Copper(II)-Mediated 2-Quinoxalinol Salens in Alcohol Oxidation and C-H Activation: A Greener Approach

by

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Abstract

Reduction of waste production in chemical processes is the idea of greener chemistry by using less toxic or benign methods and eliminating purification steps. Because of this, using a catalytic rather than stoichiometric method is much preferred. In this dissertation, 2-quinoxalinol salen (salqu) copper(II) complexes are used in selective oxidation of alcohols and in C-H functionalization.

The oxidation of propargylic alcohols was investigated using *tert*-butyl hydroperoxide (TBHP) as the oxidant. This catalytic system produced excellent yields (up to 99 %) of α,β-acetylenic carbonyl compounds from a wide variety of substrates within a short reaction time (1 h). This catalytic protocol can also be used with propargylic alcohols that contain alkyl groups in the α-position, which can be difficult to oxidize selectively using other available oxidation methods. Excellent selectivity was achieved for the oxidation of propargylic alcohols over that of isolated hydroxy groups, triple bonds or propargylic methylene groups.

The work continued using a water-soluble version of salqu copper(II) complex considering the principles of green and sustainable chemistry. First, the water-soluble salqu copper(II) complex was designed and then synthesized in multistep organic synthesis. It was found that this catalytic system is capable of performing selective oxidation of propargylic, benzylic and allylic alcohols in water effectively. This reaction constitutes of a rare example of propargylic alcohol oxidation in water, and this process is

considered greener through the elimination of the use of hazardous organic solvents, toxic metals, and high catalyst loading. The oxidation occurs in good yields (up to 99 %) with excellent selectivity for propargylic, benzylic and allylic alcohols, and the reaction is thought to go through a radical pathway.

It was also found that the water-soluble salqu copper(II) complex is an efficient catalyst for the selective functionalization of benzylic and allylic C-H bonds to the corresponding carbonyl compounds in the presence of oxidant TBHP. The reactions proceed with very low catalyst loading (1 mol %) in water and good yields (up to 96 %) can be achieved for a wide variety of substrates. Excellent selectivity was also achieved with this catalytic protocol for the activation of benzylic and allylic C(sp^3)-H bonds.

Allylic C-H activations catalyzed by 2-quinoxalinol salen copper(II) complex was also investigated under molecular oxygen to see the potential of possible replacement of TBHP with molecular oxygen. It was found that TBHP can not be substituted completely by dioxygen, but it is possible to reduce the amount of TBHP by introducing high pressures of oxygen.

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Chapter 1

Introduction

Because of increasing environmental issues associated with chemical reactions, chemists have to rethink finding ways to make catalytic reactions environmentally more benign. A perfect case for a chemical process would be conversion of neat reactants into 100 % products at room temperature and pressure without involvement of any toxic chemicals, but as we all know, this is not possible in reality. Thus, necessary steps need to be taken to reduce or eliminate the use or generation of hazardous chemical substances in designing chemical products and processes. In this regard, Paul Anastas and John Warner developed the 12 principles of green chemistry in 1998.[1] These principles can be summarized as:

1. Prevention
2. Atom economy
3. Less hazardous chemical syntheses
4. Designing safer chemicals
5. Safer solvents and auxiliaries
6. Design for energy efficiency

7. Use of renewable feedstocks

8. Reduce derivatives

9. Catalysis

10. Design for degradation

11. Real-time analysis for pollution prevention

12. Inherently safer chemistry for accident[1]

Scientists have made great strides towards realizing these goals as green chemistry has emerged as an important aspect of all chemistry.[2] One example is the development of the field of catalysis in recent years. This is a good approach towards advancing green chemistry as catalytic reagents are superior to stoichiometric reagents helping to reduce energy, cost and waste production.[3] A catalyst is a compound that increases the rate of a reaction by lowering the activation energy, but that is not consumed during the reaction.[4] Thus, catalysts can be used in small quantities and recycled. Nature uses its own catalysts called enzymes to catalyze reactions with high selectivity in biological systems. Catalysts can be categorized into two major classes: homogeneous and heterogeneous.[4] In organic chemistry, catalysts can be found as metal based catalysts and metal free catalysts.[5] Metal based catalysts consist of metal/metal salts or organometallic compounds and metal free catalysts are known as organocatalyts consisting of carbon, hydrogen, nitrogen, oxygen and other non metal elements.[5] Among those, transition metal catalysts play an important role in organic chemistry.[6]

Oxidation of organic compounds is an important class of reaction in organic chemistry as it can convert chemically less reactive organic substrates into more reactive

chemical compounds of a high oxidation state such as alcohols and carbonyl compounds. Traditional methods for the oxidation of organic compounds involve high-valent metal compounds such as MnO_2 and CrO_3.[7] These compounds are required in stoichiometric amounts and generate lots of toxic waste causing heavy burden to the environment and becoming less popular. Thus, catalytic oxidation of organic substrates has attracted much attention in recent years. In particular, different catalytic methods using transition metals have been developed for the oxidation of organic compounds. Notably, these transition metal catalysts involve metals such as V,[8] Cr,[9] Mn,[6] Fe,[10] Co,[11] Cu,[12] Ru,[13] Rh,[14] Pd,[15] and Ir.[16]

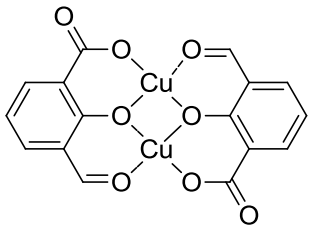
Among numerous types of transition metal catalyzed oxidations, copper-mediated reactions are of great interest due to their low toxicity, environmental abundance and effectiveness as a catalyst. Different oxidation states of copper (Cu^0, Cu^I, Cu^{II}, Cu^{III}) contributes to its chemistry and that makes it easier for copper to be involved in both one-electron and two-electron pathways via organocopper intermediates in oxidation reactions. This allows copper to be an effective catalyst in a broad range of oxidation reactions including reactions in living organisms.[17]

Copper enzymes have been observed in catalyzing oxidation reactions in biological systems.[18] These enzymes can function as oxygenases and oxidases. Oxygenases act as a source of oxygen atoms that are installed into the product and oxidases act as electron acceptors to oxidize the substrates.[19,20] Oxygenases are categorized as monooxygenases and dioxygenases depending on whether they incorporate one or two oxygen atoms into their products. For instance, phenylalanine monooxygenase and dopamine β–monooxygenase are two mammalian copper enzymes,

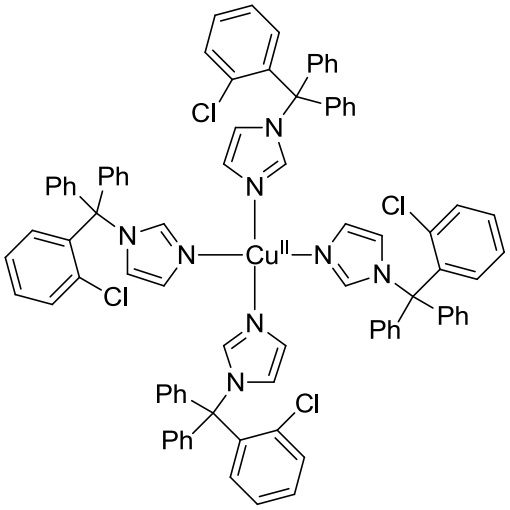
which are responsible for the synthesis of neurotransmitters. Phenylalanine monooxygenase converts phenylalanine into tyrosine, which is an essential precursor for the synthesis of dopamine.[19] Dopamine β–monooxygenase catalyzes the oxidation of dopamine into noradrenaline. Both dopamine and noradrinaline are important neurotransmitters required for the proper brain function.[21] Methane monooxygenase and ammonia monooxygenase are two oxygenases found in micro-organisms. The former is found in methanotrophic bacteria as an integral membrane protein, which is responsible for the C-H activation of methane to methanol.[18] The latter is also a membrane-bound protein, which catalyzes the oxidation of ammonia to hydroxylamine.[22] These ammonia-oxidizing bacteria are important micro-organisms involved in the nitrogen cycle.[22] Copper containing dioxygenases such as quercetinase and indole dioxygenase play a key role in the degradation of aromatic compounds in organisms.[23,24] Meanwhile, oxidases catalyze the reduction of O_2 to water or hydrogenperoxide and the oxidation of organic substrates. Galactose oxidase is a copper containing metalloenzyme, which catalyzes the oxidation of primary amines to aldehydes.[20] Copper amine oxidases convert primary amines into aldehydes in plants, animals and micro-organisms.[25]

It is challenging to mimic the chemistry of copper oxidation reactions in nature; however, copper salts and copper complexes have been used widely as effective catalysts in oxidation reactions such as epoxidation,[26-28] oxidation of alkanes,[29-31] alkenes[32,33] and alkynes,[34-37] benzyllic oxidation,[38-40] arene oxidation,[41-44] alcohol oxidation,[45-48] reaction of carbonyls,[49] sulfoxidation,[50] reactions of phenols,[51] reactions of amines,[52] reactions of enamines[53] and reactions of anilines.[54] These reactions are conducted in the presence of various oxidizing agents such as peroxides,[55] peroxyesters,[56] *m*-CPBA[57] (*meta*-

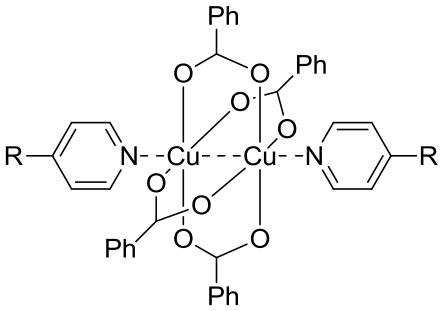
chloroperoxybenzoic acid), Oxone[58] (potassium peroxymonosulfate) and DDQ[59] (2,3-dichloro-5,6-dicyanobenzoquinone); however benign oxidants like *tert*-butyl hydroperoxide (TBHP), hydrogen peroxide and molecular oxygen have taken much attention in recent years.[60]



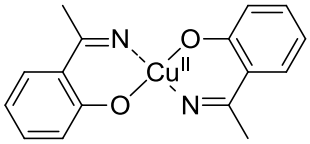
O-donor system



N-donor system



N,O-donor system



Schiff base system

Figure 1.1. Examples of copper complexes with O-donor systems,[61] N-donor systems,[62] N, O-donor systems[47] and Schiff base systems[63]

The copper based catalytic oxidation systems have been studied using various copper salts such as CuCl,[45] CuBr,[35] $CuCl_2$,[32] $CuBr_2$,[64] $Cu(OH)_2$,[65] $Cu(ClO_4)_2$,[66] $Cu(OAc)_2$,[67] $Cu(OTf)_2$[33] and $Cu(NO_3)_2$.[68] These ligand free copper systems are always handy as they are commercially available and cheap; however, copper-ligand systems are of great interest as they help to enhance overall efficiency of the reaction by increased solubility, selectivity and reduced catalyst loading. For this purpose, different ligand systems have been incorporated with copper: O-donor systems,[61] N-donor systems,[62] N, O-donor systems[47] and Schiff base systems[63] (Figure 1.1). O-donor systems can derive from ligands containing carboxylates, alkoxides or N-oxides. Ligands bearing N-containing groups such as pyridine, pyrole, pyrazole, imidazole, triazole and indole can act as N-donor systems. Meanwhile, ligands with both of these oxygen and nitrogen moieties can serve as N, O-donor systems.

Schiff bases are another type of ligand systems incorporated into copper complexes. Schiff base, named after German chemist Hugo Schiff, is a compound containing carbon-nitrogen double bond where N-atom is attached to an aryl or alkyl group except hydrogen. These compounds are easy to synthesize and capable of making stable complexes with metal ions.[69] One type of Schiff base which has attracted much attention is the salen ligand (Figure 1.2). Salen ligands are a fundamental class of organic compounds known since 1933.[70] The name salen stems from the two precursors used to synthesize the ligand: salicylaldehyde and ethylene diamine. Salen ligands contain two Schiff bases resulting in a tetradentate chelating ligand with O, N, N, O type donor system. Two O- units derive from the salicylaldehyde and the two N- units derive from the ethylene diamine, which is involved in the Schiff base.

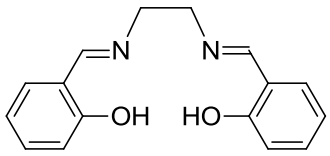


Figure 1.2. Basic structure of salen ligand

Salen ligands make very stable complexes with copper and most of the other transitions metals including Ti, V, Cr, Mn, Fe, Co, Ni, Zn, Zr, Ru and Pd.[71] Group 13 metals such as Al also make stable complexes with salen ligands.[69] Tetradentate chelating sites of the salen ligand favors the formation of distorted square planar complexes; however, distorted square pyramidal and distorted octahedral geometries are also formed depending on the coordination around the metal centre.[72] These salen-metal complexes have been applied extensively in a wide range of fields such as medicine and catalysis. For instance, palladium-salen complexes have shown high *in vitro* anti-proliferative effects against human hepatoma cancer.[73] Iron-salen complexes have been studied against human cancer cell lines including lung carcinoma, cervix epithelial carcinoma, malignant melanoma, osteosarcoma, breast adenocarcinoma, ovarian carcinoma and cisplatin-resistant ovarian carcinoma.[74] Salen complexes of manganese,[75] titanium,[76] copper[77] and cobalt[78] have also been investigated as anti-cancer agents.

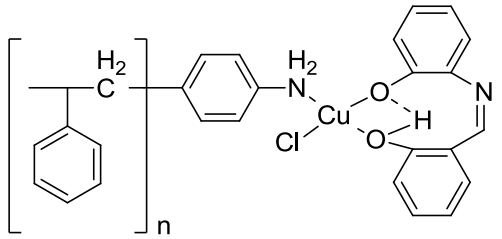
Salen-metal complexes have been applied widely as catalysts in organic reactions including asymmetric catalysis, as the production of optically pure compounds is important in pharmaceutical and fine chemical industries. In 1990, Jacobsen[79] and Katsuki[80] reported the use of chiral Mn-salen complexes for the enantioselective

epoxidation of unfuctionalized olefins. Since then, a lot of salen-metal complexes have been employed in the synthesis of enantiomerically pure compounds. For example, Ti-salen complexes catalyze the asymmetric addition of ethyl cyanoformate to aldehydes.[81] This reaction produces chiral cyanohydrins that are useful starting materials in the synthesis of natural products[81] and pharmaceutical intermediates.[82] Cyanohydrins can also be synthesized by V-salen catalyzed asymmetric cyanation of aldehydes, which is also known as Meerwein-Ponndorf-Verley cyanation.[83] Salen complexes of Ti have been reported to catalyze asymmetric sulfoxidation[84] and enantioselective oxidation of cyclic dithioacetals[85] as well.

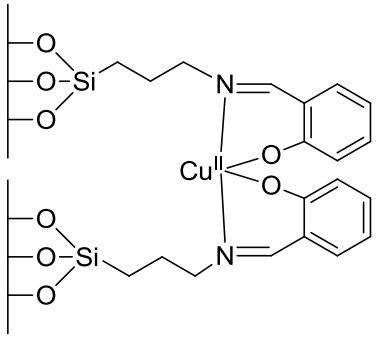
Chromium is another first raw transition metal, which makes strong complexes with salen ligands and catalyzes a wide range of asymmetric transformations such as epoxide ring opening,[86] allylation of alkyl glyoxilates,[87] hetero-Diels-Alder reaction[88] and aminolysis of epoxides.[89] Asymmetric epoxide ring opening[90] and hetero-Diels-Alder reaction[91] can also be catalyzed by chiral Co-salen complexes. In addition, Co-salen complexes are capable of catalyzing a variety of other reactions including hydrolytic kinetic resolution of terminal epoxides,[92] asymmetric Diels-Alder reaction,[93] enantioselective cyclopropanation,[94] oxidation of alcohols to corresponding carboxylic acid analogs and ketones[95] and arylation of azole heteroarenes.[96] Copper and zinc salen complexes have also been reported in asymmetric catalysis. Enantioselective alkene aziridination[97] is an example for such reaction catalyzed by Cu-salen. Meanwhile, Zn-salen complexes are known to catalyze addition of diethylzinc to aldehydes[98] and enantioselective alkynylation of ketones.[99]

In addition to first row transition metals, second row transition metals such as Zr and Ru are capable of asymmetric transformations when coordinated with salen ligands. For instance, enantioselective Baeyer-Villiger oxidation[100] can be catalyzed by Zr-salen complexes. Likewise, Ru-salen complexes can catalyze asymmetric aziridination of alkenes,[101] sulfimidation[102] and cyclopropanation of olefins.[103] Not only transition metal complexes, but also main group salen complexes such as Al-salen complex have been reported in enantioselctive catalysis. Some of those reactions include asymmetric catalysis of Michael addition reaction,[104] conjugate addition of cyanide to α,β–unsaturated imides[105] and addition of hydrogen cyanide to imines.[106]

These ligand systems featuring O-donor systems, N-donor systems, N, O-donor systems and Schiff base systems can also be found attached to solid supports in order to increase the recovery and the reusability of the catalyst. This helps to increase the turn over numbers (TON) of the reaction and, therefore, making it viable industrial process.[107] The solid support can be either polymers or inorganic oxides where active metal complexes interact with the solid support through covalent bonding or weak Coulombic forces. Most of the recently reported solid supports include polystyrene frame works[108] and mesoporous silica such as MCM-41[109] (Mobil Crystalline Materials) and SBA-15[36] (Santa Barbara Amorphous type materials) (Figure 1.3).



Polystyrene-Cu



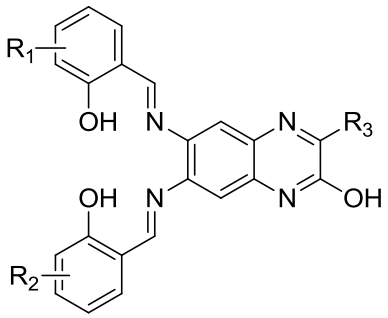
Cu-MCM-41

Figure 1.3. Solid supported copper complexes

We have developed ligands incorporating a 2-quinoxalinol into a salen backbone (Figure 1.4). Quinoxaline is a conjugated heterocyclic compound containing two nitrogen atoms (Figure 1.4). Quinoxaline derivatives are key intermediates as bioactive agents,[110,111] dyes,[112] and have been key pharmaceutical or medicinal intermediates.[113,114] The addition of 2-quinioxalinol makes the salen ligand a highly conjugated system by delocalizing the π-electrons of 2-quinoxalinol and phenolic moieties through Schiff bases. This makes the 2-quinoxalinol incorporated salen or salqu ligand fluorescence active and alters the coordination site. So these salqu ligands with different electronic

properties are expected to be of use in the development of new catalysts, sensors and pharmaceutical agents.

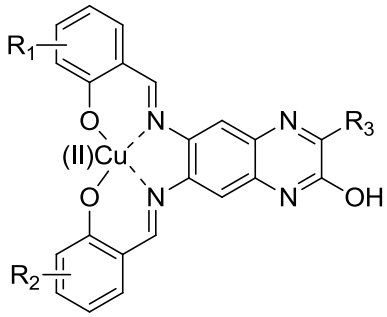
Quinoxaline 2-Quinoxalinol



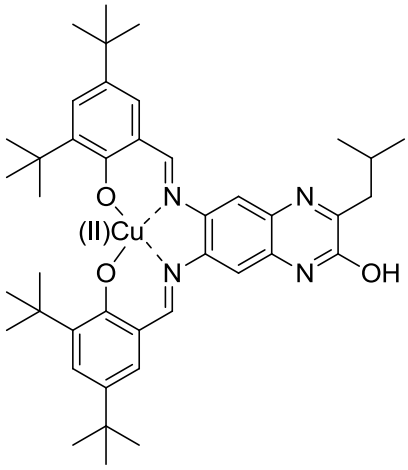
2-Quinoxalinol salen (salqu)

Figure 1.4. Structures of quinoxaline, 2-quinoxalinol and 2-quinoxalinol salen (salqu)

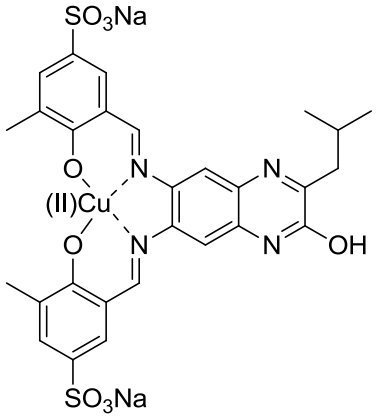
Salqu ligands are synthesized from 6,7-diamino-2-quinoxalinol and salicylaldehyde. We have coordinated salqu ligands with copper as a novel catalytic sytems for the selective oxidation of organic compounds (Figure 1.5). Previously, it was shown that 2-quinoxalinol salen copper(II) complex can work effectively as a catalytic system for the selective oxidation of benzylic methylenes to carbonyl compounds and allylic oxidations to α,β-unsaturated ketones.[115-117]



2-Quinoxalinol salen (salqu)



complex 1



complex 2

Figure 1.5 Structures of 2-quinoxalinol salen (salqu) copper(II) complexes

In this dissertation, 2-quinoxalinol salen copper(II) complexes (complex 1 and complex 2) have been used to promote the selective oxidation of alcohols and C-H functionalization (Figure 1.5). Complex 1 was used to oxidize propargylic alcohols to α,β-acetylinic carbonyl compounds using *tert*-butyl hydroperoxide (TBHP) as the

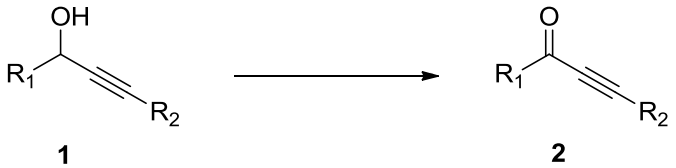
terminal oxidant. As the principles of green chemistry encourage the use of safer solvents, a water-soluble version of 2-quinoxalinol salen copper(II) complex, complex 2 (Figure 1.5) was synthesized and used with TBHP for the selective oxidation of propargylic, benzylic and allylic alcohols to their corresponding carbonyl compounds in water replacing volatile hazardous organic solvents. This work was further extended for the C-H activations of organic compounds at benzylic and allylic positions in water, still using the water soluble 2-quinoxalinol salen copper(II) catalyst. Moreover, allylic C-H activations catalyzed by complex 1 were also studied under molecular oxygen as a potential substitution for TBHP to further reduce chemical waste production in the process.

Chapter 2

Propargylic Alcohol Oxidation

The oxidation of propargylic alcohols to carbonyl compounds is of great interest due to their utility as starting materials in a wide range of organic compounds such as heterocyclic compounds,[118] aromatic compounds[119] and others.[120-132] They have also been used in the synthesis of biologically active compounds[133] like anti-cancer agents,[134] and nucleosides.[135] Direct α-oxidation of alkynes to their corresponding ketones[136-138] and some other methods using terminal alkyne as a building block[139-147] have also been reported for preparation of α,β-acetylenic ketones in addition to the oxidation of propargylic alcohols.

Scheme 2.1. Oxidation of Propargylic Alcohols

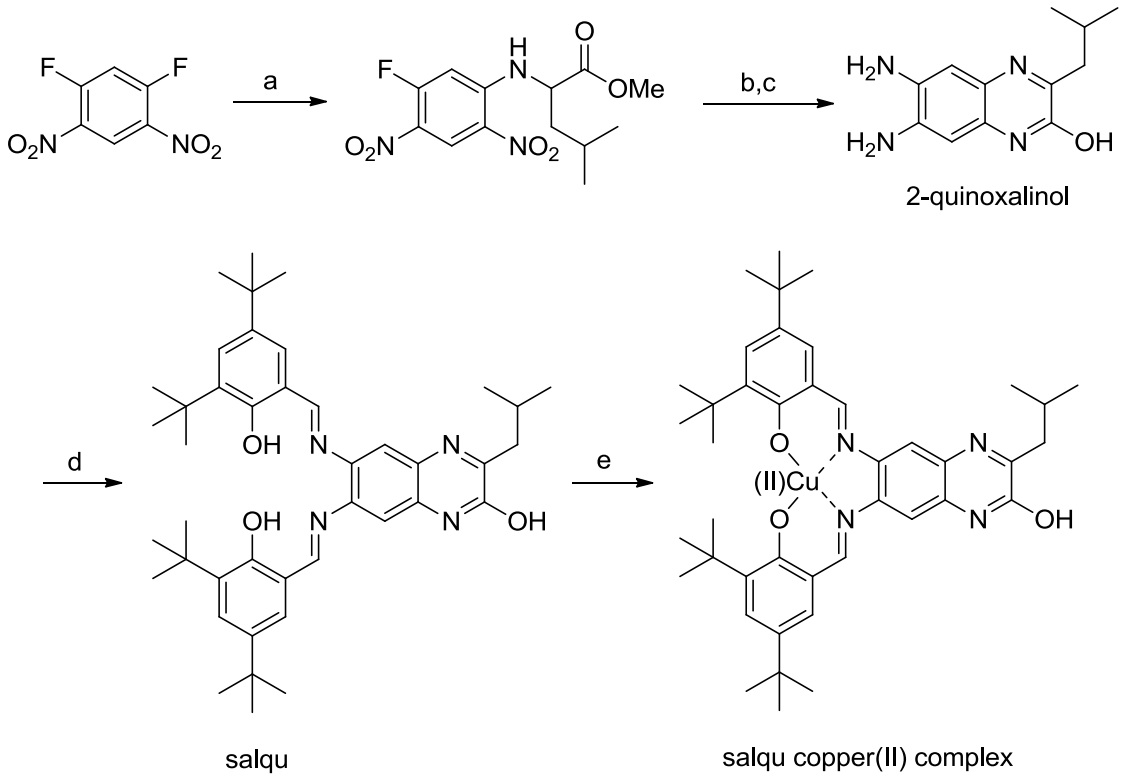


Uemura and co-workers have demonstrated the ability of an oxovanadium complex (vanadium oxyacetylacetonate)[148] and calcium phosphate-vanadate apatite[149] as catalytic systems for oxidation of propargylic alcohols under aerobic conditions. Both

these systems show good results, but produce poor to moderate yields with propargylic alcohols derived from alkyl alkynes.[148,149] Pedro and co-workers have described a cobolt(III) complex in the catalyzed aerobic oxidation of propargylic alcohols derived from aryl alkynes.[150] Meanwhile, Hanson and co-workers reported isolated examples of oxidation of propargylic alcohols using an 8-quinolinate vanadium complex with air,[151] but this system was not effective with propargylic alcohols with aryl groups at α position. In addition, the toxicity of metal involved is a major issue in both of these methodologies.[150,151] Copper has also been used in recently reported methods, as a catalyst for propargylic alcohol oxidation. For instance, ligand promoted, copper nanoparticles with *tert*-butyl hydroperoxide (TBHP) or air as the oxidant[152] and CuCl under aerobic conditions have been described.[153] These methods demonstrate the potential of copper as a catalyst in similar oxidations, but each method requires 10-20 mol % of catalyst loadings. Thus, most of these available methods require high catalyst loading (5-6 mol %,[150,153] 10-20 mol %,[152,154] and 30 mol %[149]) and long reaction times.[149-151,154] Furthermore, limitations still remain as these systems are incompatible with propargylic alcohols derived from alkyl alkynes.[149] Therefore, in the view of green and sustainable chemistry, the development of a fast, efficient and less toxic method is desirable.

Here, we describe the use of a 2-quinoxalinol salen copper(II) complex with *tert*-butyl hydroperoxide (TBHP) as the oxidant in the catalytic oxidation of propargylic alcohols to the corresponding α,β-acetylenic ketones. The 2-quinoxalinol salen copper(II) complex was synthesized following a modified reported procedure in our laboratory (Scheme 2.2).[155]

Scheme 2.2. Synthesis of 2-quinoxalinol salen copper(II) complex



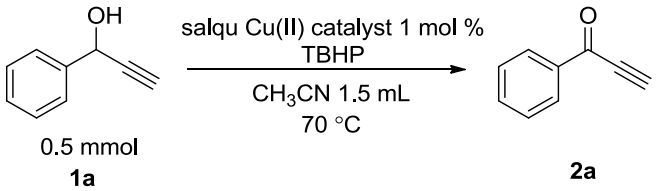
(a) THF, L-leucine methyl ester hydrochloride, DIPEA
(b) $NH_3.H_2O$, THF
(c) Pd/C, $HCOONH_4$, EtOH
(d) MeOH, 3,5-ditertbutyl-2-hydroxybenzaldehyde, TFA, reflux
(e) $Cu(OAc)_2$, DCM/MeOH, NEt_3, reflux

Synthesis of 2-quinoxalinol began by reacting 1 equiv. of 1,5-difluoro-2,4-dinitrobenzene with 1 equiv. of leucine methyl ester hydrochloride in THF. Then the remaining fluorine group was substituted with an amino group by reacting with ammonium hydroxide solution. Once the resulting product was reduced with Pd/C and $HCOONH_4$, it cyclized and oxidized to afford 2-quinoxalinol.[155] The crude mixture of 2-quinoxalinol was purified by silica gel column chromatography with ethyl acetate:hexane:ethanol (8:2:1) as the eluent.

Reaction of 2-quinoxalinol with 3,5-diterbutyl-2-hydroxybenzaldehyde in the presence of 1 drop of trifluroacetic acid (TFA) formed the tetradentate salqu ligand. Finally, the coordination of the salqu ligand to copper acetate produced the 2-quinoxalinol salen copper(II) complex.

With a 2-quinoxalinol salen copper(II) complex in hand, we began our investigation of propargylic alcohol oxidation by oxidizing commercially available 1-phenyl-2-propyn-1-ol (0.5 mmol) with TBHP (10 eq) and copper(II) catalyst (1 mol %) in CH_3CN (1.5 mL) under stirring at 70 °C for 24 h as a model system. The yield of 1-phenyl-2-propyn-1-one was low under these conditions, however, it was found to improve significantly when the reaction time was reduced (Table 2.1, entries 1-3). The yield had no considerable change when the reaction time reduced from 3 h to 1 h (Table 1, entries 1 and 2), thus the reaction time was set to 1 h to optimize the other conditions of the reaction.

Table 2.1. Oxidation of 1-phenyl-2-propyn-1-ol



Entry	TBHP portions	Time/h	Conversion of 1a (%)	GC yield of 2a (%)
1	1	1	88	56
2	1	3	90	55
3	4	24	85	41

Next, the required ratio of TBHP was determined (Figure 2.1). An increasing trend of both yield and conversion of 1-phenyl-2-propyn-1-ol was observed when the amount of oxidant was increased from 1 eq to 2.5 eq. The conversion of the starting propargylic alcohol remained the same with further increases, but the yield was found to be reduced when the TBHP was increased beyond 2.5 eq, perhaps due to the over oxidation of 1-phenyl-2-propyn-1-one. Hence, both the maximum yield and the maximum conversion of 1-phenyl-2-propyn-1-ol were observed at 2.5 eq of TBHP.

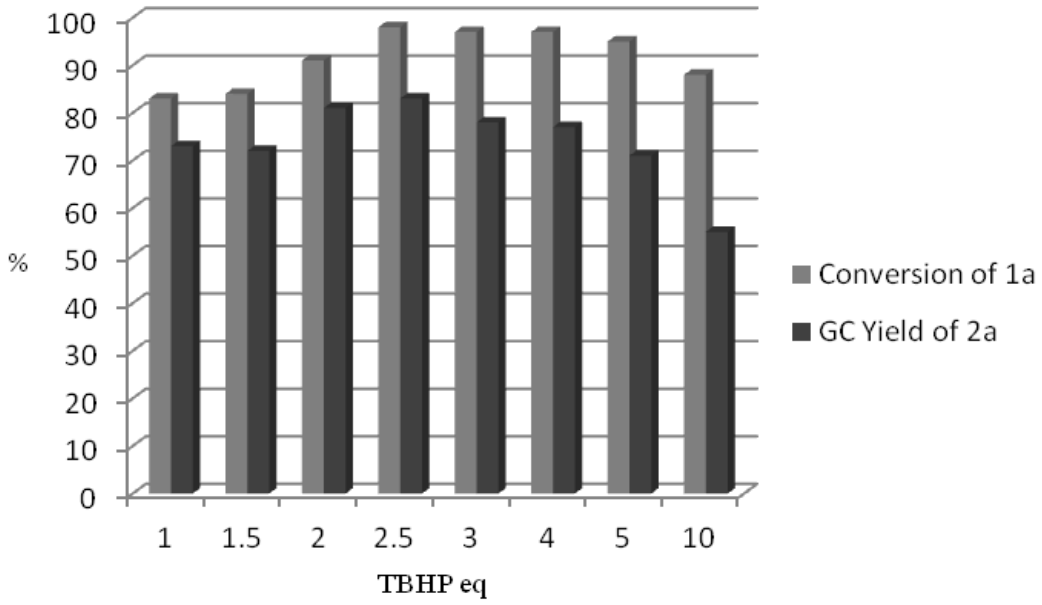


Figure 2.1. GC yields and conversions with the oxidant ratio

A solvent effect for this reaction was characterized by characterizing the reactions using different solvents (Table 2.2). The reaction in methylene chloride gave both low yield and low conversion of 1-phenyl-2-propyn-1-ol (Table 2, entry 1). Both chloroform and 1, 2-dichloroethane (DCE) produced moderate yields and good conversion of starting

propargylic alcohol (entries 2 and 3). Using acetontrile resulted in very good yields as well as good conversion; however, the use of tert-butanol and benzonitrile resulted in low yields and low conversions of 1-phenyl-2-propyn-1-ol as compared to the other solvents (entries 5 and 6).

Table 2.2. Effect of solvent[a]

Entry	Solvent	Conversion of 1a (%)	GC yield of 2a (%)
1	CH_2Cl_2	72	44
2	$CHCl_3$	97	64
3	DCE	96	62
4	CH_3CN	98	83
5	tBuOH	53	39
6	PhCN	59	45

[a]Reaction conditions: 1a (0.5 mmol), catalyst (1 mol %), TBHP (2.5 eq), solvent (1.5 mL), 70 °C, 1 h

Finally, a time profile of the oxidation of 1-phenyl-1-propyn-1-ol was examined with TBHP (2.5 eq) and copper(II) catalyst (1 mol %) in CH_3CN (1.5 mL) under stirring at 70 °C (Figure 2.2). The product yield gradually increased and levels off after 1 h of reaction time. Conversion of the 1-phenyl-2-propyn-1-ol increased and reached a maximum after 1 hour. Subsequent extension of the reaction times further reduced yields

of the desired product, presumably because of additional oxidation of the resulting carbonyl compound.

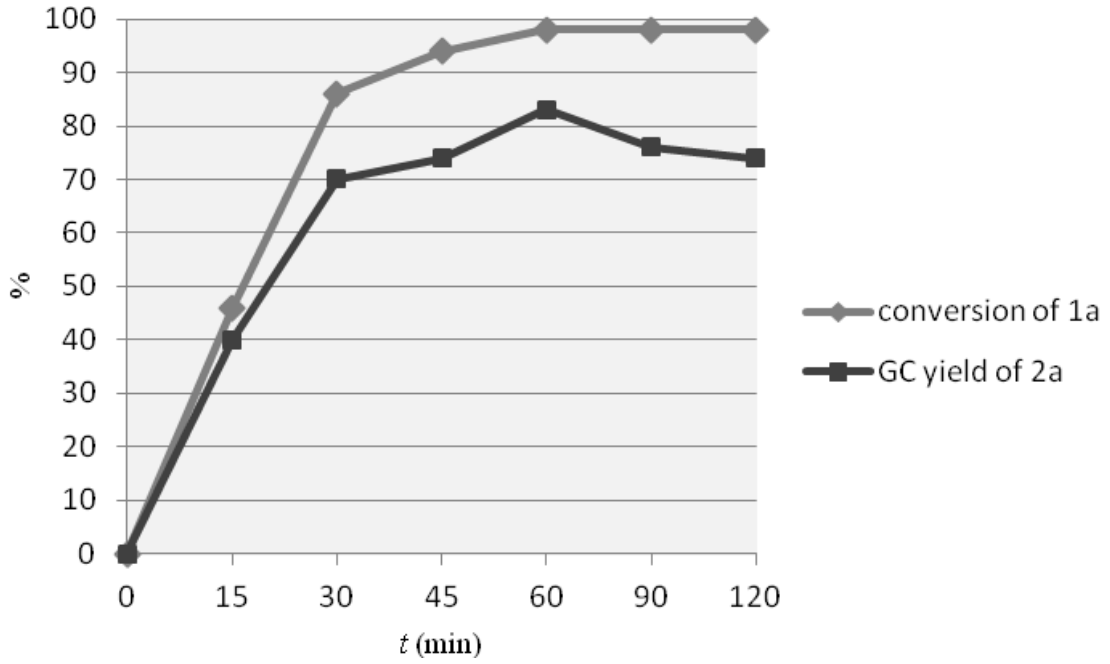


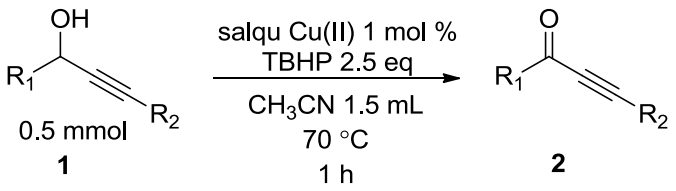
Figure 2.2. Time profile of oxidation of 1-phenyl-2-propyn-1-ol

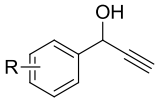
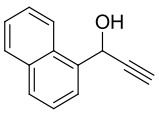
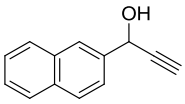
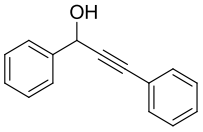
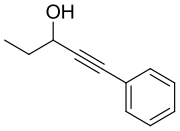
On the basis of these optimized reaction conditions, a variety of propargylic alcohol substrates were oxidized with TBHP (2.5 eq) and Cu(II) catalyst (1 mol %) in CH_3CN (1.5 mL) under stirring at 70 °C for 1 h (Table 3). First, the oxidation of propargylic alcohols with substituted aryl groups at α position was examined. Most of the propargylic alcohols with substituted aryl groups at α position were converted to the corresponding carbonyl compound in high yields (Table 2.3, entries 1, and 3-9). When Cl was substituted at the 2, 3 and 4 positions of the aryl group, increasing yields of the corresponding carbonyl compound were observed and turn over numbers were 39, 71 and

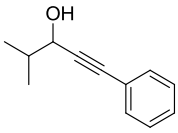
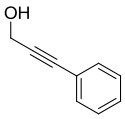
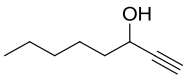
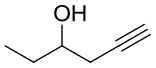
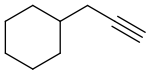
78 respectively (entries 2-4). This could be the results of steric hindrance at the ortho position.

When the 4 position of the aryl group of the propargylic alcohol was instead substituted with Br or I, the yield also increased (entries 4-6). These results reflect an electronic effect of the substituent on the aromatic ring. Electron donating groups such as methyl and tert-butyl groups produced good yields under these conditions (entries 7-8), however, a strong electron donating methoxy group produced slightly lower yield as compared to that of tert-butyl group, possibly due to over oxidation of the resulting ketone (entry 9). When an electron withdrawing nitro group was introduced at the para position, the yield was comparatively low (entry 10). Propargylic alcohols having 1-naphthyl and 2-naphthyl groups also produced good yields of corresponding carbonyl compound (entries 11 and 12), but again, the alcohol with 2-naphthyl group produced higher yield compared to that of 1-naphthyl group reflecting the importance of the effects of steric hindrance. Thus, a wide range of functional groups such as Cl, Br, I, Me, *t*-Bu, OMe, NO_2 are tolerated.

Table 2.3. Oxidation of propargylic alcohols under optimized condition with 1 mol % catalyst



Entry	Substrate		Conversion of substrate (%)	Isolated yield of 2 (%)
1		1a R= H	98	83
2		1b R= 2-Cl	86	39
3		1c R= 3-Cl	100	71
4		1d R= 4-Cl	100	78
5		1e R= 4-Br	100	82
6		1f R= 4-I	100	92
7		1g R= 4-Me	99	82
8		1h R= 4-tBu	100	95
9		1i R= 4-OMe	100	89
10		1j R= 4-NO_2	99	51
11		1k	93	82
12		1l	100	87
13		1m	100	99
14[a]		1n	100	90

15[a]		1o	100	86
16[a]		1p	88	62
17[a]		1q	90	85[b]
18[a]		r	15	_[b]
19[a]		s	7	_[b]

[a] For 5 h. [b] GC yield

When a propargylic alcohol with aryl groups at both the R_1 and R_2 positions was oxidized, it produced excellent yield under these conditions (entry 13). The oxidation of propargylic alcohols having alkyl groups at the α position gave low yields when oxidized for 1 h; however, when the reaction time was increased to 5 h, they produced good yields of corresponding ketone (entries 14, 15 and 17). Even when a primary propargylic alcohol was oxidized (H at the α position) it gave a good yield of α,β-acetylenic aldehyde under this reaction condition (entry 16).

Finally, the reaction was studied using an alkyne substrate having an isolated hydroxyl group (entry 18). In this case, no oxidized ketone was observed even after 5 h of reaction time. A small percentage of substrate conversion was observed possibly due to the oxidation of the triple bond. As this reaction is expected to go through a radical pathway, a radical formed at α carbon to a triple bond is supposed to be more stabilized

than that of an isolated carbon. Thus, that could possibly be the reason why propargylic alcohols are more reactive over homopropargylic alcohols under this reaction conditions. When an alkyne was oxidized, it resulted no α,β-acetylenic ketones (entry 19). Again, this demonstrates the selectivity of this catalyst system for propargylic alcohol oxidation and propargylic methylenes are resistant to oxidation under this catalytic protocol.

To characterize the effects of the substituent on this reaction, a correlation to Hammett constants were calculated and plotted according to equation 2.1. The correlation between log (k_X/k_H) and para-position Hammet constants showed a good fit as shown in Figure 2.3. According to these results, the propargylic alcohol oxidation was accelerated by electron-donating substituents and decelerated by electron-withdrawing substituents. The negative slope (ρ) indicates that the electron-withdrawing substituents decrease the ratio of log (k_X/k_H) resulting lower oxidized yields and that the oxidation of propargylic alcohol 1 with copper(II) catalyst is likely to be electrophilic in nature under these reaction conditions. Because of this, it stands to reason that the reaction mechanism may go through an electron deficient intermediate and thus, the electron-donating substituents help to stabilize the intermediate resulting high reaction yields.

Equation 2.1.

$\log k_X/k_H = \rho\sigma_p$

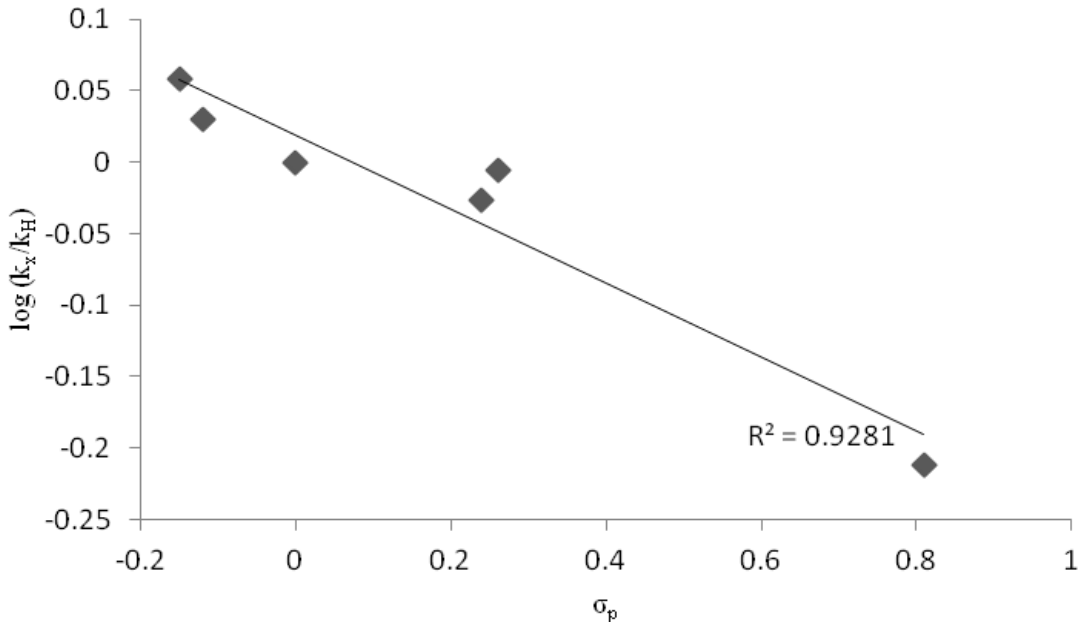


Figure 2.3. Correlation between log (k_X/k_H) and para-position Hammet constants. The substituent constants σp were taken from ref 100.[156]

In summary, we have found that 2-quinoxalinol salen or salqu copper(II) complex is efficient as a catalyst for the oxidation of propargylic alcohols to the corresponding carbonyl compounds under the oxidant TBHP. This catalytic system produced excellent selectivity for oxidation of propargylic alcohols over isolated alcohols, triple bonds, or propargylic methylenes. Excellent yields were achieved within 1 h, a significantly enhanced reaction time compared to the other available methods.[149-151,153] Most other reported methods fail the oxidation of propargylic alcohols with alkyl groups at R_1 position;[149] however, the salqu copper(II) catalyst with TBHP works well and produces

high yields. Furthermore, the use of 1 mol % catalyst for the oxidation of all types of propargylic alcohols (turn over numbers up to 99) is another advantage of this method in the view of industrial and environmental chemistry.

Elimination of hazardous organic solvents is another way to make chemical reactions environmentally benign. Thus, this work was continued using a water-soluble version of 2-quinoxalinol salen copper(II) complex in the view of green and sustainable chemistry. The synthesis of water-soluble 2-quinoxalinol salen copper(II) complex and its application for the selective alcohol oxidation is discussed in Chapter 3.

Chapter 3

Alcohol Oxidation in Water

As the use of safer solvents in reactions are encouraged by green chemistry, water based organic reactions have gained increasing interest in recent years.[157-165] Water has reported to have rate acceleration of reactions[163] and even when there is no rate acceleration, features like high heat capacity, redox stability, ease of product isolation and most importantly green aspect of it, keep scientists interested in water as a solvent over hazardous volatile organic solvents.[159,161]

In recent years, water has been used as a solvent for transition metal-catalyzed organic reactions including pericyclic reactions,[166-168] olefin metathesis,[169] carbonylation,[170] arylation,[171] hydroformylation,[172] Suzuki reaction,[173] Mizoroki-Heck reaction[174] and others;[175-178] however, the use of water as solvent for metal catalyzed radical reactions in organic synthesis is rare. Water is less reactive towards free radicals and it is relatively redox inert molecule. Hence, water could be a useful reaction medium for radical reactions as well as redox reactions of organic compounds.

Synthesis of carbonyl compounds by oxidation of alcohols is one of the important redox reactions in organic chemistry. These oxidations are typically conducted by using catalysts featuring toxic metals such as V,[148,149] Co,[150] Mo,[179] Ru,[180-182] Pd,[183,184] and

Ir.[185,186] To mitigate the harsh conditions associated with these methods, alternative approaches like Cu-catalyzed[152,154,187,188] reactions have been developed. Use of pure oxygen[149,150,153,189,190] or air[151,152,189] as oxidant for these metal-catalyzed alcohol oxidation reactions can also be seen as a greener approach. The use of water as a reaction medium for alcohol oxidation has less reported. Thus, in the view of green and sustainable chemistry, the development of a mild, less toxic and efficient method is desirable.

In this chapter, a radical reaction in water is described for the oxidation of propargylic, benzylic, and allylic alcohols to yield corresponding carbonyl compounds using a water-soluble sulfonated 2-quinoxalinol salen (sulfosalqu) copper(II) complex as a catalytic system. Thus, this study commenced by synthesizing a water-soluble 2-quinoxalinol salen copper(II) complex.

Salqu copper(II) complex can be made water-soluble by introducing polar or ionic groups at R_1, R_2 or R_3 positions (Figure 3.1).

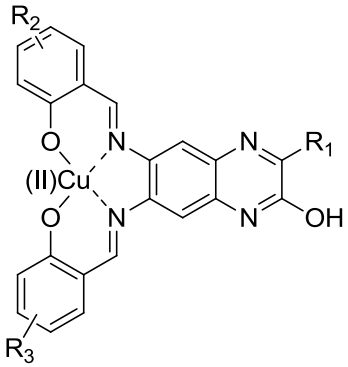
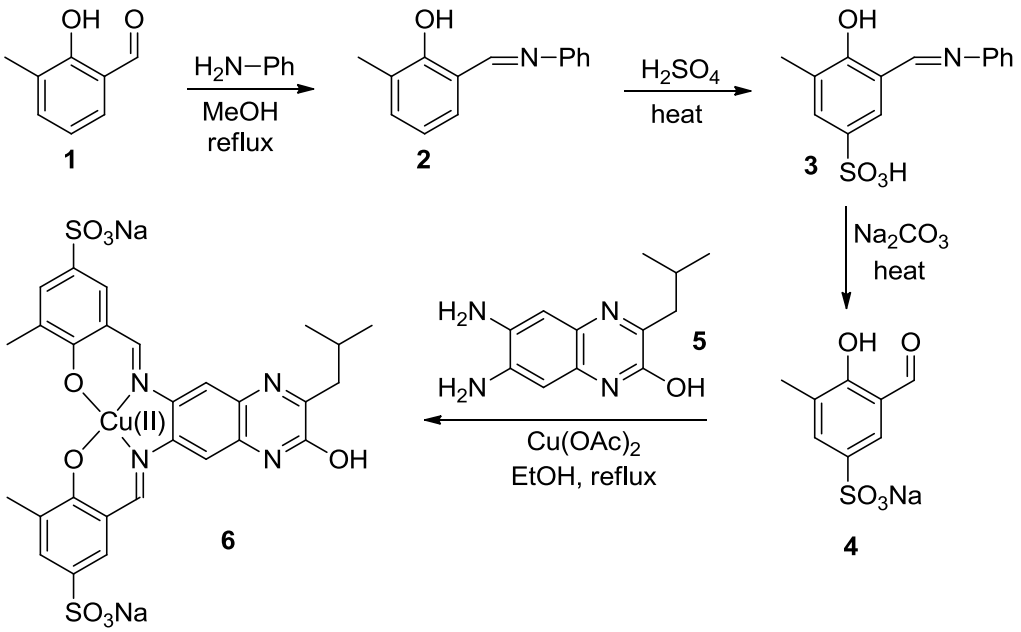


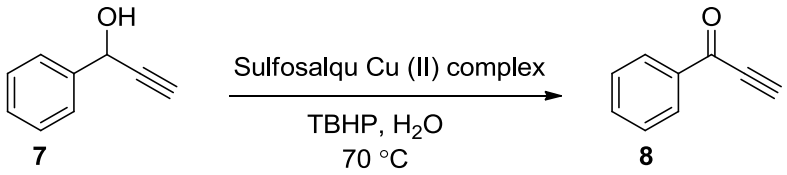
Figure 3.1. Basic structure of 2-quinoxalinol salen copper(II) complex

Here, we use a salicylaldehyde derivative with sulfonate groups to make the R_1 and R_2 groups of the complex ionic. A sulfonated 2-quinoxalinol salen (sulfosalqu) copper(II) complex was synthesized through the reaction sequence shown in scheme 3.1. The approach to sodium 3-methylsalicylaldehyde-5-sulfonate **4** requires protection of 3-methylsalicylaldehyde **1** followed by sulfonation and then deprotection of the resulting compound **3**, and this was achieved by following a modified procedure from literature.[191] Sodium 3-methylsalicylaldehyde-5-sulfonate **4** was then reacted with 2-quinoxalinol **5,** which was prepared according to the reported procedure in our laboratory,[155] and copper acetate in one-pot to yield sulfosalqu copper(II) complex **6**.

Scheme 3.1. Synthesis of sulfonated 2-quinoxalinol salen (sulfosalqu) copper(II) complex



Scheme 3.2. Oxidation of 1-phenyl-2-propyn-1-ol



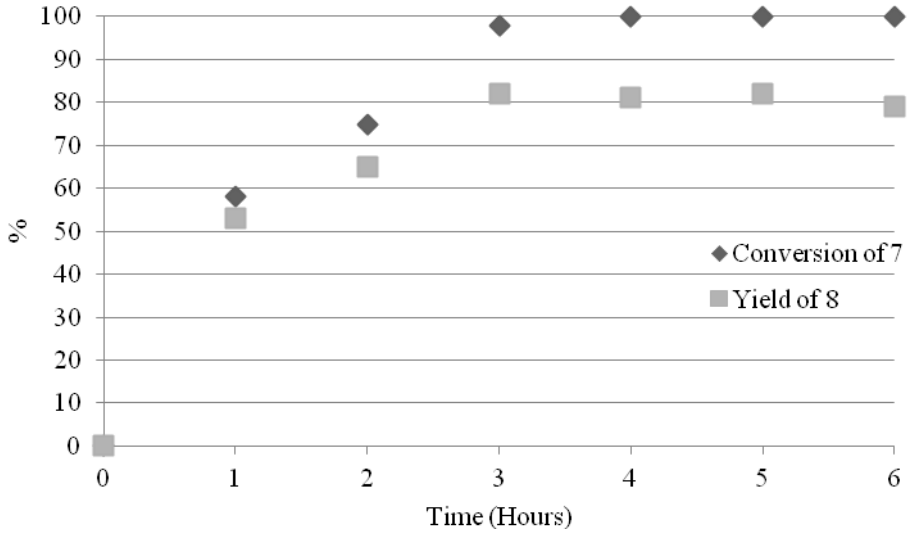


Figure 3.2. Time profile of the reaction with **7** (0.5 mmol), sulfosalqu copper(II) complex (1 mol %) and TBHP (3 eq) in H_2O at 70 °C. Yields and conversions were determined by GC with 1,2-dichlorobenzene added as an internal standard.

Using the water soluble catalyst we developed, we tested the oxidation of 1-phenyl-2-propyn-1-ol (0.5 mmol) with TBHP (3 eq) and sulfosalqu copper(II) catalyst (1 mol %) in H_2O under stirring at 70 °C for 1 h as a model system (Scheme 3.2). The yields and conversions were determined by extracting the reaction mixture to ether and then analyzing the organic layer by GC with the internal standard method. The yield of 1-phenyl-2-propyn-1-one was low under these conditions; however, it was found to improve when the reaction time was increased (Figure 3.2). Both conversions and

reaction yields reached to a maximum after 3 h and no considerable yield change occurred upon further increasing the reaction time from 3 h to 6 h. Therefore, the 3 h mark was best suited to optimize the other conditions of the reaction.

Several different oxidants were then screened for the oxidation of 1-phenyl-2-propyn-1-ol using sulfosalqu copper(II) complex (1 mol %) in water. Hydrogen peroxide, peracetic acid, and m-chloroperbenzoic acid were all ineffective oxidants towards this oxidation, affording low yields of corresponding ketone after 3 h at 70 ˚C (Figure 3.3). In contrast, TBHP was an excellent oxidant, producing high yields of 1-phenyl-2-propyn-1-one under these reaction conditions.

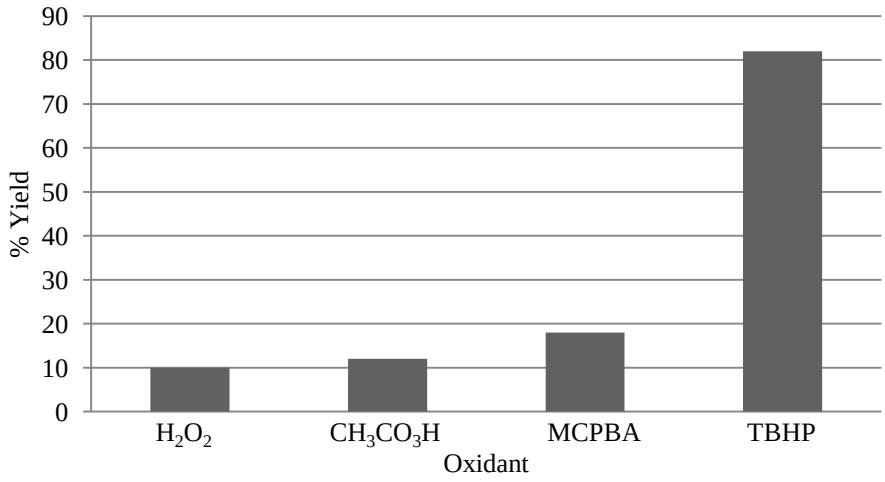


Figure 3.3. Effect of Oxidant. Conditions: **7** (0.5 mmol), sulfosalqu copper(II) complex (1 mol %) and oxidant (3 eq) in H_2O at 70 °C. Yields were determined by GC with 1,2-dichlorobenzene added as an internal standard.

As TBHP resulted in producing good yields under these conditions, we went on to analyze the effect of TBHP ratio in the reaction. Yield of 1-phenyl-2-propyn-1-one was (**8**) increased from 44 % to 82 % when the TBHP ratio was changed from 1 eq to 3 eq

(Figure 3.4); however, the addition of more TBHP equivalents did not result in a further improvement in the reaction yield.

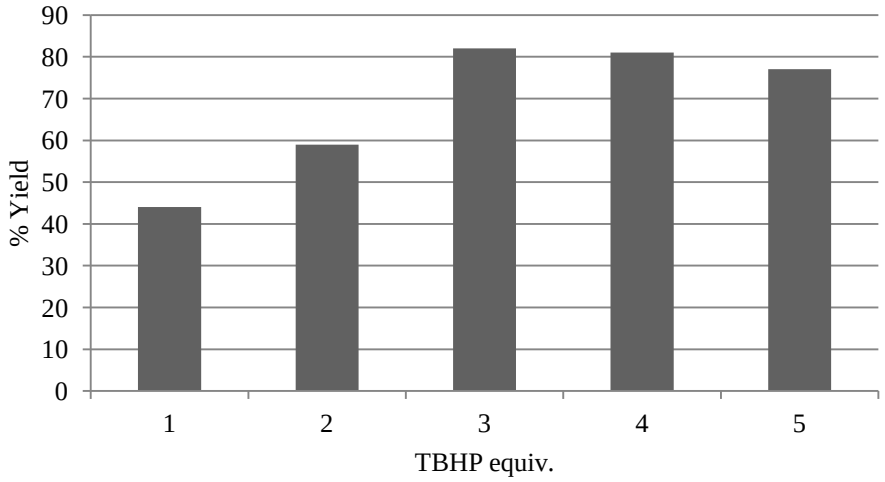


Figure 3.4. Effect of TBHP ratio. Conditions: **7** (0.5 mmol), sulfosalqu copper(II) complex (1 mol %) and TBHP in H_2O at 70 °C. Yields were determined by GC with 1,2-dichlorobenzene added as an internal standard.

Encouraged by these results, we studied the factors that control the reaction yield of 1-phenyl-2-propyn-1-ol oxidation. The reactions were performed in water at 70 °C for 3 h with 1 mol % copper(II) sulfosalqu complex and 3 eq TBHP, with 1 mol % copper(II) sulfosalqu complex alone, without a copper catalyst, and with catalytic amounts of $Cu(OAc)_2$ or $CuCl_2$ and 3 eq TBHP (Table 3.1). When the reaction was run in the absence of the catalyst, it afforded a very small yield of corresponding ketone after 3 h at 70 ˚C (entry 2), showing the important role of copper(II) sulfosalqu complex as the catalyst in this alcohol oxidation. It was also observed that the reaction barely happens in the absence of TBHP, suggesting the lack of driving force of the reaction without the oxidant TBHP (entry 3). Reactions run under normal conditions with $Cu(OAc)_2$ and

$CuCl_2$, instead of copper(II) sulfosalqu complex as the catalyst occurred in very low yields of 27 % and 30 % respectively (entries 4 and 5). Even when the amount of $Cu(OAc)_2$ was increased form 1 mol % to 5 mol %, it produced only 35 % yield (entry 4). These results suggested that the copper(II) sulfosalqu complex is responsible for the high yields, not just a copper salt alone as a catalyst.

Table 3.1. Effect of reaction condition[a]

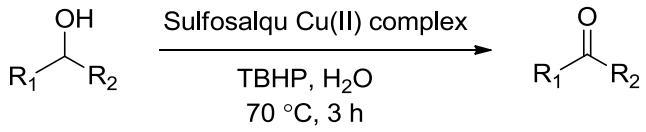
Entry	Condition	Yield of 8 (%)[b]
1	Sulfosalqu Cu(II)	82
2	No catalyst	7
3	No TBHP	0.5
4	$Cu(OAc)_2$	27 (35)
5	$CuCl_2$	30

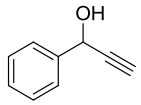
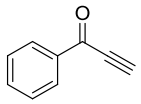
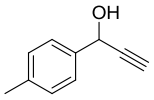
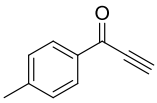
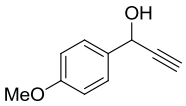
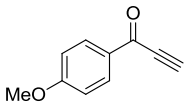
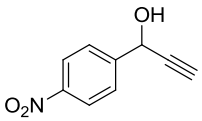
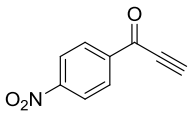
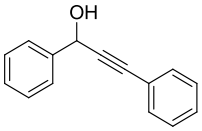
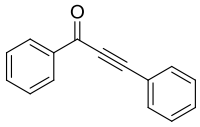
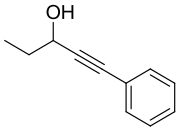
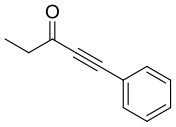
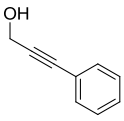
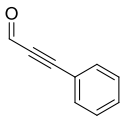
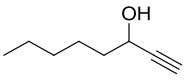
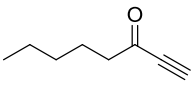
[a]Conditions: **7** (0.5 mmol), sulfosalqu copper(II) complex (1 mol %) and TBHP (3 eq) in H_2O at 70 °C for 3 h. [b]GC yields with 1,2-dichlorobenzene added as an internal standard. The value in parentheses is the yield when 5 mol % of $Cu(OAc)_2$ used.

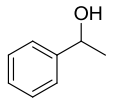
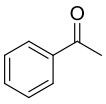
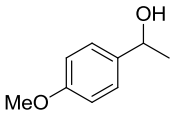
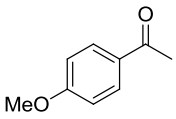
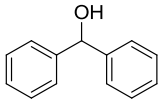
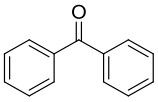
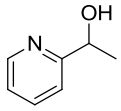
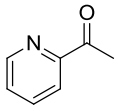
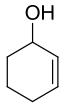
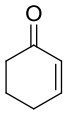
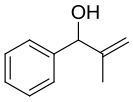
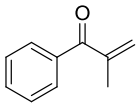
The substrate scope of the alcohol oxidation was investigated using sulfosalqu copper(II) catalyst (1 mol %) and TBHP (3 eq) in H_2O under stirring at 70 °C for 3 h (Table 3.2). The yields were determined by mass calculation of purified product after silica gel column chromatography. First, the oxidation of propargylic alcohol substrates was examined by varying the electronic properties of the arene. Substrate bearing H (entry 1) and methyl (entry 2) occurred in similar yields. However, the substrate possessing more electron-donating methoxy group (entry 3) underwent the oxidation to give much higher yield of corresponding ketone than that of latter. In contrast, moderate

yield was observed for the substrate with a nitro substituent, suggesting a significant influence of the electronic properties of the arene (entry 4).

Table 3.2. Substrate scope[a]



Entry	Substrate	Product	Yield (%)[b]
1			81
2			79
3			90
4			52
5			98 (92)
6[c]			78
7[c,d]			54
8[c]			60

9[e]			74
10[e]			92
11[e]			99
12[e]			63
13[c,d]			41
14			58

[a]Conditions: **7** (0.5 mmol), sulfosalqu copper(II) complex (1 mol %) and TBHP (3 eq) in H_2O at 70 °C for 3 h. [b]Isolated yields are shown. The value in parentheses is an isolated yield on a 5 mmol scale. [c]6 h. [d]sulfosalqu copper(II) complex (2 mol %). [e]12 h.

Meanwhile, 1,3-diphenyl-2-propyn-1-ol was oxidized to corresponding ketone in almost quantitative yield (entry 5). This reaction was also conducted on a 5 mmol scale and it gave 92 % yield of 1,3-diphenyl-propyn-1-one after purification by silica gel column chromatography with hexane:ethyl acetate as eluent (entry 5). Oxidation of propargylic alcohols containing an alkyl substituent at α position was relatively slow; however, extension of reaction time to 6 h produced high yields of desired product (entry 6). The reaction also occurred with an alcohol having only hydrogens at α position

(primary propargylic alcohol) 3-phenyl-2-propyn-1-ol to provide corresponding aldehyde in moderate yield (entry 7). In this case, over oxidation resulting 3-phenyl-2-propynal to the corresponding carboxylic acid was also observed, as the reaction medium is water. In addition, oxidation of terminal alkyne, 1-octyn-3-ol was compatible with this catalytic system affording a good yield of the corresponding ketone (entry 8).

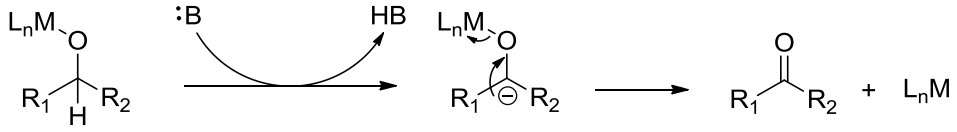
Under these conditions, oxidations of benzylic alcohols were slightly slower compared to that of propargylic alcohols; however, when the reaction time was increased to 12 h, they produced corresponding ketones in good to excellent yields (entries 9,10 and 11). 2-(1-hydroxyethyl)pyridine also underwent the oxidation on water to give a good yield of 2-acetylpyridine (entry 12). Moreover, this catalytic protocol led to the oxidation of allylic alcohols to the corresponding α,β-unsaturated ketones in moderate yields (entries 13 and 14).

In all cases, the oxidation occurred at the propargylic, benzylic and allylic positions. To study the selectivity of oxidation to these positions, a mixture of 1-phenyl-2-propyn-1-ol (0.5 mmol) and 1-octanol (0.5 mmol) was oxidized using sulfosalqu copper(II) catalyst (1 mol %) and TBHP (3 eq) in H_2O under stirring at 70 °C for 3 h. Only the oxidation of 1-phenyl-2-propyn-1-ol was observed with no formation of 1-octanal, suggesting the selectivity of this system to propargylic, benzylic and allylic positions.

To understand the role of the oxidizing agent, TBHP, oxidation of 1-phenyl-2-propyn-1-ol was examined under a nitrogen atmosphere. Treatment of 1-phenyl-2-propyn-1-ol with sulfosalqu copper(II) catalyst (1 mol %) and TBHP (3 eq) in H_2O under nitrogen at 70 °C for 3 h produced similar results as in normal atmosphere of air,

suggesting that TBHP is the only oxidant required for this reaction and oxygen from air has no role to play in the formation of active intermediates in this reaction. This was also evidenced by the fact that the reaction barely happened in the absence of TBHP.

Scheme 3.3. Decomposition of the catalyst-substrate intermediate under basic conditions



The addition of a base promoter has been reported in other similar reactions to accelerate the oxidation of alcohols when catalyzed with metal complexes using oxidants.[151,154] This is due to the rapid decomposition of the catalyst-substrate intermediate forms during the reaction under basic conditions (Scheme 3.2); however, in our case, the addition of 2 mol % NEt_3 did not affect the reaction rate. The absence of a rate change in the presence of NEt_3 suggests that the reaction may not proceed through such a catalyst-substrate intermediate in this sulfosalqu copper(II) catalytic system. Thus, we suggest that the catalytic oxidation may go through a radical intermediate under these reaction conditions and it may occur at propargylic, benzylic and allylic positions. This is supported by the fact that, in the absence of TBHP, with no radical initiator in the reaction medium the reaction had very poor production of products (Table 3.1 entry 3). To further prove this, oxidation of 1-phenyl-2-propyn-1-ol was conducted under 7 mol % of BHT (Butylated hydroxytoluene) and it only produced 5 % yield of the corresponding ketone. This suggests that the reaction barely happens in the presence of a radical inhibitor. The observed selectivity for propargylic, benzylic and/or allylic alcohol oxidation also supports the formation of a radical intermediate. Because of the

propargylic, benzylic and allylic radicals are more stable than isolated radicals, the alcohol oxidation is more preferred at those positions. This may be the reason why, a mixture of 1-phenyl-2-propyn-1-ol and 1-octanol only resulted in oxidation of 1-phenyl-2-propyn-1-ol. Moreover, experimental results showed that a substrate bearing a methoxy group (Table 3.2, entry 3) underwent the oxidation to give much higher yield of corresponding ketone. In contrast, precursor with a nitro substituent produced a low yield (Table 3.2, entries 4). This could be the result of the ability of the strong electron donors to stabilize the radical intermediates, and the consequence of strong electron withdrawing groups destabilizing the radical intermediate. Thus, it is believed that the formation of this carbon-based radical intermediate is facilitated by the sulfosalqu copper(II) complex.

In summary, we have developed a sulfonated 2-quinoxalinol salen copper(II) catalyzed, selective oxidation of propargylic, benzylic and allylic alcohols using *tert*-butyl hydroperoxide as oxidant. This reaction constitutes a rare example of alcohol oxidation in water and it makes this process greener by eliminating the use of hazardous organic solvents, toxic metals and high catalyst loading. These alcohol oxidations occur in good yields with excellent selectivity for propargylic, benzylic and allylic alcohols. Ease of product isolation by extraction is another advantage of this method.

This work was further extended for the C-H functionalization of organic compounds at benzylic and allylic positions in water and that work is discussed in Chapter 4.

Chapter 4

C-H Activation in Water

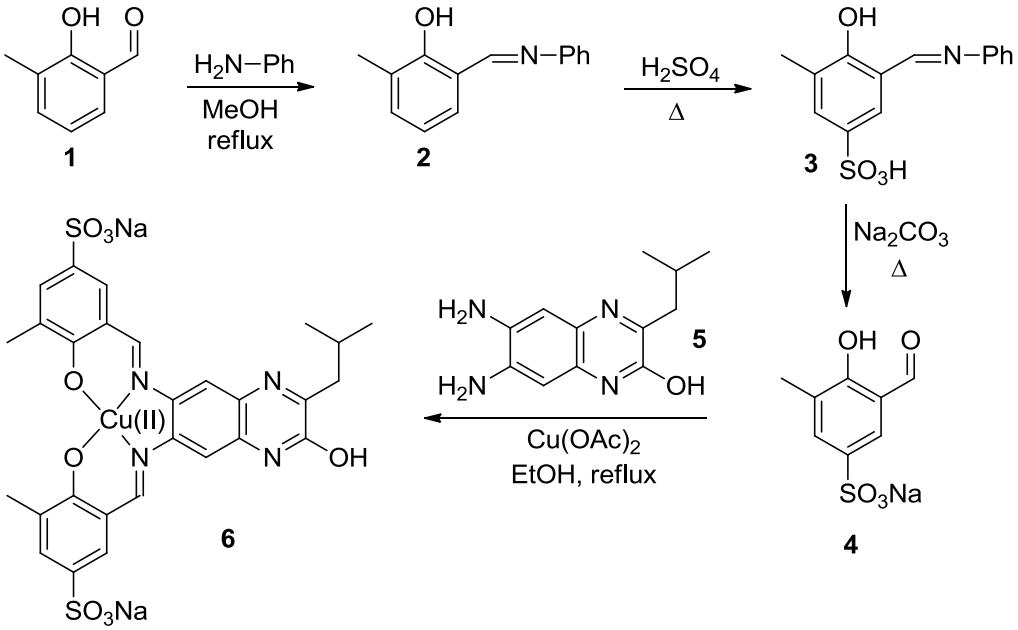
The functionalization of C-H bonds is of wide interest as it converts chemically less reactive organic substrates into more reactive chemical compounds, which are versatile building blocks in multistep organic syntheses.[192-196] These activations can occur at benzylic,[197,198] allylic[116,117,199] and aliphatic C(sp^3)-H[200,201] bonds or even at the aromatic C(sp^2)-H[202-204] bonds. Such functionalizations are typically carried out using transition metal catalyzed reactions, for example Mn,[205-207] Fe,[208,209] Co,[210,211] Ru,[195,212,213] Rh,[199,214,215] Pd,[216,217] and Ir.[200,218]

Development of environmentally friendly or greener methods is desired for these C-H functionalizations, in the view of green and sustainable chemistry. In this regard, copper-catalyzed C-H activations have been employed to eliminate the toxicity of metals involved in combination with environmentally benign oxidants such as molecular oxygen[62,219-221] and *tert*-butyl hydroperoxide.[38,40,115] Solvent-free conditions[40] and polymer supported heterogeneous catalytic sytems[39,40,220] have also been studied to make the process efficient and ecofriendly in recent years. Another approach is to use green solvents like water instead of hazardous volatile organic solvents for C-H functionalization.[222]

In this chapter, we report the extension of using copper(II) complex of sulfonated 2-quinoxalinol salen as an efficient catalyst in water for the selective functionalization of benzylic and allylic C-H bonds to the corresponding carbonyl compounds in the presence of oxidant *tert*-butyl hydroperoxide.

Sulfonated 2-quinoxalinol salen (sulfosalqu) copper(II) complex was synthesized in the same way as described in the Chapter 3 (Scheme 4.1). The approach to sodium 3-methylsalicylaldehyde-5-sulfonate **4** requires protection of 3-methylsalicylaldehyde **1** followed by sulfonation and then deprotection of the resulting compound **3**. Sodium 3-methylsalicylaldehyde-5-sulfonate **4** was then reacted with 2-quinoxalinol **5**, and copper acetate in one-pot to yield sulfosalqu copper(II) complex **6**.

Scheme 4.1. Synthesis of sulfonated 2-quinoxalinol salen (sulfosalqu) copper(II) complex



To begin our study, we examined the oxidation of diphenylmethane (0.5 mmol) using a catalytic amount of sulfosalqu copper(II) complex (1 mol %) and TBHP (3 eq) in H_2O under stirring at 70 °C for 3 h (scheme 4.2). The yields and conversions of the reaction were determined by extracting the reaction mixture to dichloromethane and then analyzing the organic layer by GC with the internal standard method. The reaction, however, did not occur efficiently under these conditions to give the corresponding ketone in good yield (Table 4.1, entry 1). Thus, the reaction time was gradually increased to improve the yield of the reaction. Both conversions and reaction yields were found to improve with the reaction time and it resulted in very good yield of benzophenone (**8**) after 24 h of reaction time (Table 1, entries 2-7).

Scheme 4.2. Oxidation of diphenylmethane

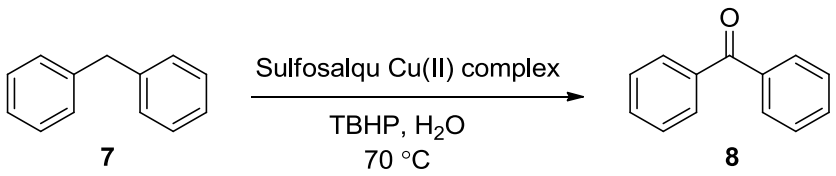


Table 4.1. Time profile of the reaction[a]

Entry	Time/h	Conversion of 7 (%)	Yield of 8 (%)
1	1	31	26
3	3	56	48
4	6	68	57
5	12	83	70
6	18	90	75
7	24	95	80

[a]Conditions: **7** (0.5 mmol), sulfosalqu copper(II) complex (1 mol %) and TBHP (3 eq) in H_2O at 70 °C. Yields and conversions were determined by GC with 1,2-dichlorobenzene added as internal standard.

This reaction was then examined with 3 eq of hydrogen peroxide as the oxidant; however, the yield of benzophenone was very low (3 mol %), under this reaction condition. Even when the amount of H_2O_2 was increased to 30 mol % it produced only 4 % yield of desired product. Thus, TBHP was continued to be used as the oxidant for the C-H functionalization.

The required amount of TBHP for the reaction was studied by oxidizing diphenylmethane (0.5 mmol) using sulfosalqu copper(II) complex (1 mol %) in H_2O under stirring at 70 °C for 24 h (Figure 4.1). The yield of benzophenone was increased when TBHP amount was increased from 1 eq to 3 eq. After 3 eq of TBHP, reaction yield reached to a maximum and produced almost similar results. The addition of additional equivalents of TBHP also did not reduce the reaction time.

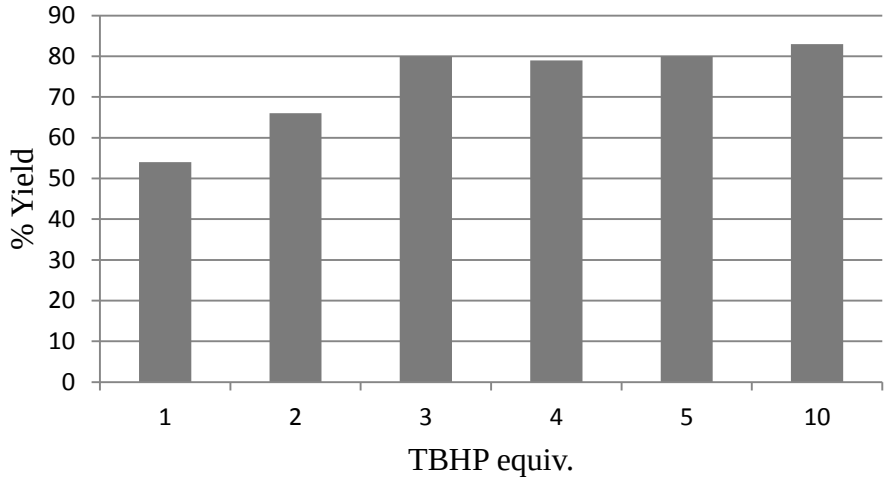
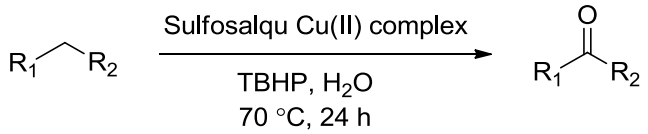
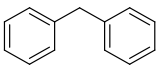
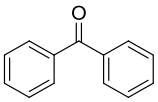
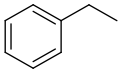
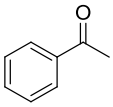
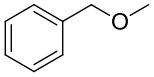
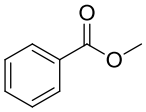
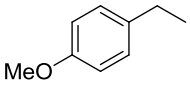
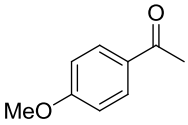
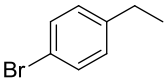
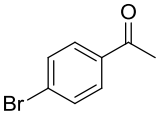
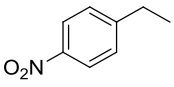
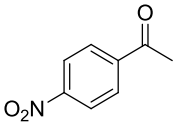
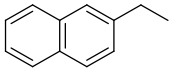
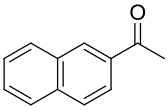
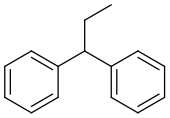
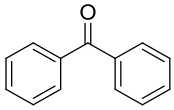
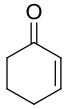
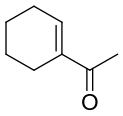
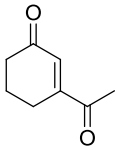
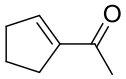
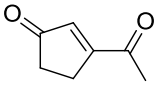
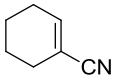
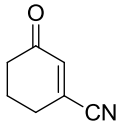


Figure 4.1. Effect of TBHP ratio. Conditions: **7** (0.5 mmol), sulfosalqu copper(II) complex (1 mol %) and TBHP in H_2O at 70 °C. Yields were determined by GC with 1,2-dichlorobenzene added as an internal standard.

Table 4.2. Substrate scope[a]



Entry	Substrate	Product	Yield (%)[b]
1			80
2			92
3			92
4			96
5			65
6[c]			56
7[c,d]			76
8[c]			62
9[e]			60

10[e]			74
11[e]			70
12[e]			56

[a]Conditions: Substrate (0.5 mmol), sulfosalqu copper(II) complex (1 mol %) and TBHP (3 eq) in H_2O at 70 °C for 24 h. [b]GC yields are shown. [c]6 h. [d]sulfosalqu copper(II) complex (2 mol %). [e]12 h.

The substrate scope of the C-H functionalization was investigated using sulfosalqu copper(II) catalyst (1 mol %) and TBHP (3 eq) in H_2O under stirring at 70 °C for 24 h (Table 4.2). First, a variety of representative benzylic substrates were oxidized. Substrates bearing electron donating R_2 groups such as –Me and –OMe produced excellent yields (entries 2 and 3). Oxidation of the ether compound provides a direct method to synthesize methyl benzoate from benzyl methyl ether (entry 3). Electronic properties of the arene were varied and the substrate bearing electron-donating methoxy group (entry 4) underwent the oxidation to give excellent yield of corresponding ketone. In contrast, reaction yields dropped when electron-withdrawing groups were introduced to the arene, indicating the importance of the electronic properties of the arene for the C-H activation. In particular, the substrate with a weak deactivating –Br group produced 65 % yield and the substrate with a strong deactivating $–NO_2$ group produced 56 % yield of their corresponding carbonyl compounds (entries 5 and 6). This could be the result of the

electron-withdrawing properties of bromo and nitro groups that could destabilize the radical intermediates form during the reaction.

When 2-ethylnaphthalene was oxidized, it still produced a good yield of corresponding ketone (entry 7). Surprisingly, 1,1-diphenylpropane was oxidized to benzophenone as the major product instead of the expected 1,1-diphenylpropanol, under this catalytic system (entry 8). This observation indicates the reaction to go through a complicated mechanism.

Having successfully functionalized benzylic C-H bonds, we examined the capability of this catalytic protocol for the allylic C-H activation. Cyclohexene was oxidized to 2-cyclohexenone in 60 % yield in water (entry 9). Allylic substrates bearing –CN groups and –Ac groups also produced moderate to good yields under this catalytic system (entries 10, 11 and 12). Formation of epoxides have also been reported in copper-catalyzed allylic oxidations.[108] No formation of epoxides, however were observed under this salqu copper(II) catalytic system when reaction mixtures were analyzed with GC/MS.

To gain more insight into the role of the salqu copper(II) catalyst and the TBHP, the oxidation of diphenylmethane was conducted in the absence of each. Withtout the addition of catalyst, oxidation using 3 eq TBHP in water at 70 °C for 24 h, resulted in very low yield. In fact 4-5 % of benzophenone was observed. Benzophenone, however did not form, when the reaction was carried out in the absence of TBHP, suggesting the importance of a radical initiator for the reaction. Thus, the reaction is thought to go through a radical mechanism. Addition of NEt_3, a base promoter, did not increase the rate

of the reaction and this is also an evidence for the possibilty of radical intermediate formation.

In conclusion, a copper(II) complex of sulfonated 2-quinoxalinol salen (sulfosalqu) has been characterized as an efficient catalyst for the selective functionalization of benzylic and allylic C-H bonds to the corresponding carbonyl compounds in the presence of oxidant *tert*-butyl hydroperoxide. The reactions proceed with 1 mol % of catalyst loading at 70 °C in water and good yields (up to 96 %) can be achieved for a variety of substrates. Use of water as the solvent makes this process environmentally benign by eliminating the volatile organic solvents. Excellent selectivity was also achieved with this catalytic protocol for the activation of benzylic and allylic $C(sp^3)$-H bonds. The reaction is thought to go through a radical pathway.

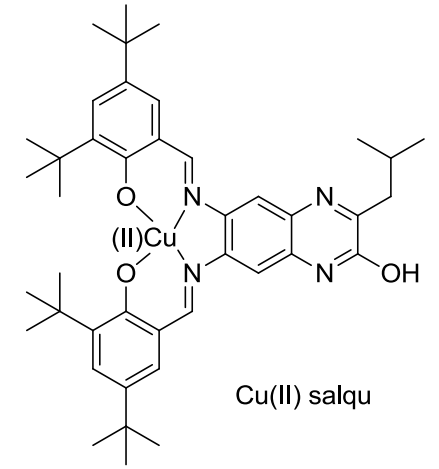
Chapter 5

C-H Activation using Salqu Copper(II) and Molecular Oxygen

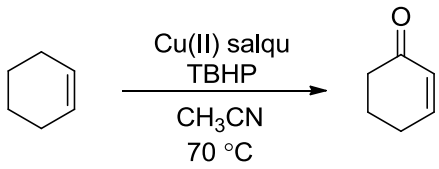
Copper-catalyzed C-H activations have been established over the years with various oxidizing agents including hydrogen peroxide,[223-226] *tert*-butyl hydroperoxide[227] (TBHP) and oxygen.[221,228] Among those, molecular oxygen is particularly attractive as it is cheap, environmentally benign and naturally abundant.[6] Oxygen has the ability to act as an electron acceptor and/or oxygen donor in these metal-catalyzed reactions.[6] The most common byproduct formed during the oxidation with molecular oxygen is water, and this increases the atom economy of the reaction when acts as the oxygen donor. Meanwhile, oxidations with TBHP can leave byproducts like *tert*-butyl alcohol, butylene or unused TBHP as organic waste.[6,229] Thus, introduction of molecular oxygen over tert-butyl hydroperoxide is desired for the 2-quinoxalinol salen (salqu) copper(II) catalyzed oxidations.

In our previous studies, we have shown that the 2-quinoxalinol salen copper(II) complex with tert-butyl hydroperoxide works as an efficient catalyst for the allylic C-H activations (Scheme 5.1).[117]

Scheme 5.1. Allylic oxidation catalyzed by Cu(II) salqu

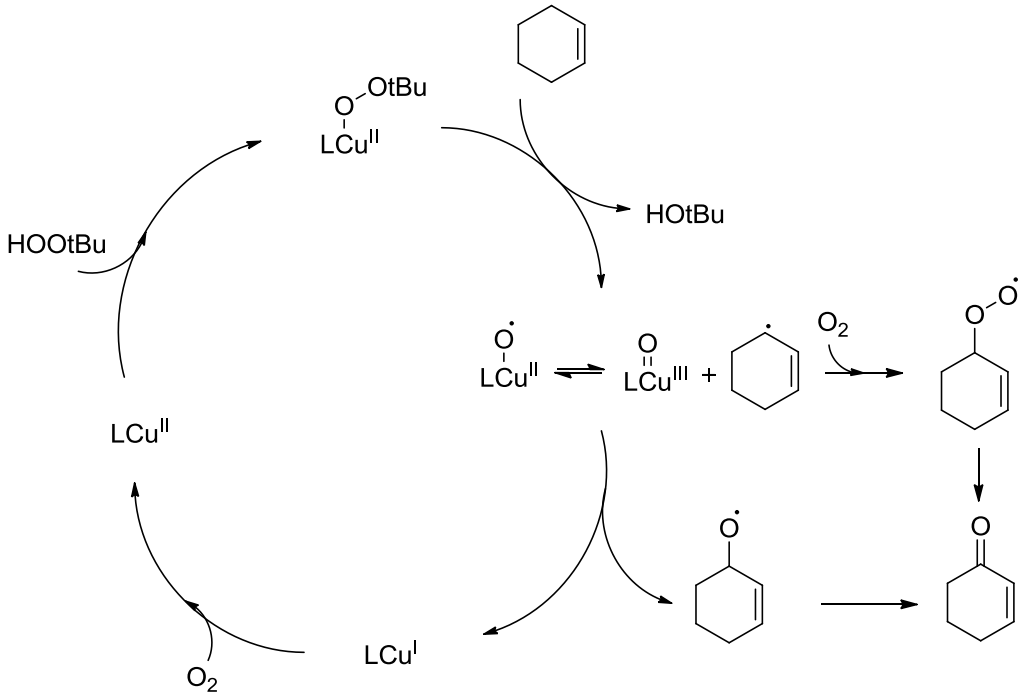


Cu(II) salqu



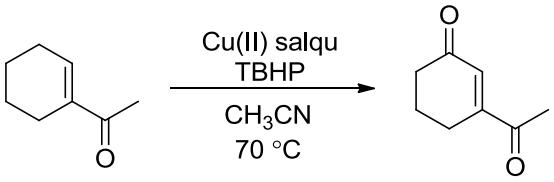
The proposed reaction mechanism for the allylic oxidation is thought to involve a Cu(II) *tert*-butyl peroxo intermediate as shown in scheme 5.2.[117] This intermediate undergoes a homolytic cleavage of O-O bond by reacting with the allylic substrate to yield allylic radical, tert-butyl alcohol and LCu(II)-O·. After this point, two possible pathways could result in the formation of enone product: (1) reaction of allylic radical with the molecular oxygen in the medium to form allylic peroxy radical and then conversion of that to enone; (2) reaction of allylic radical with the LCu(II)-O· species to form allylic oxyl radical and then conversion of that to enone. Finally, the oxidation of LCu(I) complex by molecular oxygen regenerates the LCu(II) complex, which can be recycled.

Scheme 5.2. Proposed catalytic cycle for allylic oxidation catalyzed by Cu(II) salqu[117]



According to this reaction mechanism, only one equivalent of TBHP is consumed during the reaction. Meanwhile, dioxygen acts as both an oxygen donor to incorporate oxygen atom into the enone and an electron acceptor to oxidize Cu(I) to Cu(II). As this is a radical reaction, it is challenging to prove that the reaction has only one pathway. Thus, introduction of more molecular oxygen to the reaction mixture may favor the oxidation reaction and would help to reduce the amount of chemical oxidant used in the reaction. On the basis of this assumption, here we describe the introduction of molecular oxygen for the salqu copper(II) catalyzed allylic C-H activation.

Scheme 5.3. Oxidation of 1-acetyl-1-cyclohexene catalyzed by Cu(II) salqu



We began our investigation by studying the oxidation of 1-acetyl-1-cyclohexene (0.5 mmol) using a catalytic amount of 2-quinoxalinol salen copper(II) complex (1 mol %) and TBHP (3 eq) in acetonitrile under stirring at 70 °C and 1 atm (air) for 24 h in a pressure vessel (Scheme 5.3).

Table 5.1. Effect of dioxygen[a]

Entry	O_2 pressure (atm)	Yield (%)
1	atmospheric	67
2	1	84
3	10	90
4	20	90
5	30	90

[a]Conditions: 1-acetyl-1-cyclohexene (0.5 mmol), copper(II) salqu complex (1 mol %) and 3 eq TBHP in acetonitrile at 70 °C for 24 h in a pressure vessel. Yields were determined by GC with 1,2-dichlorobenzene added as an internal standard.

The yield of the reaction was determined by analyzing the reaction mixture using GC with the internal standard method. In this method, the reaction run in the pressure vessel with 1 atm of air resulted in 67 % yield of 3-acetyl-2-cyclohexen-1-one (Table 5.1 entry 1). When the reaction ran at 1 atm of oxygen it produced 84 % yield, suggesting that the molecular oxygen clearly plays a role in the reaction by increasing the reaction yield (entry 2). Encouraged by this result, oxygen pressure was further increased to see

more improvement in the reaction yield. As the pressure was increased to 10 atm, the yield reached to 90 % (entry 3); however, the oxygen pressures beyond 10 atm did not result in a further improvement in the reaction yield (entries 4 and 5).

To study the effect of TBHP, the reaction was examined at 1 atm and 30 atm of oxygen in the absence of TBHP. Both of these experiments resulted in no reaction and it revealed two general features of the reaction: (1) molecular oxygen alone can not oxidize 1-acetyl-1-cyclohexene under this 2-quinoxalinol salen copper(II) catalytic system; (2) the presence of a radical initiator is required in order to occur the reaction. Thus, TBHP can not be replaced with oxygen as the oxidant under this catalytic protocol; however, we seek to reduce the amount of required TBHP in the reaction by introducing more molecular oxygen into the system.

Table 5.2. Effect of TBHP equivalent[a]

Entry	TBHP (eq)	O_2 pressure (atm)	Yield (%)
1	3	1	84
2	3	10	90
3	3	20	90
4	2	1	49
5	2	10	61
6	2	20	62
7	1	1	36
8	1	10	37
9	1	20	37

[a]Conditions: 1-acetyl-1-cyclohexene (0.5 mmol), copper(II) salqu complex (1 mol %) and TBHP in acetonitrile at 70 °C for 24 h in a pressure vessel. Yields were determined by GC with 1,2-dichlorobenzene added as an internal standard.

With TBHP as the radical initiator in the reaction, we turned our attention to the primary goal of this work: identifying whether oxygen could act as the main oxidizing

agent replacing most of the TBHP used in the oxidation of 1-acetyl-1-cyclohexene. The reaction was conducted with different amounts of TBHP equivalents while varying the pressure of oxygen (Table 5.2). Three equivalents of TBHP produced 84 %, 90 % and 90 % yields of 3-acetyl-2-cyclohexen-1-one at 1 atm, 10 atm and 20 atm pressure of oxygen respectively (entries 1, 2 and 3). Likewise, reactions conducted with 2 equivalent of TBHP occured in 49 % yield at 1 atm and increased to 61 % yield at 10 atm (entry 4 and 5). Again, reaction yield at 20 atm was identical to that at 10 atm (entry 6). In contrast, reactions performed with 1 equivalent of TBHP only produced low yields (~37 %) of desired product at all pressures of oxygen (entries 7, 8 and 9). As the reaction yields were relatively low with 1 equivalent of TBHP, the amount of TBHP was not further reduced in this study.

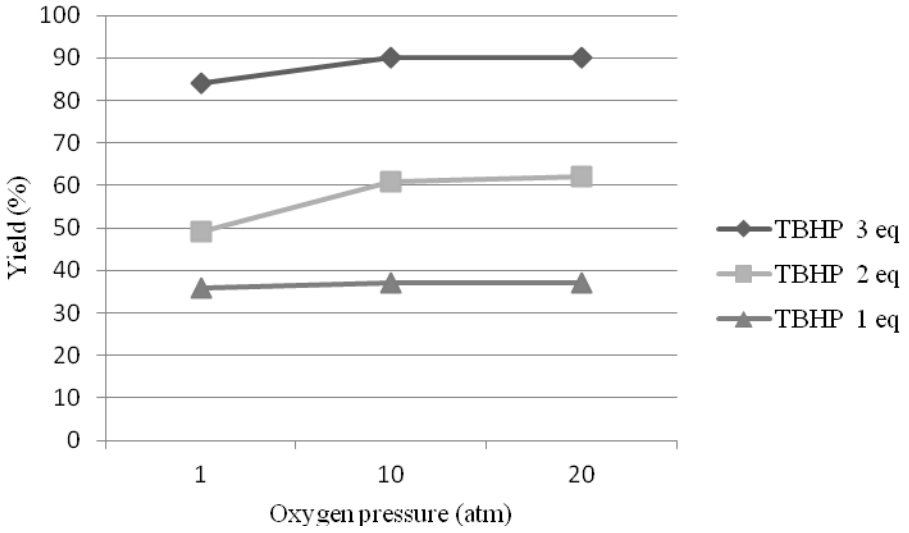


Figure 5.1. Effect of TBHP equivalent

These results were plotted in Figure 5.1 and it describes the reaction yield as a function of oxygen pressure at various amount of TBHP. According to these results, both 3 eq and 2 eq of TBHP produced greater yields compared to 1 eq of TBHP. The results

obtained at 1 eq was low and closer than expected in various pressures of oxygen in accordance with the trend obsereved at higher amounts of TBHP, and the reason for this behavior is not clear at this point. Meanwhile, 3 eq of TBHP produced 90 % of 3-acetyl-2-cyclohexen-1-one at 10 atm and 2 eq of TBHP produced 61 % yield at the same pressure of oxygen. Thus, 3 eq of TBHP produce better yields of desired product than 2 eq at the same reactions conditions.

Table 5.3. Yields of 3-acetyl-2-cyclohexen-1-one under different reaction conditions

Entry	TBHP (eq)	O_2 pressure (atm)	Yield (%)
1	3	atmospheric	67
2	2	atmospheric	39
3	2	10	61

As the primary goal of this study to reduce the amount of TBHP used in the oxidation reactions, it is worth looking at the results obtained with the 2 eq of TBHP. With 3 eq of TBHP, 1 atm of air and 24 h reaction time, a 67 % yield of 3-acetyl-2-cyclohexen-1-one was observed (Table 5.3, entry 1). Reactions run under similar conditions with 2 eq of TBHP occured in a 39 % yield (entry 2); however, the same reaction with 10 atm oxygen produced similar results to the former (entry 3). These results suggest that equivalents of TBHP required for the reaction can be reduced from 3 eq to 2 eq in the the oxidation of 1-acetyl-1-cyclohexene, at the expense of 10 atm of oxygen under this catalytic protocol. This is a 33 % less TBHP input compared to the original reaction conditions. Even though this is a higher amount of TBHP than anticipated at this point, it is still a significant amount of prevented waste at a larger scale with regard to industrial and environmental chemistry.

Table 5.4. Time profile[a]

Entry	Time (h)	Yield (%)
1	6	51
2	12	61
3	18	65
4	24	62

[a]Conditions: 1-acetyl-1-cyclohexene (0.5 mmol), copper(II) salqu complex (1 mol %) and 2 eq TBHP in acetonitrile at 70 °C and 10 atm of oxygen for 24 h in a pressure vessel. Yields were determined by GC with 1,2-dichlorobenzene added as an internal standard.

Having identified 2 eq of TBHP and 10 atm of oxygen as a better reaction condition, we established the relationship between the time of reaction and the yield (Table 5.4). Reactions were conducted with 1-acetyl-1-cyclohexene (0.5 mmol) using a catalytic amount of 2-quinoxalinol salen copper(II) complex (1 mol %) and TBHP (2 eq) in acetonitrile under stirring at 70 °C and 10 atm of oxygen for 6 h, 12 h, 18 h and 24 h in a pressure vessel. After 6 h, the yield of 3-acetyl-2-cyclohexen-1-one is 53 % and it incresed to 61 % at 12 h. Longer reaction times beyond 12 hours did not result in a further increase in the yield. Based on these results, a greener method for allylic oxidation can be achieved by using salqu copper(II) catalyst and 2 eq of TBHP at 10 atm of oxygen for 12 h.

From these results, we can conclude that molecular oxygen can not completely replace TBHP in the 2-quinoxalinol salen copper(II) catalyzed allylic oxidation; however, it is possible to reduce the amount of TBHP by using high pressures of oxygen. If the reaction happens only according to the above described reaction pathway, it should be

still possible to reduce the required amount of TBHP to 1 eq. The decomposition of TBHP during the reaction could be a reason for the need of excess amount of it. These results also seem to suggest that TBHP can not only function as the radical initiator of the reaction while oxygen perfoming the role of oxygen insertion into the enones. Thus, TBHP seems to play a bigger role in allylic oxidation than molecular oxygen under this catalytic system.

Chapter 6

Conclusions and Future Work

In this dissertation, 2-quinoxalinol salen (salqu) copper(II) complexes were used as catalysts for the selective oxidation of alcohols and C-H functionalizations in the presence of *tert*-butyl hydroperoxide as the oxidant. Two different salqu copper(II) complexes were studied for these oxidation reactions (Figure 6.1).

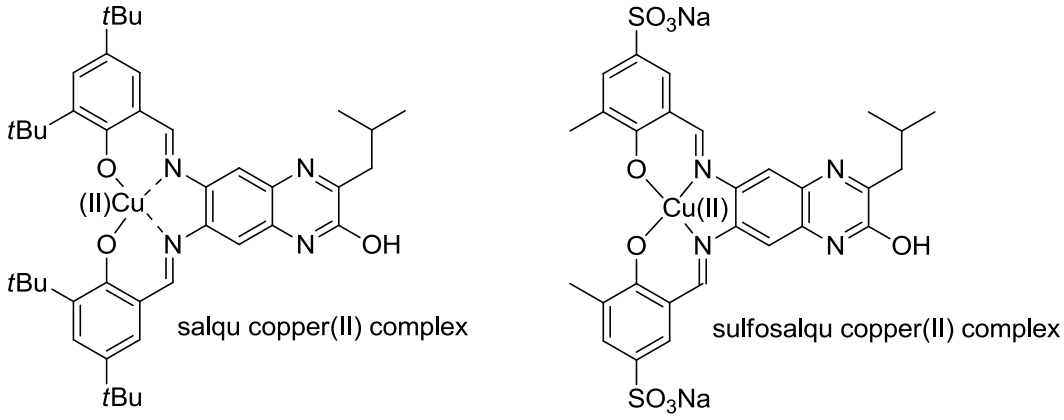


Figure 6.1. Structures of 2-quinoxalinol salen copper(II) complexes

A salqu copper(II) complex was synthesized by reacting 3,5-ditertbutyl-2-hydroxybenzaldehyde with 6,7-diamino-2-quinoxalinol and then coordinating the ligand with $Cu(OAc)_2$. This complex was used for the reactions conducted in organic solvents.

To make the salqu copper(II) complex water soluble, sulfonate groups were introduced to the ligand by reacting sulfonated salicylaldehydes with 6,7-diamino-2-quinoxalinol.

The oxidation of propargylic alcohols to the corresponding carbonyl compounds was studied with the salqu copper(II) complex. Propargylic alcohol oxidation is complicated as the triple bond can also get easily oxidized. Reaction conditions were optimized using commercially available 1-phenyl-2-propyn-1-ol and it was found that 2-quinoxalinol salen or salqu copper(II) complex is efficient as a catalyst for the oxidation of 1-phenyl-2-propyn-1-ol to 1-phenyl-2-propyn-1-one under the oxidant TBHP. Several solvents were also screened and acetonitrile produced the better results for the oxidation. Time profile of the reaction showed that the maximum yield of 1-phenyl-2-propyn-1-one can be achieved at 1 h of reaction time but, it could further react and reduce the yield if the reaction was kept running. Thus, oxidation reactions were carried out in acetonitrile with 1 mol % catalyst, 3 eq TBHP at 70 ˚C for 1 h.

Having identified the optimum reaction conditions, the substrate scope of propargylic alcohol oxidation was investigated and a variety of substrates were converted to corresponding carbonyl compounds in good to excellent yields (up to 99 %). A wide range of functional groups such as Cl, Br, I, Me, *t*-Bu, OMe and NO_2 were tolerated under this catalytic protocol. This catalytic system also produced excellent selectivity for oxidation of propargylic alcohols over isolated alcohols, triple bonds, or propargylic methylenes.

Substituents on the arene ring of the propargylic substrates also played a part in the reaction. The propargylic alcohol oxidation was accelerated by electron-donating substituents and decelerated by electron-withdrawing substituents. The correlation

between log (k_X/k_H) and para-position Hammett constants showed a negative slope (ρ) indicating that the oxidation of propargylic alcohols with salqu copper(II) catalyst is likely to be electrophilic in nature under these reaction conditions.[187]

A water soluble version of 2-quinoxalinol salen copper(II) complex was successfully synthesized to carry out oxidation reactions in water. First, the oxidation of alcohols were studied using sulfosalqu copper(II) complex. Reaction conditions were optimized using commercially available 1-phenyl-2-propyn-1-ol and it was found that sulfosalqu copper(II) complex is efficient as a catalyst in water, for the oxidation of 1-phenyl-2-propyn-1-ol to 1-phenyl-2-propyn-1-one under the oxidant TBHP. The time profile of the reaction showed that the yields up to 83 % could be achieved within 3 h of reaction time. Several different oxidants including hydrogen peroxide, peracetic acid and m-chlroperbenzoic acid were screened for the oxidation; however, TBHP produced the better results for the alcohol dehydrogenation.

Reactions carried out in the absence of saulfosalqu copper(II) complex or TBHP produced very small yields of desired product, suggesting their important role in the reaction. Also reactions ran under similar conditions with $Cu(OAc)_{2,}$ instead of saulfosalqu copper(II) complex, produced very low yields (27-35 %) even when 5 mol % of the catalyst used. This clearly indicates that the saulfosalqu copper(II) complex works as an excellent catalyst for the alcohol oxidation, in water.

Having identified the optimum conditions for the alcohol oxidation, a wide variety of propargylic, benzylic and allylic alcohols were successfully oxidized to their corresponding carbonyl compounds in good yields (up to 99 %). This is also a rare example of propargylic alcohol oxidation in water. Electron-donor groups on the arene

helped to increase the reaction yield. In contrast, electron-withdrawing groups reduced the yield of carbonyl compounds. Under these conditions, oxidation of benzylic alcohols was little slower compared to that of propargylic alcohols. Oxidation of a mixture of 1-phenyl-2-propyn-1-ol and 1-octanol showed only the oxidation of 1-phenyl-2-propyn-1-ol with no formation of 1-octanal, suggesting the selectivity of sulfosalqu copper(II) catalytic system to propargylic, benzylic and allylic positions.

Very little alcohol oxidation occurred when the reaction was carried out in the absence of TBHP. Addition of NEt_3, a base promoter, did not increase the rate of the reaction and it helps to eliminate the possibility of the reaction to go through an ionic pathway. Thus, the alcohol oxidation is more likely to go through a radical mechanism; however, it has been a challenge to isolate radical intermediates.

Sulfosalqu copper(II) complex was also found to be a good catalyst for C-H functionalization in water. Again, better results were obtained when the catalyst was in combination with TBHP. Reaction conditions were optimized using commercially available diphenylmethane and good yields of benzophenone was obtained with 3 eq of TBHP and 24 h of reaction time. Under optimized conditions, a wide variety of benzylic and allylic substrates were converted to corresponding carbonyl compounds in good to excellent yields (up to 96 %). The reaction mechanism is thought to involve radical intermediates.

To further reduce the waste production in the oxidation process, molecular oxygen was tested as a potential substituent for the oxidant TBHP in the allylic oxidations. High pressure oxygen reactions suggested that molecular oxygen cannot completely replace TBHP in the 2-quinoxalinol salen copper(II) catalyzed allylic

oxidation; however, it was showed that 33 % of the amount of TBHP can be reduced from the original reaction by introducing 10 atm of oxygen.

All these results showed that the 2-quinoxalinol salen (salqu) copper(II) complex have been an efficient catalyst for alcohol oxidations and C-H functionalizations. This catalytic system can be further improved to achieve better results including higher yields and selectivity. It is necessary to isolate and characterize radical intermediates of oxidation reactions to better understand the reaction pathway and to fine-tune the reaction conditions to achieve better selectivity.

The salqu ligand can be further modified to change the properties of the ligand and to further improve yields and selectivity. For instance, conjugation of the ligand can be increased to see whether it could help to enhance the reaction rates and yields by further stabilizing the radical intermediates formed during the oxidations. This could be achieved by 3 different ways: (1) using salicylaldehyde derivatives with higher conjugation; (2) using higher conjugated diamines instead of 2-quinoxalinol; (3) using both higher conjugated salicylaldehyde and diamine. A few possible examples are shown in figure 6.2. Ligands **A**, **B** and **C** can be synthesized by reaction of 2-hydroxy-1-naphthaldehyde with 2-quinoxalinol, by reaction of 3,5-ditertbutylsalicylaldehyde with 2,3-diaminophenazine and by reaction of 2-hydroxy-1-naphthaldehyde with 2,3-diaminophenazine respectively. These ligands with different electronic properties can be coordinated with copper and then tested for catalytic activity. In addition, these highly conjugated salqu ligands could serve as selective metal coordination systems for use in sensors and extraction applications. These studies would broaden our understanding of the salqu ligand and help us designing more efficient catalytic systems.

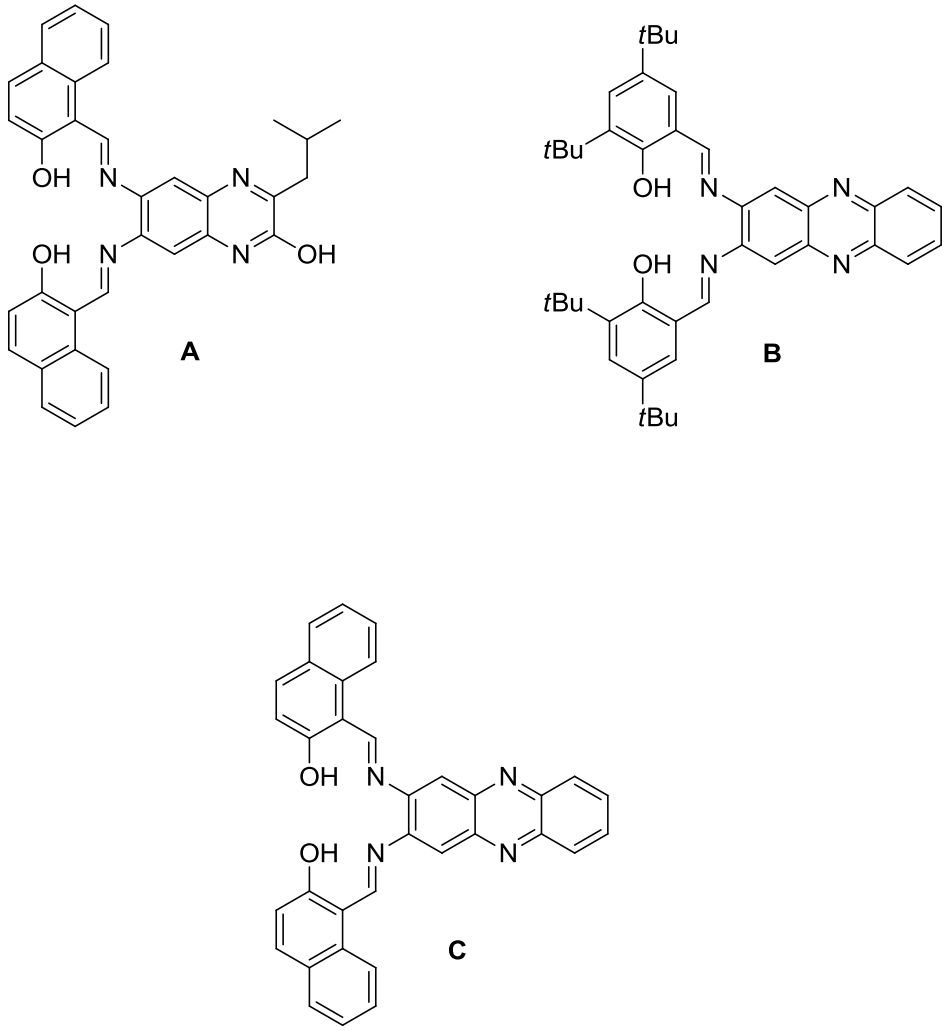
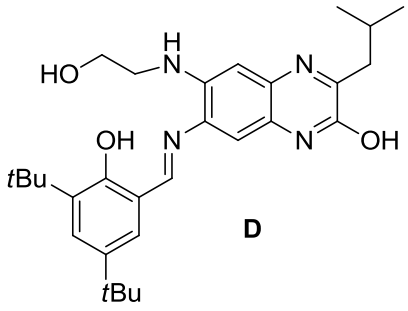


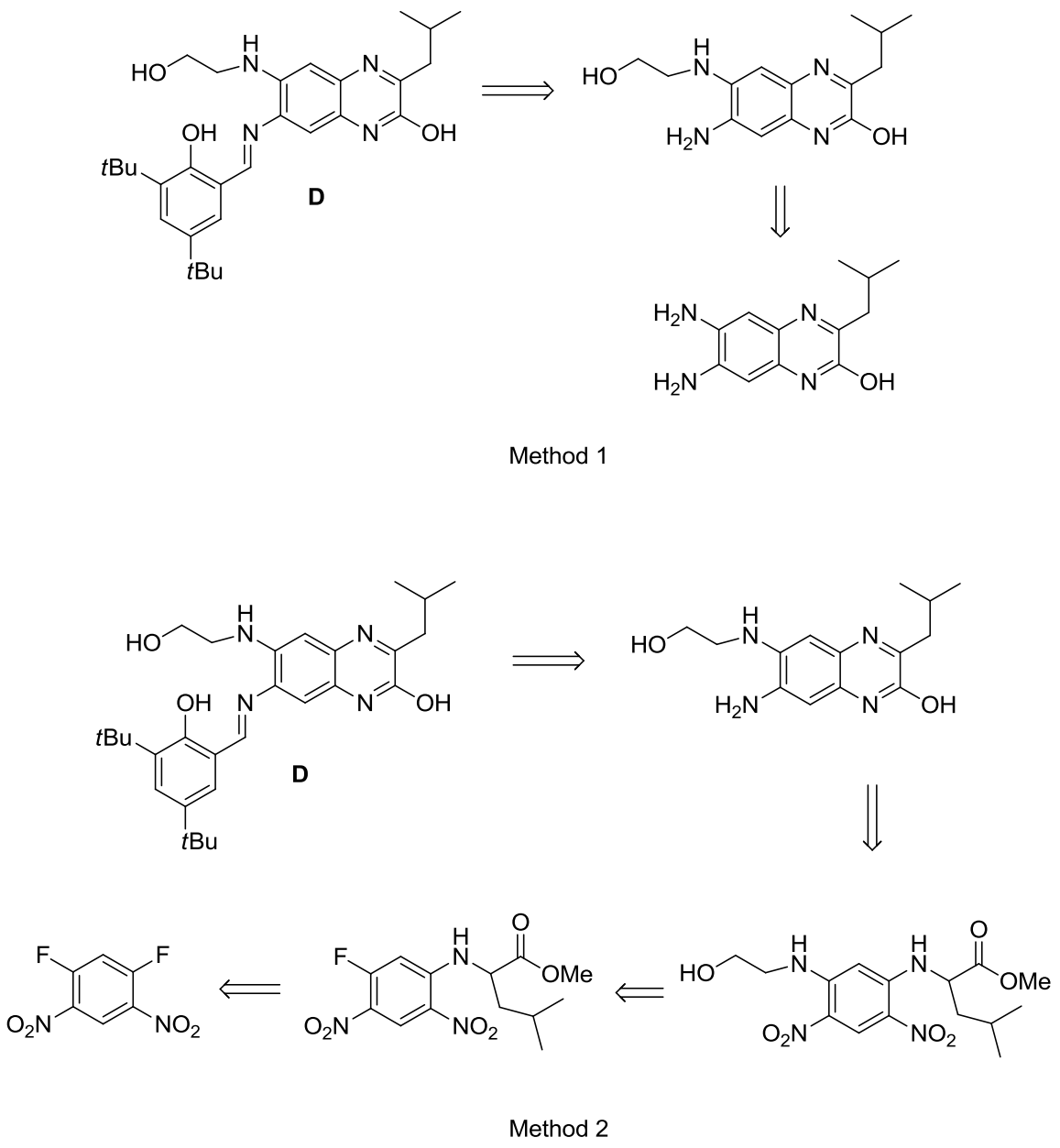
Figure 6.2. Examples for modified salqu ligands

It is also interesting to alter the coordination site of the salqu ligand by introducing a flexible chelating arm. This would allow the salqu ligand to have a less rigid pocket and change the properties of the catalytic site. Hence, it can facilitate the different geometries around the ligand rather than forcing it to be square planar at the metal center. In addition, salqu ligands with altered coordination sites could test for the selective metal extractions or in sensor applications. One possible way to incorporate a flexible arm to a salqu ligand is to replace one phenolic moiety with a non rigid coordinating moiety like ethanol (Figure 6.3). In the case of ligand **D**, flexible arm could be incorporated in two different ways: (1) reacting 2-quinoxalinol with 2-iodoethanol or 2-bromoethanol; (2) synthesizing N-sustituted 2-quinoxalinol from DFDNB (1,5-difluoro-2,4-dinitrobenzene). Retrosynthetic analysis of ligand **D** is shown in scheme 6.1.



D

Figure 6.3. Salqu ligand with a flexible arm



Scheme 6.1. Retrosynthetic analysis of ligand **D**

Another future effort is to seak to improve the reusability of the catalyst. It was found that the catalyst decomposes to some extent as the reaction proceeds. Again, a

reaction mechanism study would help to answer this problem properly. Introduction of a solid support to the salqu copper(II) catalyst is one-way to improve the reusability of the catalyst. This would help the catalyst to be easily recovered and recycled to increase the turnover numbers with regard to industrial and environmental chemistry. According to the basic structure of the salqu ligand, a solid support can be introduced at two different positions: (1) at the hydroxyl group of the 2-quinoxalinol moiety; (2) at the phenolic moiety. Two such structures are shown in figure 6.4. For this purpose, solid supports such as polystyrene frame works and mesoporous silica can be used.

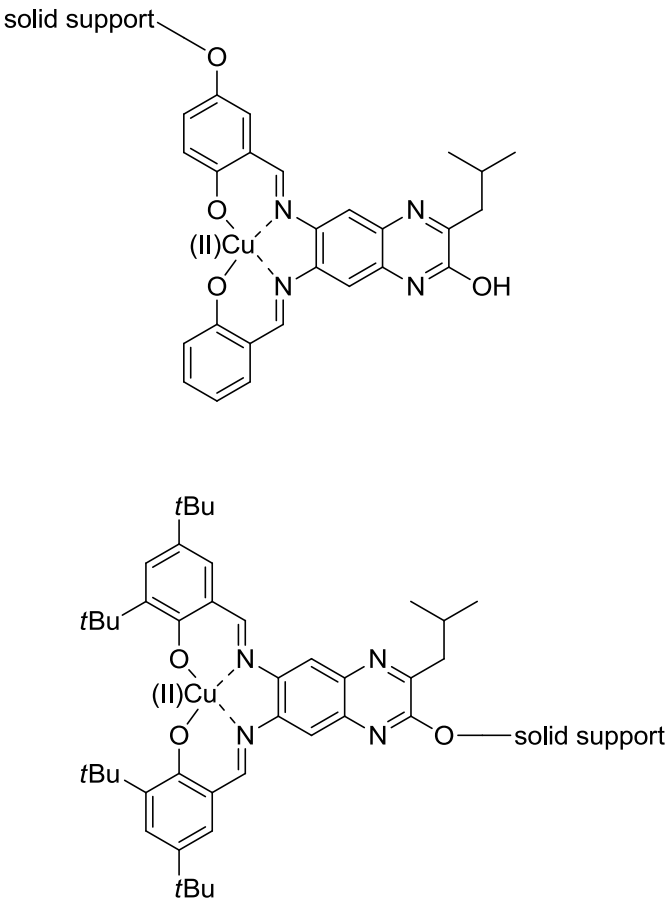


Figure 6.4. Examples for solid supported salqu copper(II) complexes

In summary, 2-quinoxalinol salen (salqu) copper(II) complexes have been efficient catalysts for alcohol oxidations and C-H functionalizations. Oxidations can be conducted both in organic solvents and in water. Experimental results suggested that the reactions undergo a radical pathway. This catalytic system has been successful in making the oxidation process greener by increasing yields and selectivity, reducing catalytic loading and reaction time and minimizing the waste production. In future efforts, isolation of radical intermediates, alteration of coordination site and enhancement of the reusability of the catalyst are of great interest.

Chapter 7

Experimental Section

General

All reagents were obtained commercially and used without purifications. Amino acid methyl esters, DFDNB, HCl (37 %), aldehydes, ammonium hydroxide (5.0 N), *tert*-butyl hydroperoxide in decane, palladium on carbon (wet, 5 %) were purchased from Aldrich. Starting materials for oxidation were purchased from Alfa Easer. All organic solvents were purchased from Fisher Scientific and were directly used for synthesis. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 at 400 MHz instrument; chemical shifts (δ) were reported in ppm relative to Me_4Si. Chromatographic purifications were performed using Fisher (60 Å, 70-230 mesh) silica gel. HRMS data were collected with electrospray ionization or chemical ionization. IR spectroscopic data were collected using SHIMADZU Inc. IR, Prestige-21 Fourier Transfer Infrared Spectrophotometer with the use of KBr solid samples and NaCl windows. GC analysis was performed on a Thermo sciencetific Trace GC Ultra instrument with flame ionization detector (FID).

General Procedure

Synthesis of 6,7-diamino-2-quinoxalinol (Scheme 2.2)

1,5-difluoro-2,4-dinitrobenzene (5 mmol) was charged in a 100-mL round-bottom flask containing leucine methyl ester (5 mmol) and 2.2 equivalent of diisopropylethylamine (11 mmol) in THF and the reaction mixture was stirred at room temperature for 12 h. Then, 6 equivalents of ammonium hydroxide (30 mmol) was added to the same reaction mixture and stirred at room temperature for an additional 5 h. The reaction solvent was removed under reduced pressure to obtain an orange color oil. This oil was dissolved in ethanol (50 mL), and $HCOONH_4$ (100 mmol) and 5 % wet Pd-C (1.6 g) were added. The reaction mixture was refluxed for 2 h and it was vacuum filtered and washed with ethanol. Then the filtrate was concentrated and the crude product was purified by silica column chromatography (ethyl acetate/hexane/ethanol, 8:2:1) to afford the yellow color 6,7-diamino-2-quinoxalinol; yield: 70 %.

Synthesis of 2-quinoxalinol salen (salqu) ligand (Scheme 2.2)

Diamino-2-quinoxalinol (2.00 mmol) was charged in a 100-mL round-bottom flask containing 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (2.5 mmol), methanol (40 mL) and trifluoroacetic acid (5 mol %). The reaction mixture was stirred at refluxing temperature for 18 h and salqu ligand precipitated in the solution. The solid was vacuum filtered and dried under vacuum. A yellow solid was obtained as the product (60 %).

Synthesis of 2-quinoxalinol salen copper(II) complex (Scheme 2.2)

2-Quinoxalinol salen ligand (0.5 mmol) dissolved in 50 mL DCM, $Cu(OAc)_2.H_2O$ (0.6 mmol) dissolved in 50 mL methanol and 3 mmol of triethylamine were mixed and stirred at refluxing temperature for 2 h. After the solvent was removed, the resulting dark red solid was washed with water and cold ether 3 times each. The solid was obtained in 86 % yield.

General procedure for synthesis of propargylic alcohols (Table 2.3, entries 2-12)

2-Chlorobenzaldehyde (2 mmol) was charged in a 100-mL round-bottom flask in a N_2 atmosphere and it was slowly treated with ethynylmagnesium bromide (2 mmol) at -20 ˚C. The reaction mixture was then stirred at -20 ˚C for 2 h. After 2 h, saturated NH_4Cl was added to the reaction mixture and the products were extracted to ether. Organic layer was concentrated and the products were purified by column chromatography with hexane/ethyl acetate.

General procedure for oxidation of propargylic alcohols (Table 2.3)

Propargylic alcohol (0.5 mmol), Cu(II) catalyst (1 mol %) and TBHP in decane (5.0 M, 0.25 mL) were stirred in acetonitrile (1.5 mL) at 70 ºC for 1 h. The reaction was monitored with TLC. After 1 h is completed, it was cooled to room temperature, the solvent was removed with a rotary evaporator, and the products were purified by column chromatography with hexane/ethyl acetate. Yields were determined by isolation of the product or by GC analysis.

Synthesis of sodium 3-methylsalicylaldehyde-5-sulfonate (Scheme 3.1)

3-methylsalicylaldehyde (10 mmol) was charged in a 50-mL round-bottom flask containing aniline (10 mmol) in methanol (10 mL) and the reaction mixture was stirred at reflux temperature for 18 h. Then, solvent was removed under reduced pressure to obtain an orange color oil of protected salicylaldehyde; yield: 97 %. To this compound was added five times its weight of concentrated sulfuric acid, and the mixture was heated at 110 ˚C for 2 h. After cooling, it was poured into ice-pieces to induce crystallization of N-phenyl-3-methylsalicylaldimine-5-sulfonic acid. A yellow precipitate formed and it was then filtered and washed with ice-water and dried under vacuum to afford the sulfonated salicylaldehyde product; yield: 65 %. N-phenyl-3-methylsalicylaldimine-5-sulfonic acid was dissolved in boiling distilled water, and then anhydrous Na_2CO_3 was added until the evolution of carbon dioxide ceased. Then the mixture was boiled vigorously for 2 h. After cooling the mixture to 0 ˚C, it was filtered and washed with ethanol to give 3-methylsalicylaldehyde-5-sulfonate as a pale yellow solid; yield: 65 %.

Synthesis of sulfonated 2-quinoxalinol salen copper(II) complex (Scheme 3.1)

2-quinoxalinol (1 mmol) was charged in a 100-mL round-bottom flask containing 3-methylsalicylaldehyde-5-sulfonate (2.5 mmol), $Cu(OAc)_2 \cdot H_2O$ (1.1 mmol) and a drop of trifluoroacetic acid in ethanol (40 mL), and the reaction mixture was stirred at reflux temperature for 4 h. Then the reaction mixture was filtered and the precipitate was washed with cold ethanol and dichlromethane. Thereafter the solid was collected and dried under vacuum to afford the sulfosalqu copper(II) complex; yield: 60 %.

General procedure for the oxidation of alcohols (Table 3.2)

Alcohol (0.5 mmol), the Cu(II) catalyst (1 mol %), and TBHP (1.5 mmol) were stirred in water (1.5 mL) at 70 °C for 3 h. The reaction was monitored by TLC. After 3 h, the mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The product was purified by column chromatography (hexane/ethyl acetate). Yields were determined by isolating the product or by using GC analysis, and the isolated products were characterized by ^{1}H and ^{13}C NMR spectroscopy.

General procedure for the C-H activations (Table 4.2)

Diphenylmethane (0.5 mmol), the Cu(II) catalyst (1 mol %), and TBHP (1.5 mmol) were stirred in water (1.5 mL) at 70 °C for 24 h. The reaction was monitored by TLC. After 24 h, the reaction mixture was cooled to room temperature, and the products were extracted to dichloromethane. The yields were determined by GC analysis of the organic layer with the internal standard method.

General procedure for the allylic C-H activations with oxygen (Scheme 5.3)

1-acetyl-1-cyclohexene (0.5 mmol), the Cu(II) catalyst (1 mol %), and TBHP (1.5 mmol) were stirred in acetonitrile (1.5 mL) at 70 °C and 1-20 atm (oxygen) for 24 h in a pressure vessel. After 24 h, the reaction mixture was cooled to room temperature, and the yields were determined by GC analysis of the reaction mixture with the internal standard method.

Data Section

6,7-Diamino-2-quinoxalinol (Scheme 2.2). ^{1}H NMR (400MHz, DMSO): δ 11.74 (s, 1 H), 6.78 (s, 1 H), 6.34 (s, 1 H), 5.37 (bs, 2 H), 4.60 (bs, 2 H), 2.52 (d, 2H), 2.13 (m, 1 H), 0.88 (d, *J* = 6.8 Hz, 6 H). ^{13}C NMR (400 MHz, DMSO): δ 155.3, 153.1, 140.1, 132.7, 126.0, 125.7, 111.1, 96.8, 41.7, 26.8, 23.0.

2-Quinoxalinol salen (salqu) ligand (Scheme 2.2). ^{1}H NMR (400 MHz, CDCl3): δ 13.23 (s, 1H), 13.14 (s, 1H), 12.04 (bs, 1H), 8.58 (s,1H), 8.48 (s, 1H), 7.47 (s, 1H), 7.22 (d, 2H), 7.22 (d, 2H), 7.06 (m, 2H), 6.89 (s, 1H),2.57 (d, J = 7.1 Hz, 2H), 2.12 (m, 1H), 1.22 (s, 9H), 1.19 (s, 9H), 1.12 (s, 9H), 1.11 (s,9H), 0.83 (d, J = 6.6 Hz, 6H). ^{13}C NMR (100 MHz, CDCl3): δ 166.6, 164.1, 161.4, 158.4,158.1, 155.6, 144.4, 140.4, 138.7, 136.9, 136.8, 131.3, 128.5, 128.0, 127.0, 126.8, 118.2,118.0, 117.8, 105.4, 42.0, 34.9, 34.0, 31.3, 29.3, 26.5, 22.6.

2-Quinoxalinol salen copper(II) complex (Scheme 2.2). IR (solid): 3429, 2955, 2909, 2868, 1661, 1556, 1524, 1495, 1462, 1423, 1385, 1202 cm-1. UV-Vis (CHCl3): 327 (ε = 20 000 M-1 cm^{-1}), 450 nm (ε = 13 000 M-1 cm-1). Formula (M + H): C42H55N4O3Cu. HRMS: (M + H) calcd. 726.3570, found 726.3575.

3-Methylsalicylaldehyde-5-sulfonate (Scheme 3.1). ^{1}H NMR (400MHz, D_2O): δ 9.91 (s, 1 H), 7.94 (dd, *J* = 2.4, 0.8 Hz, 1 H), 7.80 (dd, *J* = 2.4, 0.8 Hz, 1 H), 2.24 (s, 3 H). ^{13}C NMR (400 MHz, D_2O): δ 197.6, 162.5, 134.0, 133.0, 128.7, 128.6, 119.4, 14.6. HRMS (EI-negative) m/z: $[(M - Na]^-$ calcd. 215.0014, found 215.0015.

Sulfonated 2-quinoxalinol salen copper(II) complex (Scheme 3.1). ^{1}H NMR spectrum was featureless due to its paramagnetism. IR (cm^{-1}) 3430 (br), 2957, 2925, 2869, 1668, 1607, 1538, 1441, 1383, 1176, 1119, 1041, 470, 402. HRMS (EI-negative) m/z: $[(M + H) – 2 Na]^-$ calcd. 688.0359, found 688.0361, $[M – 2 Na]^{2-}$ calcd. 343.5140, found 343.5119.

1-(2-Chlorophenyl)-2-propyn-1-ol (1b, Entry 2, Table 2.3). ^{1}H NMR (400MHz, $CDCl_3$): δ 7.77 (dd, *J* = 7.2, 1.6 Hz, 1 H), 7.26-7.40 (m, 3 H), 5.83 (dd, *J* = 5.6, 2.4 Hz, 1 H), 3.01 (d, *J* = 5.6 Hz, 1 H), 2.66 (d, *J* = 2.4 Hz, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 137.3, 132.6, 129.8, 129.7, 128.2, 127.3, 82.4, 74.9, 61.6. IR (cm^{-1}) 3372 (br), 3297, 3069, 2910, 1472, 1440, 1274, 1190, 1031, 952, 816, 755, 644. HRMS (EI) m/z, calcd. 166.0185, found 166.0185.

1-(3-Chlorophenyl)-2-propyn-1-ol (1c, Entry 3, Table 2.3). ^{1}H NMR (400MHz, $CDCl_3$): δ 7.55 (s, 1 H), 7.40-7.43 (m, 1 H), 7.31-7.32 (m, 2 H), 5.42 (dd, *J* = 6.0, 2.4 Hz, 1 H), 3.02 (d, *J* = 6.0 Hz, 1 H), 2.70 (d, *J* = 2.4 Hz, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 141.8, 134.5, 129.9, 128.6, 126.8, 124.8, 82.9, 75.3, 63.6. IR (cm^{-1}) 3373 (br), 3297, 3065, 2884, 1598, 1577, 1474, 1431, 1192, 1023, 786, 689. HRMS (EI) m/z, calcd. 166.0185, found 166.0173.

1-(4-Chlorophenyl)-2-propyn-1-ol (1d, Entry 4, Table 2.3). ^{1}H NMR (400MHz, $CDCl_3$): δ 7.44 (dt, *J* = 8.8, 2.4 Hz, 2 H), 7.34 (dt, *J* = 8.8, 2.4 Hz, 2 H), 5.39 (s, 1 H), 3.35 (d, *J* = 3.6 Hz, 1 H), 2.68 (d, *J* = 2.4 Hz, 1 H). ^{13}C NMR (400 MHz,

$CDCl_3$): δ 138.4, 134.3, 128.7, 128.1, 83.1, 75.2, 63.5. IR (cm^{-1}) 3373 (br), 3297, 3069, 2881, 1648, 1588, 1490, 1404, 1255, 1092, 1013, 949, 836, 791, 673. HRMS (EI) m/z, calcd. 166.0185, found 110.0179.

1-(4-Bromophenyl)-2-propyn-1-ol (1e, Entry 5, Table 2.3). ^1H NMR (400MHz, $CDCl_3$): δ 7.50 (dt, *J* = 8.4, 2.4 Hz, 2 H), 7.39 (dt, *J* = 8.4, 2.4 Hz, 2 H), 5.39 (dd, *J* = 6.0, 2.0 Hz, 1 H), 3.02 (d, *J* = 6.0 Hz, 1 H), 2.68 (d, *J* = 2.0 Hz, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 138.9, 131.7, 128.3, 122.5, 83.0, 75.2, 63.6. IR (cm^{-1}) 3374 (br), 3294, 3094, 2880, 1645, 1591, 1486, 1403, 1256, 1010, 949, 831, 786, 666. HRMS (EI) m/z, calcd. 209.9680, found 209.9626.

1-(4-Iodophenyl)-2-propyn-1-ol (1f, Entry 6, Table 2.3). ^1H NMR (400MHz, $CDCl_3$): δ 7.73 (dt, *J* = 8.4, 2.4 Hz, 2 H), 7.31 (dt, *J* = 8.4, 2.4 Hz, 2 H), 5.42 (dd, *J* = 6.4, 2.0 Hz, 1 H), 2.69 (d, *J* = 2.0, Hz, 1 H), 2.37 (d, *J* = 6.4 Hz, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 139.6, 137.7, 128.5, 94.3, 82.9, 75.2, 63.8. IR (cm^{-1}) 3362 (br), 3284, 3087, 2889, 1481, 1393, 1021, 1006, 945, 850, 783, 670. HRMS (EI) m/z, calcd. 257.9542, found 257.9600.

1-(p-Tolyl)-2-propyn-1-ol (1g, Entry 7, Table 2.3). ^1H NMR (400MHz, $CDCl_3$): δ 7.45 (d, *J* = 8.0 Hz, 2 H), 7.22 (d, *J* = 8.0 Hz, 2 H), 5.42 (s, 1 H), 2.98 (d, *J* = 5.6 Hz, 1 H), 2.68 (d, *J* = 2.0 Hz, 1 H), 2.40 (s, 3 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 138.3, 137.3, 129.3, 126.6, 83.8, 74.6, 64.1, 21.2. IR (cm^{-1}) 3375 (br), 3291, 3095, 3027, 2922, 1513,

1414, 1275, 1179, 1016, 948, 816, 761, 651. HRMS (EI) m/z, calcd. 146.0732, found 146.0758.

1-(4-Tertbutylphenyl)-2-propyn-1-ol (1h, Entry 8, Table 2.3). ^{1}H NMR (400MHz, $CDCl_3$): δ 7.51 (dt, *J* = 8.4, 2.0 Hz, 2 H), 7.45 (dt, *J* = 8.4, 2.0 Hz, 2 H), 5.44 (dd, *J* = 6.0, 2.0 Hz, 1 H), 2.83 (d, *J* = 6.0 Hz, 1 H), 2.68 (d, *J* = 2.0 Hz, 1 H), 1.37 (s, 9 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 151.6, 137.2, 126.4, 125.6, 83.8, 74.6, 64.1, 34.6, 31.3. IR (cm^{-1}) 3505 (br), 3267, 3056, 2957, 1510, 1460, 1415, 1363, 1268, 1012, 942, 843, 804, 698. HRMS (EI) m/z, calcd. 188.1201, found 188.1191.

1-(4-Methoxyphenyl)-2-propyn-1-ol (1i, Entry 9, Table 2.3). ^{1}H NMR (400MHz, $CDCl_3$): δ 7.47 (dt, *J* = 8.8, 2.0 Hz, 2 H), 6.91 (dt, *J* = 8.8, 2.0 Hz, 2 H), 5.41 (dd, *J* = 6.0, 2.4 Hz, 1 H), 3.82 (s, 3 H), 2.67 (d, *J* = 2.4 Hz, 1 H), 2.56 (d, *J* = 6.0 Hz, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 159.7, 132.4, 128.1, 114.0, 83.7, 74.6, 63.9, 55.3. IR (cm^{-1}) 3403 (br), 3287, 3072, 2958, 2838, 1610, 1512, 1463, 1250, 1175, 1031, 948, 834, 766, 650. HRMS (EI) m/z, calcd. 162.0681, found 162.0664.

1-(4-Nitrophenyl)-2-propyn-1-ol (1j, Entry 10, Table 2.3). ^{1}H NMR (400MHz, $CDCl_3$): δ 8.23 (d, *J* = 8.4 Hz, 2 H), 7.23 (d, *J* = 8.4 Hz, 2 H), 5.74 (dd, *J* = 6.0, 2.0 Hz, 1 H), 2.82 (d, *J* = 6.0 Hz, 1 H), 2.74 (d, *J* = 2.0 Hz, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 147.8, 146.7, 127.4, 123.8, 82.3, 75.9, 63.3. IR (cm^{-1}) 3502 (br), 3295, 3110, 2898, 1600, 1505, 1348, 1184, 1054, 942, 856, 743, 704, 675, 638. HRMS (EI) m/z, calcd. 177.0426, found 177.0419.

1-(1-Naphthyl)-2-propyn-1-ol (1k, Entry 11, Table 2.3). ^{1}H NMR (400MHz, $CDCl_3$): δ 8.30 (d, *J* = 8.4, Hz, 1 H), 7.87-7.92 (m, 3 H), 7.48-7.62 (m, 3 H), 5.65 (dd, *J* = 6.0, 2.4 Hz, 1 H), 2.76 (d, *J* = 2.4 Hz, 1 H), 2.41 (d, *J* = 6.0 Hz, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 135.1, 134.0, 130.4, 129.5, 128.8, 126.5, 125.9, 125.2, 124.6, 123.8, 83.2, 75.5, 62.7. IR (cm^{-1}) 3295 (br), 3173, 3046, 2865, 1597, 1510, 1470, 1259, 1062, 1000, 940, 777, 643, 685. HRMS (EI) m/z, calcd. 182.0732, found 182.0737.

1-(2-Naphthyl)-2-propyn-1-ol (1l, Entry 12, Table 2.3). ^{1}H NMR (400MHz, $CDCl_3$): δ 8.02 (s, 1 H), 7.85-7.90 (m, 3 H), 7.67 (dd, *J* = 8.4, 1.6 Hz, 1 H), 7.50-7.54 (m, 2 H), 5.65 (dd, *J* = 6.4, 2.4 Hz, 1 H), 2.75 (d, *J* = 6.4 Hz, 1 H), 2.47 (d, *J* = 2.4 Hz, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 137.3, 133.3, 133.1, 128.6, 128.2, 127.7, 126.4, 126.4, 125.5, 124.4, 83.4, 75.1, 64.5. IR (cm^{-1}) 3364 (br), 3277, 3051, 1653, 1599, 1418, 1368, 1275, 1019, 975, 864, 824, 742, 644. HRMS (EI) m/z, calcd. 182.0732, found 182.0733.

1-Phenyl-2-propyn-1-one (2a, Entry 1, Table 2.3). ^{1}H NMR (400MHz, $CDCl_3$): δ 8.17-8.20 (m, 2 H), 7.63-7.68 (m, 1 H), 7.50-7.54 (m, 2 H), 3.45 (s, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 177.4, 136.1, 134.5, 129.7, 128.7, 80.7, 80.2. IR (cm^{-1}) 3234, 3061, 2094, 1646, 1596, 1578, 1451, 1314, 1264, 1174, 1006, 698. HRMS (EI) m/z, calcd. 130.0419, found 130.0414.

1-(2-Chlorophenyl)-2-propyn-1-one (2b, Entry 2, Table 2.3). ^{1}H NMR (400MHz, $CDCl_3$): δ 8.11-8.13 (m, 1 H), 7.39-7.51 (m, 3 H), 3.49 (s, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 175.9, 134.5, 133.9, 133.8, 133.3, 131.7, 126.8, 81.3, 81.1. IR (cm^{-}

^{1}) 3231, 3068, 2961, 2089, 1655, 1586, 1465, 1435, 1235, 999, 732. HRMS (EI) m/z, calcd. 164.0029, found 164.0060.

1-(3-Chlorophenyl)-2-propyn-1-one (2c, Entry 3, Table 2.3). ^{1}H NMR (400MHz, $CDCl_3$): δ 8.13-8.14 (m, 1 H), 8.04-8.07 (m, 1 H), 7.60-7.63 (m, 1 H), 7.45-7.49 (m, 1 H), 3.50 (s, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 176.0, 137.6, 135.0, 134.4, 130.0, 129.5, 127.7, 81.5, 79.8. IR (cm^{-1}) 3251, 3070, 2930, 2097, 1652, 1537, 1426, 1242, 1035, 898, 781, 736. HRMS (EI) m/z, calcd. 164.0029, found 163.9994.

1-(4-Chlorophenyl)-2-propyn-1-one (2d, Entry 4, Table 2.3). ^{1}H NMR (400MHz, $CDCl_3$): δ 8.12 (dt, *J* = 8.8, 2.4 Hz, 2 H), 7.50 (dt, *J* = 8.8, 2.4 Hz, 2 H), 3.47 (s, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 176.0, 141.2, 134.5, 131.0, 129.1, 81.2, 79.9. IR (cm^{-1}) 3221, 2921, 2099, 1636, 1587, 1259, 1092, 1009, 843, 752. HRMS (EI) m/z, calcd. 164.0029, found 164.0015.

1-(4-Bromophenyl)-2-propyn-1-one (2e, Entry 5, Table 2.3). ^{1}H NMR (400MHz, $CDCl_3$): δ 8.03 (dt, *J* = 8.8, 2.0 Hz, 2 H), 7.66 (dt, *J* = 8.8, 2.4 Hz, 2 H), 3.48 (s, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 176.2, 134.9, 132.1, 131.0, 130.1, 81.2, 79.9. IR (cm^{-1}) 3218, 3089, 2097, 1637, 1581, 1398, 1259, 1173, 1068, 1005, 840, 748, 672. HRMS (EI) m/z, calcd. 207.9524, found 207.9498.

1-(4-Iodophenyl)-2-propyn-1-one (2f, Entry 6, Table **3**). ^{1}H NMR (400MHz, $CDCl_3$): δ 7.85-7.90 (m, 4 H), 3.48 (s, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 176.6,

138.1, 135.4, 130.0, 103.2, 81.2, 79.9. IR (cm^{-1}) 3219, 3081, 2100, 1632, 1579, 1392, 1260, 1176, 1002, 840, 737, 673. HRMS (EI) m/z, calcd. 255.9385, found 255.9365.

1-(p-Tolyl)-2-propyn-1-one (2g, Entry 7, Table 2.3). ^{1}H NMR (400MHz, $CDCl_3$): δ 8.05 (dt, *J* = 8.4, 2.0 Hz, 2 H), 7.29 (dt, *J* = 8.4, 2.0 Hz, 2 H), 3.43 (s, 1 H), 2.43 (s, 3 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 177.0, 145.7, 133.8, 129.8, 129.4, 80.5, 80.4, 21.8. IR (cm^{-1}) 3248, 3035, 2925, 2859, 2096, 1649, 1603, 1410, 1258, 1177, 1008, 835, 743, 684. HRMS (EI) m/z, calcd. 144.0575, found 144.0568.

1-(4-Tertbutylphenyl)-2-propyn-1-one (2h, Entry 8, Table 2.3). ^{1}H NMR (400MHz, $CDCl_3$): δ 8.11 (dt, *J* = 8.8, 2.0 Hz, 2 H), 7.52 (dt, *J* = 8.8, 2.0 Hz, 2 H), 3.43 (s, 1 H), 1.36 (s, 9 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 177.0, 158.6, 133.7, 129.7, 125.7, 80.4, 80.3, 35.3, 31.0. IR (cm^{-1}) 3251, 2965, 2870, 2095, 1649, 1605, 1463, 1410, 1262, 1186, 1109, 1002, 851, 767, 699. HRMS (EI) m/z, calcd. 186.1045, found 186.1042.

1-(4-Methoxyphenyl)-2-propyn-1-one (2i, Entry 9, Table 2.3). ^{1}H NMR (400MHz, $CDCl_3$): δ 8.15 (dt, *J* = 8.8, 2.0 Hz, 2 H), 6.98 (dt, *J* = 8.8, 2.0 Hz, 2 H), 3.91 (s, 3 H), 3.39 (s, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 175.9, 164.8, 132.1, 129.6, 113.9, 80.4, 80.0, 55.6. IR (cm^{-1}) 3264, 3251, 2992, 2093, 1640, 1600, 1511, 1424, 1271, 1171, 1024, 841, 759, 685. HRMS (EI) m/z, calcd. 160.0524, found 160.0536.

1-(4-Nitrophenyl)-2-propyn-1-one (2j, Entry 10, Table **3**). ^{1}H NMR (400MHz, $CDCl_3$): δ 8.33-8.39 (m, 4 H), 3.62 (s, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 175.4,

151.1, 140.1, 130.6, 123.9, 82.8, 79.6. IR (cm^{-1}) 3282, 3104, 2098, 1660, 1603, 1522, 1346, 1235, 1005, 855, 717, 669. HRMS (EI) m/z, calcd. 175.0269, found 175.0259.

1-(1-Naphthyl)-2-propyn-1-one (2k, Entry 11, Table 2.3). ^{1}H NMR (400MHz, $CDCl_3$): δ 9.23 (dd, *J* = 8.8, 0.8 Hz, 1 H), 8.64 (dd, *J* = 7.2, 1.2 Hz, 1 H), 8.12 (d, *J* = 8.0 Hz, 1 H), 7.93 (dt, *J* = 8.4, 0.8 Hz, 1 H), 7.68-7.72 (m, 1 H), 7.58-7.62 (m, 2 H), 3.46 (s, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 178.8, 135.7, 135.5, 133.8, 131.9, 130.7, 129.2, 128.6, 126.9, 125.9, 124.4, 81.6, 79.4. IR (cm^{-1}) 3215, 2927, 2089, 1638, 1570, 1509, 1434, 1275, 1232, 1184, 1107, 930, 774, 629. HRMS (EI) m/z, calcd. 180.0575, found 180.0581.

1-(2-Naphthyl)-2-propyn-1-one (2l, Entry 12, Table 2.3). ^{1}H NMR (400MHz, $CDCl_3$): δ 8.77 (s, 1 H), 8.16 (dd, *J* = 8.6, 2.0 Hz, 1 H), 8.03 (d, *J* = 8.0 Hz, 1 H), 7.93 (d, *J* = 4.4 Hz, 1 H), 7.91 (d, *J* = 3.6 Hz, 1 H), 7.60-7.68 (m, 2 H), 3.52 (s, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 177.3, 136.3, 133.7, 133.3, 132.3, 129.9, 129.3, 128.6, 127.9, 127.1, 123.6, 80.6, 80.4. IR (cm^{-1}) 3217, 3060, 2091, 1640, 1622, 1465, 1352, 1281, 1186, 1125, 1005, 941, 831, 760, 717. HRMS (EI) m/z, calcd. 180.0575, found 182.0587.

1,3-Diphenyl-2-propyn-1-one (2m, Entry 12, Table 2.3). ^{1}H NMR (400MHz, $CDCl_3$): δ 8.23-8.26 (m, 2 H), 7.61-7.70 (m, 3 H), 7.40-7.54 (m, 5 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 178.0, 136.8, 134.2, 133.1, 130.8, 129.6, 128.7, 128.6, 120.1, 93.1, 86.9. IR (cm^{-1}) IR (cm^{-1}) 3052, 3027, 2200, 1634, 1596, 1578, 1488, 1445, 1315, 1209, 1012, 761, 689. HRMS (EI) m/z, calcd. 206.0732, found 206.0704.

1-Phenyl-1-pentyn-3-one (2n, Entry 12, Table 2.3). ^{1}H NMR (400MHz, $CDCl_3$): δ 7.55-7.58 (m, 2 H), 7.35-7.47 (m, 3 H), 2.69 (q, *J* = 7.2 Hz, 1 H), 1.21 (t, *J* = 7.2 Hz, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 188.5, 133.0, 130.6, 128.6, 120.0, 90.6, 87.6, 38.8, 8.1. IR (cm^{-1}) 3062, 2980, 2938, 2200, 1676, 1489, 1409, 1352, 1258, 1160, 1112, 1046, 958, 759, 689. HRMS (EI) m/z, calcd. 159.0810, found 159.0823.

4-Methyl-1-phenyl-1-pentyn-3-one (2o, Entry 12, Table 2.3). ^{1}H NMR (400MHz, $CDCl_3$): δ 7.48-7.51 (m, 2 H), 7.27-7.39 (m, 3 H), 2.66 (septet, *J* = 6.4 Hz, 1 H), 1.18 (d, *J* = 6.4 Hz, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 192.2, 133.0, 130.6, 128.6, 120.1, 91.6, 86.8, 43.1, 18.0. IR (cm^{-1}) 3067, 2975, 2934, 2674, 2199, 1691, 1601, 1452, 1323, 1289, 1177, 1060, 935, 759, 710, 689. HRMS (EI) m/z, calcd. 173.0966, found 173.0970.

1-Octyn-3-one (2p, Entry 12, Table 2.3). ^{1}H NMR (400MHz, $CDCl_3$): δ 3.22 (s, 1 H), 2.58 (t, *J* = 7.6 Hz, 2 H), 1.68 (quint, *J* = 7.6 Hz, 2 H), 1.31 (m, 4 H), 0.90 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 187.6, 81.4, 78.3, 45.4, 31.0, 23.4, 22.3, 13.8. HRMS (EI) m/z, calcd. 125.0966, found 125.0957.

1-Phenyl-2-propyn-1-one (Entry 1, Table 3.2). ^{1}H NMR (400MHz, $CDCl_3$): δ 8.17-8.20 (m, 2 H), 7.63-7.68 (m, 1 H), 7.50-7.54 (m, 2 H), 3.45 (s, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 177.4, 136.1, 134.5, 129.7, 128.7, 80.7, 80.2.

1-(p-Tolyl)-2-propyn-1-one (Entry 2, Table 3.2). ^{1}H NMR (400MHz, $CDCl_3$): δ 8.05 (dt, *J* = 8.4, 2.0 Hz, 2 H), 7.29 (dt, *J* = 8.4, 2.0 Hz, 2 H), 3.43 (s, 1 H), 2.43 (s, 3 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 177.0, 145.7, 133.8, 129.8, 129.4, 80.5, 80.4, 21.8.

1-(4-Methoxyphenyl)-2-propyn-1-one (Entry 3, Table 3.2). ^{1}H NMR (400MHz, $CDCl_3$): δ 8.15 (dt, *J* = 8.8, 2.0 Hz, 2 H), 6.98 (dt, *J* = 8.8, 2.0 Hz, 2 H), 3.91 (s, 3 H), 3.39 (s, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 175.9, 164.8, 132.1, 129.6, 113.9, 80.4, 80.0, 55.6.

1-(4-Nitrophenyl)-2-propyn-1-one (Entry 4, Table 3.2). ^{1}H NMR (400MHz, $CDCl_3$): δ 8.33-8.39 (m, 4 H), 3.61 (s, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 175.4, 151.1, 140.1, 130.6, 123.9, 82.8, 79.6.

1,3-Diphenyl-2-propyn-1-one (Entry 5, Table 3.2). ^{1}H NMR (400MHz, $CDCl_3$): δ 8.24-8.26 (m, 2 H), 7.63-7.73 (m, 3 H), 7.42-7.56 (m, 5 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 178.0, 136.8, 134.2, 133.1, 130.8, 129.6, 128.7, 128.6, 120.1, 93.1, 86.9.

1-Phenyl-1-pentyn-3-one (Entry 6, Table 3.2). ^{1}H NMR (400MHz, $CDCl_3$): δ 7.58-7.60 (m, 2 H), 7.38-7.49 (m, 3 H), 2.72 (q, *J* = 7.2 Hz, 1 H), 1.23 (t, *J* = 7.2 Hz, 1 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 188.7, 133.0, 130.6, 128.6, 120.0, 90.6, 87.6, 38.8, 8.1.

3-Phenyl-2-propyn-1-al (Entry 7, Table 3.2). ^{1}H NMR (400MHz, $CDCl_3$): δ 9.44 (s, 1 H), 7.62 (d, *J* = 7.2 Hz, 2 H), 7.51 (t, *J* = 7.2 Hz, 1 H), 7.42 (t, *J* = 7.2 Hz, 2 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 176.5, 133.3, 131.3, 128.7, 119.4, 95.1, 88.4.

1-Octyn-3-one (Entry 8, Table 3.2). ^{1}H NMR (400MHz, $CDCl_3$): δ 3.22 (s, 1 H), 2.58 (t, *J* = 7.6 Hz, 2 H), 1.68 (quint, *J* = 7.6 Hz, 2 H), 1.31 (m, 4 H), 0.90 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 187.6, 81.4, 78.3, 45.4, 31.0, 23.4, 22.3, 13.8.

Acetophenone (Entry 9, Table 3.2). ^{1}H NMR (400MHz, $CDCl_3$): δ 7.96 (d, *J* = 7.2 Hz, 2 H), 7.57 (t, *J* = 7.2 Hz, 1 H), 7.46 (t, *J* = 9.2 Hz, 2 H), 2.61 (s, 3 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 198.1, 137.1, 133.1, 128.5, 128.3, 26.6.

1-(4-Methoxyphenyl)ethanone (Entry 10, Table 3.2). ^{1}H NMR (400MHz, $CDCl_3$): δ 7.92 (d, *J* = 8.8 Hz, 2 H), 6.92 (d, *J* = 8.8 Hz, 2 H), 3.85 (s, 3 H), 2.54 (s, 3 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 196.8, 163.4, 130.5, 130.2, 113.6, 55.4, 26.3.

Benzophenone (Entry 11, Table 3.2). ^{1}H NMR (400MHz, $CDCl_3$): δ 7.82 (d, *J* = 7.6 Hz, 4 H), 7.59 (t, *J* = 7.6 Hz, 2 H), 7.49 (t, *J* = 7.6 Hz, 4 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 196.7, 137.6, 132.4, 130.0, 128.3.

2-Acetylpyridine (Entry 12, Table 3.2). ^{1}H NMR (400MHz, $CDCl_3$): δ, 8.68 (d, *J* = 4.8 Hz, 1 H), 8.04 (d, *J* = 7.6 Hz, 1 H), 7.83 (t, *J* = 7.6 Hz, 1 H), 7.46 (m, 1 H), 2.72 (s, 1 H) ^{13}C NMR (400 MHz, $CDCl_3$): δ 200.1, 153.5, 148.9, 136.5, 127.1, 121.6, 25.8.

2-Cyclohexenone (Entry 13, Table 3.2). ^{1}H NMR (400MHz, $CDCl_3$): δ 6.99 (m, 1 H), 5.99 (m, 1 H), 2.39 (m, 2 H), 2.32 (m, 2 H), 2.01 (m, 2 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 199.7, 150.7, 129.8, 38.0, 25.6, 22.7.

2-Methyl-1-phenyl-2-propen-1-one (Entry 14, Table 3.2). ^{1}H NMR (400MHz, $CDCl_3$): δ 7.75 (m, 2 H), 7.54 (m, 1 H), 7.44 (m, 2 H), 5.92 (s, 1 H), 5.64 (s, 1 H), 2.09 (s, 3 H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 198.4, 143.7, 137.7, 132.0, 129.4, 128.1, 127.1, 18.6.

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