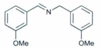
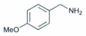
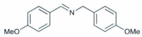
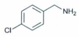
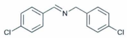
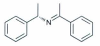
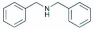
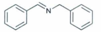
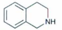
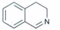
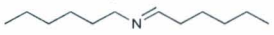
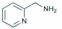
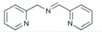
[c] 12 h reaction time.

4-2-2 Aerobic dehydrogenation of primary and secondary benzylic amines

With the optimized reaction conditions above in hand, a wide range of primary and secondary benzylic amine aerobic dehydrogenations were investigated using the $CuBr_2$-TEMPO catalytic system (Table 4-2). The electronic properties of substituents had no significant effect on the conversions and selectivities. This differs from a previously reported CuCl-catalyzed reaction where reaction selectivity was affected by substituents.[28] All the benzylic amines studied whether containing electron-withdrawing or electron-donating groups were smoothly oxidized to the corresponding imines (Table 4-2, entries 1-5). This contrasts with a recently reported V_2O_5-H_2O_2 catalytic system, where significantly different reaction conditions were needed for the two classes of substrate with benzyl amines bearing electron donating groups being significantly less reactive than those containing electron withdrawing groups.[53] Also, when using this Cu(II)/TEMPO catalytic system, the *p*-methoxy benzylamine substrates achieved slightly faster reaction rates compared with *p*-chloro benzylamine (Table 4-2, entries 4 and 5). 80% GC-MS conversion was achieved in 8 h for the oxidation of *p*-methoxy benzylamine, whereas 72% conversion was obtained for the oxidation of *p*-chloro benzylamine in 8 h. This is possibly due to a faster transamination for the phenylmethanimine intermediate when a more basic (electron-donating) amine is used (Figure 4-1). Unfortunately, the $CuBr_2$-TEMPO catalyst system was inactive for the oxidation of (R)-1-phenylethanamine (Table 4-2, entry 6). This could be explained by the steric demands of the β-methyl group of the amine, which would hinder the formation of the crucial species **III** in the proposed catalytic cycle (Figure 4-1). For such a substrate, it would be challenging for C_α-H abstraction by the coordinated TEMPO to occur. However, some secondary amines could be converted to their corresponding imines in good to excellent yields. However, the reaction conditions were more demanding than for the self-condensation of benzylic amines. In order to achieve high conversions, higher catalyst loadings and reaction temperatures were essential (Table 4-2, entries 7 and 8). If the catalyst loading was decreased to 5 mol% for the oxidation of dibenzylamine, the conversion dramatically dropped to 50% (see Appendix 3). From this graph of catalyst loading and conversion (see Appendix 3), the reaction appears to be first order in $CuBr_2$-TEMPO but more studies are needed to confirm this and to determine the relative reaction orders for both catalyst and co-catalyst. Also, dibenzylamine could not be transformed to the imine at room temperature. Kinetic studies showed a first-order dependence for the reaction rate on the dibenzylamine concentration at 45 °C (see Appendix 3). Under optimised conditions, *N*-benzylidene-benzylamine could be isolated in 94% yield from dibenzylamine (Table 4-2, entry 7), whereas only 66% yield is obtained under neat reaction conditions using CuCl.[28] However, the $CuBr_2$-TEMPO catalytic system reported herein was not effective for the self-coupling of non-activated aliphatic amines, only a small amount of the resulting imine was detected (Table 4-2, entry 9). No reactions were observed for some functional amines studied such as 2-picolylamine (Table 4-2, entry 10). This could be explained by strong coordination of N-donors to the copper centre and a difficulty in dissociating these to yield a vacant site at the metal centre for subsequent TEMPO coordination (Figure 4-1, II→III).

Very recently, Patil and Adimurthy reported CuCl-catalyzed aerobic oxidation of amines to imines under neat conditions with 0.5 mol% catalyst loading.[28] The simple CuCl catalyst system could oxidize benzylic amines to imines efficiently and moderately oxidize aliphatic and functional amines to the corresponding imines. However, a higher reaction temperature was required compared with the system reported here. Also, for the oxidation of electron-donating benzyl amines, the selectivities for the imine products were not notable. As shown in Table 4-2, entry 4, only 78% selectivity was obtained due to the formation of *p*-methoxy benzaldehyde as a by-product. No benzaldehyde by-products were observed in the reactions reported here. However, this catalytic system

Table 4-2. $CuBr_2$-TEMPO catalyzed primary and secondary benzylic amines[a]

Entry	Substrate	Product	Yield (%) [b]
1			87 (88[d])
2			94
3			93
4			94(80[c]) (72[d])
5			76(72[c])
6			0
7			94[e,f] (66[d])
8			92[e,f]
8			5[c] (50[d], NMR yield)
9			0 (32[d])

[a] Reaction conditions, unless otherwise stated: benzylamine (4 mmol), catalyst (0.10 mmol), solvent (9 ml), air (1 atm), 25 °C, 12 h.

[b] Isolated yield.

[c] GC conversion, 8 h.

[d] Under conditions reported in ref. 28; entry 4, 78% selectivity (92% combined yield of imine and aldehyde).

[e] 7.5 mol% catalyst loading.

[f] 45 °C reaction temperature.

uses TEMPO as a co-catalyst. This is a disadvantage, as TEMPO is the most expensive component in the catalytic system. It would be desirable if TEMPO could be efficiently recycled and reused. Chung and Toy reported a recyclable PEG-modified Cu/TEMPO catalyst for selective aerobic alcohol oxidation.[54] The development of a recyclable Cu/TEMPO catalyst system or another reusable non-precious metal-based catalyst system for aerobic oxidation reactions of amines is underway.

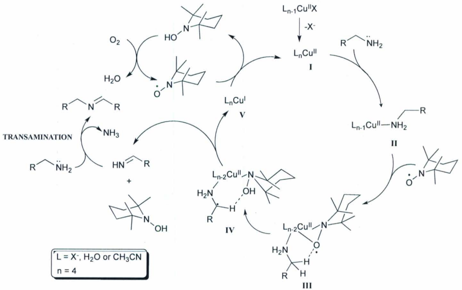
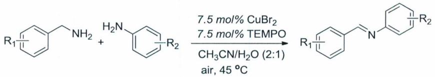


Figure 4-1. Proposed mechanism for $CuBr_2$-TEMPO catalyzed oxidation of benzyl amines, postulated loss and coordination of L throughout the cycle omitted from image for clarity.

Through the studies reported above, a reaction mechanism is proposed for the condensation of benzyl amines using Cu(II)/TEMPO catalysts (Figure 4-1). The mechanism is very similar to that reported by Sheldon et al. for $CuBr_2$(bipyridine)-TEMPO catalyzed aerobic alcohol oxidation.[52] Initially, a Cu^{II} species **I** coordinates with the amine and the intermediate complex **II** is formed. Complex **II** coordinates with TEMPO to form species **III,** which is crucial for the catalytic cycle. C-H abstraction from the amine by the coordinated TEMPO molecule is the next step and the radical intermediate **IV** is formed which is stabilized by hydrogen bonding to the second β-hydrogen atom and the oxygen atom of TEMPO-H. Then TEMPO-H and intermediate imine, RCH=NH, dissociate from the radical species **IV** by single proton transfer. This results in the formation of a Cu(I) complex **V**. The product is obtained by transamination of RCH_2NH_2 and the imine intermediate RCH=NH. The Cu(II) complex **I** and TEMPO are regenerated by the oxidation of Cu(I) complex **V** and TEMPOH with oxygen and thus the catalytic cycle is completed. It should be noted that Patil and Adimurthy propose two possible mechanisms for their related CuCl-catalyzed amine oxidation reactions.[28] Given the formation of benzaldehyde by-products in some of their reactions and the lack of a more significant difference in reactivity between amines bearing electron-donating and -withdrawing groups, it was proposed that path 2 in their mechanism dominates and that path 1 (reaction of the methanimine intermediate with an amine) occurs to a lesser extent. The methanimine intermediates in the proposed cycle, Figure 4-1, must be short-lived, as no benzaldehyde products were observed despite the use of water as a co-solvent in the reactions. Therefore, the two catalytic systems (CuCl cf. Cu(II)/TEMPO) likely involve different catalytic cycles and most definitely different rate determining steps. It should be noted that some biomimetic approaches to amine oxidation (models for copper amine oxidase enzymes) have also been reported,[14, 55] and may share some mechanistic details with the system reported here. However, further studies are needed to elucidate the mechanism in more detail and with greater accuracy. Especially in light of recent studies concerning alcohol oxidation using $CuBr_2$/bipyridine/TEMPO and mechanistic insights therein,[56] a bimetallic catalytic mechanism cannot be excluded at this stage.

4-2-3 Oxidative coupling of benzylamines with anilines

Benzylamines also reacted with anilines to form *N*-benzylidene-anilines with moderate to good conversions under optimized reaction conditions (Scheme 4-2, Table 4-3). Generally, the oxidative coupling reactions proceeded smoothly with 7.5 mol% catalyst loading at 45 °C under air. As previously reported by Török,[57] it is likely that the homo-coupling products benzylidene-benzylamines were formed first and then reacted with the anilines by transamination to form *N*-benzylidene-anilines. The reaction rates for benzylamines bearing electron-donating groups with aniline were slightly faster in comparison with electron-withdrawing variants (Table 4-3, entries 1-4). This is



Scheme 4-2 .$CuBr_2$-TEMPO catalyzed oxidative coupling of benzylamines with anilines.

Table 4-3. $CuBr_2$-TEMPO catalyzed oxidative coupling of benzylamines with anilines.[a]

Entry	R_1	R_2	Time (h)	Conv.(%)[b]
1	H	H	12	48 (18[c])
2	*p*-Me	H	12	58
3	*p*-OMe	H	12	64
4	*o*-Cl	H	18	44
5	H	*o*-CH_3	12	66 (*p*-CH_3 14[c])
6	*o*-Cl	*o*-CH_3	12	55
7	H	*p*-OMe	12	73 (74[c])
8	*p*-Me	*p*-OMe	12	78
9	*o*-OMe	*p*-Br	24	38[d]
10	*o*-OMe	*p*-NO_2	24	16[d]
11	H	2,6-CH_3	24	n.r.

[a] Reaction conditions, unless otherwise stated: benzylamine (4 mmol), aniline (4 mmol), $CuBr_2$ (0.3 mmol), TEMPO (0.3 mmol), solvent (6 ml CH_3CN and 3 ml H_2O), air (1 atm), 45 °C.

[b] Conversion determined by GC using dodecane as an internal standard. n.r. = no reaction.

[c] Yields of unsymmetrical imine under conditions reported in ref. 28: entry 1, 23% selectivity (78% combined yield of symmetrical and unsymmetrical imines); entry 5, 17% selectivity (82% combined yield of symmetrical and unsymmetrical imines).

[d] 75 °C reaction temperature.

probably due to faster formation of the homo-coupling benzylidene-benzylamine intermediates. In these reactions, the electronic properties of the anilines used had a significant effect on the catalytic activities (Table 4-3, entries 5-10). The reaction rates for electron-rich anilines with benzylamines were much faster than for others. For *p*-bromoaniline and *p*-nitroaniline, only 38% and 16% conversions were achieved even at 75 °C after 24 h (Table 4-3, entries 9 and 10). This is likely due to the reduced basicity of the anilines containing electron-withdrawing moieties, which makes the transamination step challenging. In addition to such electronic effects, strong steric effects were also seen and no conversion was observed when 2,6-dimethylaniline was used as a partner in the reaction (Table 4-3, entry 11). It should also be noted that after prolonged reaction times, some benzaldehyde and benzonitrile by-products were seen to form via GC-MS analysis. This contrasts with the self-coupling of benzyl-amines reported herein (Table 2) where no benzaldehyde products were observed. In general, although isolated yields were not obtained in this study, the selectivity towards the cross-coupled product appears to be moderately better than reactions catalyzed using CuCl with identical or similar substrates (Table 4-3, entries 1 and 5). A more diverse study of substrate scope and determination of isolated yields are needed in order to further understand this interesting reaction.

4-2-4 CuBr-TEMPO catalyzed cross-dehydrogenative coupling of anilines

Cross-dehydrogenative coupling is an efficient method for C−C bond formations beyond functional group transformations.[58] It has also been recognized as an important method to form N-N bonds. Notable examples have been developed for the aerobic oxidative coupling of anilines to azo derivatives.[59-61] The $CuBr_2$-TEMPO catalytic system is also active for the oxidative homo-coupling of anilines to diphenyldiazenes to some extent but if $CuBr_2$ is replaced with CuBr the catalyst system becomes more active (Scheme 4-3).

Scheme 4-3.CuBr ($CuBr_2$)-TEMPO catalyzed oxidative coupling of benzylamines with anilines.

CuBr-TEMPO catalyzed aerobic oxidative dehydrogenative coupling of some representative anilines was investigated. As shown in Table 4-4, some electron-donating anilines could be smoothly oxidized to form the self-coupling azo compounds (Table 4-4, entries 2-4). However, the homocoupling of anilines with electron-withdrawing substituents proceeded to a very limited extent (Table 4-4, entries 5 and 6). Furthermore, sterically-demanding substituents in the 2-position or di-substituted 2,6-anilines led to lower or no yield of the oxidative coupling products (Table 4-4, entries 7 and 8). In the previous research by Zhang and Jiao,[61] CuBr was used with 3 equiv pyridine in toluene using air or O_2 (1 atm) as the oxidant. In contrast to their work, in this study high yields were observed for the dehydrogenative coupling of *p*-methoxy aniline (66% *cf.* 91%). Therefore, the mechanisms at play in the two systems are likely different and a radical mechanism is likely to dominate in the method described here. However, further mechanistic studies are required to understand and further develop Cu-catalyzed dehydrogenative couplings of anilines.

Table 4-4. CuBr-TEMPO catalyzed aerobic oxidative dehydrogenative coupling of anilines.[a]

Entry	R	Time (h)	Yield[b] (%)
1	H	24	86
2	*o*-CH_3	24	89
3	3,5-dimethyl	18	92
4	*p*-OCH_3	18	91[c]
5	*p*-Br	48	8[d]
6	*p*-NO_2	48	n.r.[e]
7	*o*-$C(CH_3)_3$	48	n.r.[e]
8	*2,6*-dimethyl	48	n.r.[e]

[a] Standard reaction conditions: anilines (4 mmol), aniline (4 mmol), CuBr (0.15 mmol), TEMPO (0.15 mmol), solvent (9 ml CH_3CN), air (1 atm), 60 °C.

[b] Isolated yield. n.r. = no reaction.

[c] 60% yield when using $CuBr_2$.

[d] 75 °C reaction temperature.

[e] 85 °C reaction temperature.

4-3 Experimental

4-3-1 General experimental information

Amines and other chemicals were purchased from Aldrich and Alfa and were used without further purification. The ^{1}H NMR spectra of the imines and azo compounds were acquired on a Bruker AVANCE 500 MHz spectrometer. The ^{13}C NMR spectra were obtained on a Bruker AVANCE III 300 MHz spectrometer equipped with a BBFO probe. Chemical shifts were reported in ppm using the tetramethylsilane ($\delta = 0$ ppm) in $CDCl_3$ or Acetone-d_6 as an internal standard. Conversions were determined by GC-MS (Gas Chromatography Mass Spectrometry) analyses using an Agilent Technologies 7890 GC system coupled to an Agilent Technologies 5975C mass selective detector (MSD). Dodecane was used as an internal standard. The GC system was equipped with electronic pressure control, split/splitless and on-column injectors, and an HP5-MS column. HRMS is equipped with Waters GC system and GCT Premier Micromass system. IR spectra were acquired with a Bruker-Alfa spectrometer.

4-3-2 General procedure for the synthesis of imines

The oxidation reactions were carried out under air in a 25 ml three-necked round-bottom flask equipped with a magnetic stirrer. Typically, 4.0 mmol benzylamine was dissolved in 6 ml acetonitrile and 3 ml water. 0.10 mmol (22 mg) of $CuBr_2$ and 0.10 mmol (16 mg) TEMPO were then added leading to a blue solution. The reaction mixture was stirred vigorously at room temperature for 12 h. After reaction completion, the mixture was extracted with diethyl ether. Then the organic layer was washed with water and brine. The organic phase was dried with anhydrous magnesium sulfate and filtered through a short silica column. After concentrating under vacuum, the product was obtained without further purification.

***N*-(benzylidene)benzylamine**. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.33 (s, 1H), 7.77-7.74 (m, 2H), 7.39-7.35 (m, 3H), 7.34-7.26 (m, 4H), 7.25-7.21 (m, 1H), 4.78 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 161.84, 139.16, 136.00, 130.65, 128.50, 128.40, 128.18, 127.88, 126.88, 64.93 ppm.

2-Methoxy-*N*-(2-methoxybenzylidene)benzylamine. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.84 (s, 1H), 8.03 (d, *J* = 7.3 Hz, 1H), 7.40-7.28 (m, 2H), 7.22 (t, *J* = 7.3 Hz, 1H), 7.03-6.81 (m, 4H), 4.82 (s, 2H), 3.84 (s, 3H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 155.73, 155.24, 154.01, 128.82, 126.09, 125.12, 124.94, 124.46, 121.85, 117.77, 117.53, 108.04, 107.20, 56.65, 52.75, 52.51 ppm.

3-Methoxy-*N*-(3-methoxybenzylidene)benzylamine. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.33 (s, 1H), 7.38 (s, 1H), 7.34-7.22 (m, 3H), 6.98-6.90 (m, 3H), 6.80 (d, *J* = 8.3 Hz, 1H), 4.78 (s, 2H), 3.82 (s, 3H), 3.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 160.36, 158.24, 158.11, 139.17, 135.92, 127.94, 127.86, 120.01, 118.68, 115.93, 111.99, 110.80, 110.02, 63.25, 53.81, 53.64 ppm.

4-Methoxy-*N*-(4-methoxybenzylidene)benzylamine. ^{1}H NMR (Acetone-d_6, 500 MHz): δ = 8.36 (s, 1H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.3 Hz, 2H), 3.83 (s, 2H), 3.76 (s, 2H); ^{13}C NMR (Acetone-d_6, 75 MHz):

δ = 162.77, 161.27, 159.72, 133.21, 130.67, 130.07, 114.96, 114.71, 65.11, 56.05, 55.78 ppm.

4-Methyl-*N*-(4-methylbenzylidene)benzylamine. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.34 (s, 1H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.25-7.13 (m, 6H), 4.76 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 161.68, 140.96, 136.51, 136.36, 133.63, 129.30, 129.15, 128.24, 127.95, 64.81, 21.51, 21.10 ppm.

2-Chloro-*N*-(2-chlorobenzylidene)benzylamine. ^{1}H NMR ($CDCl_3$, 500 MHz):δ = 8.86 (s, 1H), 8.11(d, *J* = 7.5 Hz, 1H), 7.43-7.20 (m, 7H), 4.94 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 158.84, 135.94, 134.42, 132.53, 132.22, 130.89, 128.97, 128.80, 128.48, 127.59, 127.46, 126.17, 126.06, 61.32 ppm.

4-Chloro-*N*-(4-chlorobenzylidene)benzylamine. ^{1}H NMR ($CDCl_3$, 500 MHz):δ = 8.33 (s, 1H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 2H), 7.32-7.25 (m, 4H), 4.76 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 160.81, 137.60, 136.86, 134.44, 132.81, 129.44, 129.24, 128.91, 128.62, 64.15 ppm.

3,4-Dihydroisoquinoline. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.33 (s, 1H), 7.35 (td, *J* = 7.2, 1.1 Hz, 1H), 7.31-7.26 (m, 2H), 7.15 (d, *J* = 7.3 Hz, 1H), 3.79-3.76 (m,2H), 2.75 (t, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 160.33, 136.30, 131.05, 128.49, 127.43. 127.20, 127.09, 47.41, 25.04 ppm.

4-3-3 General procedure for the preparation of benzylideneanilines

The oxidative coupling reactions were carried out under air in a 25 ml reaction tube using a Radleys Carousel ReactorTM equipped with a magnetic stirrer. Typically, 2.0 mmol benzylamine and aniline were dissolved in 6 ml acetonitrile and 3 ml water. 0.15 mmol (33 mg) of $CuBr_2$ and 0.15 mmol (23 mg) TEMPO were then added leading to a blue solution. The reaction mixture was stirred vigorously at 45 °C for 12 h. After completion, the reaction mixture was extracted with diethyl ether. Then the organic layer was washed with water and brine. The conversion was determined by GC-MS based on aniline.

4-3-4 General procedure for the synthesis of diazenes

The oxidative homo-coupling of anilines to diphenyldiazenes were carried out under air in a 25 ml reaction tube using a Radleys Carousel ReactorTM equipped with a magnetic stirrer. Typically, 4-methoxybenzenamine (548 mg, 4.00 mmol) was dissolved in 9 ml acetonitrile; CuBr (21 mg, 0.15 mmol) and TEMPO (23 mg, 0.15 mmol) were then added. The reaction mixture was stirred vigorously at 60 °C for 18 h. After completing, the reaction mixture was extracted with diethyl ether. Then the organic layer was washed with water and brine. The organic phase was dried with anhydrous magnesium sulfate and filtered through a short silica column. After concentrating under vacuum, the product was obtained without further purification.

(*E*)-1,2-Diphenyldiazene. ^1H NMR ($CDCl_3$, 500 MHz): $\delta = 7.97\text{-}7.87$ (m, 4H), 7.55-7.44 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 152.65, 130.97, 129.08, 122.83$ ppm; IR (neat):

ν = 3061, 1581, 1482, 1452, 1298, 1220, 925, 771, 685 cm^{-1}. HRMS (TOF MS EI+) m/z calcd for $C_{12}H_{10}N_2$ 182.0845, found 182.0844.

(*E*)-1,2-Di-*o*-tolyldiazene. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.62 (d, *J* = 8.0 Hz,, 2H), 7.38-7.29 (m, 4H), 7.28-7.23 (m, 2H), 2.74 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 151.10, 137.97, 131.27, 130.69, 126.37, 115.85, 17.63 ppm; IR (neat): ν = 2924, 1596, 1477, 1192, 1150, 1039, 768, 715 cm^{-1}. HRMS (TOF MS EI+) m/z calcd for $C_{14}H_{14}N_2$ 210.1157, found 210.1156.

(*E*)-1,2-Bis(3,5-dimethylphenyl)diazene. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.52 (s, 4H), 7.11 (s, 2H), 2.44 (s, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 152.90, 138.74, 132.51, 120.54, 21.26 ppm; IR (neat): ν = 2914, 1608, 1442, 1292, 1038, 903, 853 cm^{-1}. HRMS (TOF MS EI+) m/z calcd for $C_{16}H_{18}N_2$ 238.1470, found 238.1469.

(*E*)-1,2-Bis(4-methoxyphenyl)diazene. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.88 (d, *J* = 9.0 Hz, 2H), 7.70 (d, *J* = 9.0 Hz, 4H), 3.89 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 161.56, 147.07, 124.34, 114.16, 55.57 ppm; IR (neat): ν = 3413, 1592, 1579, 1496, 1249, 841 cm^{-1}. HRMS (TOF MS EI+) m/z calcd for $C_{14}H_{14}N_2$ 242.1059, found 242.1055.

4-4 Conclusions

In conclusion, a simple catalyst system for $CuBr_2$-TEMPO catalyzed aerobic oxidation of amines has been developed. Primary and secondary benzylic amines can be oxidized to the corresponding imines in excellent yields. A possible reaction mechanism has been proposed. The same catalytic system is also efficient for oxidative cross-coupling of benzylamines and anilines. Notably, CuBr-TEMPO is an efficient catalyst system for aerobic oxidative dehydrogenative couplings of electron-donating anilines to yield azo compounds in good yields.

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Chapter 5

Conclusions and proposed future work

5-1 Conclusions

Chapter 1 included an overview of the background chemistry and literature reviews related to the research reported in this thesis. The main purpose of the research was to develop a green chemical process based on the principles of Green Chemistry. The application of polymer-supported catalysts, $scCO_2$ as a green reaction medium and Cu-catalyzed aerobic oxidations were highlighted.

A series of tetradentate pyridyl-imine ligands and the corresponding copper compounds were synthesized and characterized. PDMS-derived pyridyl-imine ligands and the copper complex with a low molecular weight siloxane group proved to be soluble in $scCO_2$. The results of PGSE NMR experiments and computational studies revealed that the chelating pyridyl-imine ligands with siloxane groups could form [1+1] metallocycles, although [2+2] metallocycles could not be conclusively ruled out.

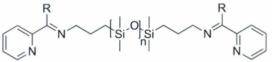
A range of primary and secondary alcohols were effectively oxidized to the corresponding aldehydes and ketones using $CuBr_2$ with TEMPO and the tetradentate PDMS derived pyridyl-imine ligand. The aerobic oxidation reactions could be carried out in pure water to some extent. However, the catalytic system did not oxidize cyclic secondary alcohols efficiently.

$CuBr_2$-TEMPO was found to be an efficient catalyst system for the aerobic dehydrogenation of primary and secondary benzylic amines to the corresponding imines. CuBr-TEMPO proved to be effective for aerobic oxidative dehydrogenative couplings of electron-donating anilines to yield azo compounds.

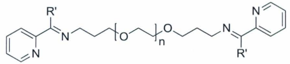
5-2 Proposed future work

As reported in Chapters 2 and 3, the PDMS-derived ligand **L1** was soluble in $scCO_2$. **L1** showed the best activity with $CuBr_2$ and TEMPO for the aerobic oxidation of alcohols in aqueous media. However, [Cu(**L1**)](PF_6) was insoluble in pure $scCO_2$. It would be worth testing the solubility of [Cu(**L1**)](PF_6) and some other metal complexes of **L1** in $scCO_2$ with co-solvents such as acetonitrile and methanol. If soluble, the [Cu(**L1**)](PF_6)-catalyzed reactions such as alcohol oxidation reaction could be performed in $scCO_2$ with a co-solvent media. Then, it might be possible to recycle the homogeneous catalyst through adjusting pressure. In addition, it might also be possible to prepare heterogeneous catalysts using the current ligands and copper complexes. As previously reported by Kerton and co-workers, PDMS-derived phosphine-containing ligands and their resulting Pd complexes could be readily absorbed on silica and formed heterogeneous catalysts which could be easily recycled and reused.[1-2]

The ligands presented in Chapters 2 and 3 could be modified as well (Figure 5-1). For example, if ketones are used in the place of aldehydes during their synthesis, the carbon of the imine would bear a substituent. Also, polymeric ligand **L1** could be modified to contain a different backbone such as PEG. The corresponding PEG-derived ligand should be water soluble, which would be useful for reactions using water as a reaction medium.



R = CH_3, C_6H_5



R' = H, CH_3, C_6H_5

Figure 5-1. Modified ligands which can be used in the future.

As shown in Chapters 3 and 4, TEMPO played an important role in Cu-catalyzed aerobic oxidation reactions of alcohols and amines. TEMPO is the most expensive component in those catalyst systems. It would be desirable if TEMPO could be efficiently recycled and reused. Great progress has been made in heterogeneous catalysis using supported TEMPO/M including polymer-supported TEMPO/M and silica-supported TEMPO/M.[3] It may be effective to use these approaches within the Cu-catalyzed oxidation system. Ionic liquid (IL)-supported TEMPO has been reported for alcohol oxidation reactions.[4-6] It should be promising to develop and employ an IL-supported TEMPO system for the oxidative dehydrogenation of amines and anilines. In such cases, it might be possible to recycle the TEMPO. A Cu/TEMPO catalytic system has recently been used in aerobic oxidation of lignin model compounds.[7] Therefore, a recyclable Cu/TEMPO/IL system might be useful in future biomass transformations.

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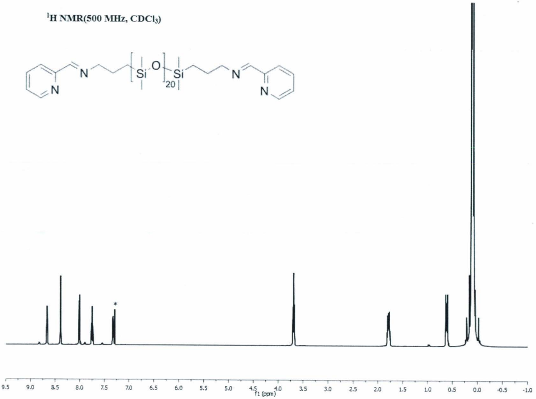
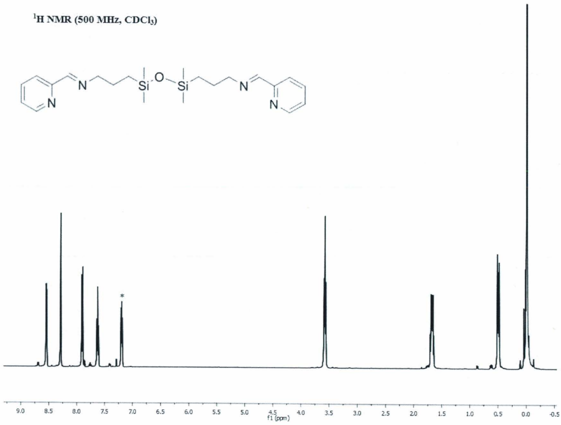
Appendix 1

<u>^{1}H NMR spectrum of **L1**</u>

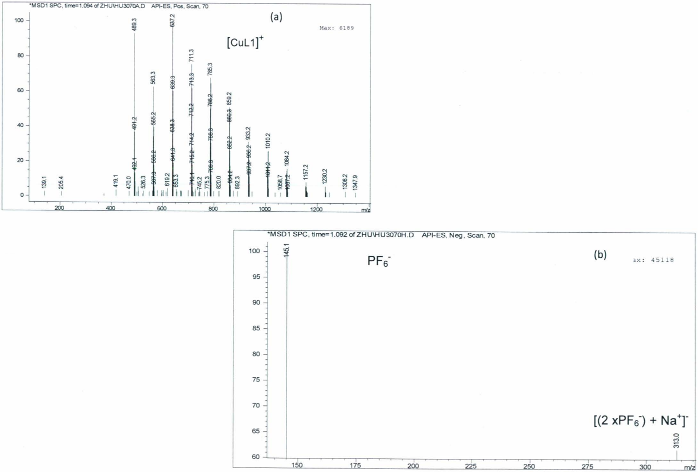


^{1}H NMR spectrum of **L2**

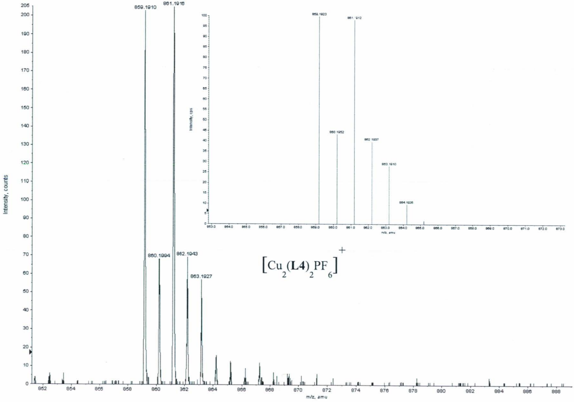
^{1}H NMR (500 MHz, CDCl$_3$)



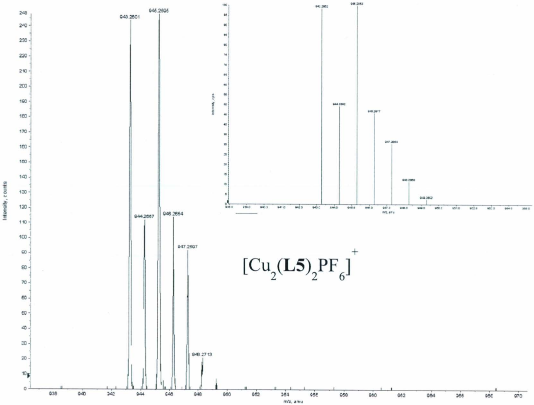
ESI Mass Spectra of Cu(**L1**)](PF$_6$) (a) positive scan, (b) negative scan



High mass region of MALDI-TOF mass spectrum for $[Cu_2(\mathbf{L4})_2](PF_6)_2$, inset theoretical isotope pattern for $\{[Cu_2(\mathbf{L4})_2](PF_6)\}^+$

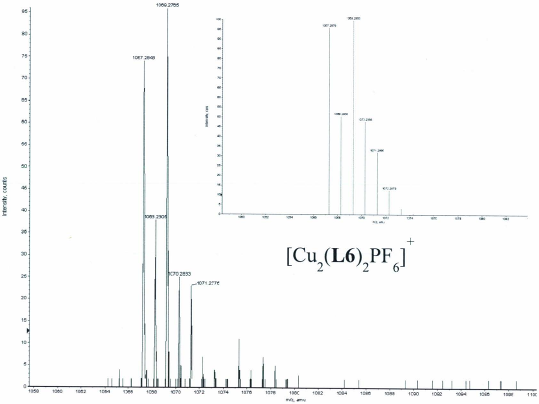


High mass region of MALDI-TOF mass spectrum for $[Cu_2(\mathbf{L5})_2](PF_6)_2$, inset theoretical isotope pattern for $\{[Cu_2(\mathbf{L5})_2](PF_6)\}^+$



High mass region of MALDI-TOF mass spectrum for $[Cu_2(L6)_2](PF_6)_2$, inset theoretical isotope pattern for

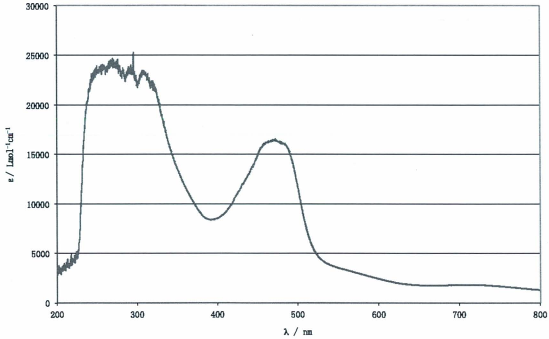
$\{[Cu_2(L6)_2](PF_6)\}^+$



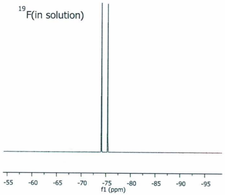
1069.2765
1067.2848
1068.2305
1070.2833
1071.2776
Intensity, counts
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
1058
1060
1062
1064
1066
1068
1070
1072
1074
1076
1078
1080
1082
1084
1086
1088
1090
1092
1094
1096
1098
1100
m/z, amu
1069.2863
1067.2879
1068.2900
1070.2886
1071.2866
1072.2879
Intensity, cps
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
80
85
90
95
100
1060
1062
1064
1066
1068
1070
1072
1074
1076
1078
1080
1082
m/z, amu
$[Cu_2(\mathbf{L6})_2PF_6]^+$

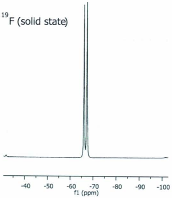
UV-Vis spectrum of $[Cu(\mathbf{L2})](PF_6)$ in CH_2Cl_2

For MLCT: $\varepsilon = 16\ 000\ Lmol^{-1}cm^{-1}$, $\lambda = 475nm$

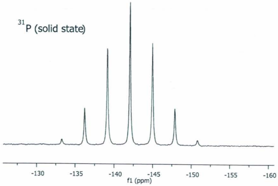


Solid-state NMR spectra for $[Cu(CH_3CN)_4](PF_6)$


^{19}F(in solution)

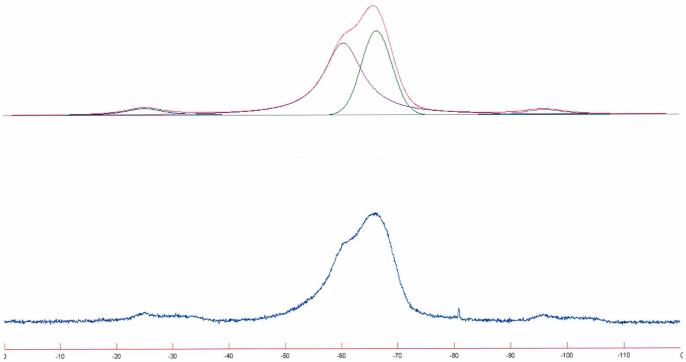

^{19}F (solid state)

	d (ppm)	J_{P-F} (Hz)	T_2^* (ms)
solution	-74.77	711.12	72.02
solid	-66.68	713.45	1.98

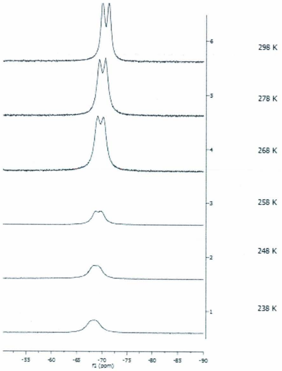

^{31}P (solid state)

d (ppm)	J_{P-F} (Hz)	T_2^* (ms)
-142.01	709.12	5.18

Expanded and modeled ^{19}F MAS NMR spectrum of [Cu(**L1**)](PF$_6$)

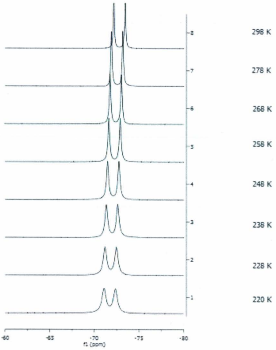


VT ^{19}F solution NMR spectra for [Cu(**L1**)](PF6)



Temperature (K)	(ppm)	J_{P-F} (Hz)	T_2^* (ms)
298	-70.7	724.9	0.63
278	-70.0	724.3	0.47
268	-69.7	710.3	0.44
258	-69.3	707.5	0.37
248	-68.8	708.9	0.31
238	-68.3	716.2	0.27

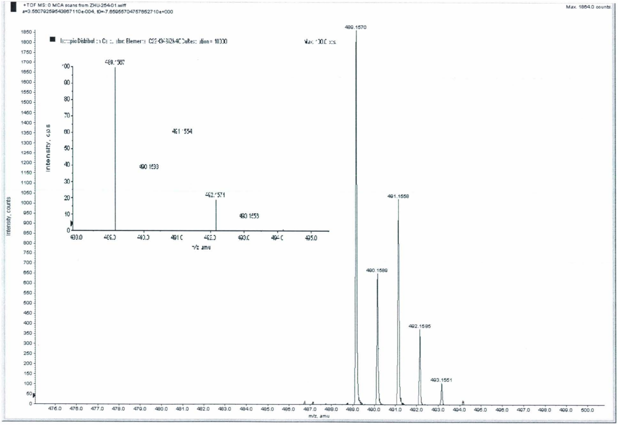
VT ^{19}F solution NMR spectra for [Cu(**L2**)](PF$_6$)



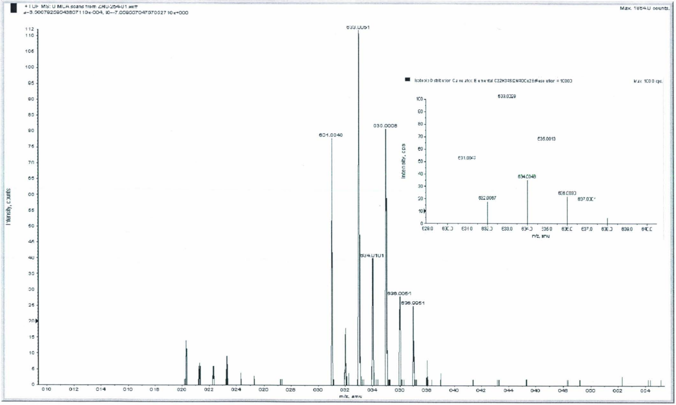
Temperature (K)	(ppm)	J_{P-F} (Hz)	T_2^* (ms)
298	-72.8	712.8	4.7
278	-72.5	712.96	3.41
268	-72.4	712.97	2.9
258	-72.3	713.39	2.4
248	-72.1	713.42	1.98
238	-71.98	713.52	1.6
228	-71.8	713.8	1.28
220	-71.72	713.34	1.05

Appendix 2

Experimental and theoretic isotope distribution of $[Cu(\mathbf{L2})]^+$

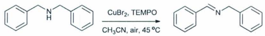


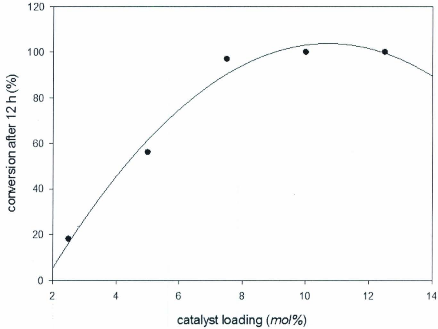
Experimental and theoretic isotope distribution of $[Cu_2(\mathbf{L2})Br]^+$



Appendix 3

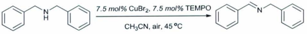
Screening with different catalyst loading for oxidation of dibenzylamine

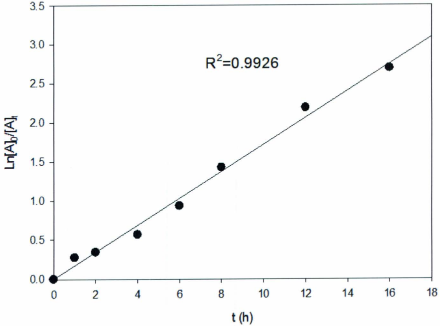




The effect of catalyst to substrate ration on the conversion for the oxidation of dibenzylamine. Reaction conditions: dibenzylamine (4 mmol), 9 ml CH_3CN, air (1 atm), 45 °C, 12 h. Conversions were determined by GC using dodecane as an internal standard.

Kinetic study of the oxidation of dibenzylamine





Time-dependence of substrate concentration for the oxidation of dibenzylamine. Reaction conditions: dibenzylamine (4 mmol), $CuBr_2$ (0.3 mmol), TEMPO (0.3 mmol), 9 ml CH_3CN, air (1 atm), 45 °C.

Kinetic studies showed a first-order dependence for the reaction rate on the dibenzylamine concentration. $k_{obs} = 0.17\ h^{-1}$.