Copper(II) 2-Quinoxalinol Salen Type Ligands as Catalysts for C-H Oxidation Reactions

by

Clayton Carlisle Black

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Approved by

Anne E. V. Gorden, Chair, Associate Professor of Chemistry and Biochemistry
Stewart Schneller, Professor of Chemistry and Biochemistry
Christian Goldsmith, Associate Professor of Chemistry and Biochemistry
Evangelos Miliordos, Assistant Professor of Chemistry and Biochemistry
Carlos Carrero, Assistant Professor of Chemical Engineering

Abstract

C-H oxidation is a powerful tool that has changed the face of synthetic organic chemistry over the last several years. Here, we explore the oxidation of alkynes to α,β-acetylenic carbonyls using only 1 mol % of an inexpensive Cu(II) 2-quinoxalinol salen catalyst with *tert*-butyl hydroperoxide (TBHP) as the oxidant in 4 hours. These reactions proceed under mild conditions (70 °C) with excellent selectivity, producing yields as high as 78 %. The optimized conditions were used with a variety of alkyne substrates to prepare the desired α,β-acetylenic ketones. Further, we report the ability to do these reactions in aqueous systems using a sulfonated version of the 2-quinoxalinol salen with good yields, thus reducing the need for volatile organic solvents and promoting "green chemistry."

Next, we investigate the use of salen type ligand supports for copper in C-H oxidation catalysis. The oxidation of allylic, propargylic, and benzylic C-H bonds is explored. A series of different ligands were tested in an effort to optimize these C-H oxidations. Derivatives of salen were prepared by altering the aldehyde and diamine starting materials. Upon investigation, the Cu(II) 2-quinoxalinol complex produced the best overall yields. This catalyst can be easily prepared in 5 synthetic steps from abundant starting materials.

Finally, oxidative Mannich reactions can be catalyzed using the Cu(II) 2-quinoxalinol salen catalyst and *tert*-butyl hydroperoxide as the oxidant. Coupling between tertiary amines and carbon-based nucleophiles was found to be highly efficient utilizing this method. Under mild conditions, a range of both cyclic and open chain tertiary amines were investigated as substrates, resulting in yields up to 98 %. A radical reaction mechanism was proposed proceeding through a

single electron transfer as the rate determining step. This method provides one alternative to more expensive and/or toxic catalysts.

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List of Abbreviations

Acac	acetylacetonate
ACN	Acetonitrile
DCM	dichloromethane
DFT	density functional theory
EtOH	Ethanol
H	Hour
H_2O_2	Hydrogen peroxide
MeCN	Acetonitrile
MeOD	deuterated methanol
MeOH	Methanol
Pd/C	palladium on carbon
Salqu	2-quinoxaminol salen
TBAI	tetrabutylammonium iodide
TBHP	Tert-butylhydroperoxide
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	trimethyl silane
UV	Ultraviolet
VOS	Volatile organic solvent

Chapter 1 Introduction

Introduction to Green Chemistry

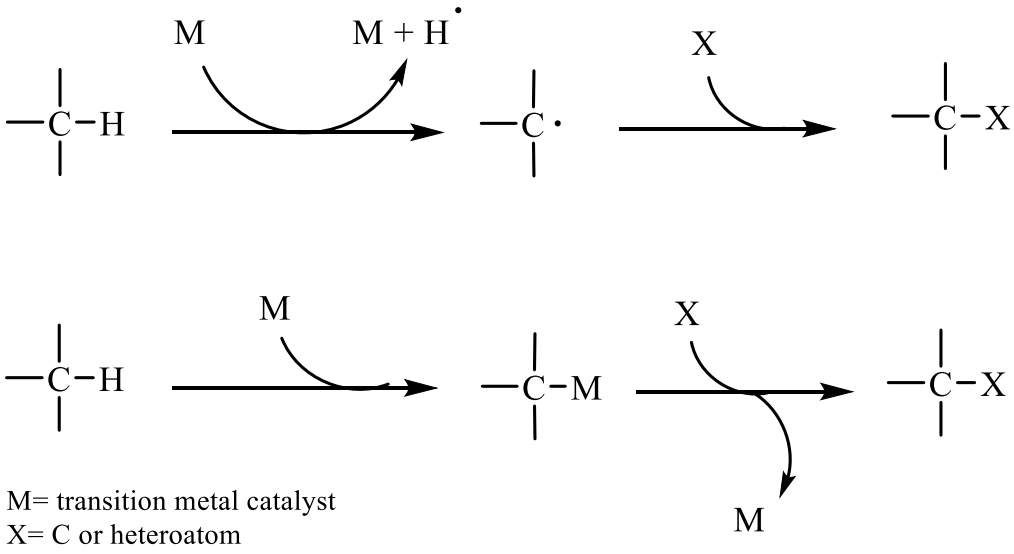
The fast-paced, high energy-dependent demands of the modern consumer has led to a booming chemical industry; however, this dramatic increase in production also has its drawbacks. According to the United States Environmental Protection Agency (EPA), chemical industries produce approximately 7.6 billion tons of hazardous waste each year.[1] This number continues to grow at an alarming rate. Due to the growing societal concern about the potential impacts of the chemical industry on health and the environment, chemists world-wide are searching for ways to make reactions more environmentally friendly or "greener."[2] Green chemistry is best represented by the 12 principles as defined by Anastas and Warner.[3] These 12 principles have set the standard for scientists who are looking to lower the harsh impacts associated with hazardous substances. As a summary, these principles address preventing waste and reducing toxic resources used for chemical transformations. We are concerned with all these principles, but in particular we would like to maximize atom economy, use safer reaction conditions, and use catalysis as a way to increase product yield and lower waste production.[4]

Key to this idea of waste reduction by reducing materials used is the use of catalysts in reaction schemes. Over 90 % of all materials produced in industrial settings are

done so with the use of some catalyst over the course of the synthesis.[5] A catalyst can speed up a reaction, reduce the energy required for that reaction, and/or direct the regio- or stereochemistry of products thereby serving to improve the overall atom economy of the reaction.[6] Catalysts do this by lowering the overall energy of activation of a synthetic transformation by changing the mechanism of the reaction. The use of catalytic amounts of transition metals provides one alternative to stoichiometric reagents that are traditionally used. Catalyst can direct the outcome of a reaction which leads to the reduction of unwanted products, waste, costs, and energy.[7]

C-H Activation

Redox active transition metals are commonly employed for various types of catalysts. In particular, transition metals have shown to be a great choice for Carbon-Hydrogen (C-H) activation in chemical synthesis.[8–13] C-H bonds are typically considered inert and not reactive due to the high bond dissociation energy.[14] In fact, Professor Robert Bergman once referred to C-H activation as "the holy grail of organic synthesis." He stated that no other chemical transformation can match the importance of selective C-H activation.[15] C-H activation involves the cleavage of an unreactive carbon hydrogen bond to either form a carbon radical intermediate or a carbon-metal bond (**Scheme 1.1**). The carbon can then be functionalized with a new C-X bond, where X can be oxygen, carbon, nitrogen or other heteroatoms.[16] The ability to functionalize seemingly unreactive and inert C-H bonds, using transition metal catalysts, has completely changed the field of organic synthesis and opened a range of new options.



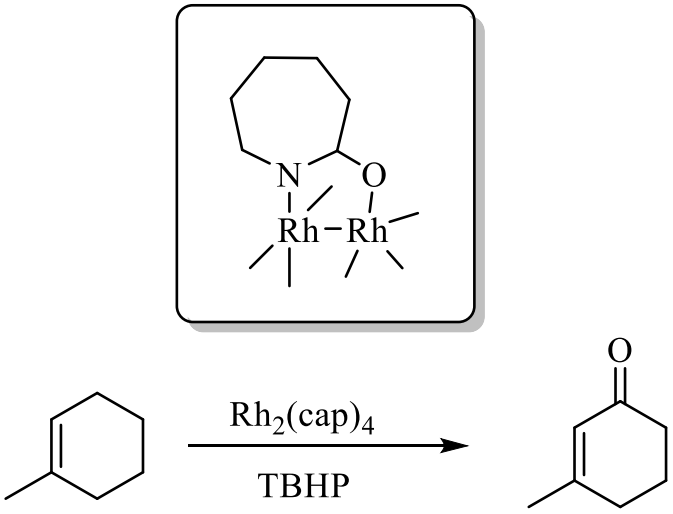
Scheme 1.1. Types of C-H activation.

With the ability to directly activate unreactive C-H bonds, without first having to incorporate some other functionality into the carbon bond, the amount of overall steps in a synthetic scheme could be greatly reduced.[17] This in turn can potentially drive down the cost of different manufacturing processes and drug syntheses while also reducing the overall amounts of waste generated. In particular, C-H activation could reduce separation and purification steps. Much research is being done in the field of C-H activation, especially for improving large-scale industrial synthesis. Academic researchers, in strong collaboration with many industrial and pharmaceutical companies, have initiatives to develop new methods of C-H activation.[18] Because of these collaborations, the potential benefits from C-H activation are becoming more practical each year.[19]

Oxidation Reactions

One class of C-H activation involves oxidation of C-H bonds.[20] Through oxidation of C-H bonds, chemists are able to install more reactive functional groups, such as alcohols and carbonyl compounds, that can be used as synthetic handles for introducing molecular diversity. Although useful, oxidation reactions can pose great challenges. Traditional oxidation reactions require stoichiometric amounts of strong oxidants, such as $KMnO_4$ and CrO_3, which are considered toxic.[21] For example, the Jones oxidation, using chromic acid, is a common method used for oxidizing alcohols to ketones or carboxylic acids.[22] Because the chromium oxidant is consumed in this transformation, this oxidation requires the use of stoichiometric amounts of chromium (IV) which is carcinogenic.[23] Although the yields for this transformation are usually high, the reaction is considered not safe to run on large scale because of its extreme exothermicity.[24] It is also difficult to control the selectivity of oxidation, and it is not uncommon to have undesired over-oxidation. Lastly, high levels of corrosive sulfuric acid are used for this oxidation.[24] Therefore, researchers are continuously investigating ways to improve the use of transition metals as catalysts for oxidation.

As a very active field of research, there are many examples of transition metals used for oxidation reactions including Pd, Cr, Mn, V, Co, Ir, and Ru.[21,25–29] In one example, Doyle and co-workers first demonstrated the use of dirhodium(II) caprolactamate ($Rh_2(cap)_4$) as a catalyst for allylic oxidation reactions in 2004.[30] $Rh_2(cap)_4$ in the presence of *tert*-butyl hydroperoxide (TBHP), was found to oxidize a wide range of olefin substrates to the corresponding enones in as little as 1 h with yields up to 92 % (**Scheme 1.2**). The

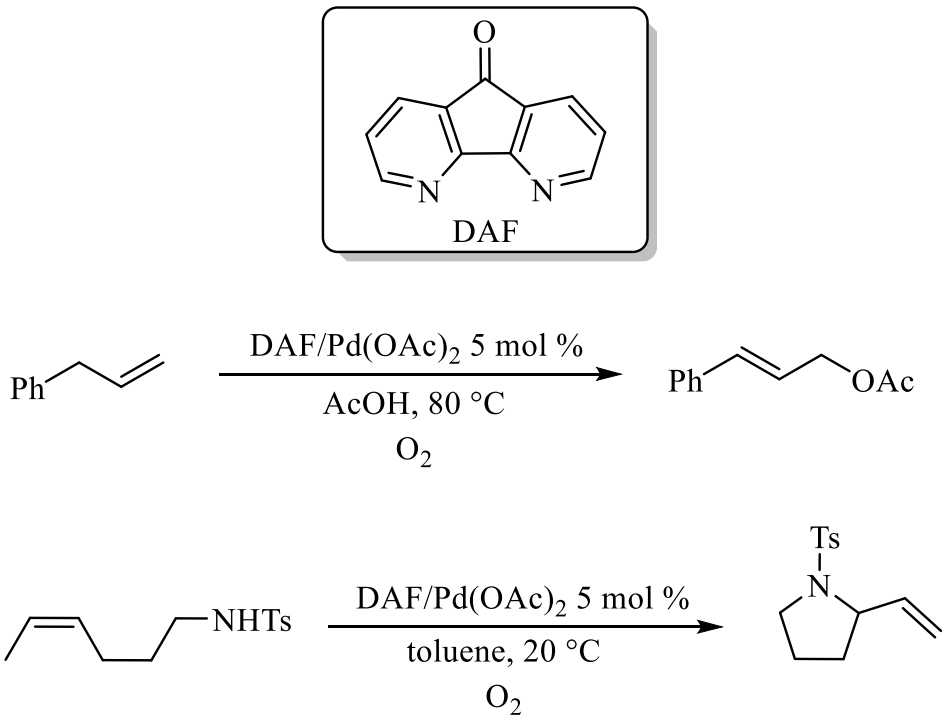


Scheme 1.2. Allylic oxidations with dirhodium caprolactamate.

ability of rhodium to promote facile redox reactions make it a highly sought-after metal for catalysis. While a useful transformation, rhodium is a very expensive metal even when used in catalytic amounts. The cost associated with this precious metal limits its practical use in both pharmaceuticals and industry.[31]

Vanadium (for example as $VO(acac)_2$ or $VOCl_3$) has also been used as a catalyst for a range of oxidation reactions.[32] These reactions include epoxidation of allylic alcohols, oxidation of heteroatoms, oxidative desilylation, and oxidative coupling.[32] For example, V_2O_5 is the industrial catalyst for the oxidation of sulfur in the production of sulfuric acid.[33] A recent review article by Delferro covers many of the applications of vanadium catalysis.[34] Vanadium is generally a less toxic metal, but in some forms, it can pose a threat to human health.[35]

Palladium is another widely used catalyst for oxidation reactions. In 2011, Gao used $PdCl_2$ for the oxidation of alcohols to ketones.[36] This aerobic oxidation worked well on both benzylic and aliphatic alcohol oxidations. More recently, Stahl and coworkers have used a Pd(II) catalyst for C-H oxidation reactions. In this work, they were able to demonstrate allylic C-H acetoxylation on terminal alkenes and intramolecular aza-Wacker type cyclization with the Pd(II) catalyst (**Scheme 1.3**).[37] In these transformations, palladium is reduced to Pd(0) while the substrate is oxidized. In many cases Pd(0) can be reoxidized to Pd(II) utilizing O_2 as the oxidant. A wide range of other oxidations using palladium catalyst were well covered in a recent review article by Stahl.[38] Although some of these reactions work well with O_2 as the oxidant, they typically require higher catalyst loading (10 mol %) and several additives.[38] Also, recent studies show an increasing concern about the long term toxic effects associated with palladium at the cellular level.[39] This study, along with others, limits the use of palladium for the production of products because of concerns with trace metal contamination.[40]



Scheme 1.3. Allylic C-H acetoxylation and aza-Wacker oxidative cyclization with Pd(II) catalyst.

While several examples of catalytic C-H systems have been discussed here, this is not an exhaustive list. However, many of these oxidations require expensive or toxic metals such as rhodium or palladium. Unfortunately, the high cost and toxicity associated with these precious metals limit their use in industrial scale synthesis.[35,40] Our interest lies in using inexpensive, earth-abundant, and environmentally friendly metals, such as copper, as catalysts for oxidation reactions. The ability of copper to access different oxidation states (Cu^0, Cu^I, Cu^{II}, Cu^{III}) allows copper to be used in a wide range of oxidations.[41] By utilizing this inexpensive and less toxic metal, this promotes the concept of "Green" or "Greener" chemistry for further reducing environmental impacts.[3] For comparison, one ounce of rhodium currently costs over $10,000 and is rising daily, and one ounce of palladium costs

$1854, while the price of copper is a mere $2.66 per pound.[42] We know that copper can be used to replace these expensive catalysts because nature has demonstrated the use of copper for catalysis throughout many biological systems.[43–48] For example, particulate methane monooxygenase (pMMO) is a copper-containing enzyme found in bacteria that is able to oxidize methane to methanol.[49] This transformation is a widely sought after method to reduce greenhouse gas by creating a liquefied fuel for ease of transportation and storage. Typically, this process is very expensive and consumes a lot of energy; however, pMMO can accomplish this transformation under ambient conditions.[50,51] Utilizing copper in simplified ligand systems can also provide an opportunity to better understand the function of copper in metalloenzymes.[47]

Although these catalysts work well in nature, it can be hard to understand and mimic the active site of these enzymes in a laboratory setting (**Figure 1.1**).[52] In some cases, simple copper salts, such as CuI, CuCl, CuBr, $CuCl_2$, $CuBr_2$, $Cu(OH)_2$, $Cu(ClO_4)_2$, $Cu(OAc)_2$, $Cu(OTf)_2$, and $Cu(NO_3)_2$, are able to be used for catalysis without the use of a ligand.[41,53–63] For example, Chai and co-workers used $Cu(OTf)_2$ for diacetoxylation of olefins producing yields up to 85 % with 10 mol % of catalyst and $PhI(OAc)_2$ as the oxidant.[64] The proposed mechanism of this reaction is believed to go through a Cu(III)/Cu(I) catalytic cycle where the Cu(II) salt is first oxidized by $PhI(OAc)_2$ to Cu(III) which then undergoes reductive elimination to Cu(I).[64] Wang and coworkers have demonstrated the use of Cu(II) acetate for oxidative cross-coupling reactions of arenes and boronic acids.[65] While still a novel transformation, this reaction requires the use of an intramolecular directing group and very high catalyst loading (30 mol %).[65]

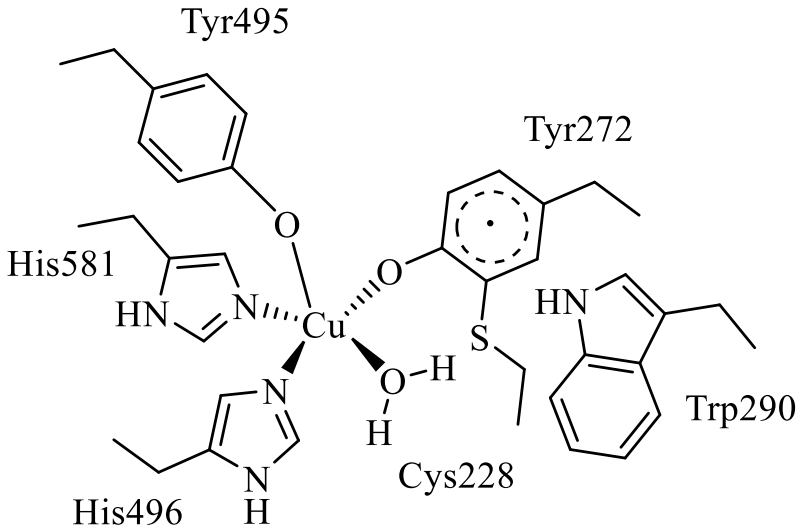
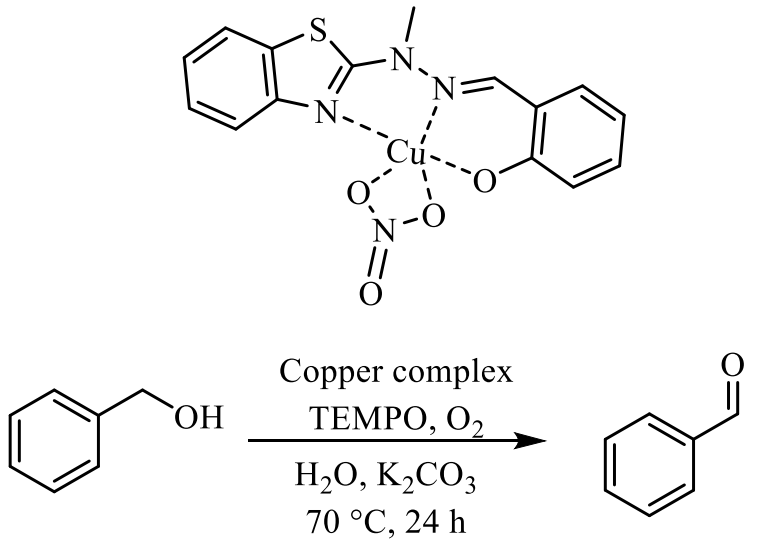


Figure 1.1. Active site of copper containing enzyme galactose oxidase.

Simple copper salts are useful because they are readily commercially available, but an organic ligand catalyst support can enhance the overall efficiency of oxidation reactions by stabilizing intermediates, increasing solubility, and increasing selectivity of the metal center.[66] In many examples, chemist are able to decrease catalyst loading by utilizing copper-ligand systems while still obtaining an increased overall product yield compared to employing simple copper salts. Copper complexes have been used for a wide range of oxidation reactions including oxidations of alkanes, alkenes, and alkynes, epoxidation, alcohol oxidation, benzylic oxidation, arene oxidation, sulfoxidation, and more. These examples range from ligands containing O-donors, N-donors, N,O-donors, or Schiff base systems.[67–80] Several copper complexes with these ligands have been discussed in a recent review article by Kozlowski.[81]

Imine Ligands

Here, we have chosen to focus on ligand supports that contain an imine donor, these are of interest due to the ease of preparation and low costs. Schiff base ligands in particular have drawn much attention in the last several years.[82] A Schiff base is a functional group containing a carbon-nitrogen double bond where the nitrogen is bound to an alkyl or aryl group.[83] These functional groups are typically prepared by condensation of an amine and aldehyde to form the imine. Schiff bases are strong chelators with many transition metals, including copper. In fact, these ligands are often used to extract copper metal ions.[84] Part of the increased observed stability with this class of ligands is due to the Schiff bases acting as π acceptors. Sigma electron density from the imine can be transferred to the metal while π electron density can be transferred from the metal to the empty π* orbital of the imine.[85] Recently, Patroniak and coworkers used a Cu(II) Schiff base catalyst for the oxidation of benzyl alcohols, producing high yields with 5 mol % catalyst loading (**Scheme 1.5**).[86] In another example, the oxidation of cyclohexane was carried out with a Cu(II) Schiff base ligand to produce the corresponding cyclohexanone using H_2O_2 as the oxidant; however, this catalyst produced low yields (up to 21 %) even in the presence of various promotors.[87] This type of functional group can be found in other classes of ligands such as salen ligands.



Scheme 1.4. Benzylic oxidation with a Cu(II) Schiff base ligand system.

Salen Ligands

Salen ligands are used abundantly throughout the literature. Historically, salen ligands are any of a class of tetradentate (O, N, N, and O) Schiff base chelators.[88] The term "salen" comes from an abbreviation of the starting materials, salicylaldehyde ("sal") and ethylenediamine ("en"), used to make the simplest ligand in this class of imines or Schiff bases (**Figure 1.2**).[88] Salen ligands are able to make stable complexes with various transition metals, including copper. These stable transition metal complexes have been used in a wide range of reactions including epoxide ring-opening, asymmetric epoxidation, hetero Diels-Alder reactions, enantioselective sulfimidation, ring-opening polymerizations, and many more.[89–94]

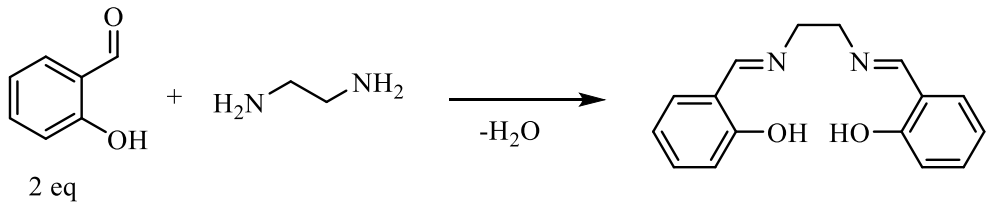
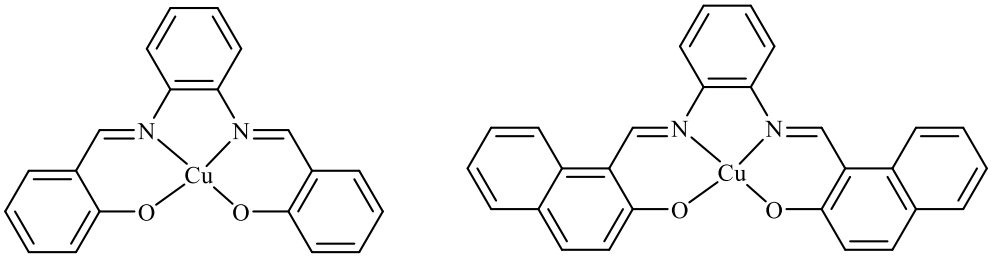


Figure 1.2. Simple salen ligand synthesis.

Most notably, Jacobson's catalyst is a salen Mn complex for asymmetric epoxidation of olefins which is still widely used in synthetic chemistry today.[95] More recently, Poltowictz and colleagues used simple salen with various transition metals for the oxidation of cycloalkanes with O_2.[96] This example produced low yields and was not very selective, producing both the corresponding alcohol and ketone. In an effort to increase selectivity while also increasing overall yield, modifications of simple salen ligands is being investigated by several research groups.[88]

Modifications of salen ligands can be attained through derivatization of either the diamine or aldehyde starting materials.[88] For example, replacing ethylenediamine with diaminobenzene will produce a phenyl backbone termed salophen (**Figure 1.3**). Copper salophen has been used as a catalyst for oxidations[97,98], cross coupling reactions[99,100], and arylations.[101] Also, changing the aldehyde can results in a modified salen structure, such as napthyl salen (**Figure 1.3**).[100] Other modifications have been done by placing salen into a solid support system such as a polymer or zeolite.[102,103] Solid supports can help with the removal of the catalyst after the reaction takes place, leading to a decrease in purification steps. These types of supports are increasingly popular in industrial scale synthesis.[104]



Cu Salophen Cu Napthyl salen

Figure 1.3. Examples of modified salen ligands.

We first became interested in incorporating the salen coordinating subunit with a heterocycle backbone to modify the electronic properties of simple salen. The hypothesis was that in doing so it would help increase solubility, alter the coordinating electronics, increase the stability of radical intermediates through delocalization of charge across the ligand, and provide additional opportunities for asymmetrical functionalization of the ligand. We chose to look at incorporating a quinoxalinol backbone into the salen molecule. Thus, 2-quinoxalinol salen (salqu) can be synthesized starting from commercially available 1,5-difluro-2,4-dinitrobenzene and L-leucine methyl ester (**Figure 1.4**). Salqu is synthesized in 5 steps which can then be complexed with different metals (Cu, Mn, Ni, Co, UO_2).[105]

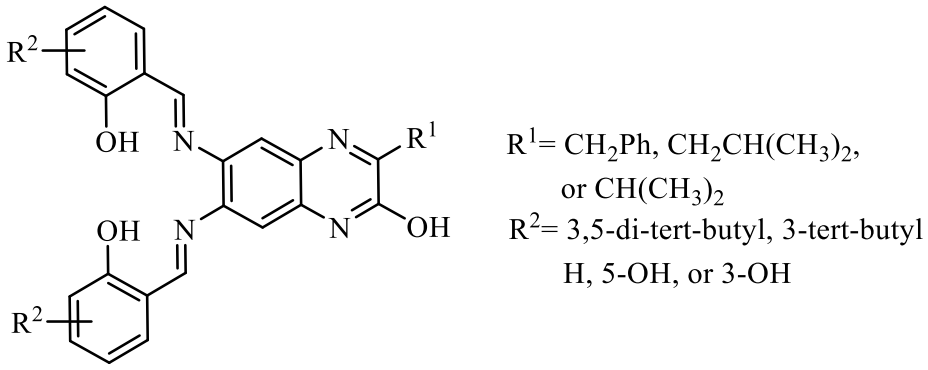
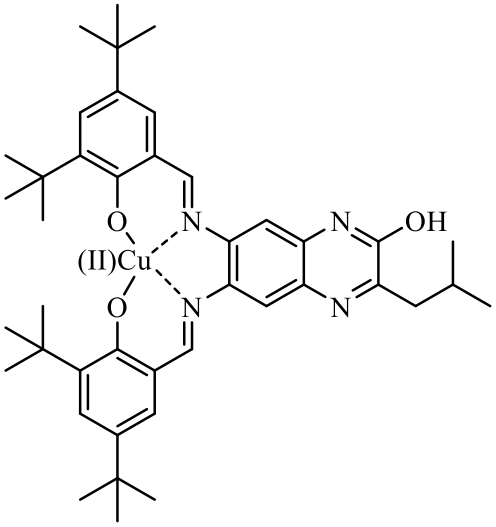
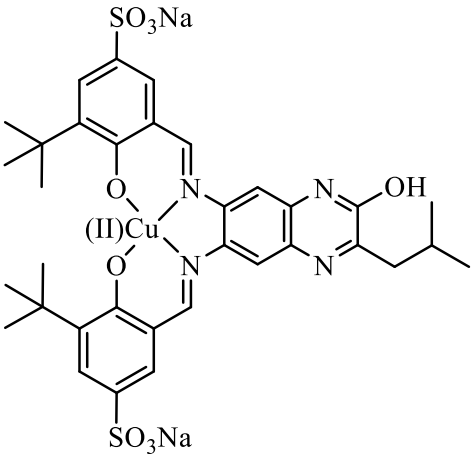


Figure 1.4. 2-Quinoxalinol salen ligand.

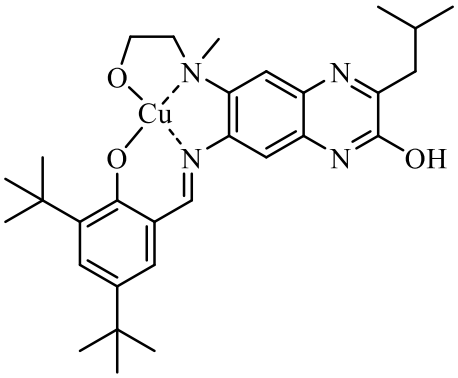
Previously, copper salqu has been shown to be an efficient catalyst for the oxidation of benzylic and allylic C-H bonds;[105,106] however, room to explore with this class of ligands exists, in particular in the field of C-H activation. Here, the Cu(II)-salqu (**complex 1**) has been studied in the oxidation of propargylic C-H bonds to α,β-acetylenic ketones. Also, the oxidation of 3° amines to imines with Cu(II)-salqu was investigated. In these examples, mechanistic studies elucidate the role of Cu(II)-salqu and allow us to propose mechanisms for the catalysis. Other derivatives of salen were synthesized and compared to Cu(II)-salqu; including a water soluble catalyst (**complex 2**), a less ridged binding pocket (**complex 3**), and a pyrazine backbone (**complex 4**) (**Figure 1.5**). The goal of this project is to provide a cost-effective, more efficient, and less toxic catalyst for C-H oxidation reactions.



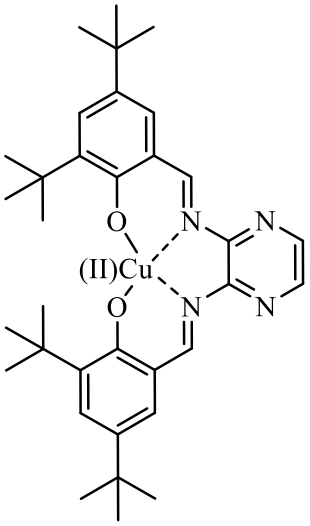
Complex 1
Salqu



Complex 2
Sulfosalqu



Complex 3
Salflex



Complex 4
Pyrasal

Figure 1.5. Cu(II)-Salqu structure and derivatives.

References

(1) US EPA. *EPA's Guide for Industrial Waste Management*; 1992.

(2) A. Sheldon, R. Fundamentals of Green Chemistry: Efficiency in Reaction Design. *Chem. Soc. Rev.* **2012**, *41* (4), 1437–1451. https://doi.org/10.1039/C1CS15219J.

(3) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press, 1998.

(4) Anastas, P. T.; Kirchhoff, M. M.; Williamson, T. C. Catalysis as a Foundational Pillar of Green Chemistry. *Appl. Catal. Gen.* **2001**, *221* (1), 3–13. https://doi.org/10.1016/S0926-860X(01)00793-1.

(5) Hagen, J. *Industrial Catalysis: A Practical Approach, 2nd Edition*; Wiley-VCH: Weinheim, Germany, 2006.

(6) Rothenberg, G. *Catalysis: Concepts and Green Applications*; John Wiley & Sons, 2015.

(7) Hagen, J. *Industrial Catalysis: A Practical Approach*; John Wiley & Sons, 2015.

(8) Shang, R.; Ilies, L.; Asako, S.; Nakamura, E. Iron-Catalyzed C(Sp2)–H Bond Functionalization with Organoboron Compounds. *J. Am. Chem. Soc.* **2014**, *136* (41), 14349–14352. https://doi.org/10.1021/ja5070763.

(9) Hwang, H.; Kim, J.; Jeong, J.; Chang, S. Regioselective Introduction of Heteroatoms at the C-8 Position of Quinoline N-Oxides: Remote C–H Activation Using N-Oxide as a Stepping Stone. *J. Am. Chem. Soc.* **2014**, *136* (30), 10770–10776. https://doi.org/10.1021/ja5053768.

(10) Yang, G.; Lindovska, P.; Zhu, D.; Kim, J.; Wang, P.; Tang, R.-Y.; Movassaghi, M.; Yu, J.-Q. Pd(II)-Catalyzed Meta-C–H Olefination, Arylation, and

Acetoxylation of Indolines Using a U-Shaped Template. *J. Am. Chem. Soc.* **2014**, *136* (30), 10807–10813. https://doi.org/10.1021/ja505737x.

(11) Xiao, K.-J.; Lin, D. W.; Miura, M.; Zhu, R.-Y.; Gong, W.; Wasa, M.; Yu, J.-Q. Palladium(II)-Catalyzed Enantioselective C(Sp3)–H Activation Using a Chiral Hydroxamic Acid Ligand. *J. Am. Chem. Soc.* **2014**, *136* (22), 8138–8142. https://doi.org/10.1021/ja504196j.

(12) Chan, K. S. L.; Fu, H.-Y.; Yu, J.-Q. Palladium(II)-Catalyzed Highly Enantioselective C–H Arylation of Cyclopropylmethylamines. *J. Am. Chem. Soc.* **2015**, *137* (5), 2042–2046. https://doi.org/10.1021/ja512529e.

(13) Chen, G.; Gong, W.; Zhuang, Z.; Andrä, M. S.; Chen, Y.-Q.; Hong, X.; Yang, Y.-F.; Liu, T.; Houk, K. N.; Yu, J.-Q. Ligand-Accelerated Enantioselective Methylene C(Sp3)–H Bond Activation. *Science* **2016**, *353* (6303), 1023–1027. https://doi.org/10.1126/science.aaf4434.

(14) Blanksby, S. J.; Ellison, G. B. Bond Dissociation Energies of Organic Molecules. *Acc. Chem. Res.* **2003**, *36* (4), 255–263. https://doi.org/10.1021/ar020230d.

(15) Arndtsen, B. A.; Bergman, R. G.; Mobley, T. A.; Peterson, T. H. Selective Intermolecular Carbon-Hydrogen Bond Activation by Synthetic Metal Complexes in Homogeneous Solution. *Acc. Chem. Res.* **1995**, *28* (3), 154–162. https://doi.org/10.1021/ar00051a009.

(16) Crabtree, R. H. Alkane C–H Activation and Functionalization with Homogeneous Transition Metal Catalysts: A Century of Progress—a New Millennium in Prospect. *J. Chem. Soc. Dalton Trans.* **2001**, *0* (17), 2437–2450. https://doi.org/10.1039/B103147N.

(17) Chuang, K. V.; Xu, C.; Reisman, S. E. A 15-Step Synthesis of (+)-Ryanodol. *Science* **2016**, *353* (6302), 912–915. https://doi.org/10.1126/science.aag1028.

(18) Davies, H. M. L.; Morton, D. Collective Approach to Advancing C–H Functionalization. *ACS Cent. Sci.* **2017**, *3* (9), 936–943. https://doi.org/10.1021/acscentsci.7b00329.

(19) Davies, H. M. L.; Morton, D. Recent Advances in C–H Functionalization. *J. Org. Chem.* **2016**, *81* (2), 343–350. https://doi.org/10.1021/acs.joc.5b02818.

(20) Newhouse, T.; Baran, P. S. If C-H Bonds Could Talk: Selective C-H Bond Oxidation. *Angew. Chem. Int. Ed.* **2011**, *50* (15), 3362–3374. https://doi.org/10.1002/anie.201006368.

(21) Muzart, J. Chromium-Catalyzed Oxidations in Organic Synthesis. *Chem. Rev.* **1992**, *92* (1), 113–140. https://doi.org/10.1021/cr00009a005.

(22) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. 13. Researches on Acetylenic Compounds. Part I. The Preparation of Acetylenic Ketones by Oxidation of Acetylenic Carbinols and Glycols. *J. Chem. Soc. Resumed* **1946**, No. 0, 39–45. https://doi.org/10.1039/JR9460000039.

(23) Wang, Y.; Su, H.; Gu, Y.; Song, X.; Zhao, J. Carcinogenicity of Chromium and Chemoprevention: A Brief Update. *OncoTargets Ther.* **2017**, *10*, 4065–4079. https://doi.org/10.2147/OTT.S139262.

(24) Tojo, G.; Fernandez, M. I. *Oxidation of Alcohols to Aldehydes and Ketones: A Guide to Current Common Practice*; Springer Science & Business Media, 2006.

(25) Selander, N.; J. Szabó, K. Catalysis by Palladium Pincer Complexes. *Chem. Rev.* **2011**, *111* (3), 2048–2076. https://doi.org/10.1021/cr1002112.

(26) Punniyamurthy, T.; Velusamy, S.; Iqbal, J. Recent Advances in Transition Metal Catalyzed Oxidation of Organic Substrates with Molecular Oxygen. *Chem. Rev.* **2005**, *105* (6), 2329–2364. https://doi.org/10.1021/cr050523v.

(27) Cahiez, G.; Moyeux, A. Cobalt-Catalyzed Cross-Coupling Reactions. *Chem. Rev.* **2010**, *110* (3), 1435–1462. https://doi.org/10.1021/cr9000786.

(28) Suzuki, T. Organic Synthesis Involving Iridium-Catalyzed Oxidation. *Chem. Rev.* **2011**, *111* (3), 1825–1845. https://doi.org/10.1021/cr100378r.

(29) Naota, T.; Takaya, H.; Murahashi, S.-I. Ruthenium-Catalyzed Reactions for Organic Synthesis. *Chem. Rev.* **1998**, *98* (7), 2599–2660. https://doi.org/10.1021/cr9403695.

(30) Catino, A. J.; Forslund, R. E.; Doyle, M. P. Dirhodium(II) Caprolactamate: An Exceptional Catalyst for Allylic Oxidation. *J. Am. Chem. Soc.* **2004**, *126* (42), 13622–13623. https://doi.org/10.1021/ja045330o.

(31) *The Role of the Chemical Sciences in Finding Alternatives to Critical Resources: A Workshop Summary*; National Research Council, 2012. https://doi.org/10.17226/13366.

(32) Hirao, T. Vanadium in Modern Organic Synthesis. *Chem. Rev.* **1997**, *97* (8), 2707–2724. https://doi.org/10.1021/cr960014g.

(33) Herrmann, C. V. Contact Process for Manufacturing Sulphuric Acid. US2357195A, August 29, 1944.

(34) Langeslay, R. R.; Kaphan, D. M.; Marshall, C. L.; Stair, P. C.; Sattelberger, A. P.; Delferro, M. Catalytic Applications of Vanadium: A Mechanistic Perspective.

Chem. Rev. **2019**, *119* (4), 2128–2191. https://doi.org/10.1021/acs.chemrev.8b00245.

(35) Ghosh, S. K.; Saha, R.; Saha, B. Toxicity of Inorganic Vanadium Compounds. *Res. Chem. Intermed.* **2015**, *41* (7), 4873–4897. https://doi.org/10.1007/s11164-014-1573-1.

(36) Wang, L.-Y.; Li, J.; Lv, Y.; Zhang, H.-Y.; Gao, S. Aerobic Alcohol Oxidation Using a PdCl2/N,N-Dimethylacetamide Catalyst System under Mild Conditions. *J. Organomet. Chem.* **2011**, *696* (20), 3257–3263. https://doi.org/10.1016/j.jorganchem.2011.07.019.

(37) Jaworski, J. N.; McCann, S. D.; Guzei, I. A.; Stahl, S. S. Detection of Palladium(I) in Aerobic Oxidation Catalysis. *Angew. Chem. Int. Ed.* **2017**, *56* (13), 3605–3610. https://doi.org/10.1002/anie.201700345.

(38) Wang, D.; Weinstein, A. B.; White, P. B.; Stahl, S. S. Ligand-Promoted Palladium-Catalyzed Aerobic Oxidation Reactions. *Chem. Rev.* **2018**, *118* (5), 2636–2679. https://doi.org/10.1021/acs.chemrev.7b00334.

(39) Hosseini, M.-J.; Jafarian, I.; Farahani, S.; Khodadadi, R.; Tagavi, S. H.; Naserzadeh, P.; Mohammadi-Bardbori, A.; Arghavanifard, N. New Mechanistic Approach of Inorganic Palladium Toxicity: Impairment in Mitochondrial Electron Transfer. *Metallomics* **2016**, *8* (2), 252–259. https://doi.org/10.1039/C5MT00249D.

(40) Garrett, C. E.; Prasad, K. The Art of Meeting Palladium Specifications in Active Pharmaceutical Ingredients Produced by Pd-Catalyzed Reactions. *Adv. Synth. Catal.* **2004**, *346* (8), 889–900. https://doi.org/10.1002/adsc.200404071.

(41) Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozlowski, M. C. Aerobic Copper-Catalyzed Organic Reactions. *Chem. Rev.* **2013**, *113* (8), 6234–6458. https://doi.org/10.1021/cr300527g.

(42) U.S. Market Price 12/3/2019 https://www.nasdaq.com/market-activity/commodities/hg%3Acmx (accessed Dec 3, 2019).

(43) Steventon, G. B.; Mitchell, S. C. Mouse Recombinant Phenylalanine Monooxygenase and the S-Oxygenation of Thioether Substrates. *J. Biochem. Mol. Toxicol.* **2009**, *23* (2), 119–124. https://doi.org/10.1002/jbt.20274.

(44) Han, J.-S.; Ahn, C.-M.; Mahanty, B.; Kim, C.-G. Partial Oxidative Conversion of Methane to Methanol Through Selective Inhibition of Methanol Dehydrogenase in Methanotrophic Consortium from Landfill Cover Soil. *Appl. Biochem. Biotechnol.* **2013**, *171* (6), 1487–1499. https://doi.org/10.1007/s12010-013-0410-0.

(45) Han, P.; Li, M.; Gu, J.-D. Biases in Community Structures of Ammonia/Ammonium-Oxidizing Microorganisms Caused by Insufficient DNA Extractions from Baijiang Soil Revealed by Comparative Analysis of Coastal Wetland Sediment and Rice Paddy Soil. *Appl. Microbiol. Biotechnol.* **2013**, *97* (19), 8741–8756. https://doi.org/10.1007/s00253-013-5169-2.

(46) Comai, S.; Costa, C. V. L.; Ragazzi, E.; Bertazzo, A.; Allegri, G. The Effect of Age on the Enzyme Activities of Tryptophan Metabolism along the Kynurenine Pathway in Rats. *Clin. Chim. Acta* **2005**, *360* (1), 67–80. https://doi.org/10.1016/j.cccn.2005.04.013.

(47) Solomon, E. I.; Heppner, D. E.; Johnston, E. M.; Ginsbach, J. W.; Cirera, J.; Qayyum, M.; Kieber-Emmons, M. T.; Kjaergaard, C. H.; Hadt, R. G.; Tian, L.

Copper Active Sites in Biology. *Chem. Rev.* **2014**, *114* (7), 3659–3853. https://doi.org/10.1021/cr400327t.

(48) Johnson, B. J.; Yukl, E. T.; Klema, V. J.; Klinman, J. P.; Wilmot, C. M. Structural Snapshots from the Oxidative Half-Reaction of a Copper Amine Oxidase: Implications for O2 Activation. *J. Biol. Chem.* **2013**, *288* (39), 28409–28417. https://doi.org/10.1074/jbc.M113.501791.

(49) Ross, M. O.; MacMillan, F.; Wang, J.; Nisthal, A.; Lawton, T. J.; Olafson, B. D.; Mayo, S. L.; Rosenzweig, A. C.; Hoffman, B. M. Particulate Methane Monooxygenase Contains Only Mononuclear Copper Centers. *Science* **2019**, *364* (6440), 566–570. https://doi.org/10.1126/science.aav2572.

(50) Khirsariya, P.; Mewada, R. K. Single Step Oxidation of Methane to Methanol–Towards Better Understanding. *Procedia Eng.* **2013**, *51*, 409–415. https://doi.org/10.1016/j.proeng.2013.01.057.

(51) Chan, S. I.; Yu, S. S.-F. Copper Protein Constructs for Methane Oxidation. *Nat. Catal.* **2019**, *2* (4), 286–287. https://doi.org/10.1038/s41929-019-0268-9.

(52) Tkac, J.; Vostiar, I.; Gemeiner, P.; Sturdik, E. Indirect Evidence of Direct Electron Communication between the Active Site of Galactose Oxidase and a Graphite Electrode. *Bioelectrochemistry* **2002**, *56* (1), 23–25. https://doi.org/10.1016/S1567-5394(02)00043-9.

(53) Mannam, S.; Sekar, G. CuCl Catalyzed Selective Oxidation of Primary Alcohols to Carboxylic Acids with Tert-Butyl Hydroperoxide at Room Temperature. *Tetrahedron Lett.* **2008**, *49* (15), 2457–2460. https://doi.org/10.1016/j.tetlet.2008.02.031.

(54) Gogoi, A.; Guin, S.; Rout, S. K.; Patel, B. K. A Copper-Catalyzed Synthesis of 3-Aroylindoles via a Sp3 C–H Bond Activation Followed by C–C and C–O Bond Formation. *Org. Lett.* **2013**, *15* (8), 1802–1805. https://doi.org/10.1021/ol400692b.

(55) Wang, J.; Liu, C.; Yuan, J.; Lei, A. Copper-Catalyzed Oxidative Coupling of Alkenes with Aldehydes: Direct Access to α,β-Unsaturated Ketones. *Angew. Chem. Int. Ed.* **2013**, *52* (8), 2256–2259. https://doi.org/10.1002/anie.201208920.

(56) Komiya, N.; Naota, T.; Oda, Y.; Murahashi, S.-I. Aerobic Oxidation of Alkanes and Alkenes in the Presence of Aldehydes Catalyzed by Copper Salts and Copper-Crown Ether. *J. Mol. Catal. Chem.* **1997**, *117* (1), 21–37. https://doi.org/10.1016/S1381-1169(96)00263-4.

(57) V. Rokade, B.; K. Malekar, S.; Ramaiah Prabhu, K. A Novel Oxidative Transformation of Alcohols to Nitriles : An Efficient Utility of Azides as a Nitrogen Source. *Chem. Commun.* **2012**, *48* (44), 5506–5508. https://doi.org/10.1039/C2CC31256E.

(58) Hayashi, Y.; Komiya, N.; Suzuki, K.; Murahashi, S.-I. Copper-Catalyzed Aerobic Oxidative Functionalization of C–H Bonds of Alkanes in the Presence of Acetaldehyde under Mild Conditions. *Tetrahedron Lett.* **2013**, *54* (21), 2706–2709. https://doi.org/10.1016/j.tetlet.2013.03.074.

(59) Tao, C.; Liu, F.; Zhu, Y.; Liu, W.; Cao, Z. Copper-Catalyzed Aerobic Oxidative Synthesis of Aryl Nitriles from Benzylic Alcohols and Aqueous Ammonia. *Org. Biomol. Chem.* **2013**, *11* (20), 3349–3354. https://doi.org/10.1039/C3OB00002H.

(60) Huang, L.; Jiang, H.; Qi, C.; Liu, X. Copper-Catalyzed Intermolecular Oxidative [3 + 2] Cycloaddition between Alkenes and Anhydrides: A New Synthetic Approach

to γ-Lactones. *J. Am. Chem. Soc.* **2010**, *132* (50), 17652–17654. https://doi.org/10.1021/ja108073k.

(61) Wu, F.; Stewart, S.; Ariyarathna, J. P.; Li, W. Aerobic Copper-Catalyzed Alkene Oxyamination for Amino Lactone Synthesis. *ACS Catal.* **2018**, *8* (3), 1921–1925. https://doi.org/10.1021/acscatal.7b04060.

(62) Tran-Vu, H.; Daugulis, O. Copper-Catalyzed Carboxylation of Aryl Iodides with Carbon Dioxide. *ACS Catal.* **2013**, *3* (10), 2417–2420. https://doi.org/10.1021/cs400443p.

(63) Evans, R. W.; Zbieg, J. R.; Zhu, S.; Li, W.; MacMillan, D. W. C. Simple Catalytic Mechanism for the Direct Coupling of α-Carbonyls with Functionalized Amines: A One-Step Synthesis of Plavix. *J. Am. Chem. Soc.* **2013**, *135* (43), 16074–16077. https://doi.org/10.1021/ja4096472.

(64) Seayad, J.; Seayad, A. M.; Chai, C. L. L. Copper-Catalyzed Diacetoxylation of Olefins Using $PhI(OAc)_2$ as Oxidant. *Org. Lett.* **2010**, *12* (7), 1412–1415. https://doi.org/10.1021/ol902813m.

(65) Zhang, Q.; Liu, Y.; Wang, T.; Zhang, X.; Long, C.; Wu, Y.-D.; Wang, M.-X. Mechanistic Study on Cu(II)-Catalyzed Oxidative Cross-Coupling Reaction between Arenes and Boronic Acids under Aerobic Conditions. *J. Am. Chem. Soc.* **2018**, *140* (16), 5579–5587. https://doi.org/10.1021/jacs.8b01896.

(66) Grützmacher, H. Cooperating Ligands in Catalysis. *Angew. Chem. Int. Ed.* **2008**, *47* (10), 1814–1818. https://doi.org/10.1002/anie.200704654.

(67) Adhikary, C.; Bera, R.; Dutta, B.; Jana, S.; Bocelli, G.; Cantoni, A.; Chaudhuri, S.; Koner, S. Catalytic Efficacy of Schiff-Base Copper(II) Complexes: Synthesis, X-

Ray Structure and Olefin Oxidation. *Polyhedron* **2008**, *27* (6), 1556–1562. https://doi.org/10.1016/j.poly.2008.01.030.

(68) Nandi, M.; Roy, P.; Uyama, H.; Bhaumik, A. Functionalized Mesoporous Silica Supported Copper(ii) and Nickel(ii) Catalysts for Liquid Phase Oxidation of Olefins. *Dalton Trans.* **2011**, *40* (46), 12510–12518. https://doi.org/10.1039/C1DT10157A.

(69) Goberna-Ferrón, S.; Lillo, V.; Galán-Mascarós, J. R. [Cu(L-Prolinate)$_2$]: A Catalyst for Environmentally Friendly Oxidation of Alkanes and Alkenes with H_2O_2 and O_2. *Catal. Commun.* **2012**, *23* (Supplement C), 30–33. https://doi.org/10.1016/j.catcom.2012.03.007.

(70) Kirillova, M. V.; Kirillov, A. M.; Mandelli, D.; Carvalho, W. A.; Pombeiro, A. J. L.; Shul'pin, G. B. Mild Homogeneous Oxidation of Alkanes and Alcohols Including Glycerol with Tert-Butyl Hydroperoxide Catalyzed by a Tetracopper(II) Complex. *J. Catal.* **2010**, *272* (1), 9–17. https://doi.org/10.1016/j.jcat.2010.03.017.

(71) Kirillov, A. M.; Kirillova, M. V.; Shul'pina, L. S.; Figiel, P. J.; Gruenwald, K. R.; Guedes da Silva, M. F. C.; Haukka, M.; Pombeiro, A. J. L.; Shul'pin, G. B. Mild Oxidative Functionalization of Alkanes and Alcohols Catalyzed by New Mono- and Dicopper(II) Aminopolyalcoholates. *J. Mol. Catal. Chem.* **2011**, *350* (1–2), 26–34. https://doi.org/10.1016/j.molcata.2011.08.028.

(72) Zhu, M.; Wei, X.; Li, B.; Yuan, Y. Copper-Triethanolamine Complex as Efficient and Active Catalyst for Selective Oxidation of Alkylarenes to Phenyl Ketones by Tert-Butylhydroperoxide. *Tetrahedron Lett.* **2007**, *48* (52), 9108–9111. https://doi.org/10.1016/j.tetlet.2007.10.135.

(73) Ma, Z.; Wang, X.; Wei, S.; Yang, H.; Zhang, F.; Wang, P.; Xie, M.; Ma, J. Cu (I) Immobilized on Functionalized SBA-15: A Recyclable Catalyst for the Synthesis of 1,3-Diynes Using Terminal Alkynes without Base. *Catal. Commun.* **2013**, *39* (Supplement C), 24–29. https://doi.org/10.1016/j.catcom.2013.04.012.

(74) Dhakshinamoorthy, A.; Alvaro, M.; Garcia, H. Metal Organic Frameworks as Efficient Heterogeneous Catalysts for the Oxidation of Benzylic Compounds with T-Butylhydroperoxide. *J. Catal.* **2009**, *267* (1), 1–4. https://doi.org/10.1016/j.jcat.2009.08.001.

(75) Neeli, C. K. P.; Narani, A.; Marella, R. K.; Rama Rao, K. S.; Burri, D. R. Selective Benzylic Oxidation of Alkylaromatics over Cu/SBA-15 Catalysts under Solvent-Free Conditions. *Catal. Commun.* **2013**, *39* (Supplement C), 5–9. https://doi.org/10.1016/j.catcom.2013.04.023.

(76) King, A. E.; Huffman, L. M.; Casitas, A.; Costas, M.; Ribas, X.; Stahl, S. S. Copper-Catalyzed Aerobic Oxidative Functionalization of an Arene C−H Bond: Evidence for an Aryl-Copper(III) Intermediate. *J. Am. Chem. Soc.* **2010**, *132* (34), 12068–12073. https://doi.org/10.1021/ja1045378.

(77) Yang, L.; Lu, Z.; S. Stahl, S. Regioselective Copper-Catalyzed Chlorination and Bromination of Arenes with O_2 as the Oxidant. *Chem. Commun.* **2009**, *0* (42), 6460–6462. https://doi.org/10.1039/B915487F.

(78) Pérez, Y.; Ballesteros, R.; Fajardo, M.; Sierra, I.; del Hierro, I. Copper-Containing Catalysts for Solvent-Free Selective Oxidation of Benzyl Alcohol. *J. Mol. Catal. Chem.* **2012**, *352* (Supplement C), 45–56. https://doi.org/10.1016/j.molcata.2011.10.009.

(79) Sarmah, P.; Das, B. K.; Phukan, P. Novel Dicopper(II)-Tetracarboxylates as Catalysts for Selective Oxidation of Benzyl Alcohols with Aqueous TBHP. *Catal. Commun.* **2010**, *11* (10), 932–935. https://doi.org/10.1016/j.catcom.2010.03.005.

(80) Gamba, I.; Palavicini, S.; Monzani, E.; Casella, L. Catalytic Sulfoxidation by Dinuclear Copper Complexes. *Chem. – Eur. J.* **2009**, *15* (47), 12932–12936. https://doi.org/10.1002/chem.200902451.

(81) Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozlowski, M. C. Aerobic Copper-Catalyzed Organic Reactions. *Chem. Rev.* **2013**, *113* (8), 6234–6458. https://doi.org/10.1021/cr300527g.

(82) Abu-Dief, A. M.; Mohamed, I. M. A. A Review on Versatile Applications of Transition Metal Complexes Incorporating Schiff Bases. *Beni-Suef Univ. J. Basic Appl. Sci.* **2015**, *4* (2), 119–133. https://doi.org/10.1016/j.bjbas.2015.05.004.

(83) Chemistry, I. U. of P. and A. IUPAC Gold Book - Schiff bases (Schiff's bases) http://goldbook.iupac.org/html/S/S05498.html (accessed Sep 13, 2017). https://doi.org/10.1351/goldbook.S05498.

(84) Nilash, M. M.; Hashemzadeh, A.; Fakhari, A. R.; Amini, M. M. Novel Schiff Base-Functionalized Metal–Organic Framework Nanoparticles for Dispersive Solid Phase Extraction of Copper Ions from Vegetable and Water Samples. *Anal. Methods* **2019**, *11* (20), 2683–2691. https://doi.org/10.1039/C9AY00304E.

(85) Cotton. *ADVANCED INORGANIC CHEMISTRY, 6TH ED*; Wiley India Pvt. Limited, 2007.

(86) Czepa, W.; Fik, M. A.; Witomska, S.; Kubicki, M.; Consiglio, G.; Pawluć, P.; Patroniak, V. Simple Schiff-Base Cu(II) Complexes as Efficient Catalysts for

Benzyl Alcohol Oxidation. *ChemistrySelect* **2018**, *3* (32), 9504–9509. https://doi.org/10.1002/slct.201801550.

(87) Buvaylo, E. A.; Kokozay, V. N.; Vassilyeva, O. Yu.; Skelton, B. W.; Nesterova, O. V.; Pombeiro, A. J. L. Copper(II) Complex of the 2-Pyridinecarbaldehyde Aminoguanidine Schiff Base: Crystal Structure and Catalytic Behaviour in Mild Oxidation of Alkanes. *Inorg. Chem. Commun.* **2017**, *78*, 85–90. https://doi.org/10.1016/j.inoche.2017.03.008.

(88) Cozzi, P. G. Metal–Salen Schiff Base Complexes in Catalysis: Practical Aspects. *Chem. Soc. Rev.* **2004**, *33* (7), 410–421. https://doi.org/10.1039/B307853C.

(89) Jacobsen, E. N.; Kakiuchi, F.; Konsler, R. G.; Larrow, J. F.; Tokunaga, M. Enantioselective Catalytic Ring Opening of Epoxides with Carboxylic Acids. *Tetrahedron Lett.* **1997**, *38* (5), 773–776. https://doi.org/10.1016/S0040-4039(96)02414-8.

(90) Ready, J. M.; Jacobsen, E. N. Highly Active Oligomeric (Salen)Co Catalysts for Asymmetric Epoxide Ring-Opening Reactions. *J. Am. Chem. Soc.* **2001**, *123* (11), 2687–2688. https://doi.org/10.1021/ja005867b.

(91) Zulauf, A.; Mellah, M.; Schulz, E. New Chiral Thiophene−Salen Chromium Complexes for the Asymmetric Henry Reaction. *J. Org. Chem.* **2009**, *74* (5), 2242–2245. https://doi.org/10.1021/jo802769y.

(92) Holbach, M.; Weck, M. Modular Approach for the Development of Supported, Monofunctionalized, Salen Catalysts. *J. Org. Chem.* **2006**, *71* (5), 1825–1836. https://doi.org/10.1021/jo051919+.

(93) Nishikori, H.; Katsuki, T. Mn-Salen Catalyzed Enantioselective Sulfimidation. *Appl. Catal. Gen.* **2000**, *194*, 475–477. https://doi.org/10.1016/S0926-860X(99)00393-2.

(94) Hosseini Nejad, E.; van Melis, C. G. W.; Vermeer, T. J.; Koning, C. E.; Duchateau, R. Alternating Ring-Opening Polymerization of Cyclohexene Oxide and Anhydrides: Effect of Catalyst, Cocatalyst, and Anhydride Structure. *Macromolecules* **2012**, *45* (4), 1770–1776. https://doi.org/10.1021/ma2025804.

(95) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. Enantioselective Epoxidation of Unfunctionalized Olefins Catalyzed by Salen Manganese Complexes. *J. Am. Chem. Soc.* **1990**, *112* (7), 2801–2803. https://doi.org/10.1021/ja00163a052.

(96) Pamin, K.; Pozzi, G.; Tabor, E.; Bukowski, W.; Połtowicz, J. Oxidation of Cycloalkanes with Molecular Oxygen in the Presence of Salen Metallocomplexes in Thermomorphic Conditions. *Catal. Commun.* **2013**, *39*, 102–105. https://doi.org/10.1016/j.catcom.2013.04.026.

(97) Chen, T.; Cai, C. Selective Oxidation of Benzyl Alcohols to Aldehydes with a Salophen Copper(II) Complex and *tert*-Butyl Hydroperoxide at Room Temperature. *Synth. Commun.* **2015**, *45* (11), 1334–1341. https://doi.org/10.1080/00397911.2015.1015034.

(98) Asraf, M. A.; Ezugwu, C. I.; Zakaria, C. M.; Verpoort, F. Homogeneous Photochemical Water Oxidation with Metal Salophen Complexes in Neutral Media. *Photochem. Photobiol. Sci.* **2019**, *18* (11), 2782–2791. https://doi.org/10.1039/C9PP00254E.

(99) Sahani, A. J.; Jayaram, R. V.; Burange, A. S. C-Se Cross-Coupling of Arylboronic Acids and Diphenyldiselenides over Non Precious Transition Metal (Fe, Cu and Ni) Complexes. *Mol. Catal.* **2018**, *450*, 14–18. https://doi.org/10.1016/j.mcat.2018.02.028.

(100) Sabarinathan, S.; Vasuki, G.; Rao, P. S. Chiral Cu(II) Salen Complexes Catalyzed Aerobic Oxidative Biaryl Coupling-Probing the Reaction by EPR. *Eur. J. Chem.* **2010**, *1* (4), 360–367. https://doi.org/10.5155/eurjchem.1.4.360-367.221.

(101) Liu, Y.; Zhang, Q.; Ma, X.; Liu, P.; Xie, J.; Dai, B.; Liu, Z. Salen-Cu(II) Complex Catalyzed N-Arylation of Imidazoles under Mild Conditions. *Int. J. Org. Chem.* **2013**, *3* (3), 720–726. https://doi.org/10.4236/ijoc.2013.33023.

(102) Mehta, J. P.; Parmar, D. K.; Godhani, D. R.; Nakum, H. D.; Desai, N. C. Heterogeneous Catalysts Hold the Edge over Homogeneous Systems: Zeolite-Y Encapsulated Complexes for Baeyer-Villiger Oxidation of Cyclohexanone. *J. Mol. Catal. Chem.* **2016**, *421*, 178–188. https://doi.org/10.1016/j.molcata.2016.05.016.

(103) Finelli, A.; Hérault, N.; Crochet, A.; Fromm, K. M. Threading Salen-Type Cu- and Ni-Complexes into One-Dimensional Coordination Polymers: Solution versus Solid State and the Size Effect of the Alkali Metal Ion. *Cryst. Growth Des.* **2018**, *18* (2), 1215–1226. https://doi.org/10.1021/acs.cgd.7b01769.

(104) Naber, J. E.; de Jong, K. P.; Stork, W. H. J.; Kuipers, H. P. C. E.; Post, M. F. M. Industrial Applications of Zeolite Catalysis. In *Studies in Surface Science and Catalysis*; Weitkamp, J., Karge, H. G., Pfeifer, H., Hölderich, W., Eds.; Zeolites and Related Microporous Materials: State of the Art 1994 - Proceedings of the 10th International Zeolite Conference, Garmisch-Partenkirchen, Germany, 17-22 July

1994; Elsevier, 1994; Vol. 84, pp 2197–2219. https://doi.org/10.1016/S0167-2991(08)63783-0.

(105) Wu, X.; Gorden, A. E. V. 2-Quinoxalinol Salen Copper Complexes for Oxidation of Aryl Methylenes. *Eur. J. Org. Chem.* **2009**, *2009* (4), 503–509. https://doi.org/10.1002/ejoc.200800928.

(106) Li, Y.; Lee, T. B.; Wang, T.; Gamble, A. V.; Gorden, A. E. V. Allylic C–H Activations Using Cu(II) 2-Quinoxalinol Salen and *tert*-Butyl Hydroperoxide. *J. Org. Chem.* **2012**, *77* (10), 4628–4633. https://doi.org/10.1021/jo300372q.

Chapter 2 Propargylic oxidation with Cu(II)-Salqu

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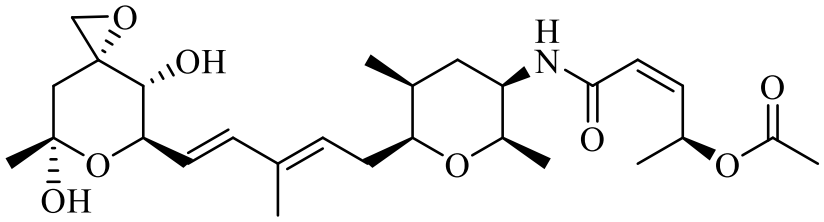
Introduction

The ability to directly install an oxygen onto a C-H bond through C-H oxidation reactions is potentially very useful in synthetic organic chemistry as it could allow the incorporation of additional functionality; however, being able to do so selectively has proven to be a great challenge. Much of the research in this area has exploited transition metal catalysis to overcome the high activation requirements of these types of reactions.[1–6] While several examples of C-H oxidation reactions exist, very few examples of propargylic oxidations have been reported. Some examples reported previously include the use of expensive transition metals such as rhodium, high catalyst loading, long reaction times, or the need for multiple additives.[7–12] The propargylic oxidation of alkynes has also been demonstrated with the use of a copper salt (e.g., $CuCl_2$) and *tert*-butyl hydroperoxide (TBHP); however, these reactions required very long reaction times (24 h), were done under an atmosphere of O_2, and were found to produce only modest yields (15-74 %).[13]

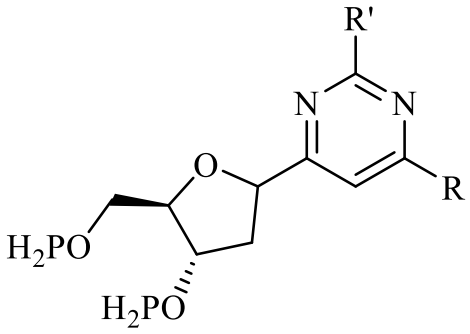
The synthesis of α,β-acetylenic ketones is of wide interest as they present novel starting materials for the synthesis of heterocycles, nucleosides, aromatic compounds, and

have been incorporated into the synthetic schemes of some anticancer agents.[14–20] For example, FR901464 is a natural product synthesized from an α,β-acetylenic ketone and has demonstrated potent anticancer activity against multiple human cancer cell types (**Figure 2.1**).[21–23] A range of complex C-nucleosides that have been shown to exhibit some biological activity have been synthesized using α,β-acetylenic ketones as the starting material (**Figure 2.1**).[24,25] Because of the wide range of potential building blocks available from this class of compound, and the limited scope of reactions currently available to prepare them, we investigated new means for the oxidation of propargylic C-H bonds.

Recently, we have reported the use of a Cu(II)-2-quinoxalinol salen (salqu) catalyst in combination with *tert*-butyl hydroperoxide (TBHP) to facilitate propargylic alcohol oxidations.[26] These reactions were done on a variety of different substrates producing good yields. As this method was highly successful when applied to allylic C-H bonds and propargylic alcohols, we reasoned that the combination of salqu and TBHP should also facilitate C-H oxidation of propargylic groups lacking an alcohol.



FR901464



C-nucleoside

Figure 2.1. Biological relevant molecules synthesized from α,β-acetylenic ketones.

Here, we describe the use of a Cu(II)-salqu catalyst for the direct oxidation of alkynes to α,β-acetylenic ketones. These reactions are carried out in mild conditions using only 1 mol % of Cu(II) catalyst at 70 °C, obtaining yields up to 78 % in very good time (4 h). These reactions can be run in either acetonitrile or aqueous media by using a sulfonated water-soluble version of the catalyst (**complex 2**).

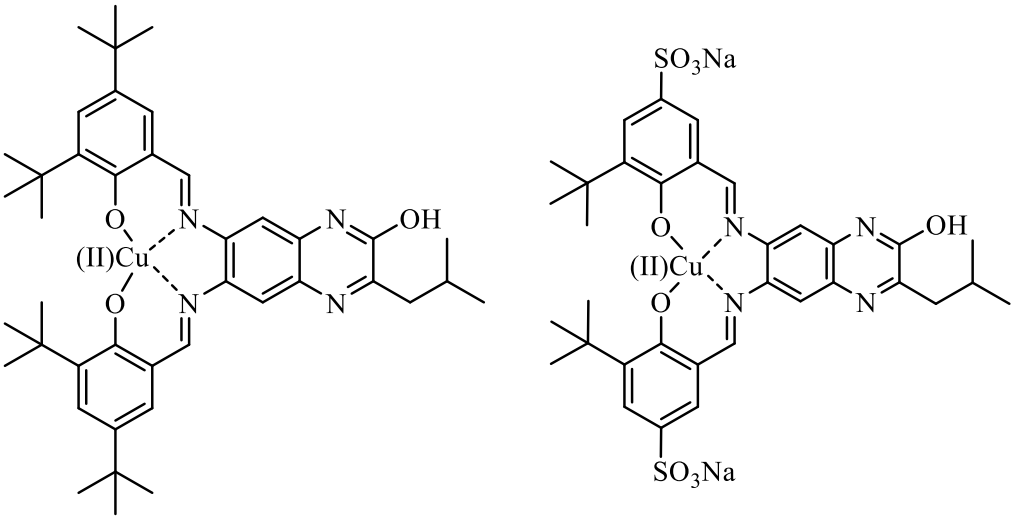


Figure 2.2. **Complex 1** (left) Cu(II) 2-quinoxalinol salen (salqu) catalyst. **Complex 2** (right) sulfonated 2-quinoxalinol salen (sulfosalqu) catalyst.

Results and Discussion

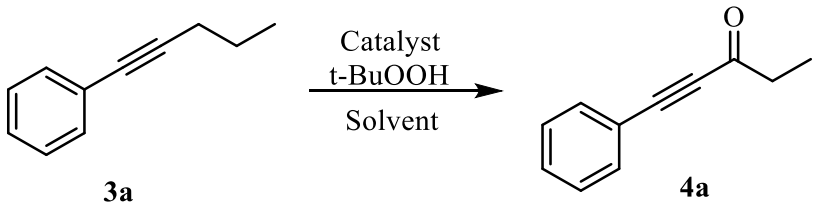
In preliminary studies, 1-phenyl-1-pentyne was used as a model substrate for the oxidation and optimization of reactions. The oxidation of 1-phenyl-1-pentyne (0.5 mmol) using 1.0 mol % of the catalyst **1** in acetonitrile (10 mL) was effective with dropwise addition of TBHP (4 equivalents) at 70 °C. This afforded the α,β-acetylenic ketone **4a** in 78 % yield in just 4 h (**Table 2.1** entry 1).

Encouraged by these results, several reaction conditions were screened to optimize the yield. Other previously reported examples of oxidation reactions including different transition metal catalysts with TBHP as the oxidant, have used the addition of base as a way to accelerate the reaction rate.[27–29] However, in our case the use of base (K_2CO_3) as

additive leads to a decrease in overall yield (**Table 2.1** entries 2 and 3). This could indicate that the decomposition of *tert*-butylperoxy ether does not occur in our reaction mechanism. In an effort to help increase the oxidative capabilities of TBHP, the use of tetrabutylammonium iodide (TBAI) as a cooxidant was employed, but this was also found to result in a significant decrease in overall yield (**Table 2.1** entry 4).[30] TBAI can act as a radical initiator in the presence of TBHP, but it could also be leading to radical termination when Cu(II) salqu is used, thus terminating the reaction.[31] Reducing the temperature also gave lower yields (**Table 2.1** entry 5). When heat was removed from the reaction, only a trace yield of product was produced (**Table 2.1** entry 6). The added heat likely supplies the needed activation energy for the initiation of radical formation.

In exploring the use of different solvents, the use of dichloromethane (DCM) led to a much lower yield, even when running the reaction for an extended period- up to 24 h (entries 7 and 8). Acetonitrile likely gives the highest yield due to having a high oxygen solubility (8.1 mM at 25 °C).[32] As expected, running this reaction using degassed solvent under an inert N_2 atmosphere, leads to a significant decrease in yield (entry 14). This discovery is in agreement with previous studies of Cu(II) salqu for allylic oxidations and helps describe our proposed mechanism.[33] In this case, dissolved oxygen in the solvent could be acting as a co-oxidant for propargylic oxidations.

Table 2.1. Optimization of the reaction conditions.



3a **4a**

Entry	Catalyst[a]	Solvent	T °C	Time	Additive[b]	Yield (%)[c]
1	**Complex 1**	**CH_3CN**	**70**	**4 h**		**78**
2	Complex **1**	CH_3CN	50	1 h	K_2CO_3	26
3	Complex **1**	CH_3CN	50	24 h	K_2CO_3	15
4	Complex **1**	CH_3CN	50	4 h	TBAI	4
5	Complex **1**	CH_3CN	50	4 h		47
6	Complex **1**	CH_3CN	RT	24 h		trace
7	Complex **1**	CH_2Cl_2	40	4 h		17
8	Complex **1**	CH_2Cl_2	40	24 h		45
9	None	CH_3CN	70	4 h		8
10	$Cu(OAc)_2$ 10 mol %	H_2O	80	6 h		26
11	$Cu(acac)_2$ 10 mol %	H_2O	80	4 h		31
12	$Cu(NO_3)_2$ 10 mol %	H_2O	80	4 h		17
13	Complex **2**	H_2O	80	4 h		64
14	Complex **1**	CH_3CN[d]	70	4 h		18

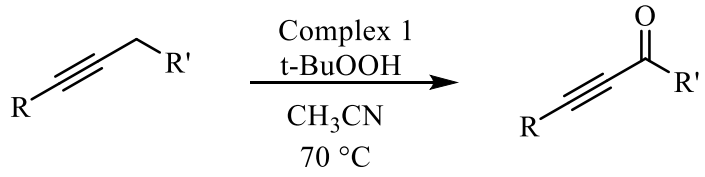
[a] 1 mol % unless otherwise stated. [b] 50 mol %. [c] GC yields using internal standard method.

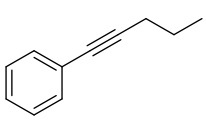
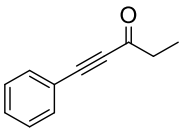
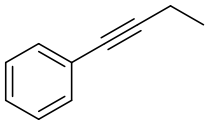
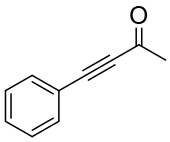
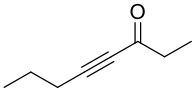
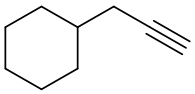
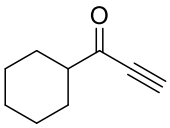
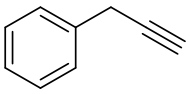
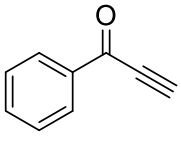
[d] N_2 atmosphere, degassed solvent.

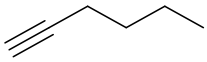
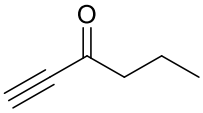
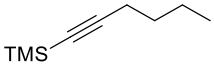
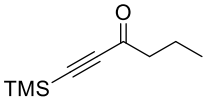
Employing simple Cu(II) salts (**Table 2.1** entries 10-12), under comparable conditions even when added with much higher catalyst loading (10 %), resulted in only modest yields (17-31 %) after 4-6 h. The absence of any metal catalyst gave a lower yield of 8 % (**Table 2.1** entry 9). These examples show the importance of a catalyst for this transformation. In particular, the ligand support of Cu(II) salqu provides a more optimal yield compared to copper salts is in agreement with our hypothesis. Throughout the optimization, entry 1 - using acetonitrile at 70 °C, 1 mol % Cu(II) salqu catalyst, and 4 equivalents of TBHP - gave the best overall yield within a reaction time of 4 hours.

To test the scope of this oxidation, a series of different functionalized substrates were oxidized using the conditions previously optimized with 1-phenyl-1-pentyne. The results of these are given in **Table 2.2** as isolated yields. Shortening the length of the R' group resulted in a slight decrease in isolated yield (**Table 2.2** entry 2). Symmetric substrate **3c** gives one example that this reaction works in the absence of aromatic compounds while also producing a good isolatable yield. However, the same reaction with the terminal alkynes **3d** and **3f** resulted in lower yields even when the time was increased to 16 h or 20 h. Previous reports have also demonstrated low yields and longer reaction times when oxidizing these types of terminal alkynes.[8–11,34] This could be due to competition from a Glaser coupling reaction in the presence of the copper catalyst.[35] In addition, the steric bulk of the cyclohexane found in **3d** could inhibit hydrogen radical abstraction at the propargylic position.

Table 2.2. Substrate scope of various alkynes.



Entry	Substrate		Product		Yield[b]
1		3a		4a	78
2		3b		4b	71
3		3c		4c	68
4[c]		3d		4d	13[e]
5		3e		4e	77

6[d]		3f		4f	23[e]
7		3g		4g	36[e] 57[d,e]

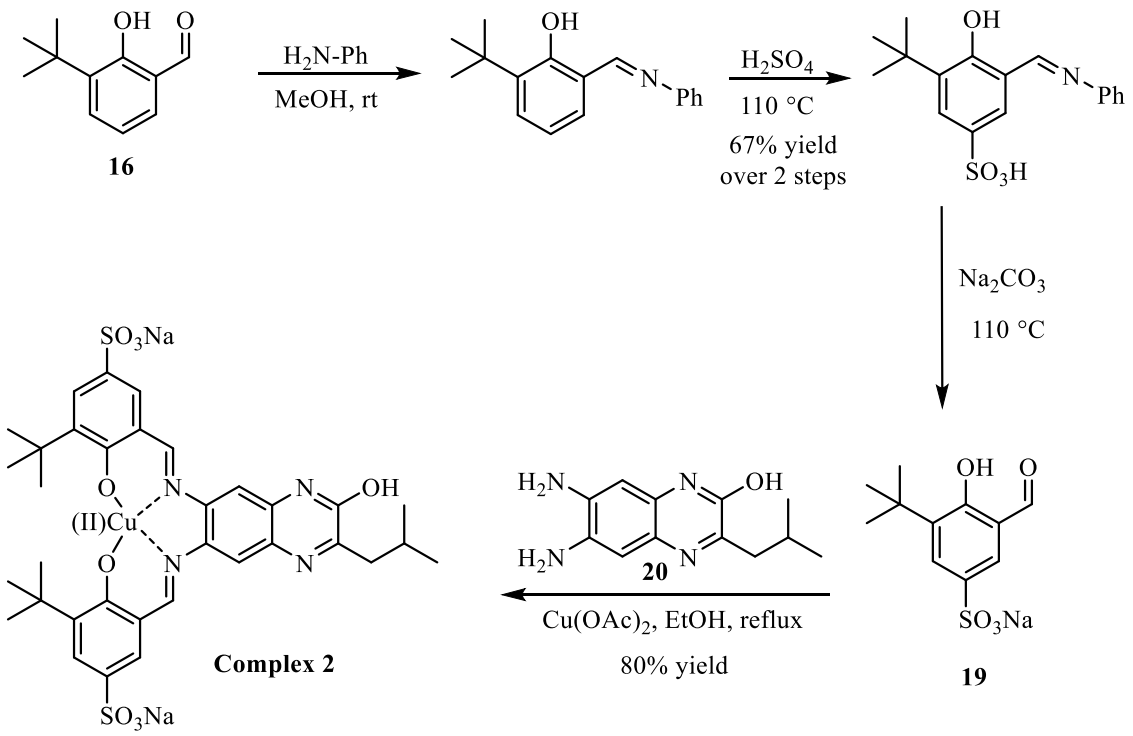
[a]Reaction conditions: substrate (0.5 mmol), CH_3CN (10 mL), TBHP (2 mmol), complex 1 (1 mol %), 70 °C, 4 h. [b] Isolated yields. [c] 20 h. [d] 16 h. [e] GC Yield.

To overcome the potential competing Glaser coupling reaction, terminal alkynes can be protected with trimethyl silane (TMS) following standard protection procedures (**3g**).[36] By doing this, we were able to decrease the reaction time significantly from 16 h to 4 h while also increasing the overall yield (**4g**). Allowing the reaction to proceed for 16 h, in order to better compare with the terminal alkyne reactivity, leads to an overall yield more than double the unprotected terminal alkyne (57 %). This provides one alternative method to be able to utilize this chemistry in the presence of terminal alkynes with limited additional effort from the protection step.

Entry 5 (**Table 2.2**) shows an example of a substrate with a C-H bond that is both benzylic and propargylic activated resulting in oxidation with an isolated yield of 77 %. Because our catalyst has been shown to oxidize benzylic C-H bonds, we would expect a higher yield with the added functional group; however, the added bulk of the aromatic compound may hinder the reactive site of the molecule leading to a smaller yield than

desired. For the symmetrical alkyne (**Table 2.2** entry 3) we only observed oxidation on one side of the alkyne without the undesired over oxidation. This is likely due to the electron withdrawing effect of the ketone once oxidation occurs, hindering the formation of the propargylic radical species needed for second oxidation cycle.

Although acetonitrile gave the optimal yield for this transformation, it does have its drawbacks when used in large scale production. While recent studies have shown the importance of acetonitrile in the pharmaceutical industry, they also examine the challenges associated with using this solvent in large scale manufacturing.[37] Due to some of the poor environmental effects associated with this solvent, and in an effort to address this, we set out to run these reactions in water using a sulfonated water soluble version (sulfosalqu) of Cu(II)-salqu. Water is a much safer solvent when compared to organic solvents such as acetonitrile.[38] The water soluble ligand (**complex 2**) was synthesized following a modified version of the synthetic procedure previously described.[39] This synthesis follows **Scheme 2.1**. First, 3-tertbutylsalicylaldehyde (**16**) must be protected with aniline which can then subsequently be sulfonated using H_2SO_4. Deprotection can be readily achieved using aqueous Na_2CO_3 to afford aldehyde **19**. Aldehyde **19** can then be templated with 2-quinoxalinol (**20**) and $Cu(OAc)_2$ to yield **complex 2**.



Scheme 2.1. Synthesis of Cu(II)-sulfosalqu.

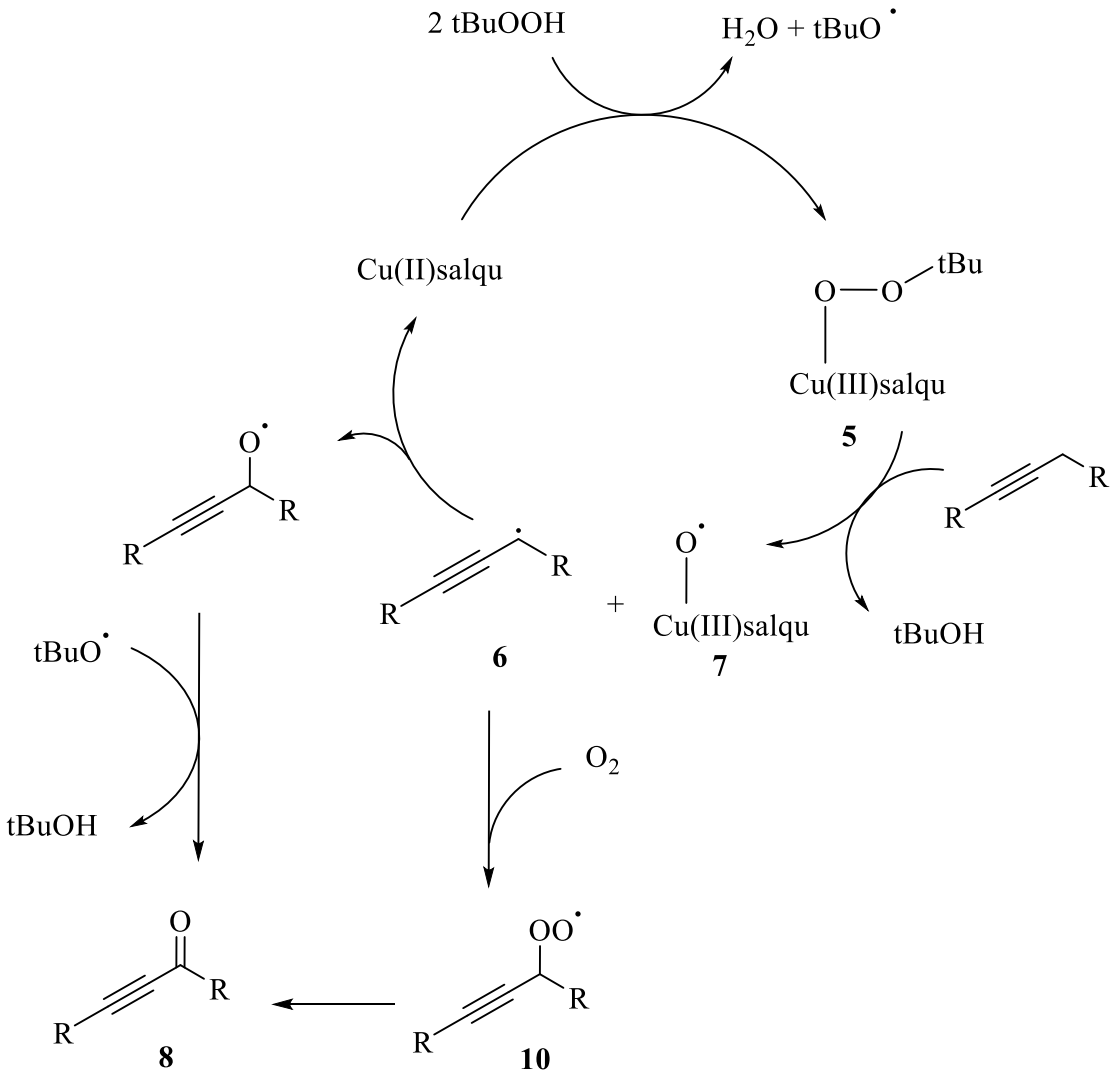
To demonstrate the potential utility of these reactions in water, our initial model substrate (**3a**) was tested using **complex 2** (1 mol %) as the catalyst. This reaction was carried out utilizing the "on water" emulsion method coined by Barry Sharpless.[40] **Complex 2** was also found to act as the catalyst for the oxidation of **3a** in just 4 hours resulting in a yield of 64 % (**Table 2.1** entry 13). A few other substrates (**3b** and **3c**) gave similar yields (60 % and 51 % respectively) in the aqueous solvent system. Using the aqueous system, we can reduce or eliminate the use of volatile organic solvents (VOS) which have the potential to increase hazards in large scale oxidation reactions.[41,42]

Running these reactions in water provides a greener and safer approach without sacrificing much of the yield. It also greatly increases the ease of product isolation because the reaction is done in an "on water" fashion.[40] Subsequent to oxidation, once the stirring has stopped, the substrate separates from the water and can easily be removed from the catalyst/aqueous solution by means of a separatory funnel. The water catalyst layer can then be recycled and reused in a second oxidation reaction leading to lower waste generation. This is in keeping with the principles of "Green Chemistry."[43]

Although some might not consider water as a green solvent, several methods have been developed for the treatment of contaminated water.[43,44] Water is the most abundant solvent on earth and what nature chooses as its solvent throughout a wide range of oxidation reactions. Also, water has a high heat capacity, is redox stable, and has a much lower environmental impact compared to organic solvents.[45–47] The greenest approach would be to run all reactions without the use of solvent; however, this is not practical in many cases.[46] Here we have provided a new method for the oxidation of propargylic C-H bonds in both organic and aqueous media.

Based on the findings here and previous studies with Cu(II)-salqu, we speculate this reaction goes through a radical mechanism (**Scheme 2.2**).[33] Starting with TBHP binding to Cu(II)-salqu (**5**), this complex then likely reacts with the alkyne and undergoes homolytic cleavage of the O—O bond producing *tert*-butyl alcohol (observed by HRMS), Cu(III)-salqu—O˙(**7**), and a propargylic radical species (**6**). This cycle can then follow 2 pathways. In one pathway, Cu(III)-salqu—O˙ can undergo reductive cleavage to produce the α,β-acetylenic ketone (**8**) and Cu(II)-salqu. In the other pathway, **6** will react with O_2

to form **10** and the loss of oxygen produces **8**. This could explain why when degassed solvent and an inert atmosphere is used, the yield is decreased. Increasing the equivalents of the oxidant TBHP added to the reaction does not further increase the reaction rate or isolable yields. Although, only 2 equivalents of TBHP is consumed in the proposed mechanism, 4 equivalents are likely required due to decomposition of TBHP at higher temperatures.



Scheme 2.2. Proposed catalytic cycle for propargylic oxidation catalyzed by Cu(II)-salqu.

Conclusion

In summary, we have here reported the use of the Cu(II) salqu catalyst for oxidation of propargylic C-H bonds to α,β-acetylenic ketones. After optimizing the conditions, up to 78 % isolated yield using only 1 mol % of catalyst was achieved. A series of alkyne substrates were oxidized including ones containing aromatic groups. However, terminal alkynes posed a challenge with our catalyst which can be combatted with the use of TMS group to regain appreciable yields. Also, we have demonstrated that these reactions can be carried out in water using a slightly modified water-soluble catalyst as an alternative to volatile organic solvents.

Experimental Section

Materials.

Except when otherwise stated, all reagents were purchased from Alfa Aesar and used without further purification. Acetonitrile (CH_3CN) and dichloromethane (DCM) were purchased from BDH, stored under argon, and dispensed from a solvent purification system. Ethyl acetate was purchased from EMD. Hexanes was purchased in bulk from Macron and used without further purification. The *tert*-Butyl hydroperoxide oxidant (70 % in H_2O or 5.5 M in decane) was purchased from Sigma Aldrich and refrigerated. Deuterated chloroform ($CDCl_3$) was purchased from Cambridge Isotopes.

Instrumentation.

^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ at 600 or 400 MHz instrument; chemical shifts (δ) were reported in parts per million (ppm) relative to Me_4Si. Chromatographic purifications were performed using Fisher (60 Å, 70-230 mesh) silica gel. HRMS data were collected with electronspray ionization. GC analysis was performed on a Thermo Scientific Trace GC Ultra instrument with flame ionization detector (FID).

Synthesis.

6,7-diamino-2-quinoxalinol.

Following a modification of published procedure.[48] 1,5-difluoro-2,4,-dinitrobenzene (4.0 mmol), L-leucine methyl ester (4.0 mmol) were added to a round bottom flask (150 mL) containing ethanol (30 mL) and THF (30 mL). Diisopropylethylamine (8.8 mmol) was added and the reaction mixture was stirred for 24 h at room temperature. Ammonium hydroxide (30 mmol) was added and the reaction continued to stir at room temperature for an additional 24 h. The solvent was removed under reduced pressure to produce a viscous yellow oil. The oil was dissolved in ethanol (40 mL), ammonium formate (80 mmol), and 5 % Pd-C (1.24 g) was added. The reaction was brought to reflux for 2 h and filtered through celite. The filtrate was concentrated under reduced pressure. The product was purified by flash column chromatography (8:2:1 ethyl acetate/hexanes/ethanol) to yield a dark yellow solid (75%) that matched the reported ^{1}H and ^{13}C NMR spectrum.[49]

2-quinoxalinol salen (salqu) ligand.

6,7-diamino-2-quinoxalinol (0.88 mmol) was charged in a round bottom flask (100 mL) containing methanol (20 mL), 3,5-di-tert-butyl-2-hydroxybenzaldehyde (3.53 mmol), and trifluoracetic acid (2 drops). The reaction was heated to reflux and stirred for 4 h. Once cooled to room temperature, the precipitate was filtered and washed with cold methanol 3 times to yield a yellow solid (79 %) that matched the reported ^{1}H and ^{13}C NMR spectrum.[49]

Copper(II) Salqu (Complex 1).

Following a modification of previously published procedure.[48] 2-quinoxalinol salen (0.7 mmol) was charged in a round bottom flask (250 mL) containing methanol (60 mL), dichloromethane (60 mL) and triethylamine (0.5 mL). $Cu(OAc)_2$ (0.77 mmol) was dissolved and the reaction mixture was heated to reflux and stirred for 5 h. The precipitate was washed with water and cold ether 3 times each to yield a dark red solid (81 %).

2-quinoxalinol salen (sulfosalqu) copper(II) complex 2.

The Cu(II) sulfosalqu complex **2** was synthesized and characterized following a modified published procedure.[39]

1-(Trimethylsilyl)-1-hexyne (3g).

1-hexyne (25 mmol, 2.87 mL) was added to a round bottom flask (100 mL) containing THF (25 mL), the reaction was cooled to -78 °C and n-Butyllithium (27.5 mmol, 10.58 mL) was added dropwise over 1 h. Next, TMSCl (25 mmol, 3.27 mL) was added to the reaction, the temperature was maintained at -78 °C for 0.5 h and slowly raised to room temperature over 1 h. The reaction was then quenched with NH_4Cl (aq) and extracted with

Et_2O three times. The product was then dried over $MgSO_4$ and matched the previously published spectra.[36]

Representative procedure for propargylic oxidations.

2-quinoxalinol salen (1 mol %) was added to a round bottom flask (25 mL), followed by CH_3CN (10 mL), alkyne (0.5 mmol), and dropwise addition TBHP (4 equiv). The reaction was heated to 70 °C and stirred for 4 h. The solvent was then evaporated under reduced pressure and the product was purified by flash column chromatography on silica gel (95:5 hex/EtOAc) to afford a clear or yellow oil.

1-Pentyn-3-one, 1-phenyl: R*f* 0.2 (95:5 hexanes/EtOAc); **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 7.56-7.58 (m, 2H), 7.36-7.47 (m, 3H), 2.70 (q, 2H), 1.22 (t, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ: 188.7, 133.0, 130.7, 128.6, 120.0, 90.7, 87.6, 38.9, 8.2.

3-Butyn-2-one, 4-phenyl: R*f* 0.22 (95:5 hexanes/EtOAc); **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 7.57-7.58 (m, 2H), 7.45-7.48 (m, 1H), 7.38-7.40 (m, 2H), 2.46 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ: 184.7, 133.1, 130.8, 128.6, 119.9, 90.3, 88.3, 32.8.

4-Octyn-3-one: R*f* 0.6 (95:5 hexanes/EtOAc); **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 2.55 (q, 2H), 2.34 (t, 2H), 1.61 (q, 2H), 1.14 (t, 3H), 1.02 (t, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ: 188.9, 94.1, 80.8, 38.8, 21.3, 20.9, 13.4, 8.1.

2-Propyn-1-one, 1-phenyl: R*f* 0.4 (95:5 hexanes/EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ: 8.08-8.10 (m, 2H), 7.54-7.58 (m, 1H), 7.41-7.45 (m, 2H), 3.37 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ: 177.4, 136.2, 134.5, 129.7, 128.7, 80.8, 80.3.

2-Propyn-1-one, 1-cyclohexyl: HRMS (EI): *m/z* calcd. for $C_9H_{12}O$ 136.0888, found 136.0903.

1-Hexyn-3-one: HRMS (EI): *m/z* calcd. for, C_6H_7O 95.0497, found 95.0487.

1-Hexyn-3-one, 1-(trimethylsilyl): HRMS (EI): *m/z* calcd. for, $C_8H_{13}OSi$ 153.0742, found 153.0736.

References

(1) Shang, R.; Ilies, L.; Asako, S.; Nakamura, E. Iron-Catalyzed C(Sp2)–H Bond Functionalization with Organoboron Compounds. *J. Am. Chem. Soc.* **2014**, *136* (41), 14349–14352. https://doi.org/10.1021/ja5070763.

(2) Hwang, H.; Kim, J.; Jeong, J.; Chang, S. Regioselective Introduction of Heteroatoms at the C-8 Position of Quinoline N-Oxides: Remote C–H Activation Using N-Oxide as a Stepping Stone. *J. Am. Chem. Soc.* **2014**, *136* (30), 10770–10776. https://doi.org/10.1021/ja5053768.

(3) Yang, G.; Lindovska, P.; Zhu, D.; Kim, J.; Wang, P.; Tang, R.-Y.; Movassaghi, M.; Yu, J.-Q. Pd(II)-Catalyzed Meta-C–H Olefination, Arylation, and Acetoxylation of Indolines Using a U-Shaped Template. *J. Am. Chem. Soc.* **2014**, *136* (30), 10807–10813. https://doi.org/10.1021/ja505737x.

(4) Xiao, K.-J.; Lin, D. W.; Miura, M.; Zhu, R.-Y.; Gong, W.; Wasa, M.; Yu, J.-Q. Palladium(II)-Catalyzed Enantioselective C(Sp3)–H Activation Using a Chiral Hydroxamic Acid Ligand. *J. Am. Chem. Soc.* **2014**, *136* (22), 8138–8142. https://doi.org/10.1021/ja504196j.

(5) Chan, K. S. L.; Fu, H.-Y.; Yu, J.-Q. Palladium(II)-Catalyzed Highly Enantioselective C–H Arylation of Cyclopropylmethylamines. *J. Am. Chem. Soc.* **2015**, *137* (5), 2042–2046. https://doi.org/10.1021/ja512529e.

(6) Chen, G.; Gong, W.; Zhuang, Z.; Andrä, M. S.; Chen, Y.-Q.; Hong, X.; Yang, Y.-F.; Liu, T.; Houk, K. N.; Yu, J.-Q. Ligand-Accelerated Enantioselective Methylene C(Sp3)–H Bond Activation. *Science* **2016**, *353* (6303), 1023–1027. https://doi.org/10.1126/science.aaf4434.

(7) Yeon Ryu, J.; Heo, S.; Park, P.; Nam, W.; Kim, J. Alkyne Oxidation by Nonheme Iron Catalysts and Hydroperoxides. *Inorg. Chem. Commun.* **2004**, *7* (4), 534–537. https://doi.org/10.1016/j.inoche.2004.02.010.

(8) Nait Ajjou, A.; Ferguson, G. An Unprecedented Highly Efficient Solvent-Free Oxidation of Alkynes to α,β-Acetylenic Ketones with Tert-Butyl Hydroperoxide Catalyzed by Water-Soluble Copper Complex. *Tetrahedron Lett.* **2006**, *47* (22), 3719–3722. https://doi.org/10.1016/j.tetlet.2006.03.140.

(9) Zhao, Y.; Ng, A. W. T.; Yeung, Y.-Y. Mild Propargylic Oxidation Using a Diacetoxyiodobenzene/Tert-Butyl Hydroperoxide Protocol. *Tetrahedron Lett.* **2014**, *55* (31), 4370–4372. https://doi.org/10.1016/j.tetlet.2014.06.032.

(10) Pérollier, C.; Sorokin, A. B. Preparation of α,β-Acetylenic Ketones by Catalytic Heterogeneous Oxidation of Alkynes. *Chem. Commun.* **2002**, *0* (14), 1548–1549. https://doi.org/10.1039/B204122G.

(11) McLaughlin, E. C.; Doyle, M. P. Propargylic Oxidations Catalyzed by Dirhodium Caprolactamate in Water: Efficient Access to α,β-Acetylenic Ketones. *J. Org. Chem.* **2008**, *73* (11), 4317–4319. https://doi.org/10.1021/jo800382p.

(12) Horn, E. J.; Rosen, B. R.; Chen, Y.; Tang, J.; Chen, K.; Eastgate, M. D.; Baran, P. S. Scalable and Sustainable Electrochemical Allylic C–H Oxidation. *Nature* **2016**, *533* (7601), 77–81. https://doi.org/10.1038/nature17431.

(13) Li, P.; Fong, W. M.; Chao, L. C. F.; Fung, S. H. C.; Williams, I. D. A Convenient Synthesis of α,β-Acetylenic Ketones. *J. Org. Chem.* **2001**, *66* (11), 4087–4090. https://doi.org/10.1021/jo015534c.

(14) Tseng, J.-C.; Chen, J.-H.; Luh, T.-Y. A Convenient Synthesis of Tetrasubstituted Furans from Propargylic Dithioacetals. *Synlett* **2006**, *2006* (08), 1209–1212. https://doi.org/10.1055/s-2006-939686.

(15) Zhang, X.; Sarkar, S.; Larock, R. C. Synthesis of Naphthalenes and 2-Naphthols by the Electrophilic Cyclization of Alkynes. *J. Org. Chem.* **2006**, *71* (1), 236–243. https://doi.org/10.1021/jo051948k.

(16) Van den Hoven, B. G.; Ali, B. E.; Alper, H. Chemo- and Regioselective Cyclohydrocarbonylation of α-Keto Alkynes Catalyzed by a Zwitterionic Rhodium Complex and Triphenyl Phosphite. *J. Org. Chem.* **2000**, *65* (13), 4131–4137. https://doi.org/10.1021/jo000230w.

(17) Karpov, A. S.; Müller, T. J. J. Straightforward Novel One-Pot Enaminone and Pyrimidine Syntheses by Coupling-Addition-Cyclocondensation Sequences. *Synthesis* **2003**, *2003* (18), 2815–2826. https://doi.org/10.1055/s-2003-42480.

(18) Trost, B. M.; Sorum, M. T.; Chan, C.; Rühter, G. Palladium-Catalyzed Additions of Terminal Alkynes to Acceptor Alkynes. *J. Am. Chem. Soc.* **1997**, *119* (4), 698–708. https://doi.org/10.1021/ja9624937.

(19) Lumbroso, A.; Catak, S.; Sulzer-Mossé, S.; De Mesmaeker, A. Efficient Access to Functionalized Cyclobutanone Derivatives Using Cyclobuteniminium Salts as Highly Reactive Michael Acceptors. *Tetrahedron Lett.* **2015**, *56* (19), 2397–2401. https://doi.org/10.1016/j.tetlet.2015.02.112.

(20) G. Kundu, N.; K. Dasgupta, S. Synthesis of 5-(Acylethynyl)Uracils and Their Corresponding 2′-Deoxyribonucleosides through Palladium-Catalysed Reactions.

J. Chem. Soc. Perkin 1 **1993**, *0* (21), 2657–2663. https://doi.org/10.1039/P19930002657.

(21) Thompson, C. F.; Jamison, T. F.; Jacobsen, E. N. FR901464: Total Synthesis, Proof of Structure, and Evaluation of Synthetic Analogues. *J. Am. Chem. Soc.* **2001**, *123* (41), 9974–9983. https://doi.org/10.1021/ja016615t.

(22) Ghosh, A. K.; Chen, Z.-H.; Effenberger, K. A.; Jurica, M. S. Enantioselective Total Syntheses of FR901464 and Spliceostatin A and Evaluation of Splicing Activity of Key Derivatives. *J. Org. Chem.* **2014**, *79* (12), 5697–5709. https://doi.org/10.1021/jo500800k.

(23) Nakajima, H.; Hori, Y.; Terano, H.; Okuhara, M.; Manda, T.; Matsumoto, S.; Shimomura, K. New Antitumor Substances, FR901463, FR901464 and FR901465. *J. Antibiot. (Tokyo)* **1996**, *49* (12), 1204–1211. https://doi.org/10.7164/antibiotics.49.1204.

(24) Adlington, R. M.; Baldwin, J. E.; Pritchard, G. J.; Spencer, K. C. Synthesis of Novel C-Nucleosides with Potential Applications in Combinatorial and Parallel Synthesis. *Tetrahedron Lett.* **2000**, *41* (4), 575–578. https://doi.org/10.1016/S0040-4039(99)02078-X.

(25) Jan Štambaský; Hocek, M.; Pavel Kočovský. C-Nucleosides: Synthetic Strategies and Biological Applications. *Chem. Rev.* **2009**, *109* (12), 6729–6764. https://doi.org/10.1021/cr9002165.

(26) Weerasiri, K. C.; Gorden, A. E. V. Oxidation of Propargylic Alcohols with a 2-Quinoxalinol Salen Copper(II) Complex and Tert-Butyl Hydroperoxide. *Eur. J. Org. Chem.* **2013**, *2013* (8), 1546–1550. https://doi.org/10.1002/ejoc.201201394.

(27) Yu, J.-Q.; Corey, E. J. A Mild, Catalytic, and Highly Selective Method for the Oxidation of α,β-Enones to 1,4-Enediones. *J. Am. Chem. Soc.* **2003**, *125* (11), 3232–3233. https://doi.org/10.1021/ja0340735.

(28) Catino, A. J.; Forslund, R. E.; Doyle, M. P. Dirhodium(II) Caprolactamate: An Exceptional Catalyst for Allylic Oxidation. *J. Am. Chem. Soc.* **2004**, *126* (42), 13622–13623. https://doi.org/10.1021/ja045330o.

(29) Kornblum, N.; DeLaMare, H. E. THE BASE CATALYZED DECOMPOSITION OF A DIALKYL PEROXIDE. *J. Am. Chem. Soc.* **1951**, *73* (2), 880–881. https://doi.org/10.1021/ja01146a542.

(30) Wu, X.-F.; Gong, J.-L.; Qi, X. A Powerful Combination: Recent Achievements on Using TBAI and TBHP as Oxidation System. *Org. Biomol. Chem.* **2014**, *12* (31), 5807–5817. https://doi.org/10.1039/C4OB00276H.

(31) Chen, R.; Chen, J.; Zhang, J.; Wan, X. Combination of Tetrabutylammonium Iodide (TBAI) with Tert-Butyl Hydroperoxide (TBHP): An Efficient Transition-Metal-Free System to Construct Various Chemical Bonds. *Chem. Rec.* **2018**, *18* (9), 1292–1305. https://doi.org/10.1002/tcr.201700069.

(32) Achord, J. M.; Hussey, C. L. Determination of Dissolved Oxygen in Nonaqueous Electrochemical Solvents. *Anal. Chem.* **1980**, *52* (3), 601–602. https://doi.org/10.1021/ac50053a061.

(33) Li, Y.; Lee, T. B.; Wang, T.; Gamble, A. V.; Gorden, A. E. V. Allylic C–H Activations Using Cu(II) 2-Quinoxalinol Salen and Tert-Butyl Hydroperoxide. *J. Org. Chem.* **2012**, *77* (10), 4628–4633. https://doi.org/10.1021/jo300372q.

(34) Muzart, J.; Piva, O. Oxidation of Alkynes into Conjugated Acetylenic Ketones with Tert-Butyl Hydroperoxide Catalyzed by ChromiumVI Oxide. *Tetrahedron Lett.* **1988**, *29* (19), 2321–2324. https://doi.org/10.1016/S0040-4039(00)86048-7.

(35) Glaser, C. Untersuchungen Über Einige Derivate Der Zimmtsäure. *Justus Liebigs Ann. Chem.* **1870**, *154* (2), 137–171. https://doi.org/10.1002/jlac.18701540202.

(36) Blug, M.; Piechaczyk, O.; Fustier, M.; Mézailles, N.; Le Floch, P. Protodesilylation of 2,6-Disubstituted Silyphosphinines. Experimental and Theoretical Study. *J. Org. Chem.* **2008**, *73* (8), 3258–3261. https://doi.org/10.1021/jo800105b.

(37) McConvey, I. F.; Woods, D.; Lewis, M.; Gan, Q.; Nancarrow, P. The Importance of Acetonitrile in the Pharmaceutical Industry and Opportunities for Its Recovery from Waste. *Org. Process Res. Dev.* **2012**, *16* (4), 612–624. https://doi.org/10.1021/op2003503.

(38) Hartonen, K.; Riekkola, M.-L. Chapter 2 - Water as the First Choice Green Solvent. In *The Application of Green Solvents in Separation Processes*; Pena-Pereira, F., Tobiszewski, M., Eds.; Elsevier, 2017; pp 19–55. https://doi.org/10.1016/B978-0-12-805297-6.00002-4.

(39) Weerasiri, K. C.; Gorden, A. E. V. Cu(II) 2-Quinoxalinol Salen Catalyzed Oxidation of Propargylic, Benzylic, and Allylic Alcohols Using Tert-Butyl Hydroperoxide in Aqueous Solutions. *Tetrahedron* **2014**, *70* (43), 7962–7968. https://doi.org/10.1016/j.tet.2014.08.050.

(40) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. "On Water": Unique Reactivity of Organic Compounds in Aqueous Suspension.

Angew. Chem. Int. Ed. **2005**, *44* (21), 3275–3279. https://doi.org/10.1002/anie.200462883.

(41) Stahl, S. S.; Alsters, P. L. *Liquid Phase Aerobic Oxidation Catalysis: Industrial Applications and Academic Perspectives*; John Wiley & Sons, 2016.

(42) Osterberg, P. M.; Niemeier, J. K.; Welch, C. J.; Hawkins, J. M.; Martinelli, J. R.; Johnson, T. E.; Root, T. W.; Stahl, S. S. Experimental Limiting Oxygen Concentrations for Nine Organic Solvents at Temperatures and Pressures Relevant to Aerobic Oxidations in the Pharmaceutical Industry. *Org. Process Res. Dev.* **2015**, *19* (11), 1537–1543. https://doi.org/10.1021/op500328f.

(43) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press, 1998.

(44) Simon, M.-O.; Li, C.-J. Green Chemistry Oriented Organic Synthesis in Water. *Chem. Soc. Rev.* **2012**, *41* (4), 1415–1427. https://doi.org/10.1039/C1CS15222J.

(45) Lindström, U. M. Stereoselective Organic Reactions in Water. *Chem. Rev.* **2002**, *102* (8), 2751–2772. https://doi.org/10.1021/cr010122p.

(46) Chanda, A.; Fokin, V. V. Organic Synthesis "On Water." *Chem. Rev.* **2009**, *109* (2), 725–748. https://doi.org/10.1021/cr800448q.

(47) Butler, R. N.; Coyne, A. G.; Cunningham, W. J.; Moloney, E. M. Water and Organic Synthesis: A Focus on the In-Water and On-Water Border. Reversal of the In-Water Breslow Hydrophobic Enhancement of the Normal Endo-Effect on Crossing to On-Water Conditions for Huisgen Cycloadditions with Increasingly Insoluble Organic Liquid and Solid 2π-Dipolarophiles. *J. Org. Chem.* **2013**, *78* (7), 3276–3291. https://doi.org/10.1021/jo400055g.

(48) Li, Y.; Wu, X.; Lee, T. B.; Isbell, E. K.; Parish, E. J.; Gorden, A. E. V. An Effective Method for Allylic Oxidation of Δ5-Steroids Using Tert-Butyl Hydroperoxide. *J. Org. Chem.* **2010**, *75* (5), 1807–1810. https://doi.org/10.1021/jo902637k.

(49) Wu, X.; Gorden, A. E. V. An Efficient Method for Solution-Phase Parallel Synthesis of 2-Quinoxalinol Salen Schiff-Base Ligands. *J. Comb. Chem.* **2007**, *9* (4), 601–608. https://doi.org/10.1021/cc070021q.

Chapter 3 Cu(II) Salen Type Ligands for Oxidation Reactions

Introduction

Previous research has demonstrated the use of a copper 2-quinoxalinol salen (Cu(II)-salqu) metal complex (**complex 1**) as an oxidative catalyst. **Complex 1**, in combination with TBHP, has proven of use in many types of oxidation catalysis including, allylic, benzylic, and propargylic oxidations with yields ranging from 36-99 % (**Figure 3.1**).[1–7] Also, the Cu(II)-salqu (**complex 1**) was found to be air stable and easy to prepare utilizing inexpensive, earth abundant transition metal copper.[8] These reactions are very selective for the corresponding ketone in examples where oxidation could also form an alcohol, epoxide, or carboxylic acid. Cu(II)-salqu (**complex 1**) oxidation reactions are typically carried out in acetonitrile, but a water soluble analogue has also been prepared with similar high-yielding results (41-99 % yield).[2] Although these oxidations work well on many substrates, some of these reactions require longer reactions times (18 h) and produce only modest yields (47 %).

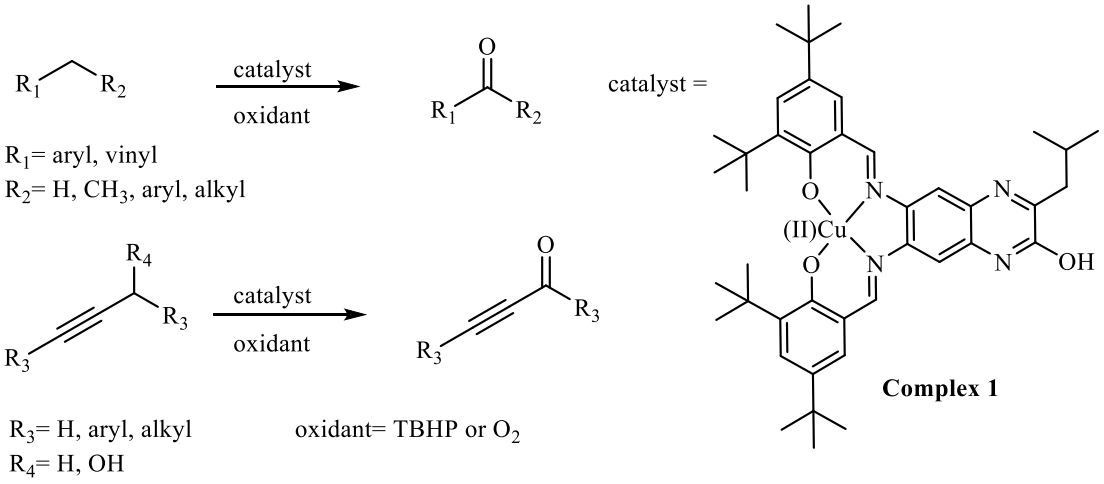


Figure 3.1. Previous catalytic oxidations with Cu(II) salqu (**complex 1**).

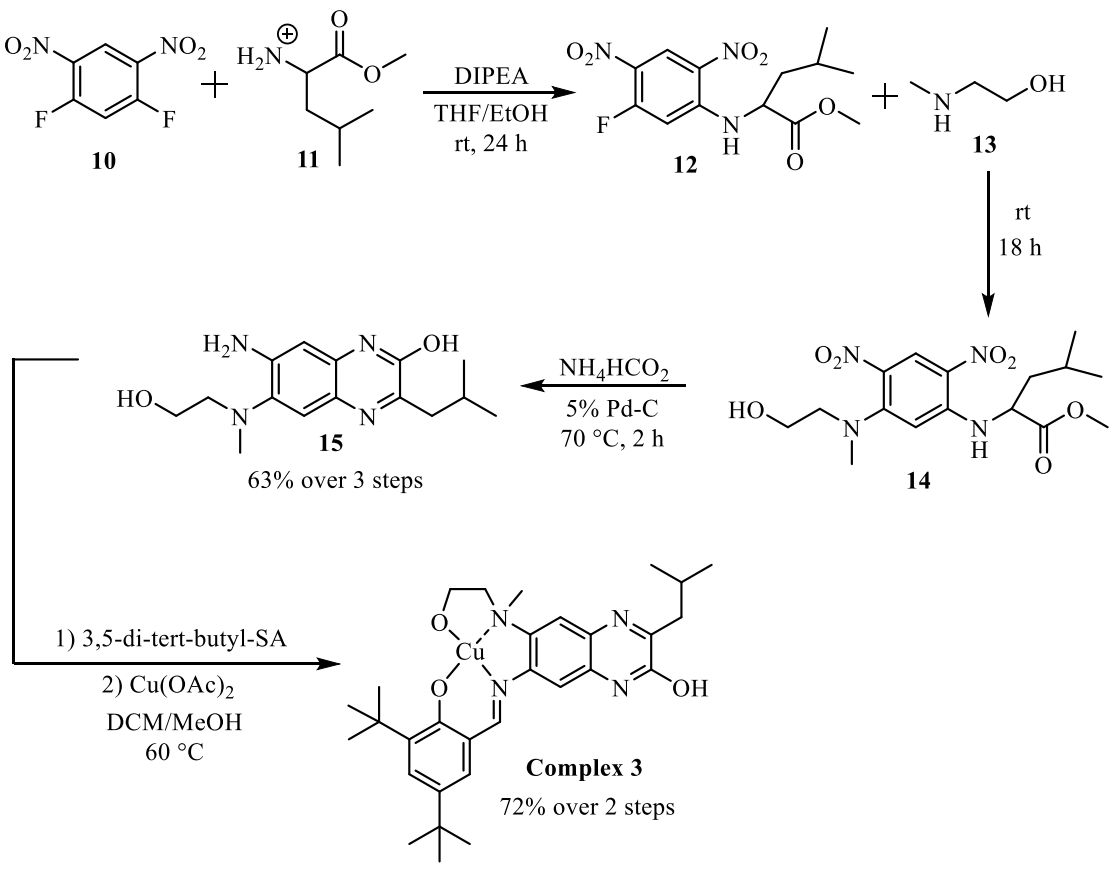
Previous studies with Cu(II)-salqu (**complex 1**) suggest that the metal changes oxidation states from Cu(II) to either Cu(I) or Cu(III).[3,7] If copper is being reduced to copper(I), this could help explain some of the reactions that result in lower yield. The rigid binding site of salqu requires the copper to be square planar, which is a preferred geometry for d^9 Cu(II), but d^{10} Cu(I) prefers to be in a tetrahedral coordination environment.[9] This could lead to the degradation of the catalyst with time, reducing turnover numbers with recycling of Cu(II)-salqu. Here, we have chosen to explore other derivatives and analogs of Cu(II)-salqu to better understand the role of this ligand and examine the catalytic pathway. In this chapter, the synthesis and characterization of two new copper complexes is carried out and tested as a catalyst for C-H oxidation reactions.

Results and Discussion

Flexible Binding Pocket (Complex 3)

In order to better understand the reaction mechanism, we envisioned modifying the coordination site of the Cu(II)-salqu (**complex 1**) catalyst by introducing a flexible chelating arm on one side of the ligand. In doing so, this would allow the copper to adopt different geometries during the course of the reaction more readily rather than being fixed into a square planar environment. One way to add this flexible pocket would be to replace one of the salicylaldehyde arms with an ethanolic arm (i.e. **complex 3**). We reasoned that this would increase the rates of our reactions and possibly lead to improved yields in some cases.

The "salflex" catalyst (**complex 3**) was synthesized through a series of reactions starting with commercially available 1,5-difluoro-2,4-dinitrobenzene (**10**) and L-leucine methyl ester (**11**) (**Scheme 3.1**). Substitution yields compound **12** which is subsequently subjected to a second substitution reaction using methyl amino ethanol (**13**), followed by reductive cyclization with ammonium formate and Pd/C to provide the key intermediate **15** in 63 % yield. Compound **15** was isolated and characterized by ^{1}H NMR. With **15** in hand, it was next attempted to template the asymmetric complex by using $Cu(acac)_2$ followed by the addition of 3,5-ditertbutylsalicylaldehyde (SA); however, this route proved inefficient resulting in poor yields and producing multiple impurities. **Complex 3** was successfully synthesized by first reacting the salicylaldehyde and **15**, which can be isolated by recrystallization, and then subsequently complexing the Cu(II) salt.



Scheme 3.1. Synthesis of Cu(II) salflex (**complex 3**) with a less rigid binding pocket.

Comparing the UV-Vis spectra of the salflex free base ligand with the purified copper complex (**complex 3**) shows the binding of the copper to the free base ligand (**Figure 3.2**). The free base ligand has an absorbance feature at 314 nm ($\varepsilon = 2.25 \times 10^4$ cm^{-1} M^{-1}) corresponding to the π-π* excitation. A second absorbance feature is present in the ligand at 400 nm ($\varepsilon = 2.13 \times 10^4$ cm^{-1} M^{-1}) which we attribute to intra-ligand charge transfer (ILCT). The Cu(II)-salflex (**complex 3**) exhibits a ligand to metal charge transfer (LMCT) at 490 nm ($\varepsilon = 2.26 \times 10^4$ cm^{-1} M^{-1}) with a hypsochromic shift from the ligand peak by 31

nm. The LMCT suggests that copper is bound to the ligand. Due to the paramagnetic nature of Cu(II), complex 3 was also confirmed by HRMS and elemental analysis.

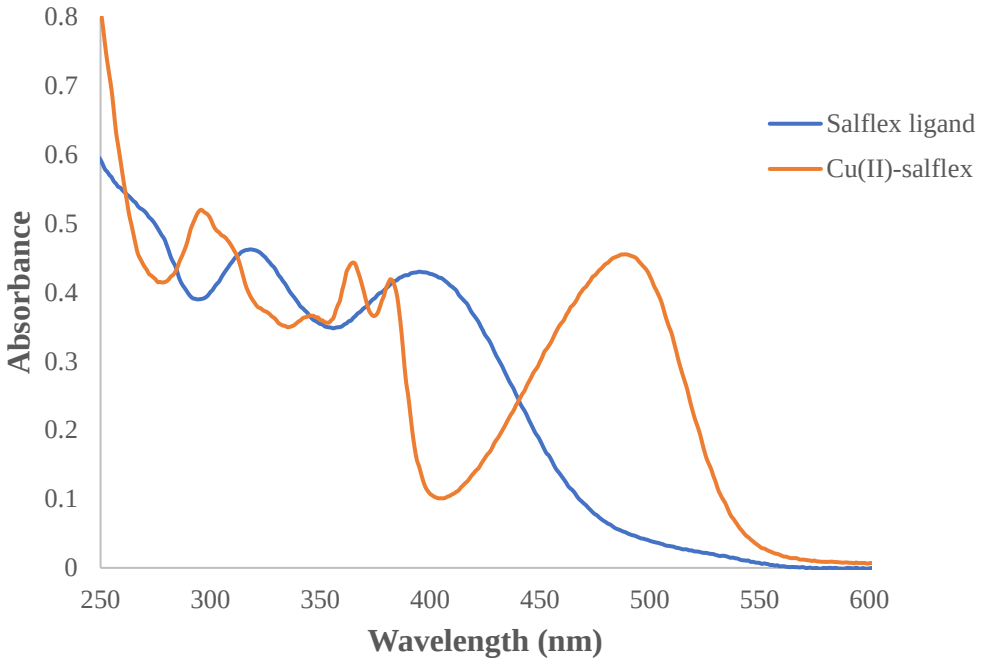
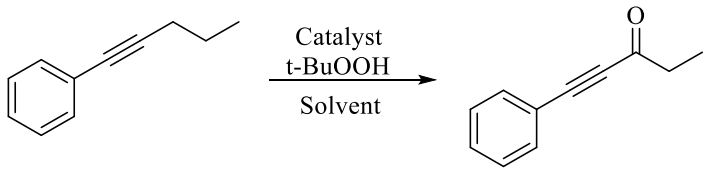


Figure 3.2. UV-Vis spectral changes of salflex ligand and Cu(II) salflex (**complex 3**) at 20 μM concentrations in DCM.

With this new catalyst in hand, investigations began on the oxidation of propargylic C-H bonds with **complex 3**. This allows for a direct comparison to the results obtained in chapter 2 of this dissertation. For this comparison, we choose to use 1-phenyl-1-pentyne as the model substrate. The reaction conditions developed with **complex 1** for the same reaction were tested- acetonitrile, TBHP (4 eq), 70 °C, for 4 h.[7] Here, we see a substantial decrease in the yield (38 %) of the corresponding α,β-acetylenic ketone as compared to when **complex 1** is used as the catalyst (78 %) (**Table 3.1** entries 1 and 7). Due to the

unreacted starting material found at the 4 h time point, we experimented with increasing the reaction time to 18 h, which did not increase the reaction yield (**Table 3.1** entry 2). Increasing the catalyst loading to 2 mol % (**complex 3**) and decreasing the temperature (50 °C) led to improved product yields (entries 3 and 4). However, a further increase of **complex 3** (up to 5 mol %) did not provide an increase in yield. When DCM is used as the solvent, a decrease in yield is observed (entry 6).

Table 3.1. Optimization of propargylic oxidations with **complex 3**



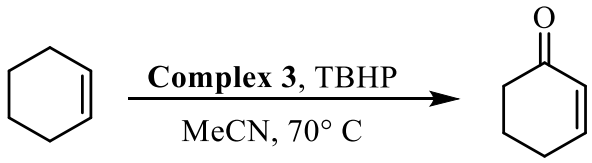
Entry	Catalyst[a]	Solvent	T °C	Time	Yield (%)[c]
1	**Complex 3**	MeCN	70	4 h	38
2	**Complex 3**	MeCN	70	18	36
3	**Complex 3** (2 mol %)	MeCN	50	3 h	47
4	**Complex 3** (2 mol %)	MeCN	50	5 h	54
5	**Complex 3** (5 mol %)	MeCN	50	4 h	45
6	**Complex 3**	DCM	40	4 h	22
7	**Complex 1**	MeCN	70	4 h	78

[a] 1 mol % unless otherwise stated, open to air. [b] 50 mol %. [c] GC yields using internal standard method.

The results from the oxidation of propargylic C-H bonds between **complex 1** and **3** show that when introducing the nonrigid binding pocket, a decrease in oxidative capability is observed. Another comparison can be made with the oxidation of allylic C-H bonds between **complex 1** and **complex 3**. To confirm this observation, we tested **complex 3** for

the allylic oxidation of cyclohexene. Using 3 equivalents of *tert*-butylhydroperoxide (TBHP) and 0.5 mol % catalyst (**complex 3**), a 25 % yield of the desired cyclohexanone product was produced in 1 h. In order to optimize these results, several different reaction conditions were screened (summary of results in **Table 3.2**). An increased catalyst loading (1 mol %) did not increase the overall yield. Also, running the reaction at 24 h as opposed to 1 did not increase the yield (23 %). Adding 1 equivalent of base, potassium carbonate (K_2CO_3) in this example, slightly increased the yield to 28 %. While still not a high yield, we began examining the effects of changing solvent. During this optimization, the highest yield obtained with **complex 3** was a mere 33 % in DCM at room temperature and 1 equivalent of K_2CO_3.

Table 3.2. Optimization of allylic oxidation with **complex 3**.



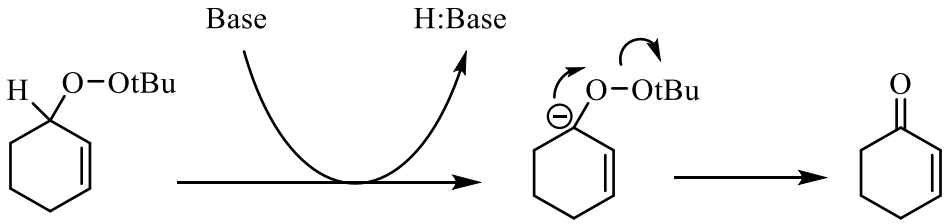
Entry[a]	**Complex 3**	Solvent	T °C	Time (h)	Additive	Yield[b] (%)
1	(0.5 mol %)	MeCN	70	1		25
2	(1 mol %)	MeCN	70	1		24
3	(0.5 mol %)	MeCN	70	24		23
4	(0.5 mol %)	MeCN	70	1	K_2CO_3	28
5	(0.5 mol %)	DCM	40	1		12
6	(0.5 mol %)	DCM	40	24		20
7	(0.5 mol %)	DCM	25	1	K_2CO_3	22
8	(0.5 mol %)	DCM	25	24	K_2CO_3	33
9	**Complex 1** (0.5 mol %)	MeCN	70	1		74
10	**Complex 1** (0.5 mol %)	MeCN	70	1	K_2CO_3	63

[a]Reaction conditions: Cyclohexene (0.5 mmol), solvent (10 mL), TBHP (1.5 mmol), complex 3 (0.5-1.0 mol %). [b]GC yield using internal standard.

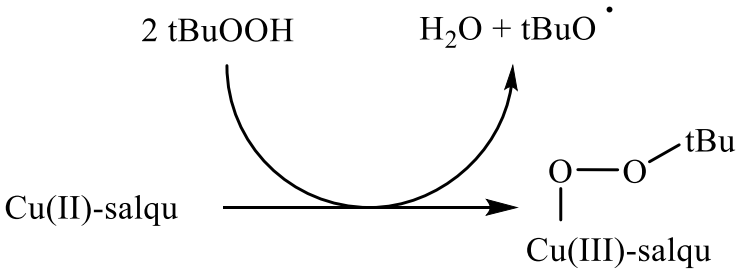
Comparing the results of allylic oxidation with **complex 3** to results obtained with Cu(II)-salqu (**complex 1**), shows a significant decrease in yield when the flexible binding pocket is introduced (**Table 3.2** entry 9). From this observation, we can draw several hypotheses. One explanation is the introduction of the flexible binding pocket eliminates one of the Schiff bases found in Cu(II)-salqu (**complex 1**). Also, the extended conjugation of Cu(II)-salqu (**complex 1**) is much greater than that of **complex 3**. This extended conjugation can help stabilize the metal center throughout the reaction pathway by allowing better spin density dispersion from the metal to the ligand. Another hypothesis is that copper(I) is not formed in the **complex 1** oxidation mechanism but rather a copper(III) species. In fact, **complex 3** could follow a different mechanism due to the ability to adapt a tetrahedral geometry.

When base (K_2CO_3) is added to the reaction containing **complex 3**, we see a slight increase in product yield; however, when base is added to the Cu(II)-salqu (**complex 1**) reaction, we see a decrease in product yield (**Table 3.2** entry 10). **Complex 3** could follow a more traditional pathway involving the accelerated decomposition of *tert*-butylperoxy ether in basic conditions (**Scheme 3.3**).[10,11] However, the lack of evidence of acceleration with base for Cu(II)-salqu (**complex 1**) means that the decomposition of *tert*-butylperoxy ether is either not a rate determining step or does not take place in the mechanism. Instead, **complex 1** could be oxidized to Cu(III) in the first step (**Scheme 3.4**). The formation of Cu(III) can be stabilized by the non-innocent salqu ligand.[12] From here, the Cu(III) species can undergo homolytic cleavage of the peroxide to form a tBu-$O^{\cdot}$. One way to test this hypothesis would be to map the reaction energies computationally; however, the large framework of Cu(II) salqu (**complex 1**) has proven difficult for these type of calculations.

To address this, we are looking into decreasing the complexity of the ligand for a model system.



Scheme 3.2. Base accelerated decomposition of tert-butylperoxy ether.

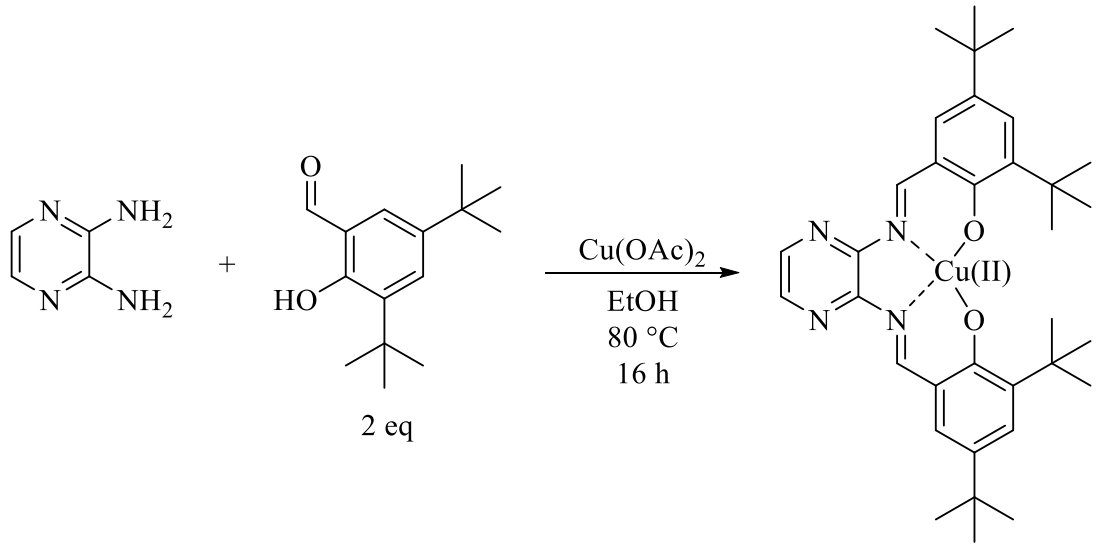


Scheme 3.3. Oxidation of **complex 1** to copper(III) with TBHP.

Pyrasal Ligand (complex 4)

An additional modification of salqu can be made through derivatization of the 2-quinoxalinol backbone. Here, we decided to synthesize a ligand containing a pyrazine backbone (**complex 4**). This new ligand can act as a model of salqu for testing the importance of the heterocyclic backbone and to reduce the number of steps required for catalyst synthesis. Direct comparisons can be made for the C-H oxidation of diphenylmethane with a library of different copper(II) containing salen derivatives.

Complex 4 was synthesized utilizing two methods with similar results, either templating $Cu(OAc)_2$ with diaminopyrazine and 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde or by preparing the ligand first and adding the copper in a second step (**Scheme 3.5**). A UV-Vis spectra of Cu(II) pyrasal (**complex 4**) was taken and compared to the free base pyrasal ligand (**Figure 3.3**). The metal complex has a new ligand to metal charge transfer (LMCT) at 455 nm ($\varepsilon = 1.52 \times 10^4$ cm^{-1} M^{-1}) with a hypsochromic shift from the ligand peak by 34 nm. The LMCT indicates that copper is bound to the ligand. HRMS and elemental analysis were also used to characterize **complex 4**.



Scheme 3.4. Synthesis of Cu(II) pyrasal (**complex 4**) by templation with $Cu(OAc)_2$.

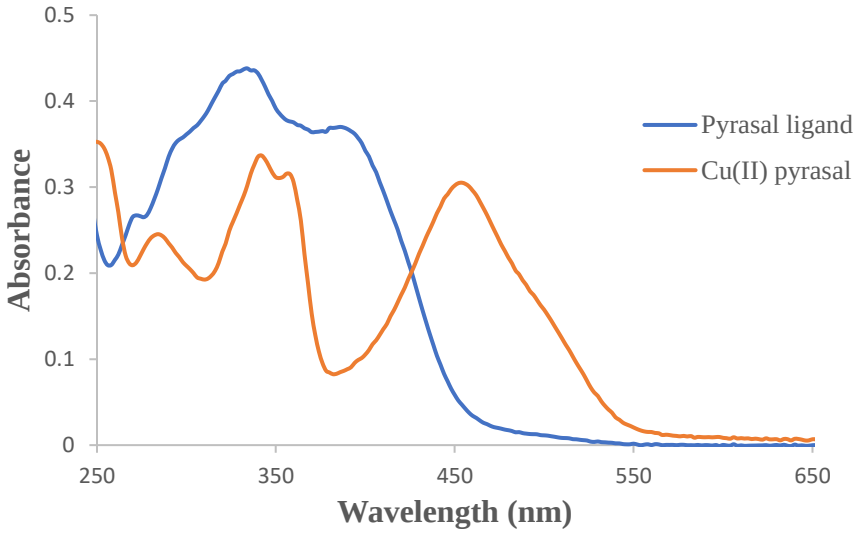


Figure 3.3. UV-Vis spectral changes of pyrasal ligand and Cu(II) pyrasal (**complex 4**) at 20 μM concentration in DCM.

With this new Cu(II) pyrasal (from pyrazine and salen) **complex 4** in hand, we began testing its efficiency as an oxidative catalyst. Cu(II) salen and Cu(II) salophen (salph) were also prepared in order to test and compare the oxidation of diphenylmethane.[13] The oxidation of diphenyl methane (2 mmol) was carried out using 3 equivalents of TBHP, 1 mol % catalyst in acetonitrile (2 mL) at 70 °C for 18 h. The isolated yields of this reaction can be summarized in **Figure 3.4**. Conditions for this reaction were kept the same for the different catalyst in order to directly compare the results.

When no catalyst is used, only 5 % of product is formed, showing that TBHP can affect the C-H oxidation without the use of catalyst but only in small yield. When simple copper salts, $Cu(OAc)_2$ and $CuCl_2$, are used in combination with TBHP, a large increase in product yield is obtained (60 and 55 %). The use of a simple salen ligand support does provide an additional slight increase in yield to 71 %. Further increasing the conjugation of the salen ligand to salophen (salph) provides a yield of 74 %. However, increasing the conjugation even further and incorporating the heterocyclic backbone of Cu(II)-salqu (**complex 1**) results in an almost quantitative yield of 99 %. The new Cu(II)-pyrasal ligand (**complex 4**) gave a yield of 87 %. The pyrazine backbone provides a better yield as compared to simple salen or salophen but it does not perform as well as Cu(II) salqu. When **complex 3** (Cu(II) salflex) is used, a decrease in yield is observed which is in agreement with our previous observations.

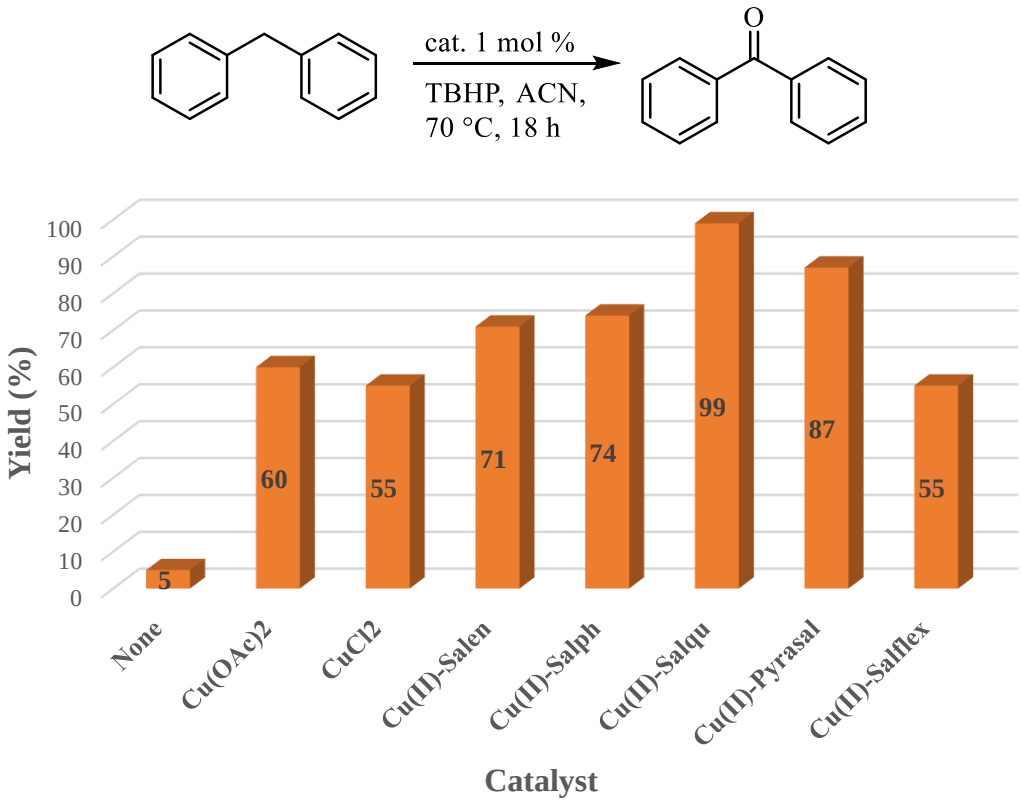


Figure 3.4. Reaction yields from benzylic oxidation of diphenylmethane.

Conclusions

The synthesis and characterization of two new salen type copper catalysts was achieved. These catalyst were used for C-H oxidation reactions and the results were compared to Cu(II) salqu (**complex 1**). In these results, we have shown that Cu(II)-salqu gives the best overall yield in the oxidation of allylic, propargylic, and benzylic C-H bonds when compared to the other salen catalyst. The introduction of a less rigid binding pocket (**complex 3**) led to a reduction in product yields. The heterocyclic backbone does help improve the oxidation yields as shown between Cu(II)-pyrasal (**complex 4**) and Cu(II)-

salph. Also, the smaller ligand framework of Cu(II)-pyrasal (**complex 4**) allows for future calculations to be done to help with understanding this mechanism.

Experimental

Materials.

Unless otherwise stated, reagents were purchased from Sigma Aldrich and used without further purification. The following reagents (source) were purchased 1,5-difluoro-2,4-dinitrobenzene (Matric Scientific), L-Leucine methyl ester (TCI), copper salts (Strem), 2,3-diaminopyrazine (Matrix Scientific), and 1-phenyl-1pentyne (Alfa Aesar). Acetonitrile (CH_3CN) and dichloromethane (DCM) were purchased from BDH, stored under argon, and dispensed from a solvent purification system. Ethyl acetate and methanol was purchased from EMD. Hexanes was purchased in bulk from Macron and used without further purification. *tert*-Butyl hydroperoxide was purchased from Sigma Aldrich and stored in a cool, dark area. Deuterated chloroform ($CDCl_3$) was purchased from Cambridge Isotopes.

Instrumentation.

^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ at 600 or 400 MHz instrument; chemical shifts (δ) were reported in parts per million (ppm) relative to Me_4Si. Chromatographic purifications were performed using Fisher (60 Å, 70-230 mesh) silica gel. HRMS data were collected with electronspray ionization. GC analysis was performed on a Thermo Scientific Trace GC Ultra instrument with flame ionization detector (FID).

UV measurements were done using a Cary 50 UV-Vis spectrometer with DCM as the solvent at room temperature.

Synthesis.

Cu(II)-salen and **Cu(II)-salph** were prepared following a previous published procedure.[14]

Cu(II)-salqu was synthesized following a previous published procedure.[6,8]

7-amino-6-[(2-hydroxyethyl)(methyl)amino]-3-(2-methylpropyl)quinoxalin-2-ol (15)

1,5-difluoro-2,4-dinitrobenzene (4.0 mmol), L-Leucine methyl ester (4.0 mmol), and *N,N*-Diisopropylethylamine (8.8 mmol) were added to a 150-mL round bottom flask charged with a stir bar and dissolved in 30 mL THF/ 30 mL EtOH. The reaction mixture was stirred at room temperature for 24 h. Next, 2-(Methylamino)ethanol (4 mmol) was added and stirred at room temperature for 24 h. The solvent was then evaporated under reduced pressure and EtOH (40 mL) was added to the reaction flask. Ammonium formate (80 mmol) and 5 % Pd-C (0.68 g) were added and the mixture was refluxed at 70 °C for 2 h. The solvent was removed under reduced pressure and the product was purified by flash column chromatography (EtOAc/hexane/EtOH 8:2:1, R_f 0.7); yield: 63 %. **^{1}H NMR (400 MHz, DMSO)**: δ 0.89 (d, 6 H), 2.14 (m, 1 H), 2.52 (d, 2 H), 2.62 (s, 3 H), 2.79 (t, 2 H), 3.54 (dd, 2 H), 5.89 (s, 2 H), 6.38 (s, 1 H), 7.16 (s, 1 H), 11.85 (s, 1 H). **HRMS** (ES) calcd. for $C_{15}H_{22}N_4O_2$ 291.1743, found 291.1501 $(M+H)^+$.

7-[(E)-[(3,5-di-tert-butyl-2hydroxyphenyl)methylidene]amino]-6-[(2-hydroxyethyl)(methyl)amino]-3-(2- methylpropyl) quinoxalin-2-ol

7-amino-6-[(2-hydroxyethyl)(methyl)amino]-3-(2-methylpropyl)quinoxalin-2-ol (0.5 mmol) and 3,5-Di-*tert*-butyl-2-hydroxybenzaldehyde (0.75 mmol) were added to a 100-mL round bottom flask charged with a stir bar and 40 mL MeOH. One drop of acetic acid was added and the reaction mixture was heated to reflux at 70 °C for 8 h. The solvent was then removed under reduced pressure and the product was purified by flash column chromatography (3:1 EtOAc/hexane, R_f 0.8); yield: 72 %. **^{1}H NMR (400 MHz, DMSO)**: δ 1.08 (d, 6 H), 1.38 (s, 9 H), 1.51 (s, 9 H), 1.64 (s, 3 H), 2.39 (m, 1 H), 2.87 (s, 3 H), 2.90 (d, 2 H), 3.25 (t, 2 H), 3.81 (s, 2 H), 7.03 (s, 1 H), 7.31 (d, 1 H), 7.54 (d, 1 H) 7.62 (s, 1H), 8.74 (s, 1 H), 11.84 (s, 1 H), 14.12 (s, 1 H). **HRMS** (ES) calcd. for $C_{30}H_{42}N_4O_3$ 507.3390, found 507.3399 $(M+H)^+$.

Cu(II)-7-[(E)-[(3,5-di-tert-butyl-2hydroxyphenyl)methylidene]amino]-6-[(2-hydroxyethyl)(methyl)amino]-3-(2- methylpropyl) quinoxalin-2-ol (Complex 3)

Flex Ligand (0.12 mmol), $Cu(OAc)_2$ (0.14 mmol), and Triethylamine (0.6 mmol) were added to a 50 mL round bottom flask charged with a stir bar and 10 mL MeOH/10 mL DCM. The reaction was heated at 60 °C for 2 h. The solvent was then removed under reduced pressure and the residue was dissolved in 10 mL DCM. The solution was then extracted 3 times with H_2O to removed Cu salts. The organic layers were collected and dried under reduced pressure; yield 98 %. **HRMS** (EI) calcd for $C_{30}H_{40}CuN_4O_3$ 468.2210, found 468.2219 (M+H). Elem. Anal. for $C_{30}H_{40}CuN_4O_3$ Calcd % (found %): C, 63.41 (63.58); H 7.10 (7.21); N 9.86 (9.58).

Pyrasal ligand

2,3-diaminopyrazine (1 mmol), 3,5-Di-tert-butyl-2-hydroxybenzaldehyde (2 mmol), and TFA (5 drops) were added to a round bottom flask (150 mL) containing DCM (20 mL) and ethanol (20 mL). The reaction was stirred at reflux for 18 h. The solvent was removed under reduced pressure and the product was then recrystallized from MeOH. The solids were filtered off and washed with MeOH 3 times to yield an orange powder (42 %). **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 13.86 (s, 2H), 9.52 (s, 2H), 8.35 (s, 2H), 7.53 (d, 2H), 7.36 (d, 2H), 1.50 (s, 18H), 1.34 (s, 18H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ: 167.48, 160.14, 148.52, 141.33, 140.68, 137.57, 129.83, 128.05, 118.25, 35.24, 34.20, 31.40, 29.40. **HRMS** (ES) calcd. For $C_{34}H_{47}N_4O_2$ 543.3699, found 543.3692 $(M+H)^+$.

Cu(II)-pyrasal (Complex 4)

2,3-diaminopyrazine (1 mmol), 3,5-Di-tert-butyl-2-hydroxybenzaldehyde (2 mmol), and $Cu(OAc)_2$ was added to a round bottom flask (150 mL) containing ethanol (50 mL). The reaction was stirred at reflux for 16 h. The solids were filtered off and washed with cold EtOH 3 times to yield a brown powder (46 %). **HRMS** (ES) calcd. for $C_{34}H_{45}CuN_4O_2$ 605.2742, found 605.2760 $(M+H)^+$. Elem. Anal. for $C_{37}H_{44}CuN_4O_2$ Calcd % (found %): C, 67.58 (67.58); H 7.34 (7.36); N 9.27 (9.12).

Representative procedure for propargylic oxidations.

Catalyst (1 mol %) was added to a round bottom flask (25 mL), followed by CH_3CN or DCM (10 mL), alkyne (0.5 mmol), and dropwise addition TBHP (4 equiv). The reaction was heated and followed by TLC. The reaction was then cooled to room temperature and 1,2-dichlorobenzene (0.5 mmol) was added as an internal standard for gas chromatography.

Yield was determined by GC. The reactions were run three times and the yields were averaged (± 3-5 %).

Representative procedure for Allylic Oxidation

Cyclohexene (0.5 mmol) and catalyst were added to a round bottom flask (50 mL) containing acetonitrile (10 mL) followed by dropwise addition of TBHP (1.5 mmol). The reaction mixture was heated and stirred until complete. The reaction was then cooled to room temperature and 1,2-dichlorobenzene (0.5 mmol) was added as an internal standard for gas chromatography. Yield was determined by GC. The reactions were ran three times and the yields were averaged (± 3-5 %).

Representative procedure for benzylic oxidation of diphenylmethane

Diphenylmethane (2 mmol), catalyst (1 mol %), and TBHP (6 mmol) were added to a round bottom flask (50 mL) containing ACN (2 mL). The reaction was heated to 70 °C and stirred for 18 h. The solvent was removed under reduced pressure and the product was purified by column chromatography to yield a clear solid. The reactions were ran three times and the yields were averaged (± 3-5 %). **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 7.47 (t, 4H), 7.60 (t, 2H), 7.80 (d, 4H).

References

(1) Weerasiri, K. C.; Gorden, A. E. V. Oxidation of Propargylic Alcohols with a 2-Quinoxalinol Salen Copper(II) Complex and Tert-Butyl Hydroperoxide. *Eur. J. Org. Chem.* **2013**, *2013* (8), 1546–1550. https://doi.org/10.1002/ejoc.201201394.

(2) Weerasiri, K. C.; Gorden, A. E. V. Cu(II) 2-Quinoxalinol Salen Catalyzed Oxidation of Propargylic, Benzylic, and Allylic Alcohols Using Tert-Butyl Hydroperoxide in Aqueous Solutions. *Tetrahedron* **2014**, *70* (43), 7962–7968. https://doi.org/10.1016/j.tet.2014.08.050.

(3) Li, Y.; Lee, T. B.; Wang, T.; Gamble, A. V.; Gorden, A. E. V. Allylic C–H Activations Using Cu(II) 2-Quinoxalinol Salen and Tert-Butyl Hydroperoxide. *J. Org. Chem.* **2012**, *77* (10), 4628–4633. https://doi.org/10.1021/jo300372q.

(4) Li, Y.; Lee, T.; Weerasiri, K.; Wang, T.; E. Buss, E.; L. McKee, M.; V. Gorden, A. E. 2-Quinoxalinol Diamine Cu(Ii) Complex: Facilitating Catalytic Oxidation through Dual Mechanisms. *Dalton Trans.* **2014**, *43* (36), 13578–13583. https://doi.org/10.1039/C4DT01562B.

(5) Wu, X.; Gorden, A. E. V. 2-Quinoxalinol Salen Copper Complexes for Oxidation of Aryl Methylenes. *Eur. J. Org. Chem.* **2009**, *2009* (4), 503–509. https://doi.org/10.1002/ejoc.200800928.

(6) Li, Y.; Wu, X.; Lee, T. B.; Isbell, E. K.; Parish, E. J.; Gorden, A. E. V. An Effective Method for Allylic Oxidation of Δ5-Steroids Using Tert-Butyl Hydroperoxide. *J. Org. Chem.* **2010**, *75* (5), 1807–1810. https://doi.org/10.1021/jo902637k.

(7) Black, C. C.; Gorden, A. E. V. Propargylic CH Activation Using a Cu(II) 2-Quinoxalinol Salen Catalyst and Tert-Butyl Hydroperoxide. *Tetrahedron Lett.* **2018**, *59* (9), 803–806. https://doi.org/10.1016/j.tetlet.2018.01.030.

(8) Wu, X.; Gorden, A. E. V. An Efficient Method for Solution-Phase Parallel Synthesis of 2-Quinoxalinol Salen Schiff-Base Ligands. *J. Comb. Chem.* **2007**, *9* (4), 601–608. https://doi.org/10.1021/cc070021q.

(9) Amendola, V.; Mangano, C.; Pallavicini, P.; Zema, M. Bistable Copper Complexes of Bis-Thia-Bis-Quinoline Ligands. *Inorg. Chem.* **2003**, *42* (19), 6056–6062. https://doi.org/10.1021/ic025690h.

(10) Yu, J.-Q.; Corey, E. J. A Mild, Catalytic, and Highly Selective Method for the Oxidation of α,β-Enones to 1,4-Enediones. *J. Am. Chem. Soc.* **2003**, *125* (11), 3232–3233. https://doi.org/10.1021/ja0340735.

(11) Catino, A. J.; Forslund, R. E.; Doyle, M. P. Dirhodium(II) Caprolactamate: An Exceptional Catalyst for Allylic Oxidation. *J. Am. Chem. Soc.* **2004**, *126* (42), 13622–13623. https://doi.org/10.1021/ja045330o.

(12) Storr, T.; Verma, P.; Pratt, R. C.; Wasinger, E. C.; Shimazaki, Y.; Stack, T. D. P. Defining the Electronic and Geometric Structure of One-Electron Oxidized Copper−Bis-Phenoxide Complexes. *J. Am. Chem. Soc.* **2008**, *130* (46), 15448–15459. https://doi.org/10.1021/ja804339m.

(13) Giorgio Cozzi, P. Metal–Salen Schiff Base Complexes in Catalysis: Practical Aspects. *Chem. Soc. Rev.* **2004**, *33* (7), 410–421. https://doi.org/10.1039/B307853C.

(14) Liu, Y.; Zhang, Q.; Ma, X.; Liu, P.; Xie, J.; Dai, B.; Liu, Z. Salen-Cu(II) Complex Catalyzed N-Arylation of Imidazoles under Mild Conditions. *Int. J. Org. Chem.* **2013**, *3* (3), 185–189. https://doi.org/10.4236/ijoc.2013.33023.

Chapter 4 Oxidative Mannich Reactions with Cu(II)-Salqu

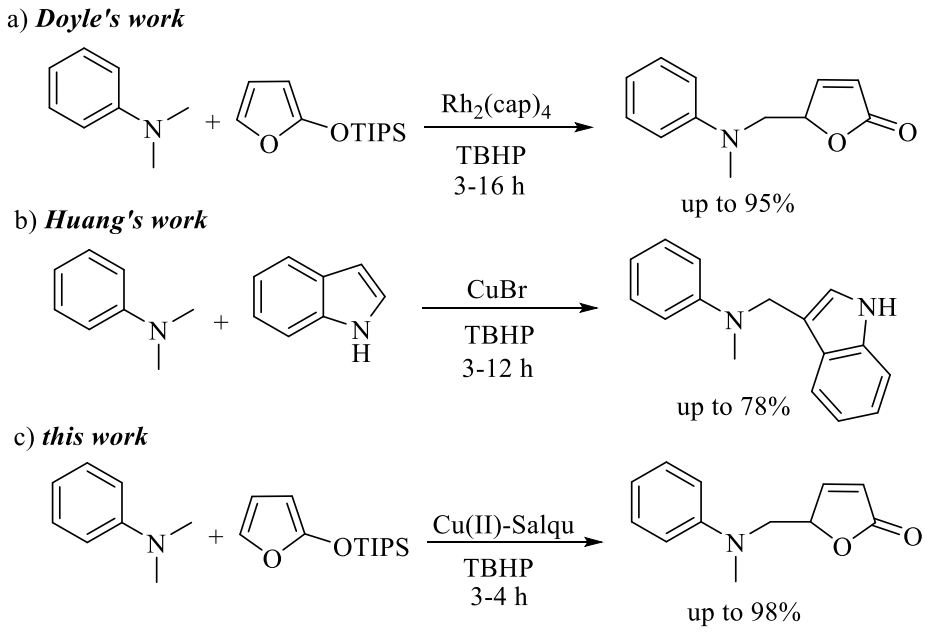
Introduction

The Mannich reaction is a very useful tool in the formation of carbon-carbon bonds. Historical syntheses of note compounds such as, the synthesis of sarain by Larry Overman[1], luciduline by David Evans[2], and strychnine by Robert Woodward[3], in each case require a key Mannich transformation in effecting the total synthesis. Despite these illustrious examples, several challenges arise when forming the iminium ion intermediate necessary for Mannich coupling reactions. Often this can require harsh reaction conditions, long reaction times, expensive transition metal catalysts, or high catalyst loading.[4–11] However, C-H oxidation could provide one direct route to forming the iminium ion using only catalytic amounts of transition metal.

In 2006, Doyle and co-workers reported a dirhodium caprolactamate catalyst for the oxidation of tertiary amines to iminium ions (**Scheme 4.1a**).[10] Yields up to 95 % could be obtained when using 2-triisopropoxysilylfuran as the nucleophile; however, these

reactions required the expensive rhodium complex as the catalyst. In 2010, the simple copper salt CuBr (5 mol %) was used by Huang and coworkers for oxidative Mannich reactions, producing modest yields from 52-78 % with indole as the nucleophile in the Mannich coupling reaction (**Scheme 4.1b**).[12] Recently, a sequence of 2 oxidative Mannich reactions were used for the construction of nortropane containing compounds while utilizing harsh reaction conditions.[13] In an effort to make reactions like these more efficient and accessible, we envisioned using a ligand supported copper catalyst for the oxidative coupling of tertiary amines.

Here, we describe the use of a Cu(II) 2-quinoxaminol salen (salqu) **complex 1** as a catalyst in oxidative Mannich type reactions. These reactions can be carried out under mild conditions, using only 1 mol % of the Cu(II) catalyst heated to 60 °C for 4 hours. Salqu can be easily prepared in 5 synthetic steps starting from 1,5-difluro-2,4-dinitrobenzene and L-leucine methyl ester.[14] Previously, we have had good results with this catalyst and TBHP for the oxidation of various activated C-H and OH bonds producing yields up to 99 %, and obtained promising results here as well.[14–17]



Scheme 4.1. Oxidative Mannich reactions with *N*,*N*-dimethylaniline.

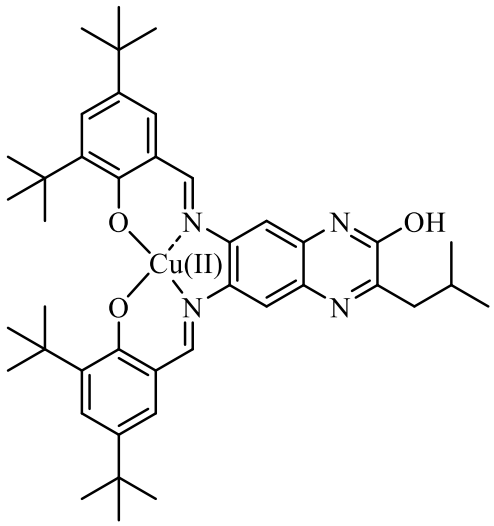


Figure 4.1. Cu(II) salqu (**complex 1**) catalyst.

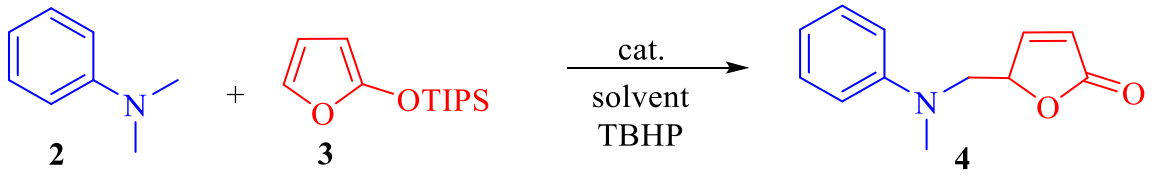
Results and Discussion

We began our investigation using *N*,*N*-dimethylaniline as the model substrate and 2-triisopropoxysilylfuran as the nucleophile for oxidative Mannich reactions (**Table 4.1**). These two reactants were chosen for ease of comparison to previous methods as well as the abundance of γ-butyrolactones throughout natural products.[18] Surprisingly, the desired product, containing a coupled γ-butyrolactone, was obtained in a 64 % yield in only 1 h using 1 mol % of **complex 1** (entry 1). With this promising initial result, it was demonstrated that Cu(II)-salqu was an effective catalyst for these reactions, the next step was to tailor the conditions to optimize the yield further.

Lengthening the reaction time in this same model reaction up to 4 hours produced an isolated yield of 98 % (entries 2-4). Base was added to observe if this would accelerate the reaction;[19] however, this only gave a trace amount of yield after 4 hours (entry 6). The lack of product yield with added base is a good indication that the mechanism does not involve the decomposition of *tert*-butylperoxy ether. We next compared the results from reactions with the Cu(II)-salqu complex to some simple copper salts. Reactions with $Cu(OAc)_2$ and $CuCl_2$ produce the desired product, but in lower overall yields, even with higher catalyst loading (entries 8-9). Although these catalysts would be ideal due to ease of availability, the Cu(II)-salqu still gives a higher overall yield and is easily prepared while also utilizing lower catalyst loading. It can also be readily isolated from products, this would be particularly important on large scale reactions. To demonstrate the importance of TBHP as the oxidant in this reaction, H_2O_2 was used as the replacement oxidant which resulted in a more modest yield of 51 % (entry 10). This is likely due to the fact that TBHP

has a higher solubility in organic solvents and forms a more stable radical compared to H_2O_2. Next, we tested the use of different solvents for the reaction. Using acetonitrile led to a lower overall yield of 52 % (entry 7). Other solvents also were tested including EtOH and DCM (entries 11-12), both of which gave lower overall yields under these conditions. The optimal yield was achieved with 1 mol % of Cu(II)-salqu, in MeOH for 4 hours (entry 4).

Table 4.1. Optimization of Reaction Conditions



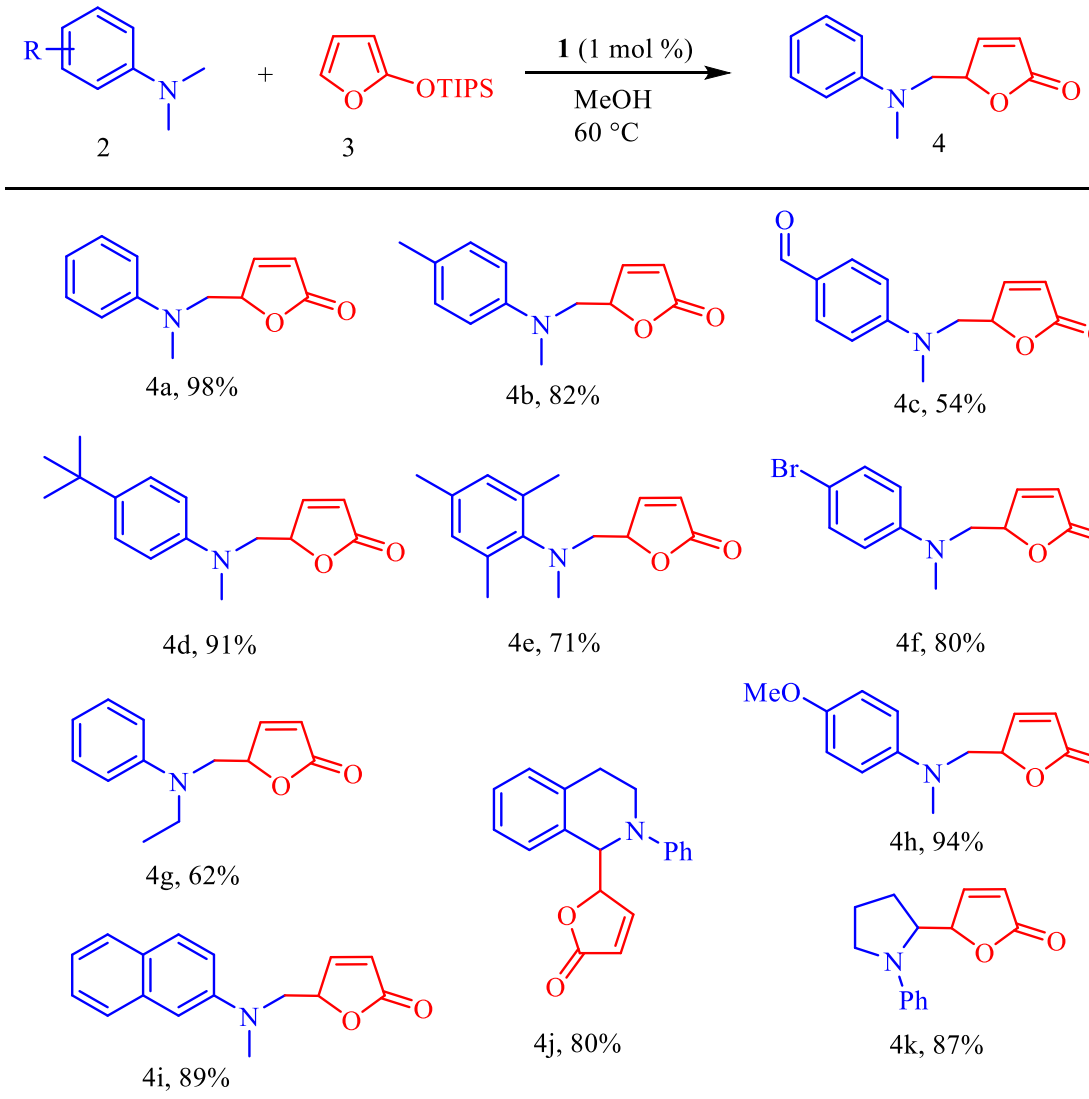
entry	catalyst	variation[a]	solvent	time (h)	yield[b] (%)
1	complex **1** (1 mol %)		MeOH	1	64[c]
2	complex **1** (1 mol %)		MeOH	2	81[c]
3	complex **1** (1 mol %)		MeOH	3	92[c]
4	complex **1** (1 mol %)		MeOH	4	98
5	complex **1** (1 mol %)	**3** (1 equiv)	MeOH	4	82
6	complex **1** (1 mol %)	K_2CO_3	MeOH	4	trace
7	complex **1** (1 mol %)		MeCN	4	52
8	$Cu(OAc)_2$ (5 mol %)		MeOH	4	62
9	$CuCl_2$ (5 mol %)		MeOH	4	60
10	complex **1** (1 mol %)	H_2O_2	MeOH	4	51
11	complex **1** (1 mol %)		EtOH	4	74
12	complex **1** (1 mol %)		DCM	4	52

[a]Reactions were done using **2** (1 mmol), **3** (0.5 mmol), TBHP (1.2 equiv), solvent (1 mL) at 60 °C. [b] Isolated yield after column chromatography. [c]GC yield using internal standard.

With these optimized conditions in hand, we next explored the scope of these reactions (**Scheme 4.2**). First, several aniline derivatives were used as substrates. The presence of a methyl group in the *para* position provided a slightly lower yield of 82 % (**4b**). The introduction of a *p*-formyl electron withdrawing group, gave a substantially lower yield of only 54 % (**4c**). This could be because of the ability of the aldehyde to undergo oxidation under these conditions leading to an ester. The formation of the ester product was detected with crude HRMS. However, these reaction conditions seem to be accelerated by the presence of electron-donating groups (such as seen in **4h**) leading to an exceptional isolated yield of 94 %. We also demonstrated the incorporation of halide functional groups (**4f**) for these reactions, which could be useful for late stage coupling reactions.

Next, we looked at the regioselectivity for the formation of the iminium ion when the disubstituted *N*-methyl, *N*-ethyl aniline is used as the substrate.[10] The coupling was found to happen exclusively on the methyl carbon giving rise to **4g** in a 62 % yield. These results are consistent with the reported acidity values by Mariano and coworkers in reactions with aniline derivatives.[20] Steric hindrance could also play a role in the regioselectivity of this reaction. To explore the utility of larger aromatic containing substrates, 2-(*N*,*N*-dimethylamino)naphthalene was tested as a substrate resulting in an isolated yield of 89 % of **4i**. Not only do open chain amines work well, cyclic amines (i.e. pyrrolidine and tetrahydroquinoline) were also found to be high yielding (80-87 %) under these conditions (**4j**-**4k**).

Scheme 4.2. Substrate Scope[a]



[a]Reaction conditions: *N*,*N*-dimethylaniline **2a** (1.0 mmol), 2-triisopropoxysilylfuran (0.5 mmol), MeOH (1 mL), Cu(II)-salqu (1 mol%), TBHP (1.2 equiv), 60 °C, 3-4 h. [b]Yields of isolated products.

To consider the electronic effects of various substituents on the reaction mechanism, kinetics studies were conducted on the *para* substituted aniline derivatives using MeOD as the nucleophile and solvent. A correlation of Hammett constants for the *p*-methoxy, *p*-methyl, *p*-formyl, *p*-bromo, and *p*-cyano anilines were plotted against $\log(k_x/k_H)$ (**Figure 4.2**).[21] The reaction rates were monitored by NMR and the linear free energy relationship was found to demonstrate a good linear fit (R^2 0.968) showing that the rate determining step is the same with the various substituents. The ρ value of -1.41 indicates the acceleration of oxidative Mannich reactions by electron-donating groups which is consistent with our reaction yields. Also, the negative ρ value indicates the buildup of an electron deficient intermediate in the rate determining step which can be stabilized by the electron donating substituents.

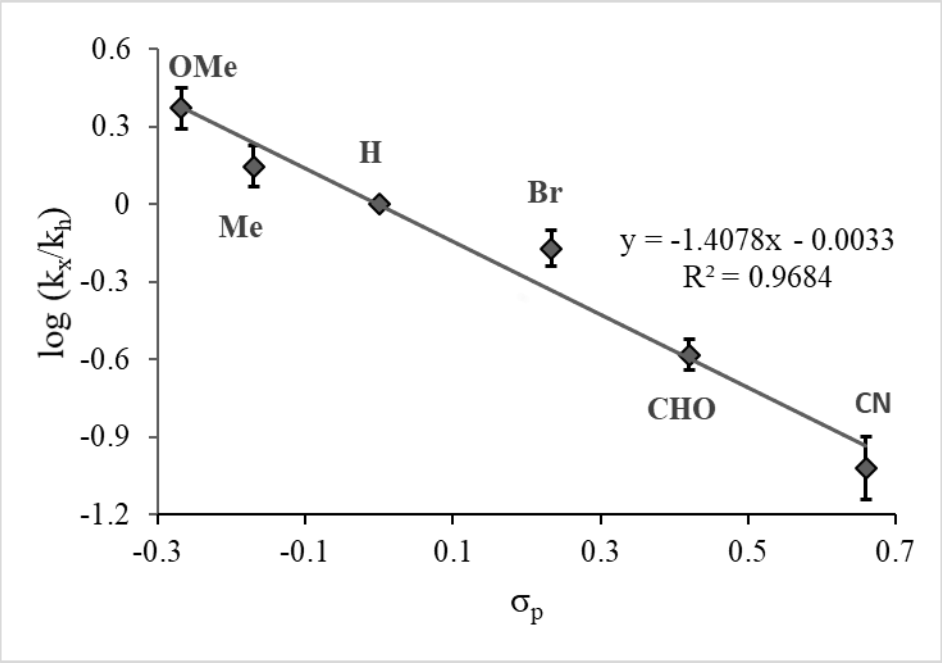


Figure 4.2. Correlation between log(k_x/k_H) and para position Hammett constants. Reaction rates monitored by NMR at room temperature in *d4*-MeOD.

Preliminary studies were done to obtain mechanistic information for this reaction. We believe that Cu(II)-salqu is oxidized by TBHP to form a Cu(III) species and a *tert*-butoxy radical (**Figure 4.3**). The formation of Cu(III) is stabilized by our non-innocent salen type ligand system.[22] Previous DFT calculations done at the B3LYP/6-311+G(d,p) level with reactions using Cu(II)-salqu show an enhanced spin density dispersion with the heterocyclic backbone as compared to simple salen.[15] This further explains the stabilization of Cu(III) by extended conjugation of the ligand compared to simple salen. From here, reductive elimination is carried out with TBHP giving a *tert*-butoxy radical and Cu(II)-

salqu. The *tert*-butoxy radical then does a single electron transfer (SET) from the lone pair on the amine. Based on the negative ρ value of -1.41 found in the linear free energy study, we believe this is the rate determining step. Here, the electron deficient amine is stabilized by electron donating substituents.[23] The *tert*-butoxy anion then carries out a proton transfer α to the amine forming *tert*-butanol and a carbon radical. Coupling of the α-amino radical and *tert*-butylperoxy radical forms intermediate **5**. We are able to confirm this pathway by the isolation of intermediate **5** and **6**.[24] To do this, the Mannich reaction was ran without adding the nucleophile 2-trisoporpoxysilyfuran. In this case, MeOH acts as the nucleophile giving rise to intermediate **6**. However, when non-nucleophilic DCM is used as the solvent, we can see coupling between *tert*-butylperoxy radical and α-amine radical. Based on this observation, it is reasonable to believe that intermediate **5** is first formed but quickly displaced by intermediate **6**. This then leads to the formation of the electrophilic iminium ion upon elimination of MeOH. The iminium ion is then intercepted by 2-trisoporpoxysilyfuran to form the coupled product **4**.

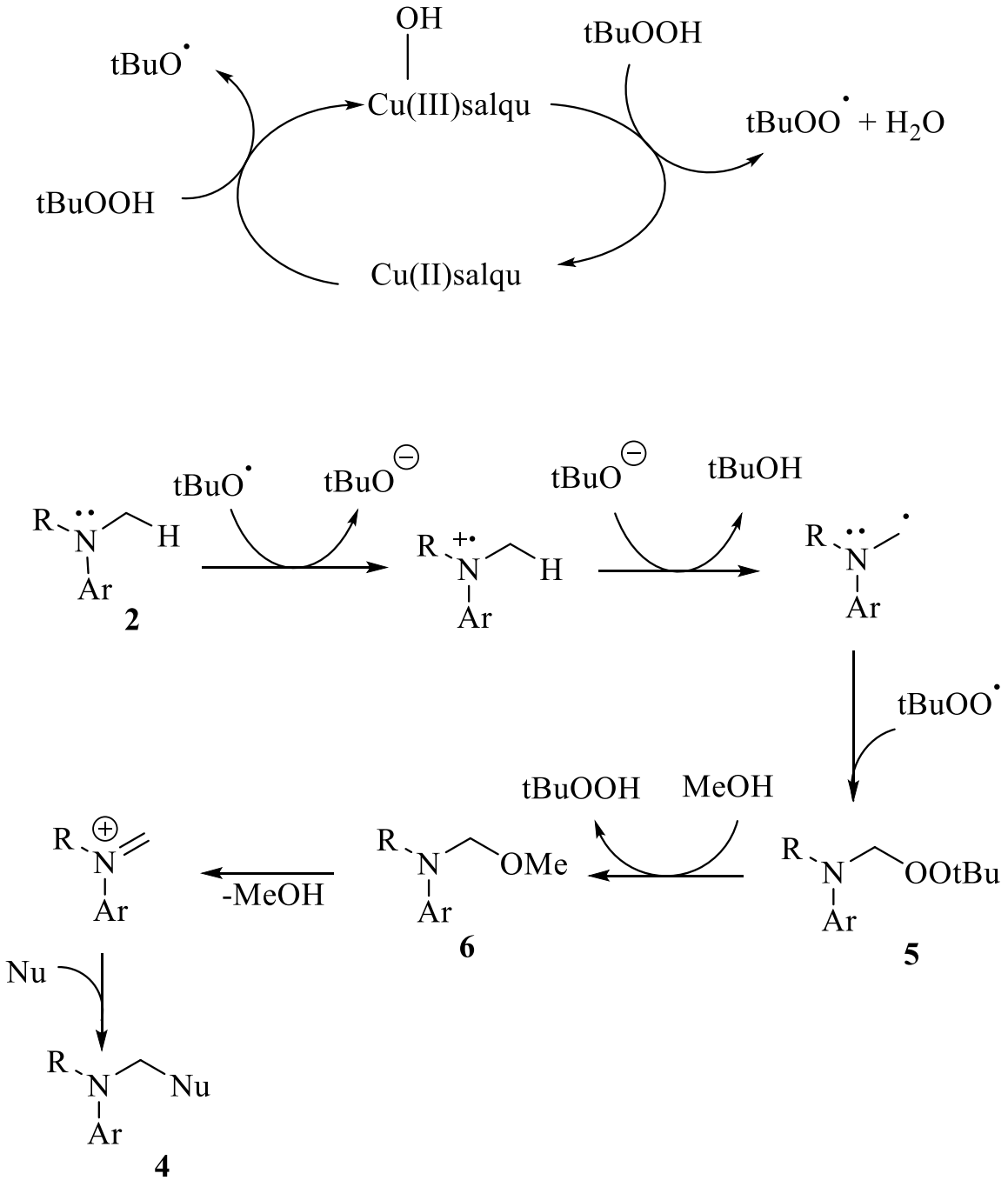


Figure 4.3. Proposed catalytic cycle of oxidative Mannich reactions using Cu(II) salqu.

Conclusion

In conclusion, we have developed a new method for oxidative Mannich reactions using only 1 mol % of an earth abundant transition metal catalyst with the Cu(II)-salqu complex. These reactions proceed under mild conditions with mild heating in as little as 4 hours. We have tested a range of different substrates including dimethylaniline derivatives as well as cyclic amines all producing good yields of the corresponding coupled product up to 98 %. A mechanism for this reaction was proposed which involved a SET as the rate determining step.

Experimental

Materials.

Except when otherwise stated, all reagents were purchased from Sigma Aldrich and used without further purification. The following reagents were purchased (source) *N*,*N*-Dimethyl-2-naphthylamine (TCI), *N*,*N*-dimethyl-p-toluidine (Alfa Aesar), 4-Methoxy-*N*,*N*-dimethylaniline (Oakwood), and 4-Bromo-*N*,*N*-dimethylaniline (Alfa Aesar). 2-Phenyl-1,2,3,4-tetrahydroisoquinoline was synthesized following a previously published procedure.[25] *N*-ethyl-*N*-methyl aniline was synthesized following a previous published procedure.[26] Acetonitrile (CH_3CN) and dichloromethane (DCM) were purchased from BDH, stored under argon, and dispensed from a solvent purification system. Ethyl acetate and methanol was purchased from EMD. Hexanes was purchased in bulk from Macron and used without further purification. tert-Butyl hydroperoxide was purchased from Sigma Aldrich and stored in a cool, dark area. Deuterated chloroform ($CDCl_3$) and methanol (d_4-MeOD) were purchased from Cambridge Isotopes.

Instrumentation.

General Methods. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ using a 600 or 400 MHz instrument; chemical shifts (δ) were reported in parts per million (ppm) relative to Me_4Si. Chromatographic purifications were performed using Fisher (60 Å, 70-230 mesh) silica gel. HRMS data were collected with electron spray ionization using a TOF analyzer.

Synthesis.

6,7-diamino-2-quinoxalinol.

Following a modification of published procedure,[27] 1,5-difluoro-2,4,-dinitrobenzene (4.0 mmol), and L-leucine methyl ester (4.0 mmol) were added to a round bottom flask (150 mL) containing ethanol (30 mL) and THF (30 mL). Diisopropylethylamine (8.8 mmol) was added and the reaction mixture was stirred for 24 h at room temperature. Ammonium hydroxide (30 mmol) was added and the reaction continued to stir at room temperature for an additional 24 h. The solvent was removed under reduced pressure to produce a viscous yellow oil. The oil was dissolved in ethanol (40 mL), ammonium formate (80 mmol), and 5 % Pd-C (1.24 g) was added. The reaction was brought to reflux for 2 h and filtered through celite. The filtrate was concentrated under reduced pressure. The product was purified by flash column chromatography (8:2:1 ethyl acetate/hexanes/ethanol) to yield a dark yellow solid (75%). Characterization of the solid was found to match that of the previously reported ^{1}H and ^{13}C NMR spectrum.[27]

2-quinoxalinol salen (salqu) ligand.

6,7-diamino-2-quinoxalinol (0.88 mmol) was charged in a round bottom flask (100 mL) containing methanol (20 mL), 3,5-di-tert-butyl-2-hydroxybenzaldehyde (3.53 mmol), and trifluoracetic acid (2 drops). The reaction was heated to reflux and stirred for 4 h. Once cooled to room temperature, the precipitate was filtered and washed with cold methanol 3 times to yield a yellow solid (79 %). Characterization of the solid was found to match that of the previously reported ^{1}H and ^{13}C NMR spectrum [27]

Copper(II) Salqu (Complex 1).

Following a modification of previously published procedure,[28] 2-quinoxalinol salen (0.7 mmol) was charged in a round bottom flask (250 mL) containing methanol (60 mL), dichloromethane (60 mL) and triethylamine (0.5 mL). $Cu(OAc)_2$ (0.77 mmol) was dissolved and the reaction mixture was heated to reflux and stirred for 5 h. The product was washed with water and cold ether 3 times each to yield a dark red solid (81 %).

Representative Procedure for Oxidative Mannich Reaction.

2-triisopropoxysilylfuran nucleophile (0.5 mmol) was added to a round bottom flask (25 mL) and dissolved in MeOH (1 mL). To this, the required *amine* (1 mmol), T-HYDRO (1.2 equiv), Cu-Salqu (1 mol %) were added. The reaction was heated, using an oil bath, to 60 °C and stirred using a stir bar for 4 h. The solvent was then evaporated under reduced pressure using a rotary evaporator, and the resulting product was purified by flash column chromatography on silica gel as indicated below. The reactions were ran three times and the yields were averaged (± 5 %).

Representative Procedure for Oxidative Mannich Reaction on 2 mmol scale.

The 2-triisopropoxysilylfuran (2.0 mmol) was added to a round bottom flask (25 mL) and dissolved in MeOH (4 mL). To this, *N*,*N*-dimethylaniline (4.0 mmol), T-HYDRO (1.2 equiv), Cu-Salqu (1 mol%) were added. The reaction was heated, using an oil bath, to 60 °C and stirred using a stir bar for 4 h. The solvent was evaporated under reduced pressure using a rotary evaporator, and 5-[(Methylphenylamino)methyl]-2(5H)-furanone was purified by flash column chromatography on silica gel (2:1 hex/EtOAc) to afford an orange oil, 94% yield (227 mg).

5-[(Methylphenylamino)methyl]-2(5H)-furanone (4a).

Purified by flash column chromatography on silica gel (2:1 hex/EtOAc) to afford an orange oil, 98% yield (99 mg). TLC R_f= 0.3 (1:1 hex/EtOAc);**^{1}H NMR** (600 MHz, $CDCl_3$) δ: 7.50 (dd, *J*=5.6, 1.5 Hz, 1H), 7.28 (t, *J*=8.0 Hz, 2H), 6.79 (t, *J*=7.3 Hz, 1H), 6.75 (d, *J*=8.0 Hz, 2H), 6.16 (dd, *J*=5.6, 1.6 Hz, 1H), 5.29 (tt, *J*=5.6, 1.6 Hz, 1H), 3.70 (t, *J*=5.6 Hz, 2H), 3.04 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ: 172.7, 154.5, 148.3, 129.4, 122.4, 117.4, 112.3, 82.0, 54.0, 39.5; **HRMS** (ES) calcd. for $C_{12}H_{14}NO_2$ 204.1025, found 204.1022 $(M+H)^+$.

5-[[Methyl(4-methylphenyl)amino]methyl]-2(5H)-furanone (4b).

Purified by flash column chromatography on silica gel to afford an orange oil, 82% yield (89.5 mg). TLC R_f= 0.5 (1:1 hexanes/EtOAc); **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 7.48 (d, *J*=5.6, 1.6 Hz, 1H), 7.06 (d, *J*=8.0 Hz, 2H), 6.64 (d, *J*=8.8 Hz, 2H), 6.13 (dd, *J*=6.0, 2.0 Hz, 1H), 5.26-5.24 (m, 1H), 3.65 (d, *J*=6.0 Hz, 2H), 2.99 (s, 3H), 2.26 (s, 3H); **^{13}C NMR**

(150 MHz, $CDCl_3$) δ: 172.7, 154.6, 146.2, 130.0, 126.8, 122.1, 112.7, 82.0, 55.4, 39.7, 20.2; **HRMS** (ES) calcd. for $C_{13}H_{16}NO_2$ 218.1181, found 218.1161 $(M+H)^+$.

4-[[(2,5-dihydro-5-oxo-2-furanyl)methyl]methylamino]benzaldehyde (4c).

Purified by flash column chromatography on silica gel to afford a yellow oil, 54% yield (62.4 mg). TLC R_f= 0.25 (1:2 hexanes/EtOAc); **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 9.76 (s, 1H), 7.75 (d, *J*=8.8 Hz, 2H), 6.75 (d, *J*=8.8 Hz, 2H), 6.18 (dd, *J*=5.6, 2.0 Hz, 1H), 5.33-5.28 (m, 1H), 3.89 (dd, *J*=15.6, 4.8 Hz, 1H), 3.73 (dd, *J*=15.3, 5.9 Hz, 1H), 3.14 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ: 190.4, 172.2, 153.5, 152.8, 132.1, 126.2, 122.9, 111.4, 81.8, 54.3, 39.9; **HRMS** (ES) calcd. for $C_{13}H_{13}NO_3Na$ 254.0793, found 254.0779 $(M+Na)^+$.

5-[[[4-(1,1-dimethylethyl)phenyl]methylamino]methyl]-2(5H)-furanone (4d).

Purified by flash column chromatography on silica gel to afford a clear oil, 91% yield (118 mg). TLC R_f= 0.25 (2:1 hexanes/EtOAc); **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 7.51 (d, *J*=5.6 Hz, 1H), 7.28 (d, *J*=8.9 Hz, 2H), 6.68 (d, *J*=8.7 Hz, 2H), 6.14 (d, *J*=4.0 Hz, 1H), 5.27 (m, 1H), 3.65 (d, *J*=4.9 Hz, 2H), 2.99 (s, 3H), 1.28 (s, 9H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ:171.9, 153.8, 144.9, 138.9, 125.2, 121.1, 110.9, 81.0, 54.2, 38.5, 32.7, 30.4; **HRMS** (ES) calcd. for $C_{16}H_{22}NO_2$ 260.1651, found 260.1647 $(M+H)^+$.

5-[[methyl(2,4,6-trimethylphenyl)amino]methyl]- 2(5*H*)-furanone (4e).

Purified by flash column chromatography on silica gel to afford a clear oil, 71% yield (87 mg). TLC R_f= 0.4 (2:1 hexanes/EtOAc); **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 7.49 (dd, *J*=4.8, 1.2 Hz, 1H), 6.84 (s, 1H), 6.82 (s, 1H), 6.13 (dd, *J*=5.5, 1.8 Hz, 1H), 5.08 (m, 1H), 3.38 (dd, *J*=13.9, 5.8 Hz, 1H), 3.28 (dd, *J*=13.9, 5.8 Hz, 1H), 2.81 (s, 3H), 2.28 (s,

3H), 2.23 (s, 6H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ: 173.4, 155.9, 146.1, 136.7, 136.6, 135.2, 129.9, 129.7, 122.0, 83.9, 59.1, 42.1, 20.8, 19.1, 19.0; **HRMS** (ES) calcd. for $C_{15}H_{20}NO_2$ 246.1494, found 246.1475 $(M+H)^+$.

5-[[(4-Bromophenyl)methylamino]methyl]-2(5H)-furanone (4f).

Purified by flash column chromatography on silica gel to afford a yellow oil, 80% yield (113 mg). TLC R_f= 0.23 (2:1 hexanes/EtOAc); **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 7.48 (dd, *J*=5.2, 1.2 Hz, 1H), 7.31 (d, *J*=8.8 Hz, 2H), 6.58 (d, *J*=8.8 Hz, 2H), 6.14 (dd, *J*=6.0, 2.0 Hz, 1H), 5.27-5.23 (m, 1H), 3.71 (dd, *J*=15.2, 5.6 Hz, 1H), 3.62 (dd, *J*=15.4, 6.1 Hz, 1H), 2.99 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ: 172.7, 154.3, 147.3, 132.1, 122.5, 113.9, 109.3, 82.0, 54.8, 39.8; **HRMS** (ES) calcd. for $C_{12}H_{13}NO_2Br$ 282.0130, found 282.0117 $(M+H)^+$.

5-[(Ethylphenylamino)methyl]-2(5H)-furanone (4g).

Purified by flash column chromatography on silica gel to afford a clear oil, 62% yield (67 mg). TLC R_f= 0.25 (3:1 hexanes/EtOAc); **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 7.51 (d, *J*=5.6 Hz, 1H), 7.26-7.24 (m, 2H), 6.74-6.70 (m, 3H), 6.16 (d, *J*=5.6 Hz, 1H), 5.28-5.24 (m, 1H), 3.69 (dd, J=15.2, 6.0 Hz, 1H), 3.5 (dd, *J*=15.2, 6.0 Hz, 1H), 3.52-3.35 (m, 2H), 1.17 (t, *J*=7.0 Hz, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ: 172.9, 155.0, 146.9, 129.6, 122.2, 117.0, 112.3, 81.9, 52.9, 45.8, 11.9; **HRMS** (ES) calcd. for $C_{13}H_{16}NO_2$ 218.1181, found 218.1178 $(M+H)^+$.

5-[[(4-methoxyphenyl)methylamino]methyl]- 2(5*H*)-furanone (4h).

Purified by flash column chromatography on silica gel to afford a clear oil, 94% yield (109 mg). TLC R_f= 0.30 (2:1 hexanes/EtOAc); **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 7.48

(dd, *J*=5.8, 2.0 Hz, 1H), 6.85 (d, *J*=9.4 Hz, 2H), 6.71 (d, *J*=9.4 Hz, 2H), 6.14 (dd, *J*=5.8, 2.0 Hz, 1H), 5.27-5.24 (m, 1H), 3.77 (s, 3H), 3.62 (d, *J*=5.8 Hz, 2H), 2.97 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ: 172.9, 154.8, 152.2, 143.0, 122.1, 114.9, 114.4, 82.1, 56.2, 55.8, 40.2; **HRMS** (ES) calcd. for $C_{13}H_{16}NO_3$ 234.1130, found 234.1135 $(M+H)^+$.

5-[[(Methyl(2-naphthyl)amino]methyl]-2(5H)-furanone (4i).

Purified by flash column chromatography on silica gel to afford a yellow oil, 89% yield (113 mg). TLC R_f= 0.22 (3:1 hexanes/EtOAc); **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 7.70 (t, *J*=9.3 Hz, 2H), 7.64 (d, *J*=8.4 Hz, 1H), 7.44 (d, *J*= 4.6 Hz, 1H), 7.38 (t, *J*=7.1 Hz, 1H), 7.24-7.22 (m, 1H), 7.01 (d, *J*=8.6 Hz, 1H), 6.90 (s, 1H), 6.09 (d, *J*=4.1 Hz, 1H), 5.28-5.24 (m, 1H), 3.75 (dd, *J*=15.7, 5.3 Hz, 2H), 3.09 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ:172.9, 154.6, 146.1, 134.8, 129.3, 127.5, 127.0, 126.6, 126.3, 122.6, 122.2, 115.5, 106.6, 82.3, 55.0, 39.9;; **HRMS** (ES) calcd. for $C_{16}H_{16}NO_2$ 254.1188, found 254.1181 $(M+H)^+$.

5-(1,2,3,4-Tetrahydro-2-phenyl-1-isoquinolinyl)-2(5H)-furanone (4j).

Purified by flash column chromatography on silica gel to afford a yellow oil, 80% yield (114 mg). TLC R_f= 0.18 (3:1 hexanes/EtOAc); **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 7.53 (d, *J*=5.6 Hz, 1H), 7.39 (d, *J*=5.6 Hz, 1H), 7.34-7.19 (m, 6H), 6.99 (d, *J*=8.4 Hz, 1H), 6.90 (d, *J*=8.4 Hz, 1H), 6.87-6.80 (m, 1H), 6.15-6.12 (m, 1H), 5.95-5.92 (m, 1H), 5.46-5.44 (m, 1H), 5.38-5.34 (m, 1H), 5.18 (d, *J*=4.4 Hz, 1H), 4.19 (d, *J*=4.4 Hz, 1H), 3.82-3.75 (m, 1H), 3.67-3.55 (m, 2H), 3.48-3.41 (m,1H), 3.20-2.90 (m, 4H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ: 172.7, 172.6, 154.8, 153.7, 149.0, 149.0, 135.8, 135.4, 132.5, 131.8, 129.7, 129.6, 128.7, 128.5, 128.2, 127.9, 127.9, 127.7, 126.5, 126.1, 124. 4, 122.7, 122.4, 118.9, 118.8, 114.6,

114.5, 86.0, 85.4, 61.8, 60.7, 44.1, 43.5, 28.5, 27.3; **HRMS** (ES) calcd. for $C_{19}H_{18}NO_2$ 292.1338, found 292.1336 $(M+H)^+$.

5-(1-Phenyl-2-pyrrolidinyl)-2(5H)-furanone (4k).

Purified by flash column chromatography on silica gel to afford a clear oil, 87% yield (99.7 mg). TLC R_f= 0.25 (2:1 hexanes/EtOAc); **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 7.48-7.42 (m, 2H), 7.30-7.24 (m, 4H), 6.80-6.73 (m, 4H), 6.57 (d, *J*=8.2 Hz, 2H), 6.19 (m, 2H), 5.40 (s, 1H), 5.02 (m, 1H), 4.37 (m, 1H), 3.85 (t, *J*=7.2 Hz, 1H), 3.63-3.57 (m, 2H), 3.20-3.16 (m, 1H), 2.15-1.60 (m, 8H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ: 173.2, 173.1, 156.3, 153.9, 147.1, 129.6, 122.9, 121.7, 117.3, 112.7, 112.4, 84.2, 82.4, 60.7, 59.2, 49.5, 49.3, 28.1, 25.2, 24.2, 23.3; **HRMS** (ES) calcd. for $C_{14}H_{16}NO_2$ 230.1181, found 230.1184 $(M+H)^+$.

***N*-(methoxymethyl)-*N*-Methylaniline.**

N,*N*-dimethylaniline (1 mmol), Cu-Salqu (1 mol %), methanol (2 mL) were placed in a round bottom flask (25 mL). The solution was stirred and TBHP (0.72 mmol) was added dropwise. The reaction was heated to reflux for 5 h. The solvent was removed under reduced pressure and the product was purified by column chromatography (10:1 ethyl acetate/hexanes). **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 7.26 (m, 2H), 6.84 (m, 2H), 6.72 (m, 1H), 4.73 (s, 2H), 3.28 (s, 3H), 3.08 (s, 3H).

***N*-(tert-butylperoxymethyl)-*N*-methylaniline.**

N,*N*-dimethylaniline (1 mmol), Cu-Salqu (1 mol %), DCM (2 mL) were placed in a round bottom flask (25 mL). The solution was stirred and TBHP (0.72 mmol) was added dropwise. The reaction was heated to reflux for 5 h. The solvent was removed under

reduced pressure and the product was purified by column chromatography (10:1 ethyl acetate/hexanes). **^{1}H NMR** (600 MHz, $CDCl_3$) δ: 7.32 (m, 2H), 6.89-6.70 (m, 3H), 5.10 (s, 2H), 3.15 (s, 3H), 1.24 (s, 9H).

Representative Procedure for Determining the Initial Reaction Rates.

A solution of *N*,*N*-dimethylaniline (0.15 mmol), with Cu(II)-salqu (1 mol %), was prepared in d_4-MeOD (1.5 mL), and 1,3,5-trichlorobenzene (0.15 mmol) was added as the internal standard. These were mixed in a vial and an aliquot of 500 µL of the solution was then added to an NMR tube. TBHP in water (28 µL) was then added to the tube and inserted immediately into the NMR at room temperature. ^{1}H scans were taken every 60 seconds for 20 minutes. The rate of oxidation was measured by the decrease in the integration value of the singlet (6 H) corresponding to the *N*,*N*-dimethyl groups of each 4-substituted aniline with respect to the internal standard, using the program Bruker Dynamic Center 2.5.6.

References

(1) Becker, M. H.; Chua, P.; Downham, R.; Douglas, C. J.; Garg, N. K.; Hiebert, S.; Jaroch, S.; Matsuoka, R. T.; Middleton, J. A.; Ng, F. W.; et al. Total Synthesis of (−)-Sarain A. *J. Am. Chem. Soc.* **2007**, *129* (39), 11987–12002. https://doi.org/10.1021/ja074300t.

(2) Scott, W. L.; Evans, D. A. Total Synthesis of (+-)-Luciduline. *J. Am. Chem. Soc.* **1972**, *94* (13), 4779–4780. https://doi.org/10.1021/ja00768a083.

(3) Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. THE TOTAL SYNTHESIS OF STRYCHNINE. *J. Am. Chem. Soc.* **1954**, *76* (18), 4749–4751. https://doi.org/10.1021/ja01647a088.

(4) Huo, C.; Wu, M.; Jia, X.; Xie, H.; Yuan, Y.; Tang, J. Aerobic Oxidative Mannich Reaction Promoted by Catalytic Amounts of Stable Radical Cation Salt. *J. Org. Chem.* **2014**, *79* (20), 9860–9864. https://doi.org/10.1021/jo5017822.

(5) Shen, Y.; Li, M.; Wang, S.; Zhan, T.; Tan, Z.; Guo, C.-C. An Efficient Copper-Catalyzed Oxidative Mannich Reaction between Tertiary Amines and Methyl Ketones. *Chem. Commun.* **2009**, No. 8, 953–955. https://doi.org/10.1039/B819657E.

(6) Wu, K.; Huang, Z.; Qi, X.; Li, Y.; Zhang, G.; Liu, C.; Yi, H.; Meng, L.; Bunel, E. E.; Miller, J. T.; et al. Copper-Catalyzed Aerobic Oxidative Coupling: From Ketone and Diamine to Pyrazine. *Sci. Adv.* **2015**, *1* (9), e1500656. https://doi.org/10.1126/sciadv.1500656.

(7) Ratnikov, M. O.; Doyle, M. P. Mechanistic Investigation of Oxidative Mannich Reaction with Tert-Butyl Hydroperoxide. The Role of Transition Metal Salt. *J. Am. Chem. Soc.* **2013**, *135* (4), 1549–1557. https://doi.org/10.1021/ja3113559.

(8) Matsuo, J.; Tanaki, Y.; Ishibashi, H. Oxidative Mannich Reaction of N-Carbobenzyloxy Amines with 1,3-Dicarbonyl Compounds. *Org. Lett.* **2006**, *8* (19), 4371–4374. https://doi.org/10.1021/ol0618095.

(9) Ratnikov, M. O.; Xu, X.; Doyle, M. P. Simple and Sustainable Iron-Catalyzed Aerobic C–H Functionalization of N,N-Dialkylanilines. *J. Am. Chem. Soc.* **2013**, *135* (25), 9475–9479. https://doi.org/10.1021/ja402479r.

(10) Catino, A. J.; Nichols, J. M.; Nettles, B. J.; Doyle, M. P. The Oxidative Mannich Reaction Catalyzed by Dirhodium Caprolactamate. *J. Am. Chem. Soc.* **2006**, *128* (17), 5648–5649. https://doi.org/10.1021/ja061146m.

(11) Condie, A. G.; González-Gómez, J. C.; Stephenson, C. R. J. Visible-Light Photoredox Catalysis: Aza-Henry Reactions via C−H Functionalization. *J. Am. Chem. Soc.* **2010**, *132* (5), 1464–1465. https://doi.org/10.1021/ja909145y.

(12) Yang, F.; Li, J.; Xie, J.; Huang, Z.-Z. Copper-Catalyzed Cross Dehydrogenative Coupling Reactions of Tertiary Amines with Ketones or Indoles. *Org. Lett.* **2010**, *12* (22), 5214–5217. https://doi.org/10.1021/ol102252n.

(13) Jo, H.; Hassan, A. H. E.; Jung, S. Y.; Lee, J. K.; Cho, Y. S.; Min, S.-J. Construction of 8-Azabicyclo[3.2.1]Octanes via Sequential DDQ-Mediated Oxidative Mannich Reactions of N-Aryl Pyrrolidines. *Org. Lett.* **2018**, *20* (4), 1175–1178. https://doi.org/10.1021/acs.orglett.8b00098.

(14) Wu, X.; Gorden, A. E. V. 2-Quinoxalinol Salen Copper Complexes for Oxidation of Aryl Methylenes. *Eur. J. Org. Chem.* **2009**, *2009* (4), 503–509. https://doi.org/10.1002/ejoc.200800928.

(15) Li, Y.; Lee, T. B.; Wang, T.; Gamble, A. V.; Gorden, A. E. V. Allylic C–H Activations Using Cu(II) 2-Quinoxalinol Salen and Tert-Butyl Hydroperoxide. *J. Org. Chem.* **2012**, *77* (10), 4628–4633. https://doi.org/10.1021/jo300372q.

(16) Black, C. C.; Gorden, A. E. V. Propargylic CH Activation Using a Cu(II) 2-Quinoxalinol Salen Catalyst and Tert-Butyl Hydroperoxide. *Tetrahedron Lett.* **2018**, *59* (9), 803–806. https://doi.org/10.1016/j.tetlet.2018.01.030.

(17) Weerasiri, K. C.; Gorden, A. E. V. Cu(II) 2-Quinoxalinol Salen Catalyzed Oxidation of Propargylic, Benzylic, and Allylic Alcohols Using Tert-Butyl Hydroperoxide in Aqueous Solutions. *Tetrahedron* **2014**, *70* (43), 7962–7968. https://doi.org/10.1016/j.tet.2014.08.050.

(18) Seitz, M.; Reiser, O. Synthetic Approaches towards Structurally Diverse γ-Butyrolactone Natural-Product-like Compounds. *Curr. Opin. Chem. Biol.* **2005**, *9* (3), 285–292. https://doi.org/10.1016/j.cbpa.2005.03.005.

(19) Yu, J.-Q.; Corey, E. J. A Mild, Catalytic, and Highly Selective Method for the Oxidation of α,β-Enones to 1,4-Enediones. *J. Am. Chem. Soc.* **2003**, *125* (11), 3232–3233. https://doi.org/10.1021/ja0340735.

(20) Zhang, X.; Yeh, S.-R.; Hong, S.; Freccero, M.; Albini, A.; Falvey, D. E.; Mariano, P. S. Dynamics of .Alpha.-CH Deprotonation and .Alpha.-Desilylation Reactions of Tertiary Amine Cation Radicals. *J. Am. Chem. Soc.* **1994**, *116* (10), 4211–4220. https://doi.org/10.1021/ja00089a010.

(21) Hansch, Corwin.; Leo, A.; Taft, R. W. A Survey of Hammett Substituent Constants and Resonance and Field Parameters. *Chem. Rev.* **1991**, *91* (2), 165–195. https://doi.org/10.1021/cr00002a004.

(22) Storr, T.; Verma, P.; Pratt, R. C.; Wasinger, E. C.; Shimazaki, Y.; Stack, T. D. P. Defining the Electronic and Geometric Structure of One-Electron Oxidized Copper−Bis-Phenoxide Complexes. *J. Am. Chem. Soc.* **2008**, *130* (46), 15448–15459. https://doi.org/10.1021/ja804339m.

(23) Goto, Y.; Watanabe, Y.; Fukuzumi, S.; Jones, J. P.; Dinnocenzo, J. P. Mechanisms of N-Demethylations Catalyzed by High-Valent Species of Heme Enzymes: Novel Use of Isotope Effects and Direct Observation of Intermediates. *J. Am. Chem. Soc.* **1998**, *120* (41), 10762–10763. https://doi.org/10.1021/ja981357u.

(24) Murahashi, S.-I.; Naota, T.; Miyaguchi, N.; Nakato, T. Ruthenium-Catalyzed Oxidation of Tertiary Amines with Hydrogen Peroxide in the Presence of Methanol. *Tetrahedron Lett.* **1992**, *33* (46), 6991–6994. https://doi.org/10.1016/S0040-4039(00)60914-0.

(25) Quach, T. D.; Batey, R. A. Ligand- and Base-Free Copper(II)-Catalyzed C−N Bond Formation: Cross-Coupling Reactions of Organoboron Compounds with Aliphatic Amines and Anilines. *Org. Lett.* **2003**, *5* (23), 4397–4400. https://doi.org/10.1021/ol035681s.

(26) Prasad, A. S. B.; Kanth, J. V. B.; Periasamy, M. Convenient Methods for the Reduction of Amides, Nitriles, Carboxylic Esters, Acids and Hydroboration of Alkenes Using NaBH4/I2system. *Tetrahedron* **1992**, *48* (22), 4623–4628. https://doi.org/10.1016/S0040-4020(01)81236-9.

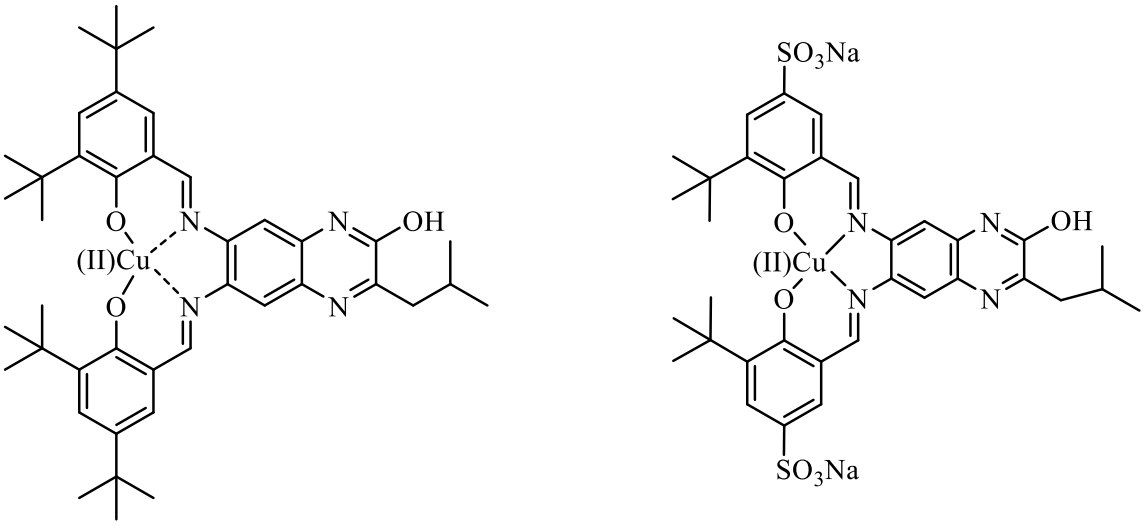
(27) Wu, X.; Gorden, A. E. V. An Efficient Method for Solution-Phase Parallel Synthesis of 2-Quinoxalinol Salen Schiff-Base Ligands. *J. Comb. Chem.* **2007**, *9* (4), 601–608. https://doi.org/10.1021/cc070021q.

(28) Li, Y.; Wu, X.; Lee, T. B.; Isbell, E. K.; Parish, E. J.; Gorden, A. E. V. An Effective Method for Allylic Oxidation of Δ5-Steroids Using Tert-Butyl Hydroperoxide. *J. Org. Chem.* **2010**, *75* (5), 1807–1810. https://doi.org/10.1021/jo902637k.

Chapter 5 Conclusions and Future Work

Conclusions

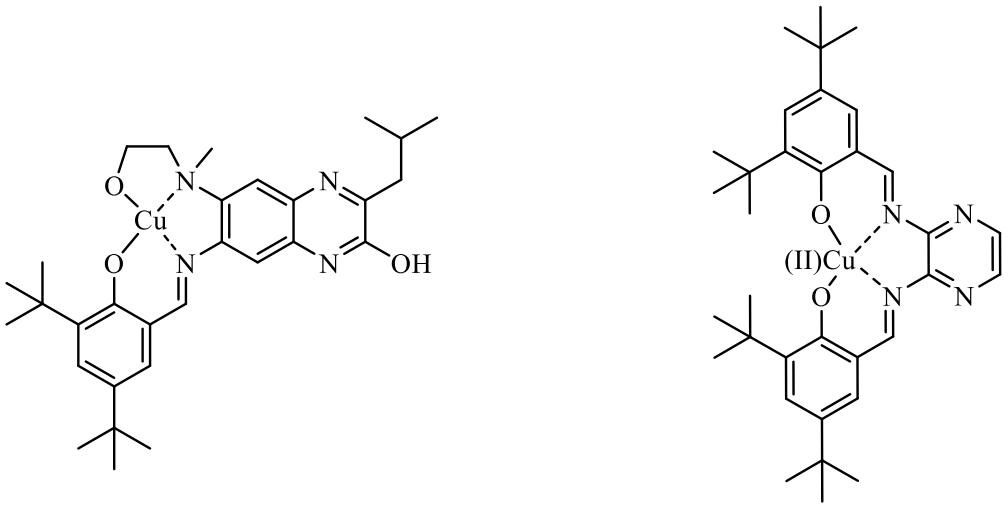
A new method was developed for the oxidation of propargylic C-H bonds using Cu(II)-salqu (**complex 1**) and TBHP. Extensive studies were done for the optimization of this transformation using 1-phenyl-1-pentyne as a model substrate. Throughout the optimization, using acetonitrile at 70 °C, 1 mol % Cu(II) salqu catalyst, and 4 equivalents of TBHP, gave the best overall yield (78 %) within a reaction time of 4 hours. This yield is very comparable to previous methods that use more expensive and toxic transition metals.[1,2] Once optimized, a substrate scope was conducted to test the versatility of this new method. Substrates containing both aromatic and aliphatic substituents worked well for this oxidation. The oxidation of terminal alkynes was addressed by first protecting the terminal C-H bond with TMS. Also, a water-soluble catalyst (**complex 2**) was used in an effort to provide an alternative to acetonitrile as the solvent. The aqueous reactions were very comparable in yield as compared to the organic solvent. This provides a much safer alternative for large scale oxidation reactions. A catalytic cycle was proposed involving two possible pathways for the oxidation of propargylic C-H bonds.



Complex 1 **Complex 2**

Figure 5.1. Cu(II) salqu (left) and sulfonated water soluble Cu(II) salqu (right).

The synthesis and characterization of 2 new salen type ligands was achieved (**complex 3** and **4**). These ligands were used to help understand the catalytic pathway of C-H oxidation reactions involving Cu(II)-salqu and TBHP. Unexpectedly, introducing a flexible binding pocket (**complex 3**) was inefficient at improving oxidations; however, we have proposed several reasons for these findings. The benzylic oxidation of diphenylmethane was carried out with a library of salen type ligands. In this study Cu(II)-salqu gave the best overall yield for the corresponding ketone. The heterocyclic backbone of Cu(II)-salqu helps to stabilize the Cu(III)/Cu(II) catalytic pathway that we believe these reactions proceed through.



Complex 3 **Complex 4**

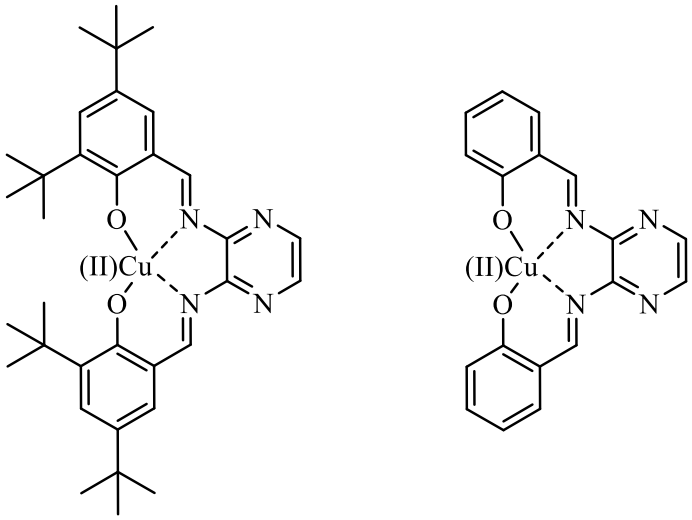
Figure 5.2. Copper(II) salen derivatives for C-H oxidation.

Next, we investigated the oxidative coupling of tertiary amines with Cu(II)-salqu. *N*,*N*-dimethylaniline can be coupled with 2-triisopropoxysilylfuran under mild conditions. Upon optimization, we are able to obtain a 98 % yield in only 4 h using 1 mol % of catalyst. A substrate scope was conducted on a wide range of cyclic and open chain tertiary amines producing yields from 54-98 %. Mechanistic studies were done including a correlation between $\log(k_x/k_H)$ and *para* position Hammett constants. From this, we determined the reaction has a buildup of an electron deficient intermediate in the rate determining step involving a SET from the amine. Also, intermediates were isolated in an effort to help determine the reaction pathway.

Future Work

Descriptors of Energy Landscape by Topological Analysis (Delta)

In an effort to better understand the mechanism of C-H oxidation reactions with Cu(II)-salqu, we have teamed up with a group of computational scientist. In this collaboration, method development is being done to help map the pathway of reactions using topological data analysis; however, the large framework of Cu(II)-salqu has proven difficult for calculating these energy landscapes. Because of the importance of the heterocyclic backbone, and the need to develop a smaller ligand, we have prepared **complex 4** as a model for Cu(II)-salqu. We have shown the effectiveness of **complex 4** in the benzylic oxidations of diphenylmethane, but much is left to be explored with this catalyst. Optimization of allylic and propargylic oxidations with **complex 4** will be done. Once optimized, we can use the experimental data as a comparison to the found computational results. We also propose the synthesis and characterization of **complex 5** as a way to further decrease the ligand framework. The di-*tert*-butyl groups are originally added to increase solubility of the ligand but should not participate in the catalytic activity. **Complex 5** can be synthesized by the condensation of salicylaldehyde and 2,3-diaminopyrazine. Once the synthesis is complete, we would then test the catalytic activity of this ligand and compare it to Cu(II)-salqu and **complex 4**.



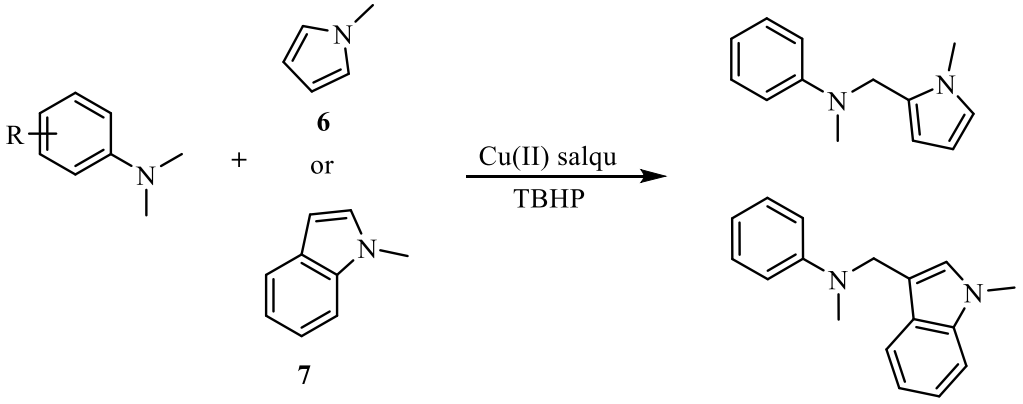
Complex 4 **Complex 5**

Figure 5.3. Cu(II)-pyrasal and proposed **complex 5** for C-H oxidations.

Oxidation of Amines

There is great interest in expanding the scope of oxidative Mannich reactions with Cu(II) salqu. A wide range of substrates were tested using 2-triisopropoxysilylfuran as the nucleophile; however, we would like to explore the use of other carbon nucleophiles for this C-C coupling reaction.[3] Because the proposed mechanism of Cu(II) salqu catalyzed oxidative Mannich reactions proceed through an electrophilic iminium ion, other nucleophiles should be available for the coupling of various compounds. Particularly, we will look at using pyrroles (**6**) and indoles (**7**) for the coupling of tertiary amines (**Scheme 5.1**). These two molecules are of interest because of their biological relevance throughout

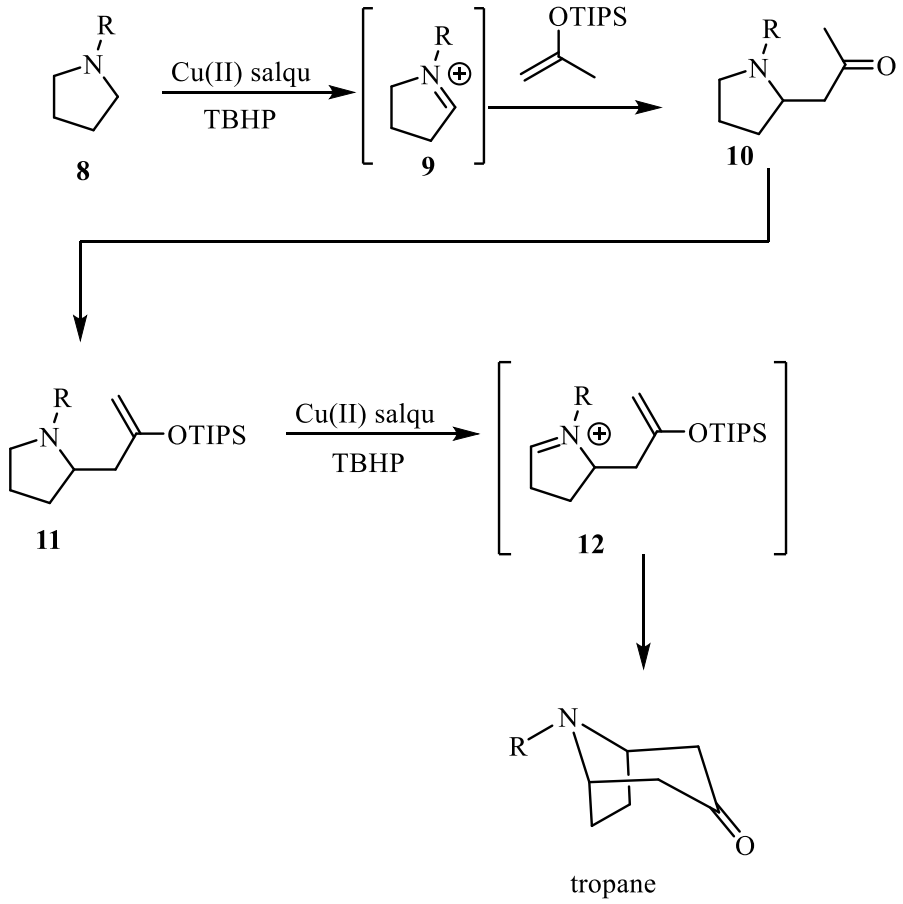
man made pharmaceuticals and natural products.[4] Previous studies have shown good results in nucleophilic reactivity of pyrrole and indole for the formation of C-C bonds.[5,6]



Scheme 5.1. Oxidative coupling reactions using *N*-methylpyrrole or *N*-methylindole as the nucleophile.

Also, of note would be the synthesis of tropane containing compounds using the oxidative Mannich chemistry developed in this dissertation. Tropane is an 8-azabicylo[3.2.1]octane that is abundant in many biologically active compounds such as atropine.[7] Some previous examples for the synthesis of tropane proceed through an intramolecular Mannich type cyclization.[8,9] Recently, Min et. al. reported the use of two oxidative Mannich reactions for the construction of tropane.[10] However, this method required strong oxidant (DDQ) and harsh reaction conditions ($LiClO_4$) at -40 °C. Here, we propose to use a milder approach for the formation of the key iminium ion intermediates (**9** and **12**). With the high yielding success with oxidizing 3° amines, we envision Cu(II) salqu with TBHP can carry out the oxidation of pyrrolidine (**8**) to the key iminium ion

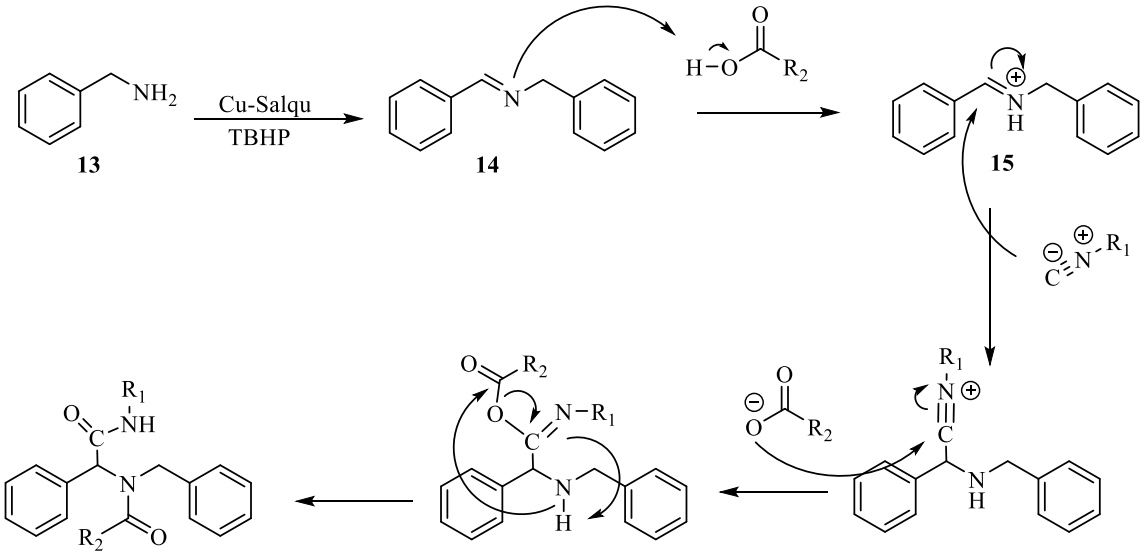
intermediate (**Scheme 5.2**). Once the electrophilic iminium is formed, a silyl enol ether could act as the nucleophile for the Mannich coupling to form compound **10**. A second intramolecular oxidative Mannich reaction can then be done on compound **11**, giving rise to tropane.



Scheme 5.2. Proposed synthesis of tropane utilizing Cu(II) salqu oxidation chemistry.

Stemming from the success with the oxidation of 3° amines, a logical extension of this program would be the oxidation of 2° and 1° amines for oxidative coupling reactions with Cu(II)-salqu. An optimization and substrate scope of various 1° and 2° amines can be tested with Cu(II) salqu and TBHP. If successful, this method could be used for a one-pot synthesis of dipeptides utilizing an oxidative Ugi reaction (**Scheme 5.2**).[11–14] Ugi reactions were first reported in 1959 by Ivar Karl Ugi, who used this method for the synthesis of bis-amides.[15,16] Since its report, much research and development has been done with this chemistry. In fact, in the last 20 years, over 1000 papers have been published on Ugi type reactions.[17–19] The proposed mechanism of Ugi type reactions proceed through an iminium ion intermediate, which we believe can be formed by oxidation chemistry with Cu(II) salqu. We envision the homocoupling of benzylamine (**13**) to *N*-benzylidine-1-phenylmethaneamine (**14**) can be carried out with Cu(II)-salqu and TBHP (**Scheme 5.3**). This oxidation should follow a similar SET mechanism as in the oxidative Mannich reactions. Once this transformation is optimized, the addition of a carboxylic acid would lead to the formation of an electrophilic iminium ion (**15**) which would then be intercepted by a nucleophilic cyano compound leading to a Ugi type mechanism. If successful, this efficient method could be used to create a wide range of different dipeptide compounds by substituting different R_1 and R_2 alkyl groups.

Ugi Type Reactions



Scheme 5.3. Synthetic strategy for Oxidative Ugi reaction with Cu(II)-salqu.

References

(1) McLaughlin, E. C.; Doyle, M. P. Propargylic Oxidations Catalyzed by Dirhodium Caprolactamate in Water: Efficient Access to α,β-Acetylenic Ketones. *J. Org. Chem.* **2008**, *73* (11), 4317–4319. https://doi.org/10.1021/jo800382p.

(2) Zhao, Y.; Ng, A. W. T.; Yeung, Y.-Y. Mild Propargylic Oxidation Using a Diacetoxyiodobenzene/Tert-Butyl Hydroperoxide Protocol. *Tetrahedron Lett.* **2014**, *55* (31), 4370–4372. https://doi.org/10.1016/j.tetlet.2014.06.032.

(3) Black, C. C.; Gorden, A. E. V. Oxidative Mannich Reactions of Tertiary Amines Using a Cu(II) 2-Quinoxalinol Salen Catalyst. *J. Org. Chem.* **2019**, *84* (15), 9806–9810. https://doi.org/10.1021/acs.joc.9b01409.

(4) Silakari, O. *Key Heterocycle Cores for Designing Multitargeting Molecules*; Elsevier, 2018.

(5) Lakhdar, S.; Westermaier, M.; Terrier, F.; Goumont, R.; Boubaker, T.; Ofial, A. R.; Mayr, H. Nucleophilic Reactivities of Indoles. *J. Org. Chem.* **2006**, *71* (24), 9088–9095. https://doi.org/10.1021/jo0614339.

(6) Nigst, T. A.; Westermaier, M.; Ofial, A. R.; Mayr, H. Nucleophilic Reactivities of Pyrroles. *Eur. J. Org. Chem.* **2008**, *2008* (14), 2369–2374. https://doi.org/10.1002/ejoc.200800092.

(7) Grynkiewicz, G.; Gadzikowska, M. Tropane Alkaloids as Medicinally Useful Natural Products and Their Synthetic Derivatives as New Drugs. *Pharmacol. Rep. PR* **2008**, *60* (4), 439–463.

(8) Hernández, A. S.; Thaler, A.; Castells, J.; Rapoport, H. Enantiospecific Synthesis of (+)- and (−)-Ferruginine from l-Glutamic Acid. Synthesis of Tropanes via Intramolecular Iminium Ion Cyclization. *J. Org. Chem.* **1996**, *61* (1), 314–323. https://doi.org/10.1021/jo9515081.

(9) Davis, F. A.; Theddu, N.; Gaspari, P. M. Asymmetric Synthesis of Substituted Tropinones Using the Intramolecular Mannich Cyclization Reaction and Acyclic N-Sulfinyl β-Amino Ketone Ketals. *Org. Lett.* **2009**, *11* (7), 1647–1650. https://doi.org/10.1021/ol9002948.

(10) Jo, H.; Hassan, A. H. E.; Jung, S. Y.; Lee, J. K.; Cho, Y. S.; Min, S.-J. Construction of 8-Azabicyclo[3.2.1]Octanes via Sequential DDQ-Mediated Oxidative Mannich Reactions of N-Aryl Pyrrolidines. *Org. Lett.* **2018**, *20* (4), 1175–1178. https://doi.org/10.1021/acs.orglett.8b00098.

(11) Dong, C.; Uematsu, A.; Kumazawa, S.; Yamamoto, Y.; Kodama, S.; Nomoto, A.; Ueshima, M.; Ogawa, A. 2,4,6-Trihydroxybenzoic Acid-Catalyzed Oxidative Ugi Reactions with Molecular Oxygen via Homo- and Cross-Coupling of Amines. *J. Org. Chem.* **2019**. https://doi.org/10.1021/acs.joc.9b01422.

(12) Ngouansavanh, T.; Zhu, J. IBX-Mediated Oxidative Ugi-Type Multicomponent Reactions: Application to the N and C1 Functionalization of Tetrahydroisoquinoline. *Angew. Chem.* **2007**, *119* (30), 5877–5880. https://doi.org/10.1002/ange.200701603.

(13) Dighe, S. U.; Kolle, S.; Batra, S. Iron-Catalysed Oxidative Ugi-Type Multicomponent Reaction Using (Arylmethyl)Amines as Imine Precursors. *Eur. J. Org. Chem.* **2015**, *2015* (19), 4238–4245. https://doi.org/10.1002/ejoc.201500464.

(14) Jiang, G.; Chen, J.; Huang, J.-S.; Che, C.-M. Highly Efficient Oxidation of Amines to Imines by Singlet Oxygen and Its Application in Ugi-Type Reactions. *Org. Lett.* **2009**, *11* (20), 4568–4571. https://doi.org/10.1021/ol9018166.

(15) Ugi, I.; Steinbrückner, C. Über Ein Neues Kondensations-Prinzip. *Angew. Chem.* **1960**, *72* (7–8), 267–268. https://doi.org/10.1002/ange.19600720709.

(16) Versammlungsberichte. *Angew. Chem.* **1959**, *71* (11), 373–388. https://doi.org/10.1002/ange.19590711110.

(17) Rocha, R. O.; Rodrigues, M. O.; Neto, B. A. D. Review on the Ugi Multicomponent Reaction Mechanism and the Use of Fluorescent Derivatives as Functional Chromophores. *ACS Omega* **2020**, *5* (2), 972–979. https://doi.org/10.1021/acsomega.9b03684.

(18) Boukis, A. C.; Reiter, K.; Frölich, M.; Hofheinz, D.; Meier, M. A. R. Multicomponent Reactions Provide Key Molecules for Secret Communication. *Nat. Commun.* **2018**, *9* (1), 1–10. https://doi.org/10.1038/s41467-018-03784-x.

(19) Chéron, N.; Ramozzi, R.; Kaïm, L. E.; Grimaud, L.; Fleurat-Lessard, P. Challenging 50 Years of Established Views on Ugi Reaction: A Theoretical Approach. *J. Org. Chem.* **2012**, *77* (3), 1361–1366. https://doi.org/10.1021/jo2021554.