β-DIKETIMINATO COPPER COMPLEXES
FOR C-H BOND FUNCTIONALIZATION

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By

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ABSTRACT

C-H amination is an attractive methodology for constructing C-N bonds from seemingly unreactive C-H bonds. This process reduces group manipulations and reaction by-products. C-H amination catalysts are usually rhodium and ruthenium-based, though many catalysts are developing based on more Earth abundant, less toxic metals (e.g., copper). Generally, these catalytic systems imply metal nitrene [M]=NR as intermediate, typically generated through iminoiodinane PhI=NR as nitrene source. This limits the amino group into electron poor moieties like N-sulfonyls or N-carbamoyls. Organoazides N₃R represent underutilized nitrene sources, which allows variable amino groups (N-alkyl, N-aryl, N-sulfonyl, N-phosphoryl, etc.) with N₂ as stoichiometric by-product. These [M]=NR species are proposed to either (a) concertedly insert the NR group into a C-H bond or (b) abstract a hydrogen atom (HAA) to produce a carbon-based radical and a metal amido species, which later captures the carbon-based radical (RC). The ability to observe, isolate and characterize these intermediates leads to development of more efficient and selective catalytic protocols.

This thesis centers on β-diketiminato copper catalyzed C-H amination using organoazides as nitrene sources. Mechanistic studies employing the isolable
intermediate dicopper alkynitrene \{[\text{Cl}_2\text{NN}]\text{Cu}\}_2(\mu-\text{N}^3\text{Bu})\) establishes the intermediacy of terminal copper nitrene \([\text{Cl}_2\text{NN}]\text{Cu}=\text{N}^3\text{Bu}\) in C-H amination via HAA / RC. Organoazide scope is explored including primary, secondary and tertiary alkylazides and arylazides. Experiments show intramolecular \(\alpha\)-H migration and diazene formation as competing reactions involving copper nitrenes.

The reactivity of \([\text{Cl}_2\text{NN}]\text{Cu}=\text{NR}\) (\(R = 1\)-adamantyl or tert-butyl) towards unactivated C-H bond is investigated. Amination is generally favored at the weaker tertiary or secondary C-H bonds. Copper nitrene \([\text{Cu}]=\text{NR}\) may also be employed as HAA reagent for functionalizing C-H bonds with functional groups (FG) other than the \([\text{Cu}]-\text{NHR}\) that results from HAA. Stoichiometric and catalytic reactions of \{[\text{Cl}_2\text{NN}]\text{Cu}\}_2(\mu-\text{NR})\) and \([\text{Cl}_2\text{NN}]\text{Cu}^{\text{II}}-\text{FG}\) (FG = N-aryl, nitromethyl, phenoxy) in ethybenzene result to new C-FG bonds.

Since nitrene (-NR) and oxo (-O) functionalities are isoelectronic, the chemistry of dicopper oxo species \([\text{Cu}]_2(\mu-\text{O})\) is also surveyed. Isolation of linked \(\beta\)-diketiminato dicopper(I) complexes is presented. Through these dicopper(I) complexes, the cooperative nature of two copper centers in activating small molecules such as dioxygen, peroxides and azides is explored in initial reactivity studies.
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RESPECTIVE CONTRIBUTIONS

Dr. Yosra Badiei’s initial efforts involving reactions of N\textsubscript{3}Ad with the stereochemical probes *cis* and *trans*-1,4-dimethylcyclohexane and her initial identification of the α-H migration pathway in copper alkynitrenes provided a helpful starting point for work in Chapter 2. Similarly, Dr. Badiei’s initial synthesis, isolation and preliminary reactivity studies of \{[Cl\textsubscript{2}NN]Cu\}\textsubscript{2}(μ-NMes) provided a convenient entry to the new work presented in Chapter 3. Dr. Ryan Hadt and Prof. Edward Solomon of Stanford University collected the resonance Raman spectra presented in Chapter 5.

Undergraduate students have been instrumental in the development of the research projects presented in this thesis. Mohammad Ali worked on the isolation of dicopper arynitrene \{[Cl\textsubscript{2}NN]Cu\}\textsubscript{2}(μ-NArp\textsuperscript{p-CN})\{[Cl\textsubscript{2}NN]Cu\} (4) and studied the reactivity of arylazides in C-H amination as presented in Chapter 3. Allison Harrigan was very adept in the isolation and characterization of the first examples of linked β-diketiminato copper complexes that were presented in Chapter 5: \{[^iPr\textsubscript{2}NN-O-Cu\textsubscript{2}](CN\textsuperscript{i}Bu)\}\textsubscript{2} (3), \{[^iPr\textsubscript{2}NN-C\textsubscript{2}-Cu\textsubscript{2}](CNAr)\}\textsubscript{2} (4) and \{[^iPr\textsubscript{2}NN-C\textsubscript{2}-Cu\textsubscript{2}](2pic)\}\textsubscript{2} (5). Sophia Chung was helpful in the study of the reactivity of 5 as shown in Chapter 5.
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CHAPTER 1

Metal Nitrenes in C-H Amination
Abstract

C-H amination has developed into a very promising synthetic protocol for organic synthesis, since this provides a direct path for introducing amino groups into seemingly unreactive C-H bonds. In this chapter, a summary of the transition metal-catalyzed C-H amination reactions of $sp^3$ C-H bonds using organic azides N$_3$R as a nitrene [NR] source is presented, with a focus on late transition metals (Groups 8 - 11). Both intramolecular and intermolecular reactions are considered. In addition, we review legitimate examples of late transition metal nitrene / imido complexes that are isolated and/or spectroscopically characterized that also engage in stoichiometric C-H amination.
Introduction

Organic compounds with carbon-heteroatom bonds are considered more valuable than those containing solely carbon-hydrogen bonds, since simple alkanes are generally not considered as functional groups. Typically, organic syntheses of these more complex functionalized organic compounds are through functional group transformations. These are mostly multi-step and energy-intensive processes that often result in synthetic by-products that add to the environmental impact of these transformations.

C-H functionalization is the direct conversion of C-H bonds to C-X bonds (X = any atom, not H). A major advantage of this process is its promise for high synthetic efficiency, which makes it generally more economically friendly. When focusing on $sp^3$ hybridized C-H bonds as targets for C-H functionalization, one needs to consider the inherent high bond dissociation energies (BDEs) of C-H bonds, which is typically around 96 - 110 kcal/mol if purely unactivated. Such C-H BDEs can be somewhat lower (75 – 95 kcal/mol) when adjacent to heteroatoms or unsaturated sites. Alkanes do not have the π-electrons and/or empty low-lying $\pi^*$ molecular orbitals present in alkenes, alkynes or aromatics, which improve coordination to metal due to greater nucleophilicity or ability to $\pi$-backbond. Instead, alkane frontier molecular orbitals consist of filled $\sigma$ and empty $\sigma^*$ levels, which are lower and higher in energy than corresponding $\pi$ and $\pi^*$ levels in unsaturated species, leading to lower reactivity. In addition, selectivity is an important issue because C-H bonds are the basic units in all molecules, making it more difficult to choose which bond to functionalize in a complex molecule. Thus, the discovery of robust catalysts for selective C-H bond functionalization is challenging but highly rewarding research.
Amines are important functional groups found in many small or complex molecules, especially in bioactive natural products and pharmaceuticals. Transition metal-catalyzed C-H aminations are typically metal nitrene-based, $[\text{M}]=\text{NR}$, although there are also examples of non-nitrene-based protocols. These metal nitrenes are generally proposed to formally insert the nitrene $[\text{NR}]$ unit into C-H bonds by two general mechanisms: asynchronous concerted and stepwise hydrogen atom abstraction / radical capture (HAA / RR) (Scheme 1.1).

**Scheme 1.1.** General mechanisms for C-H amination by metal nitrenes.

![Scheme 1.1](image)

Iminioiodinanes such as PhI=NTs are widely used nitrene sources which may be isolated or generated *in situ* from sulfonamide or carbamate precursors along with iodine(III) reagents such as PhI(OAc)$_2$ (Figure 1.1). Iminioiodinanes PhI=NR are used with a wide variety of metal complexes such as dirhodium(I/II), ruthenium(III), cobalt(II), copper(I) and iron(III) species as catalysts for nitrene (NR) transfer. A shortcoming of this methodology is the production of iodobenzene (PhI) as by-product, aside from the high costs of Rh and Ru which are the most used catalysts with this nitrene source. Related nitrene sources are the salts of $N$-halo-$p$-toluenesulfonamides (haloamides), chloramine-$T$, chloramine-$N$ or bromamine-$T$. These
salts are inexpensive and environmentally benign with sodium halide as by-product. These two types of nitrene sources are very efficient nitrene group transfer agents, although they can only introduce amino groups with electron withdrawing (e.g. tosyl) substituents.

Organic azides as nitrene sources for \( sp^3 \) C-H amination

Organic azides are atom-economical and environmentally benign nitrene sources (Figure 1.1).\textsuperscript{22,23} They are readily available or easily prepared, where R = alkyl or aryl groups that can be varied to allow for electronic and steric tunability.\textsuperscript{23} One of the earliest examples of C-H amination via organic azides is from Lwowski and Maricich\textsuperscript{22,24,25} who generated carbethoxynitrene from the photolysis of ethyl azidoformate (Scheme 1.2). The reaction of this nitrene with 2-methylbutane is more selective towards tertiary C-H bonds. Kwart and Kahn in
1967 showed copper-catalyzed nitréne group transfer reaction of cyclohexene using benzenesulfonyl azide resulting in C-H amination, aziridination and benzenesulfonyl amine as products (Scheme 1.3). The authors implicated a copper nitréne, Cu=NSO$_2$Ph, as the agent for the nitréne group transfer for the addition and insertion reactions. In this section, late transition metal-catalyzed $sp^3$ C-H amination reactions using organic azides as nitréne group transfer agent are presented, first focusing on intramolecular examples and then discussing intermolecular transformations.

**Scheme 1.2.** C-H insertion of carbethoxynitréne, generated from the photolysis of ethyl azidoformate, into 2-methylbutane.

Statistically Corrected Reactivities $1^\circ$: $2^\circ$: $3^\circ = 1: 10: 25$ (analyzed by vapor phase chromatography 5-m column, 20% cyanosilicon XF 1150 on chromosorb at 125 °C)

**Scheme 1.3.** Nitréne group transfer reaction of benzenesulfonyl azide to cyclohexene, catalyzed by copper powder.
1.2.a. Intramolecular C-H Amination

The Zhang group used cobalt porphyrin [Co\textsuperscript{II}(Por)] complexes (Figure 1.2) as catalysts for the intramolecular C-H amination of arylsulfonyl,\(^{27}\) phosphoryl\(^{28}\) and sulfamoyl azides.\(^{29}\) They found that cobalt(II) tetraphenylporphyrin [Co\textsuperscript{II}(TPP)] is suitable for catalysis of a variety of arylsulfonyl azides resulting to benzosultam derivatives with differing substitutions on the aromatic ring (Scheme 1.4).\(^{27}\) Yields are generally excellent, with tertiary C-H bonds as the most

\[ \text{Scheme 1.4} \]

![Catalysts](image)

**Figure 1.2.** Cobalt(II) porphyrin catalysts used for intramolecular C-H amination.
reactive, followed by secondary, and least is the primary ones. If the *ortho*-alkyl group of the arylsulfonyl azides is longer than ethyl, both five- and six-membered rings are formed (Scheme 1.5). They found that cobalt(II) octaethylporphyrin \([\text{Co}^{II}\text{(OEP)}]\) (Figure 1.2) is more selective for the formation of five-membered rings (73 %), along with the six-membered ring product gave an excellent combined yield of 92 %.\(^{27}\)

**Scheme 1.4.** \([\text{Co}^{II}\text{(TPP)}]\)-catalyzed intramolecular C-H amination of arylsulfonyl azides.

\[
\begin{align*}
\text{R} & \quad \text{[Co}^{II}\text{(TPP)] (2 mol %)} \\
& \quad \text{80 °C, 18 h, C}_6\text{H}_5\text{Cl} \\
\end{align*}
\]

yield = 87 - 99%

**Scheme 1.5.** Selectivity of cobalt(II) porphyrin-catalyzed formation of five- and six-membered rings from arylsulfonyl azides.

\[
\begin{align*}
\text{Pr} & \quad \text{[Co}^{II}\text{(Por)] (2 mol %)} \\
& \quad \text{80 °C, 18 h, C}_6\text{H}_5\text{Cl} \\
\end{align*}
\]

\([\text{Co}^{II}\text{(TPP)}]: A = 56\%, B = 44\%; \text{yield 94%}; [\text{Co}^{II}\text{(OEP)}]: A = 73\%, B = 27\%; \text{yield 92%}\)

They further developed Co(II) porphyrin-based catalysts for the intramolecular C-H amination of phosphoryl azides, forming the six- and seven-membered heterocycles with O-P-N connection.\(^ {28}\) Using either 2 mol % \([\text{Co}^{II}\text{(P1)}]\) or 1 mol % \([\text{Co}^{II}\text{(P2)}]\) (Figure 1.2), a series of 6-membered cyclophosphoramidates were synthesized in good yields (Scheme 1.6.a). If \(R^2\) is
longer than methyl, a mixture of *trans*- and *cis*-isomers are obtained, though diastereomeric ratios (dr) are not outstanding, except for $R^2 = \text{-CH}_2\text{Ph}$ (dr = 91/9). No aziridination product nor C-H amination product from functionalization of a primary C-H bond is observed if $R^2$ is $\text{-CH}_2\text{CH}=\text{CH}_2$. If $R^2$ is *tert*-butyl group, primary C-H bond is aminated, giving the 7-membered cyclophosphoramidates in relatively good yields (Scheme 1.6.b). Deprotection of the phosphoryl group can lead to synthetically useful 1,3- and 1,4- amino alcohols.

**Scheme 1.6.** Formation of 6- and 7-membered cyclophosphoramidates using cobalt(II) porphyrin as catalysts.

* A. Formation of 6-membered ring

![Scheme 1.6 (A)](image)

* B. Formation of 7-membered ring

![Scheme 1.6 (B)](image)

They extended the application of [Co$^{II}$(P1)] as catalyst for the intramolecular C-H amination of sulfamoyl azides that results in a variety of cyclic sulfamides through 1,6-nitrene insertion in excellent yields (Scheme 1.7). The protocol developed works well with 3° and 2° C-H bonds, as well as with stronger 1° C-H bonds. Experiments that examine the
stereospecificity of the transformations were performed on enantiomerically pure sulfamoyl azides to gain insight into the mechanism of the reaction. Product 1.7.A is obtained in low yield and fair enantiomeric excess (ee), suggesting that (a) the reaction involves radical intermediates and (b) a partial racemization of the tertiary carbon radical adjacent to the phenyl group occurred. Changing the Ph group with a bulkier alkyl group which cannot racemize, a higher yield and ee is gathered for product 1.7.B. Both products are derived from an azide of opposite configuration. Using a cyclopropyl probe, two products are obtained. The major product is the 1,6-nitrene

**Scheme 1.7.** [Co^{II}(P1)]-catalyzed synthesis of cyclic sulfamides.
insertion product containing an intact cyclopropyl unit derived from intermediate 1.7.E (Scheme 1.7.C). A minor seven-membered ring product is observed that results from the rearrangement of the cyclopropyl unit derived from intermediate 1.7.F. Removal of SO$_2$ from these sulfamide products gives the valuable 1,3-diamines. They later showed that if R$^1$ is benzyl and R$^2$ is electron-withdrawing (-CO$_2$NH$_2$, -CO$_2$Me, -CO$_2$Bu, -CN), yields and dr are improved. Deprotection of these products leads to α-amino acid derivatives.$^{30}$ Addition of (2,2,6,6-tetramethylpiperidin-1-yl)oxy (TEMPO) as trap for the carbon-based radical decreased the conversion of the azide by 10%, providing support for a stepwise mechanism with a kinetic isotope effect (KIE) of 6.6 for R$^2$ = -CO$_2$Me.

The Driver group has examined intramolecular $sp^3$ C-H amination using ortho-substituted aryl azides. They reported an Ir(I)-catalyzed amination of ortho-homobenzyl-substituted aryl azides forming indolines in good yields at ambient temperatures (Scheme 1.8).$^{31}$ Some of the indolines probably oxidized further to form indole. Electron-withdrawing R$^1$ or R$^2$ substituents on the azide improved the yields, especially with -CF$_3$ groups. It is also necessary to have one of R$^3$ or R$^4$ as aromatic group, and the other one as H. They proposed an iridium nitrenoid intermediate based on their kinetic isotope experiment (Scheme 1.8.A). They then reported Rh$_2$(esp)$_2$ (Figure 1.3) as efficient catalyst for aliphatic C-H amination with ortho-substituted arylazides as nitrene source (Scheme 1.9). In the presence of Boc$_2$O to protect the amine, they have shown both electron-rich and electron-poor arylazides can be introduced. They proposed a stepwise mechanism based on the scrambling in the product distribution upon isotope labeling experiments (Scheme 1.9.A). Using a cyclopentanone-derived arylazide resulted to an intramolecular C-H amination product from the syn C-D bond cleavage (Scheme 1.9.B).$^{32}$
Scheme 1.8. Ir(I)-catalyzed intramolecular amination of *ortho*-substituted aryl azides.

Figure 1.3. Structures of some of the catalysts discussed in section 1.2.a.
Che and co-workers showed moderate yields for the amination of C-H benzylic C-H bonds of the ortho-phenylethyl or phenylpropyl groups of the aryl azides resulting in indoline and tetrahydroquinoline products using 2 mol% iron(III) mesotetrakis(pentafluorophenyl)porphyrin chloride [Fe^{III}(F_{20}TPP)Cl] (Figure 1.3, Scheme 1.10.A).\textsuperscript{33}

Amination typically occurs at the benzylic 2° and 3° C-H bonds. They also described the synthesis of dihydroquinazolinone and quinazolinone from ortho-azidobenzamide derivatives (Scheme 1.10.B). In this case, even the 1° C-H bonds adjacent to N are aminated. Yields are moderate, ranging between 63-83%. Changing the metal to Ru, they reported the use of [Ru^{IV}(F_{20}TPP)Cl]\textsubscript{2} (Figure 1.3) in intramolecular C-H amination of phosphoryl azide, forming the five- and six-membered cyclophosphoramidates in excellent yields (Scheme 1.10.C).\textsuperscript{34}
Simple iron salts like FeBr$_2$ have been used by the Driver group as catalyst for the tandem reaction of intramolecular C-H amination and [1,2]-alkyl or aryl shift of ortho-substituted arylazides (Scheme 1.11). They found that the migratory aptitude of migrating group (MG) is in the order Me < 1° < 2° < Ph. The iron may have dual functions as nitrene group transfer catalyst and as Lewis acid for the migration step. They were able to isolate probable heterocyclic intermediates (Scheme 1.11.A and 1.11.B). The presence of A1 as the only product from the amination step, with the cyclopropyl group still intact, suggests that the C-N bond
formation from the iron nitrene intermediate is concerted; product A2 is the oxidized-migration product of A1. The Lewis acidic iron center then coordinates to the -OEt group encouraging the formation of the iminium ion, which makes the migration step non-dependent on iron. A simplified mechanistic cycle is presented in Scheme 1.12.

**Scheme 1.11.** Fe$^{II}$-catalyzed tandem C-H amination and [1,2]-migration.

Recent work by Hennessy and Betley$^{35}$ showed the wide applicability of [Fe$^{II}$(dipyrrinato)] (Figure 1.3) as catalyst for the preparation of Boc- and Fmoc-protected pyrrolidine from unactivated and mildly activated alkylazides in relatively good yields (Scheme 1.13).$^{36}$ Product yield correlates with C-H bond strength, favoring benzylic, allylic and tertiary C-H bonds. It seems that 6-membered ring (piperidine) formation is favored by having a phenyl group as activating group on the C-H bond (e.g. 1-azido-5-phenylpentane), whereas a 4-
membered ring (azetidine) is unexpectedly observed from 2-azido-2,5,5-trimethylhexane as substrate. They proposed a stepwise mechanism for the reaction, because KIE observed is around 5.0 (at 23 or 60 °C), common to a HAA / RC process (Scheme 1.13.A). Although no scrambling on the stereochemistry of the product when (R)-2-phenyl-5-azidopentane (Scheme 1.13.B) is used nor ring opening from the clock substrate (2-(4-azidobutyl)cyclopropyl)benzene (Scheme 1.13.C) are observed. While these results may suggest a concerted mechanism, the authors favor a HAA / RC mechanism in which the intermediate radical is extremely rapidly captured by the iron-amide [Fe]-NHR intermediate. They proposed a defined arrangement of the Fe-imido radical in which the imido radical lies on the plane of iron and ligand, with the bulky Ad groups

**Scheme 1.12.** Simplified mechanistic cycle for the Fe$^{II}$-catalyzed tandem C-H amination and [1,2]-migration.
slightly locking this arrangement (Figure 1.4). This requires a certain position for the C-H substrate for HAA to occur which is assisted by having it attached to iron imido moiety already (less reorganization required). Once this is achieved, RC is now much favored, resulting to a faster rate. This report poised a very promising protocol for the catalytic formation of high-valued \( N \)-heterocycles, using alkylazides.

**Scheme 1.13.** \( N \)-heterocyclic synthesis catalyzed by \([\text{Fe}^{II}(\text{dipyrrinato})]\) complex.

![Scheme 1.13](image)

Katsuki *et al.* reported a highly enantioselective intramolecular benzylic C-H amination of sulfonyl azides using the chiral \([\text{Ir}^{III}(\text{salen})]\) complex (Figure 1.3, Scheme 1.14).\(^{37}\) For various
substituted 2-ethylbenzenesulfonyl azides, a 5-membered ring is formed from reaction at the benzylic position, in high yield and good enantioselectivity. In contrast, for other 2-alkyl substituted benzenesulfonyl azides, the homobenzylic (β) C-H bond is also functionalized aside from the benzylic (α) bond, resulting to the 6-membered sultam, chemoselectivity for the 5-membered is better but ee is generally higher for the 6-membered ring. They also tried the catalyst for the cyclization of sulfamoyl azide, in low yield but high enantioselectivity (Scheme 1.14.A). Catalytic desymmetrization of prochiral sulfonyl azide gave tricyclic sultam in a moderate yield and high enantioselectivity (Scheme 1.14.B).

**Scheme 1.14.** Enantioselective synthesis of benzosultams using [Ir<sup>III</sup>(salen)] complex.
1.2.b. Intermolecular C-H Amination

Cenini, Gallo and co-workers may have started the resurgence of using azides as nitrene source towards development of catalysts for intermolecular \( sp^3 \) C-H bond amination.\(^{38} \) In conjunction with ruthenium- and cobalt-porphyrins ([Ru\(^{II}\)(TPP)CO, Ru\(^{II}\)(OEP)CO, [Co\(^{II}\)(OEP)], (see Figure 1.2 for ligand structures), they found that while larger cyclic olefins were aziridinated with \( p \)-nitrophenyl azide (N\(_3\)Ar\(^p\)-NO\(_2\)), nitrene group transfer reaction of cyclohexene gave the inserted product allylic amine, a small amount of aziridine, with aniline as the major by-product (Scheme 1.15).\(^{38} \) They also showed that the reaction is sensitive to the nature of the azide. In contrast to the reaction with N\(_3\)Ar\(^p\)-NO\(_2\) which gives aniline as the side product, use of the more electron-rich \( p \)-methoxyphenyl azide (N\(_3\)Ar\(^p\)-OMe) with [Ru\(^{II}\)(TPP)CO] as catalyst gave the allylic amine, aniline and diazene (p-OMeArN=NAr\(^p\)-OMe). Expanding on the olefin substrate for the [Co\(^{II}\)(TPP)]-catalyzed allylic amination (and aziridination), they found that allylic amination is favored over aziridination for cyclohexene and methyl-substituted cyclohexene, but not for cyclopentene and \( \alpha \)-methylstyrene (Scheme 1.15).\(^{39} \) Gallo et al. reported that allylic amination of neat olefin catalyzed by [Ru\(^{II}\)(TPP)CO] led to better yields of allylic amine products and no aziridines: cyclopentene seemed to work especially well with the catalyst, although linear terminal olefins (e.g. 1-octene) did not.\(^{40} \) Regardless of the electron-rich or electron-poor nature of the arylazide substituent, good yields of the allylic products were obtained, except for N\(_3\)Ar\(^p\)-OMe which they account to deactivation of the catalyst via possible coordination of the methoxy group of the azide. Olefins which have both allylic and benzylic C-H bonds resulted to reduced selectivity for the allylic site. Cenini et al. also reported chiral Co(II)- and Ru(II)-porphyrin complexes with TmyrtP (meso-tetrakis[(1R)-apopinen-2-yl]porphyrin) as possible catalyst for allylic amination (Figure 1.5).\(^{41} \) The yields of allylic amines of cyclohexene did not improve...
much compared with $[\text{Co}^{\text{II}}(\text{TPP})]$ and $[\text{Ru}^{\text{II}}(\text{TPP})\text{CO}]$ and aziridination is still favored over amination for $\alpha$-methylstyrene.

**Scheme 1.15.** $[\text{Co}^{\text{II}}(\text{TPP})]$-catalyzed allylic amination (and aziridination) of olefins.

**Figure 1.5.** Structures of some of the catalysts discussed in section 1.2.b.
Cenini, Gallo and co-workers continued the use of \([\text{Co}^{II}(\text{TPP})]\)\(^{42-44}\) and \([\text{Ru}^{II}(\text{TPP})\text{CO}]\)\(^{45}\) for benzylic C-H bond amination using these arylazides. For the \([\text{Co}^{II}(\text{TPP})]\)-catalyzed reactions, inserted amine products were formed in fair yields, with the aniline and diazenes as the major by-products (Scheme 1.16.A). The inserted amine product is oxidized further to imine, when \(R^1\) or \(R^2 = H\). The reaction seems to be sensitive to the nature of the \(p\)-substituents of the arylazides, the more electron-withdrawing the group is, the better the chance of isolating the inserted product and not the imine.\(^{42,43}\) Competition reactions of toluene and \(p\)-substituted tolenes with \(p\)-bromophenyl azide were done and a good correlation between the log \(k_r\) and radical effects (\(\sigma'_{JJ}\)), suggesting a mechanism that is radical-based.\(^{43}\) Gallo et al. reported the \([\text{Ru}^{II}(\text{TPP})\text{CO}]\)-catalyzed benzylic C-H amination using arylazides, with similar trends as that of observed from \([\text{Co}^{II}(\text{TPP})]\); electron-poor arylazides gave higher yields of aminated products.

**Scheme 1.16.** Benzylic C-H amination using \([\text{M}^{II}(\text{TPP})]\) as catalysts.

**A. Co-catalyzed**

\[
\begin{align*}
\text{R}^1 \text{H} & \quad \text{[Co}^{II}(\text{TPP})] \quad 70^\circ C, -\text{N}_2 \\
\text{+ N}_3\text{Ar}^X & \quad \text{R}^1\text{NHAr}^X & \quad \text{+ NH}_2\text{Ar}^X & \quad \text{+ Ar}^X\text{N}=\text{NAr}^X \\
\text{Yield 15-55\%} & \quad \text{aniline} & \quad \text{diazene} \\
\end{align*}
\]

**B. Ru-catalyzed**

\[
\begin{align*}
\text{R}^1 \text{H} & \quad \text{[Ru}^{II}(\text{TPP})\text{CO]} \quad 100^\circ C, -\text{N}_2 \\
\text{+ N}_3\text{Ar}^X & \quad \text{R}^1\text{NHAr}^X & \quad \text{+ NH}_2\text{Ar}^X \\
\text{Yield 14-80\%} & \quad \text{aniline} \\
\end{align*}
\]
The over oxidation of the inserted amine product is only observed for toluene for this system.\textsuperscript{45}

The Zhang group reported a $[\text{Co}^{\text{II}}(\text{Por})]$ complexes in intermolecular C-H amination using 2,2,2-trichloroethylcarbonyl azide ($\text{N}_3\text{Troc}$).\textsuperscript{46} Moderate to high yields of benzylic amination products were derived from various C-H substrates, which include substituted toluenes and naphthalene (Scheme 1.17). Even the quite electron deficient substrates like ethyl phenylacetate gave an $\alpha$-amino acid derivative, albeit in low yield.

Scheme 1.17. $[\text{Co}^{\text{II}}(\text{TPP})]$-catalyzed benzylic C-H amination using $\text{N}_3\text{Troc}$.

Che and co-workers also applied the iron- and ruthenium-porphyrin complexes, $[\text{Fe}^{\text{III}}(\text{F}_{20}\text{TPP})\text{Cl}]^{33}$ and $[\text{Ru}^{\text{IV}}(\text{F}_{20}\text{TPP})\text{Cl}_2]^{34}$ (Figure 1.3 for ligand structure), in benzylic and allylic C-H amination. Iron-catalyzed allylic amination of $\alpha$-methylstyrenes and $sp^3$ amination of benzylic, allylic and unactivated (in cyclic structures) C-H bonds were effected using sulfonyl and arylazides (Scheme 1.18.A).\textsuperscript{33} They also showed that microwave conditions generally decrease the time of reaction with comparable yields, especially those for saturated, unactivated C-H bonds of cyclic alkanes. On the other hand, Ru-catalyzed amination of various
hydrocarbons using bis(2,2,2-trichloroethyl) phosphorazidate gave moderate yields for benzylic, allylic and saturated 2° C-H bonds of cyclic and linear alkanes (Scheme 1.18.B). A KIE value of 2.1 is obtained using cyclohexane and cyclohexane-$d_{12}$ as substrates, which suggests a stepwise hydrogen atom abstraction / radical capture mechanism.

**Scheme 1.18.** [M(F$_{20}$TPP)]-catalyzed amination of benzylic, allylic and saturated C-H bonds using various azides.

\[
\begin{align*}
A. \quad & \begin{array}{c}
\text{CH}_3 \\
\text{Ar} = \text{aryl, sulfonyl}
\end{array} \quad + \quad \begin{array}{c}
\text{N}_3\text{Ar} \\
\text{Ar} = \text{aryl, sulfonyl}
\end{array} \\
& \xrightarrow{[\text{Fe}^{III}(\text{F}_{20}\text{TPP})\text{Cl}]} \\
\begin{array}{c}
\text{O} \\
\text{H}
\end{array} \quad \text{R}_1 \quad \text{Yields: 17-83%}
\end{align*}
\]

\[
\begin{align*}
B. \quad & \begin{array}{c}
\text{H} \\
\text{R}_1 \quad \text{R}_2
\end{array} \quad + \quad \begin{array}{c}
\text{N}_3\text{Ar} \\
\text{OCH}_2\text{CCl}_3
\end{array} \\
& \xrightarrow{[\text{Ru}^{IV}(\text{F}_{20}\text{TPP})\text{Cl}_2]} \\
\begin{array}{c}
\text{HN} \\
\text{P}(\text{OCH}_2\text{CCl}_3)_2
\end{array} \quad \text{R}_1 \quad \text{R}_2 \quad \text{Yields: 64-80%}
\end{align*}
\]

Switching to [Ru(salen)CO] (Figure 1.3 for structure of ligand, R$^2$ = C$_6$H$_5$), Katsuki et al. showed that C-H amination was effected into allylic C-H bonds by $p$-toluenesulfonyl azide ($p$-N$_3$SO$_2$C$_6$H$_4$CH$_3$). They found that allylic amination is favored over aziridination for olefins with substituents trans to the aromatic ring (Scheme 1.19). They suggested that the olefin approach the Ru-nitrenoid in a skewed-perpendicular fashion, favoring the allylic C-H bond of the E-substituent.
The Warren group showed that the application of β-diketiminato copper(I) complex [Cl₂NN]Cu (Figure 1.5) for the catalytic C-H amination of secondary and benzylic $sp^3$ C-H bonds with N₃Ad, showing the first example of using an unactivated alkylazide as nitrene source (Scheme 1.20). Heating N₃Ad in neat toluene, ethylbenzene and indane at 110 °C gave the benzylic inserted products in 90% or greater yields. With the amination of the stronger C-H bond of cyclohexane as a substrate, longer reaction times or microwave heating was required to obtain a higher conversion. Catalytic amination of ethylbenzene was also achieved even at low catalyst loading (0.05 mol%) in high yield (90 %) corresponding to a turnover number (TON) of 900. From the competition experiments employing 5 equivalents substrates showed dependence of the catalytic rate of the reaction on C-H bond dissociation energy of the benzylic and secondary $sp^3$ C-H substrate. They found that KIE values of 5.3(2) and 6.6(1) were observed for ethylbenzene

Scheme 1.19. Allylic amination using $p$-toluenesulfonyl azide and chiral [Ru(salen)CO] as catalyst.
and cyclohexane at 110 °C, respectively, consistent with their suggested stepwise pathway of hydrogen atom abstraction / radical capture (HAA / RC) mechanism. A recent kinetic and stereochemical report emphasized on the intermediacy of mononuclear [Cu]=NR as intermediates via this HAA / RC mechanism. Details on these studies are presented in Chapter 2.

**Scheme 1.20.** [Cl₂NN]Cu-catalyzed amination of benzylic and secondary $sp^3$ C-H bonds using N₃Ad.

Betley and co-workers reported the use of [Fe⁺(dipyrrinato)] complex (Figure 1.3, $Ar' = 2,4,6$-trimethylphenyl or mesityl, $L = Et_2O$) as an efficient intermolecular C-H amination catalyst for the benzylic C-H bond of toluene. Reaction with N₃Ad with toluene at RT gave a mixture of benzyladamantylamine (PhCH₂NHAd, 95%), benzyldamantylamine (PhCH=NAd, 2.8%) and adamantylamine (1.8%). Turnover for the reaction at RT was determined as 6.7, which increased to 10 upon heating to 60 °C, although further heating tended to lower TON. They also observed the formation of the 1,2-diphenylethane at higher temperatures, which they attribute to coupling of two PhCH₂• radicals, formed upon HAA of the azide-derived iron imido complex.
Polyfluoroalkanesulfonil azides are very electrophilic and reactive, but because most examples are pretty hazardous (especially the simplest version triflyl azide), these compounds are hardly used in nitrene group transfer chemistry.\(^5\) Although in recent years, the higher molecular weight versions like nonafluorobutanesulfonil azide (\(N_3SO_2CF_2CF_2CF_3\)) was found to be useful and efficient nitrene group transfer agent. Suarez and Chiara reported amination of various benzylic and cyclic substrates using \(N_3SO_2CF_2CF_2CF_3\) and dirhodium tetraacetate (\(Rh_2(OAc)_4\), Figure 1.5) as catalyst (Scheme 1.21).\(^5\) Aromatic compounds were selectively aminated at the benzylic position in moderate to good yields. No reaction was observed for aromatic substrates with substituents other than alkyl. Amination of cyclic hydrocarbons happened with a preference for the tertiary C-H bonds, although steric access may direct amination on the stronger secondary C-H bonds. They reported a KIE value of 2.47 at 90 °C for cyclohexane and cyclohexane-\(d_{12}\), suggesting a concerted nitrene insertion mechanism.

**Scheme 1.21.** Amination of benzylic and secondary or tertiary C-H bonds using nonafluorobutylsulfonil azide and dirhodium tetraacetate as catalyst.

\[
R-H + CF_3CF_2CF_2CF_2SO_2N_3 \xrightarrow{[Rh_2(OAc)_4], \text{DCE, 90 °C}} CF_3CF_2CF_2SO_2NH-CH_2R
\]

benzylic products: 47-80%

inseparable mixture (2: 3) 51 %
Late Transition Metal Nitrene Complexes That Can Participate in C-H Amination

Metal nitrenes / imidos have been proposed as intermediates for C-H amination. Both metal imido and metal nitrene possess the general formula [M]=NR; they differ on how the NR is treated as a ligand. Imido (NR²⁻) is typically used for high valent, early transition metal complexes [M]=NR while the neutral nitrene (NR) moiety is typically considered for low valent, late transition metal complexes [M]=NR. This section focuses on Group 8-11 late transition metal complexes of Ru, Rh, Fe, Co, Ni, and Cu bearing nitrene / imido ligands that are spectroscopically characterized and/or isolated, and have been implicated as reactive intermediates in sp³ C-H amination leading to some insights to the mechanism. Several reviews have appeared that comprehensively cover transition metal imido complexes (at the time of their writing) and discuss the electronics of these species. This section will center its discussion on the late transition metals complexes more commonly used in sp³ C-H amination and some investigations done to establish the mechanism of reactions. The term metal nitrene or metal imido is used in accordance to how the authors describe their [M]=NR systems.

1.3.a. Rhodium Imido Complexes

Since the seminal report of Breslow and Gellman on the use of the dimeric dirhodium tetraacetate, Rh₂(OAc)₄ (Figure 1.5), for intramolecular C-H amination of an sulfonyliminoiodinane, dirhodium(II) tetracarboxylate complexes (e.g. Rh₂(esp)₂ Figure 1.3) have become one of the efficient catalysts for intra- and intermolecular C-H amination. Muller and co-workers first described the Rh₂(OAc)₄-catalyzed C-H amination using NsN=IPh is a stereospecific reaction, with complete retention of stereochemistry (Scheme 1.22.A). A
cyclopropyl clock experiment leaned towards a concerted mechanism since there is no ring-opened product observed (Scheme 1.22.B).

**Scheme 1.22.** Rh$_2$(OAc)$_4$-catalyzed C-H amination of NsN=IPh.

A. Retention of stereochemistry

![Retention of stereochemistry](image)

B. No ring-opened product

![No ring-opened product](image)

Du Bois and colleagues made significant contributions on intramolecular$^{61-65}$ and intermolecular$^{66,67}$ C-H amination, and even application in natural product$^{68-71}$ synthesis.$^{57-59,72}$ Experimental mechanistic studies gave convincing evidence that the reaction proceeds via concerted asynchronous mechanism involving a singlet Rh-nitrene as intermediate. Intermolecular reaction of NH$_2$Tces with stoichiometric amount of external oxidant PhI(O$_2$CtBu)$_2$ and 2 mol% Rh$_2$(esp)$_2$ favors benzylic over 3° C-H bonds (Scheme 1.23.A), while reaction with cyclopropyl substrate gave an insertion product with no fragmentation of the cyclopropyl ring (Scheme 1.23.B).$^{66}$ From their recent desorption electron spray ionization mass
spectroscopy (DESI-MS) report, they have identified two short-lived transient dirhodium nitrene species, which differ in oxidation states ([Rh\textsuperscript{II}-Rh\textsuperscript{II}]=NTces and [Rh\textsuperscript{II}-Rh\textsuperscript{III}]=NTces) from the reaction of NH\textsubscript{2}Tces and adamantane, with Rh\textsubscript{2}(esp)\textsubscript{2} as catalyst and PhI(O\textsubscript{2}C\textsubscript{3}Bu\textsubscript{2}) in CH\textsubscript{2}Cl\textsubscript{2}.\textsuperscript{73} One of these nitrene species may have abstracted a H atom from adamantane or CH\textsubscript{2}Cl\textsubscript{2}, they also observed a fragment for [Rh-Rh]-NHTces. They suggest that either the reaction proceeds by concerted insertion or by a really fast radical rebound of the short-lived radical pair [Rh-Rh]-NHTces and the carboradical. DFT studies by Bach et al. showed no concerted transition state, instead they found a triplet transition state featuring a quasi linear arrangement of C-H-N (173°) (Scheme 1.24).\textsuperscript{74} Although this suggests a nonconcerted mechanism, both experimental and calculated primary KIE values (4.8 and 5.7, respectively) are quite small and may be interpreted as a stepwise mechanism between short-lived radical pairs.
Mechanistic insights on intramolecular sulfamate ester oxidation using $\text{PhI(OAc)}_2$ as external oxidant and 2 mol% $\text{Rh}_2(\text{O}_2\text{CCPh}_3)_4$ showed that qualitative intramolecular C-H amination rate goes by $3^\circ >$ ethereal, benzylic $> 2^\circ >> 1^\circ$ bonds, while aziridination is generally favored over allylic amination, indicating that a singlet nitrene is operative.$^{75}$ Radical clock experiments showed no ring-opened product and the KIE was $1.9 \pm 0.2$ (Scheme 1.25). Hammett studies showed a small degree of partial positive charge at the oxidizing carbon center of the transition state, in accord with an asynchronous, concerted transition state (TS) (Scheme 1.26). Kinetic analyses showed no dependence on the catalyst and first order on both oxidant and substrate. Although they have not clearly identified a rate-determining step, they suggested it may be the formation of the iminoidinane species. Calculations done by Zhao, Su and co-workers on the mechanism of intramolecular amination of 3-phenylpropylsulfamate ester with
three representative dirhodium catalysts (Figure 1.6) showed the nature of the C-H insertion depends on the nature of the ligand. All three reactions involved a triplet mixed-valent Rh\textsuperscript{II}-Rh\textsuperscript{III}-nitrene, with radical character on both dirhodium sites and the N\textsubscript{nitrene} atom which can participates in HAA. For the Rh\textsubscript{2}(formate\textsubscript{4})-catalyzed reaction, a spin crossover occurs leading to a closed-shell singlet electronic transition state for concerted C-H bond insertion. Because of the electron donating nature of the ligand, this leads to a better π-backbonding to the nitrene N in the Rh\textsubscript{2}((N-methyl)-formide\textsubscript{4}) and Rh\textsubscript{2}(S-nap\textsubscript{4}) complexes. With these Rh complexes, a stepwise process is functioning, with diradical intermediate from a triplet pathway of HAA followed by a radical recombination with intersystem crossing from the triplet to the open-shell singlet state.

**Scheme 1.25.** Intramolecular Rh-catalyzed amination of sulfamate ester.

A. *Clock experiment*

\[
\begin{align*}
\text{Ph} & \quad \text{H} \\
\text{NH}_2 & \quad \text{O} \\
\text{O} & \quad \text{S} \\
\text{S} & \quad \text{N} \\
\text{Ph} & \quad \text{H}
\end{align*}
\]

\[2 \text{ mol\% } \text{Rh}_2(\text{OAc})_4, \text{ PhI(OAc)}_2 \to \]

\[
\begin{align*}
\text{Ph} & \quad \text{H} \\
\text{HN} & \quad \text{S} \\
\text{O} & \quad \text{O} \\
\text{S} & \quad \text{N} \\
\text{Ph} & \quad \text{H}, \text{ 91\%}
\end{align*}
\]

B. *KIE experiment*

\[
\begin{align*}
\text{Ph} & \quad \text{H} \quad \text{D} \\
\text{NH}_2 & \quad \text{O} \\
\text{S} & \quad \text{N} \\
\text{Ph} & \quad \text{H}, \text{KIE 1.9 \pm 0.2}
\end{align*}
\]

\[2 \text{ mol\% } \text{Rh}_2(\text{OAc})_4, \text{ PhI(OAc)}_2 \to \]

\[
\begin{align*}
\text{Ph} & \quad \text{H} \quad \text{D} \\
\text{HN} & \quad \text{S} \\
\text{O} & \quad \text{O} \\
\text{S} & \quad \text{N} \\
\text{Ph} & \quad \text{H}, \text{KIE 1.9 \pm 0.2}
\end{align*}
\]
Scheme 1.26. Proposed mechanism for intramolecular Rh-catalyzed amination.

Figure 1.6. Representative Rh$_2$-complexes used by Zhang and co-workers in their theoretical studies on the mechanism of intramolecular Rh-catalyzed amination.
Next to rhodium complexes, ruthenium-catalyzed C-H amination reactions are also widely developed and applied to both intra- and intermolecular examples. Seminal studies by Che and co-workers established a series of bis(sulfonylimido)ruthenium(VI) complexes which can do C-H nitrene insertion reactions (Figure 1.7). Specifically, stoichiometric reaction of [RuVI(TPP)(NTs)2] or [RuVI(OEP)(NTs)2] with C-H substrates led to tosylamidation products in fair to good yields for unactivated, allylic and benzylic $sp^3$ C-H bonds (Scheme 1.27). Second-order rate constants were determined from these reactions, which generally increase as the C-H BDE of benzylic C-H bonds decreases. A KIE of 6 for cyclohexane / cyclohexane-$d_{10}$ and 11 for ethylbenzene / ethylbenzene-$d_{10}$ were observed when reacted with [RuVI(TPP)(NTs)2], indicating that C-H bond cleavage is involved leading to H-atom abstraction / radical capture for mechanism (Scheme 1.28). The rate constants also exhibited a subtle increase with the electron-withdrawing strength of the Y substituent of the sulfonylimido group (Figure 1.7); though the electron-poor substituents of porphyrin ring have more effect on rate, reactions with

**Scheme 1.27.** Stoichiometric tosylamidation of C-H substrates with [(por)RuVI(NTs)2] compounds.
[Ru\textsuperscript{VI}(F\textsubscript{20}TPP)(NTs)\textsubscript{2}] have greater second order rate constants\textsuperscript{79,80} They only have recently reported the isolation and X-ray structure of [Ru\textsuperscript{VI}(TMP)(NM\textsubscript{s})\textsubscript{2}] (Ms = p-methoxyphenylsulfonyl azide), showing a Ru-N\textsubscript{imido} distance 1.79(3) Å, Ru-N\textsubscript{imido}-S angle 162.5(3)o and an almost linear structure around Ru with N\textsubscript{imido}-Ru-N\textsubscript{imido} angle 175.4(2)o.\textsuperscript{81} DFT calculations shows a closed-shell singlet ground state, about 15.6 kcal/mol lower in energy than the triplet state. Further calculations on the amination of ethylbenzene and [Ru\textsuperscript{VI}(por)(NM\textsubscript{s})\textsubscript{2}] are consistent with a concerted pathway because of the lack of a carboradical intermediate in the energy profile. Nevertheless, they associated the large KIE observed with a rate-limiting C-H bond activation similar to HAA resulting to an almost linear C⋯H⋯N transition state.

**Scheme 1.28.** Proposed mechanism for the C-H amiantion of ethylbenzene using bis(sulfonylimido)ruthenium(VI).
Figure 1.7. Bis(sulfonylimido)ruthenium(VI) complexes synthesized and characterized by the Che group.
Cenini, Gallo and colleagues have isolated and characterized by X-ray the first bis(imido)ruthenium(VI) complex, \([\text{Ru}(\text{TPP})(\text{NArF}_6)_2]\) \((\text{Ar} = 3,5-\text{(CF}_3)_2\text{C}_6\text{H}_3)\) from the reaction of \([\text{Ru}^{\text{II}}(\text{TPP})\text{CO}]\) and 2 equiv N\(_3\text{ArF}_6\). This compound mediated the insertion of N\(_3\text{ArF}_6\) group stoichiometrically into benzylic and allylic C-H bonds in fair to good yields. This bis(arylimido)ruthenium(VI) compound was shown to actively catalyze the insertion of N\(_3\text{ArF}_6\) into allylic C-H bond of cyclohexene, resulting to a new Ru complex bis(amido)ruthenium(VI) \([\text{Ru}(\text{TPP})(\text{C}_6\text{H}_9\text{NArF}_6)_2]\), which is crystallographically characterized as well (Scheme 1.29).

This bis(amido)ruthenium complex accumulated only if \([\text{cyclohexene}] > [\text{azide}]\); otherwise if the azide is present in greater concentration than cyclohexene, the bis(amido)ruthenium converts cyclohexene to allylic amine regenerating the bis(imido)ruthenium complex.

Both the Blakey and Du Bois groups reported method development and mechanistic investigation involving Ru-catalyzed intramolecular C-H amination. Blakey and colleagues showed that \([\text{Ru}^{\text{II}}-\text{pybox}]^{2+}\) as a good enantioselective catalyst for sulfamate esters (Scheme 1.30). While benzylic and allylic C-H amination yields are fair (42-71 %), the ee’s are quite good (75-92 %). They proposed a \(C_2\)-symmetric cationic bis(imido)ruthenium(VI) as active species, where the preferred TS shows that one of the enantiotopic H atoms is directly pointing to the nitrene N for easy H atom abstraction. Computational studies gave a closed-shell singlet ground electronic state for the bis(imido)ruthenium(VI) complex, where the imido groups are \textit{trans} to each other and the Ru-N\textsubscript{imido} bond order is about two. The substitution of Ph into the \(\gamma\)-C-H decreases the energy barrier for intramolecular C-H amination, the Ph ring stabilizes the diradical character in the open-shell singlet TS. This change in substitution also favored H atom transfer over C-H insertion.
Scheme 1.29. Proposed mechanism for the amination of cyclohexene using [RuVI(TPP)NArF6]2.

[Scheme image with chemical structures and reactions]

[Scheme image with chemical structures and reactions]
Du Bois and co-workers reported the allylic amination of sulfamate ester using $\text{Ru}_2(\text{hp})_4\text{Cl}$ as catalyst.\textsuperscript{84} Cycloprenyl clock experiments showed no ring opened products, although a small amount of cis- and trans-isomerization was observed, suggesting a short-lived radical species as intermediate (Scheme 1.31). Calculations resulted to a pathway that starts off with a doublet state Ru-nitrenoid (with calculated spin densities of 0.82, 0.09 and 0.07 for $\text{Ru}^2$, $\text{Ru}^1$ and $N_{\text{nitrene}}$ of $\text{Ru}^2$-$\text{Ru}^1$-$N_{\text{nitrene}}$), passing through a quartet state diradical intermediate from...
HAA of the allylic C-H bond. This is followed by a radical rebound of very low energy barrier. This reactivity pattern shifts from what they have reported for Rh$_2$(esp)$_2$ catalyst, providing another possible methodology for the synthesis of amines.

**Scheme 1.31.** Cyclopropyl clock experiment and proposed intermediate in [Rh$_2$(hp)$_4$Cl]-catalyzed C-H amination.

**1.3.c. Iron Imido Complexes**

Several iron imido complexes have been isolated, with a variety of oxidation states for iron.$^{86}$ Peters and colleagues prepared pseudo-tetrahedral Fe$^{II}$,$^{87,88}$ Fe$^{III}$ $^{87,89-92}$ Fe$^{IV}$ $^{93}$ imido complexes using tripodal ligand structures like tris(phosphino)borate (Figure 1.8) and bis(phosphino)pyrazoylborate and tris(phosphino)borane derivatives of the former ligand. Smith et al. used bulky tris(carbene)borate ligands to isolate pseudotetrahedral Fe$^{III}$ and Fe$^{IV}$ imido complexes.$^{94,95}$ The non-innocent bis(imino)pyridine ligand was used by the Chirik group to
isolate iron imido complexes in square planar geometry.\textsuperscript{96,97} The reactivity patterns of these iron imido complexes are not very well-studied, although nitrene transfer to CO to form isocyanate (RN=C=O) is reported by Peters.\textsuperscript{89} Peters et al. later reported a trigonal bipyramidal iron-nitrene complex using a tris(phosphino)silyl ligand from the loss of N\textsubscript{2} of the azide adduct of the iron complex.\textsuperscript{98} This iron-nitrene transfers a nitrene group to isocyanide and azides forming carbodiimide and diazene, and an intermolecular hydrogen atom transfer (HAT) from 9,10-dihydroanthracene to form anthracene. Similarly, Smith also reported the intermolecular HAT of

\textbf{Figure 1.8.} Representative iron imido complexes that have been structurally characterized by X-ray crystallography.
LFe$^{IV}$=NAd from 9,10-dihydroanthracene to form anthracene.$^{94}$

Holland and co-workers isolated a series of β-diketiminato iron(III) imido.

**Scheme 1.32.** Proposed mechanism for the intra- and intermolecular HAT using β-diketiminato iron(III) imido.
complexes.\textsuperscript{99,100} These three-coordinate compounds have been shown to do nitrene transfer to CO and isocyanate to form isocyanate and carbodiimide (RN=C=NR’) catalytically.\textsuperscript{101,102} They also reported both intramolecular and intermolecular HAT from substrates of low BDEs\textsuperscript{103} (Scheme 1.32).\textsuperscript{104} Hydrogen atom transfer is facilitated by the coordination of tert-butylpyridine (tBupy) into the iron imido complex forming [Fe]=(NAd)(tBupy).\textsuperscript{105} Weaker C-H substrates are shown to do intermolecular HAT, these substrates react competitively faster to overcome intramolecular HAT. They also reported that bulking up the ligand, R = R’’ = Ph, leads to faster HAT of the iron(III) imido complex, the bulkier ligand tends to enclose the Fe center making the imido group more accessible to substrates.\textsuperscript{99,100} Nevertheless none of the reported iron(III) imido complexes were able to do C-H functionalization of exogenous substrates.

Using dipyrromethene as ligand, Betley and co-workers made a major advance through the isolation of iron imido complex that can genuinely perform C-H amination.\textsuperscript{35,50,106} In their initial report, reaction of [Fe\textsuperscript{II}] complex with a variety of organic azides led to a new iron complex, which is structurally characterized as an insertion product of NR group into the benzylic C-H bond of the mesityl group of the ligand, of which the NAd inserted product was characterized by X-ray crystallography (Scheme 1.33.A). They proposed the intermediacy of the high valent iron(IV) imido complex, which is competent in doing HAA / RR to form the new N-C bond.\textsuperscript{106} Switching to adamantyl instead of mesityl, they introduced new iron(II) complex that can catalyze the intermolecular C-H amination of toluene using N\textsubscript{3}Ad as nitrene source (see section 1.2.b. – discussion on catalysis).\textsuperscript{50} With the ligand that has a terphenyl substituent, a mononuclear iron imido complex when reacted with p-tert-butylphenyl azide (Scheme 1.33.B). Reaction with phenyl azide resulted to a dimeric iron imido, where the radical is delocalized in the \textit{para}-position of the NPh group in one of the iron imido moiety. Nonetheless, both iron imido
complexes were able to effect intermolecular C-H amination with toluene. They proposed based on reactivity and Mossbauer experiments that the iron imido is a high spin Fe$^{III}$ center, with the radical imido ($\bullet$NR) group antiferromagenetically coupled with it. Such intermediates are more reactive towards C-H insertion or nitrene transfer reactions as compared to other reported iron imido complexes.

**Scheme 1.33.** Intramolecular C-H amination using iron dipyrrromethene imido complex, and structures of isolated iron imido complexes of the same ligand motif.

**A. Intramolecular**

![Intramolecular Reaction Diagram]

**B. Intermolecular**

![Intermolecular Reaction Diagram]

*Terminal Iron Imido*

*Dimeric Iron Imido*
Higher coordination (5-7) iron imido complexes are more elusive and have not been isolated but implicated based on spectroscopic analyses. Que et al. observed a short-lived pseudoocctahedral iron(IV) tosylimido of the N,N-bis(2-pyridylmethyl)bis(2-pyridyl)methylamine (N4Py), as identified from Fe K-edge X-ray absorption (XAS), extended X-ray absorption fine structure (EXAFS) and Mossbauer spectroscopies (Figure 1.9). The Fe-NTs bond is best described as a Fe=N double bond. Goldberg and co-workers proposed an iron(IV) imido [FeIV(TBP8Cz+)(NTs)]2+, generated from the reaction of [FeIII(TBP8Cz)] (TBP8Cz = octakis(4-tert-butylphenyl)corrolazinato) and chloramine-T (Na+TsNCl-), which is identified from Mossbauer and EPR experiments. This species is established as an iron(IV) center antiferromagnetically coupled to the Cz-π-cation radical. It is able to efficiently transfer the nitrene group into PPh3 resulting to TsN=PPh3 and the two-electron-reduced form [FeIII(TBP8Cz)] as products. A seven-coordinate iron imido (or bis(imido)) [FeII(qpy)(NTs)(X)]2+ (X = NTs, solvent or anion) is proposed by Che and colleagues as intermediate in the C-H amination of benzylic and allylic C-H bonds with sulfamate esters and PhI(OAc)2 as oxidant, catalyzed by [FeII(qpy)(MeCN)2](ClO4)2 (qpy = 2,2':6',2":6":2":6":2":6":-quinquepyridine). Observance of ions [Fe(qpy)(NTs)2]2+ and [Fe(qpy)(NTs)]2+ in electron spray (ESI)-MS and DFT studies suggest the possibility of these species as active species for C-H amination, with the calculated energy barrier for HAA around 14-16 kcal/mol, consistent with the observed high reactivity of the iron(II) as catalyst. On the other hand, an iron(V) bis(imide) [LFeV(NAd)2] complex was reported by Power and colleagues from the reaction of [LFe(η⁶-C₆H₆)] and 2 equiv N₃Ad. When another azide is used N₃Ar (Ar = N₃C₆H₃-2,6-Mes₂), the iron bis(imido) complex is able to abstract a H atom from the ortho CH₂-H of the mesityl substituent, resulting to benzylic radicals. These radicals couple giving the isolable dimeric iron(II) amido/aryl complex.
1.3.d. Cobalt Imido Complexes

Peters et al. isolated a terminal cobalt(III) imido complex with the tris(phosphino)borate ligand that is capable of isocyanate formation upon reaction with CO (Figure 1.10). With a tris(carbene) ligand, Smith et al. showed a rather different way to synthesize cobalt(III) imido complex from the proton coupled electron transfer reaction between the cobalt(II) amido [Co\textsuperscript{II}] \(-\text{NH}^\text{tBu}\) complex and 2,4,6-tri(tert-butyl)phenoxy radical, this cobalt-imido is unfortunately not
reactive to even weak C-H bonds (Figure 1.10).\textsuperscript{112} Meyer and co-workers reported that their cobalt imido complex with tris(carbene) ligand undergoes intramolecular nitrene group transfer to the carbene C of the ligand. Warren and colleagues have isolated both terminal cobalt(III) imido and a tetrahedral cobalt(III) imido bridged dimer from the reaction of the β-diketiminato Co(I) precursor and two kinds of organic azides.\textsuperscript{113} Use of 1-adamantylazide gave the terminal [Co\textsuperscript{III}] imido, while the arylazide 3,5-dimethylphenylazide gave the imido bridged dimer (Figure 1.10). Jones \textit{et al.} showed another three-coordinate cobalt(III) imido complex with guanidato

\textbf{Figure 1.10.} Structures of isolated cobalt imido complexes.
ligand (Figure 1.10). It was the work of Theopold and co-workers who first observed C-H bond activation of a cobalt(III) imido complex with a tris(pyrazolyl)borate as ligand (Scheme 1.34). In their initial report, the isolation of [Co] alkyl complex (Scheme 1.34.A) and a cobalt amide dimer (Scheme 1.34.B) led them to propose a hydrogen atom transfer reaction of the intermediate cobalt imido [Co]=NSiMe₃ resulting to activation of the ligand. Then, the radical formed either couple with the Co center or with another alkyl radical giving the dimer. They have further isolated a cobalt imido complex of adamantyl imide (Scheme 1.35). While this compound reacts with CO to form isocyanate, it is more interesting that it can abstract an H atom, then the resulting cobalt amido and the alkyl radical couple to form the cobalt amine complex.

Betley and colleagues reported the isolation of three-coordinate cobalt alkylimido of tert-butyl imide complex using the dipyrrin ligand (Figure 1.11.A). This complex can do imido group transfer to PMe₂Ph producing the phosphoimide, although no C-H activation was shown for this complex. When an arylazide N₃Mes (mesityl or 2,4,6-trimethylphenyl azide) is reacted with precursor Co(I) dipyrrin complex, instead of a cobalt imide, they isolated a metallacycloindoline cobalt complex (Figure 1.11.B). They proposed that the cobalt mesitylimido complex does a very facile HAT then coupling of Co center and the mesityl radical of the imido subsituent, similar to what Theopold et al. reported for their cobalt system (Scheme 1.34.A).
Scheme 1.34. Radical-like reactivity of tris(pyrazoyl)borate cobalt imido.
**Scheme 1.35.** Isolation of the cobalt amine complex from cobalt imido complex.

**Figure 1.11.** Isolation cobalt imido and cobalt indoline complexes of dipyrrin ligand.

*Scheme 1.35.* Isolation of the cobalt amine complex from cobalt imido complex.

*Figure 1.11.* Isolation cobalt imido and cobalt indoline complexes of dipyrrin ligand.
Zhang and colleagues extensively study the application of cobalt-porphyrin complexes in both aziridination and C-H amination. Although they do not have an X-ray structure of an isolated [Co]=NR, they reported the intermediacy of cobalt(III) nitrene species in the cobalt(II) porphyrin-catalyzed C-H amination of organic azide, through a series of EPR and DFT studies. Following their report on the amination of benzylic substrates using N₃Troc using [Co^{II}](TPP) catalyst (Scheme 1.17), they modeled this reaction using ethylbenzene and methyl azidoformate with a simple [Co^{II}](por) complex (Scheme 1.36). Calculations are consistent with a radical-based mechanism, with a radical anion-like nitrene ligand of the cobalt nitrene intermediate. This species is detected from the X-band EPR spectrum of the reaction of the

Scheme 1.36. Proposed catalytic cycle for [Co^{II}(por)]-based C-H amination with azide.
[Co\textsuperscript{II}(TPP)] catalyst and excess N\textsubscript{3}Ts, an isotropic \( S = \frac{1}{2} \) signal with \( g \) value of 2.004 and \( A_{\text{iso}} \) of 24.7 and 10.0 MHz for Co and N respectively is observed.

1.3.e. Nickel Imido Complexes

The Hillhouse group made great contributions to the advancement of the chemistry of nickel-imido and of first row late transition metal imido complexes in general. In 2001, they reported a terminal nickel(II) imido of diphospino (dtbpe) ligand (Figure 1.12).\textsuperscript{120} They later showed this to be a good imido group transfer agent to CO, isocyanides and ethylene to form isocyanate, carbodiimide and aziridine products.\textsuperscript{121,122} Starting from the azido adduct \([(\text{dtbpe})\text{Ni}][\eta^2-\text{N}_3\text{R}] (\text{R} = 1\text{-adamantyl (Ad), 2,4,6-trimethylphenyl (Mes)), (dtbpe)Ni^{\text{II}}=\text{NR}} complexes with accompanying loss of dinitrogen (N\textsubscript{2}) (Figure 1.12).\textsuperscript{123} They also showed that nickel(II) imido \((\text{dtbpe})\text{Ni}^{\text{II}}-\text{Ndmp} (\text{dmp} = 2,6\text{-dimesitylphenyl}) can be prepared from nickel(I) amido by HAA of the 2,4,6-tris(\text{tert}-\text{butyl})phenoxy \((\tilde{\text{S}}\text{MesO•}) radical (Figure 1.12).\textsuperscript{124}

Oxidation of \((\text{dtbpe})\text{Ni}^{\text{II}}=\text{NAd} and (\text{dtbpe})\text{Ni}^{\text{II}}=\text{Ndmp gave access to nickel(III) imidos} [(\text{dtbpe})\text{Ni}^{\text{III}}=\text{NAd}]^+ and [(\text{dtbpe})\text{Ni}^{\text{III}}=\text{Ndmp}]^+ (Figure 1.12).\textsuperscript{125} These complexes can do HAA from solvent ether or \(^8\text{Bu}_3\text{SnH} to form the corresponding nickel(II) amido [(\text{dtbpe})\text{Ni}^{\text{II}}=\text{NHAd}]^+ and [(\text{dtbpe})\text{Ni}^{\text{II}}-\text{NHdmp}]^+. Using \( N \)-heterocyclic carbene (NHC) ligand, they are able to isolate dinickel complexes with bridging imido ligand (Figure 1.12).\textsuperscript{126} The \{(\text{IPr})\text{NiCl}\}_2(\mu-\text{NMes}) complex reacts with isocyanide to form carbodiimide. With a bulkier NHC, they have isolated a two-coordinate terminal nickel(II) imido \((\text{IPr}^*)\text{Ni}^{\text{II}}=\text{Ndmp}^127 Apart from nitrone group transfer to CO to form isocyanate, this nickel(II) imido can also impart C-H amination to ethylene via a \([2+2]\) cycloaddition forming a azametallacyclobutane complex, followed by a 1,2-hydride shift or \( \beta \)-hydride elimination (Scheme 1.37).
Figure 1.12. Isolated nickel imido complexes from the Hillhouse group.
Employing β-diketiminato ligands, the Warren group has isolated a series of terminal nickel imido and dinickel imido bridged complexes (Figure 1.13). Dinuclear complexes \([\text{Me}_2\text{NN}]\text{Ni}_2(\mu-\text{NAd})\) and \([\text{Me}_3\text{NN}]\text{Ni}_2(\mu-\text{NAr})\) form carbodiimide from reaction with isocyanide. Whereas, the terminal nickel imido complex \([\text{Me}_3\text{NN}]\text{Ni}=\text{NAd}\) was shown to do

**Scheme 1.37.** C-H amination of ethylene imparted by a nickel(II) imido complex.

**Figure 1.13.** Isolated and characterized β-diketiminato nickel imido and dinickel bridged imido complexes from the Warren group.
nitrene group transfer to isocyanide, CO, PMe₃ and even to cobaltocene. Interestingly, this terminal nickel imido was shown in an initial report to do HAA from 1,4-cyclohexadiene to give the nickel(II) amido and benzene. In a more recent report, they have shown that this terminal nickel(III) imido can actually do C-H amination with benzylic C-H substrates like toluene, ethylbenzene and indane. Rigorous kinetic and theoretical studies led to a mechanism that is consistent with intermediacy of radical species (Scheme 1.38). It is clear that the mechanism starts off with HAA of the terminal nickel(III) imido resulting to the carboradical and a nickel(II) amido [Me₂NN]Ni\textsuperscript{II}-NHAd. The next step is rather complicated and depends on the C-H substrates. With toluene and ethylbenzene, radical rebound between the carboradical and the nickel(II) amido complex, with a competing radical capture of the carboradical by the terminal nickel(III) imide occur (Scheme 1.38.A). In the case of indane, a radical rebound may occur resulting to nickel(I) amine [Me₃NN]Ni(NH(R)Ad) followed by subsequent reaction of this radical with the nickel(II) amido complex.

**Scheme 1.38.** Proposed mechanism for the C-H amination of benzylic C-H substrates by β-diketiminato nickel(III) imido complex.

**A. Ethylbenzene and Toluene**

\[
\begin{align*}
&[\text{Ni}^\text{III}] = \text{NAd} \\
\overset{\text{HAA}}{\rightarrow} & & [\text{Ni}^\text{II}] \text{Ni} \text{NHAd} + R^* \\
\end{align*}
\]

**B. Indane**

\[
\begin{align*}
&[\text{Ni}^\text{III}] = \text{NAd} \\
\overset{\text{HAA}}{\rightarrow} & & [\text{Ni}^\text{II}] \text{Ni} \text{NHAd} + R^* \\
\end{align*}
\]

\[
\begin{align*}
&\text{[Ni}^\text{I}]\text{(NH(R)Ad)} + [\text{Ni}^\text{III}] = \text{NAd} \\
\rightarrow & & \text{[Ni]} + \text{NH(R)Ad}
\end{align*}
\]

\[\text{[Ni]} = [\text{Me}_3\text{NN}]	ext{Ni}\]
nickel(I) amine and terminal nickel(III) imido gives the dinuclear\([\{\text{Me}_3\text{NN}\}\text{Ni}]_2(\mu-\text{NAd})\) and the inserted product of indane (Scheme 1.38.B).

### 1.3.f Copper Nitrene Complexes

Although no terminal copper nitrene complex has been isolated and structurally characterized, several experimental studies have suggested their intermediacy in C-H amination. Early studies by Vedernikov and Caulton showed the presence of both dicopper imido species \([(\text{LCu})_2(\text{NTs})(\text{BAR}_4^F)]^+\) and copper amide \([\text{LCu}^{\text{II}}\text{-NHTs}]^+\) in the ESI-MS of the reaction mixture of \((\text{LCu})\text{BAR}_4^F\) and PhI=NTs (L = pyridinophane ligand, \(\text{BAR}_4^F = \text{tetrakis}(3,5-\text{bis}(\text{trifluoromethyl})\text{phenyl})\text{borate})\) (Figure 1.14). They rationalized that both species are formed from the monocopper imido \([\text{LCu}^{\text{III}}(\text{N}\cdot\text{Ts})]^+\) when a) it interacts with another \(\text{LCu}^+\) giving the dicopper species and b) does an HAA from a solvent giving the copper amide.

Nicholas, Houk et al. presented a series of stereochemical and theoretical studies to validate the presence of a terminal copper imido species from the reaction of \((\text{diimine})\text{Cu}(\text{NCCH}_3)\)PF\(_6\) and halo-\(p\)-substitutedsulfonamides \((4-\text{R-C}_6\text{H}_4\text{SO}_2\text{NClNa}^+).\) Amination of cis- and trans-4-\(\text{tert}\)-butyl-1-phenylcyclohexane using chloramine-T and chloramine-N (R = Me and NO\(_2\), respectively) gave a 1:1 mixture of the inserted products at the tertiary, benzylic site (Scheme 1.39.A). Reaction with a radical clock substrate gave both the ring-opened and the cyclopropylamino products (Scheme 1.39.B). Nevertheless, in conjunction with their calculations, they concluded that the mechanism is via stepwise, HAA / RC pathway.
facilitated by a triplet ground state copper imido species. This triplet state copper imido species has spin density mostly localized on \( N_{\text{imido}} \) (1.180) than in Cu (0.437), which upon HAA generates a radical pair that rebounds to form the amine product.

**Scheme 1.39.** Stereochemical C-H amination experiments using (dimiinine)Cu\(^+\) and chloramine-T.

A. 4-tert-butyl-1-phenylcyclohexane

![Reaction Scheme A](image1)

B. Radical Clock

![Reaction Scheme B](image2)

Ligand A

Ligand B
Warren and co-workers have reported the isolation of β-diketiminato dicopper nitrenes (Figure 1.15).\textsuperscript{48,134} The compound \([\text{Me}_3\text{NN}]\text{Cu}\twoheadrightarrow\text{Cu}(\mu\text{-NAr})\) undergoes nitrene group transfer to \(\text{CN}^\text{Bu}\) and \(\text{PMe}_3\) to produce the corresponding isocyanate and phosphoimide.\textsuperscript{134} Interestingly, through a series of ligand exchange reactions, they provided evidence that the terminal copper nitrene form can be generated from the dicopper nitrene (Scheme 1.40). In their succeeding report, they reported the isolation of \([\text{Me}_3\text{NN}]\text{Cu}\twoheadrightarrow\text{Cu}(\mu\text{-NAd})\), although this dicopper nitrene compound is quite thermally sensitive as it decomposed at RT to form an amine bridged copper species.\textsuperscript{48} Working on with other ligand to overcome this possibly intramolecular C-H amination, they isolated the dicopper nitrene \([\text{Cl}_2\text{NN}]\text{Cu}\twoheadrightarrow\text{Cu}(\mu\text{-NAd})\).\textsuperscript{48} This dicopper nitrene \([\text{Cl}_2\text{NN}]\text{Cu}\twoheadrightarrow\text{Cu}(\mu\text{-NAd})\) proved to be a competent aminating species for indane, toluene and cyclohexane (Scheme 1.41.A). They proposed that these amination reactions are actually mediated by terminal copper nitrene \([\text{Cl}_2\text{NN}]\text{Cu}=\text{NAd}\), which is the dissociated form, along with the monocopper species \([\text{Cl}_2\text{NN}]\text{Cu}\), of the dicopper nitrene species (Scheme 1.41.B). This is similar in concept to the formation of dicopper imido species reported by Vedernikov and Caulton.\textsuperscript{133} Stoichiometric KIE experiment using ethylbenzene isotopomers gave a value of

\textbf{Figure 1.15.} Structures of the isolated β-diketiminato dicopper nitrene complexes.
5.1(2), which is within the range of KIE reported for HAA / RC mechanism of the Ru imido compounds.\(^79\)\(^80\) Calculations reveal a singlet biradical ground state with molecular orbital occupancy of 1.5 e\(^-\) and 0.5 e\(^-\) for Cu-N\(_{\text{nitrene}}\) \(\pi\) and \(\pi^*\), respectively. Careful mechanistic experimentations through kinetic and stereochemical studies on C-H amination with these dicopper nitrenes are recently reported, establishing a stepwise mechanism via HAA / RR with terminal copper nitrene as intermediate.\(^49\) These results are presented in detail in Chapter 2.

**Scheme 1.40.** Ligand exchange reaction of dicopper nitrene through the intermediacy of a terminal copper nitrene.

\[
\begin{align*}
\text{C}_6\text{D}_6 & \quad - \quad [\text{Me}_3\text{NN}]\text{Cu} & \quad + \quad [\text{Me}_2\text{Al}]\text{Cu} \\
\{[\text{Me}_3\text{NN}]\text{Cu}\}_2(\mu-\text{NAr}) & \quad \Leftrightarrow \quad [\text{Me}_3\text{NN}]\text{Cu} = \text{NAr} & \quad \Leftrightarrow \quad [\text{Me}_3\text{NN}]\text{Cu}(\mu-\text{NAr})\text{Cu}[\text{Me}_2\text{Al}]
\end{align*}
\]

Ray *et al.* reported the identification of a Lewis acid adduct of copper-tosylnitrene.\(^135\) With Sc(O\(\text{Tf}\))\(_3\) as the Lewis acid, \([(\text{triamine})\text{Cu (Sc(O\(\text{Tf}\))_3)]^+\) was detected from the reaction of (triamine)Cu\(^+\) and the iminoiodinane 2-\(^1\)BuSO\(_2\)C\(_6\)H\(_4\)I=NTs (Scheme 1.42). Resonance Raman (rR) spectrum displays three bands at 579, 660 and 887 cm\(^{-1}\), consistent with a Cu\(^{\text{III}}\)-NTs/ Cu\(^{\text{II}}\)-
N•Ts core, while X-ray absorption spectroscopy (XAS) data are more consistent with a Cu\textsuperscript{III} center rather than Cu\textsuperscript{II}. Along with DFT studies, these spectroscopic data suggest a \( \kappa^2\text{-N,O} \) binding of the NTs group to the Cu center. This copper nitrene species is very active towards C-H amination of C-H substrates, amination of toluene can be done at -90 °C and cyclohexane at RT, with yields of 21% and 35%, respectively. They proposed a stepwise HAA / RR

**Scheme 1.41.** Stoichiometric C-H amination of benzylic and \( sp^3 \) C-H bonds using \([\{\text{Cl}_2\text{NN}]\text{Cu}\}_2(\mu\text{-NAd})\), proposed to proceed via a terminal nitrene intermediate.

**A. Stoichiometric Reaction**

\[
\begin{align*}
\text{R-H} + [\text{Cu}]\text{--}[\text{Cu}] \quad &\quad 80 \text{ °C or RT} \\
\{[\text{Cl}_2\text{NN}]\text{Cu}\}_2(\mu\text{-NAd}) &\rightarrow 2 [\text{Cu}] + \text{RN(H)Ad}
\end{align*}
\]

**B. Proposed Generation of Terminal Nitrene**

\[
\{[\text{Cl}_2\text{NN}]\text{Cu}\}_2(\mu\text{-NAd}) \overset{\text{Scheme 1.41}}{\rightleftharpoons} [\text{Cl}_2\text{NN}]\text{Cu} = \text{NAd} + [\text{Cl}_2\text{NN}]\text{Cu}
\]

**Scheme 1.42.** Synthesis of Lewis acid stabilized \([\text{triamine(Cu)}(\kappa^2\text{-N,O-Nts})]^+\).

N•Ts core, while X-ray absorption spectroscopy (XAS) data are more consistent with a Cu\textsuperscript{III} center rather than Cu\textsuperscript{II}. Along with DFT studies, these spectroscopic data suggest a \( \kappa^2\text{-N,O} \) binding of the NTs group to the Cu center. This copper nitrene species is very active towards C-H amination of C-H substrates, amination of toluene can be done at -90 °C and cyclohexane at RT, with yields of 21% and 35%, respectively. They proposed a stepwise HAA / RR
mechanism for C-H amination, rate limiting HAA step based on the linear relationship of rate and BDEs of the substrate used.

Conclusion

C-H amination is clearly still a developing field of research. Several protocols have been developed, which center on the intermediacy of metal nitrene / imido [M]=NR species. Most of the developed protocols involve Ru or Rh-based catalyst, but because of the current high price of such metals, focus is shifting towards the more Earth abundant metals Fe, Co, Ni and Cu. Also, finding a wider scope of nitrogen sources to impart wider range of amine products is still on the tasks. Among the key challenges that are still needed to be addressed are regioselectivity, chemoselectivity and stereoselectivity, without a major lessening of the inherent C-H bond reactivity. These challenges also drive the proper design of metal catalyst structure towards isolation of putative metal nitrene / imido species, to provide better understanding of the mechanism of the C-H amination reaction.

References


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CHAPTER 2

Mechanistic Insights on C-H Amination by β-Diketiminato Copper Alkynitrenes

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Abstract

We examine important reactivity pathways relevant to stoichiometric and catalytic C-H amination via isolable \( \beta \)-diketiminato dicopper alkynitrene intermediates \([\text{Cl}_2\text{NN}C\text{u}]_2(\mu-\text{NR})\). Kinetic studies involving the stoichiometric amination of ethylbenzene by \([\text{Cl}_2\text{NN}C\text{u}]_2(\mu-\text{N}^t\text{Bu})\) (3) demonstrate that the terminal nitrene \([\text{Cl}_2\text{NN}C\text{u}=\text{N}^t\text{Bu}\) is the active intermediate in C-H amination. Initial rates exhibit saturation behavior at high ethylbenzene loadings and an inverse dependence on the copper species \([\text{Cl}_2\text{NN}C\text{u}]\), both consistent with dissociation of a \([\text{Cl}_2\text{NN}C\text{u}]\) fragment from 3 prior to C-H amination via \([\text{Cl}_2\text{NN}C\text{u}=\text{N}^t\text{Bu}\). C-H amination experiments employing 1,4-dimethylcyclohexane and benzylic radical clock substrate support a stepwise H-atom abstraction / radical rebound pathway. Dicopper nitrenes \([\text{Cu}]_2(\mu-\text{NCHRR'})\) derived from 1° and 2° alkylazides are unstable towards tautomerization to copper(I) aldimine complexes \([\text{Cu}](\text{HN=CRR'})\), rendering 1° and 2° alkynitrene complexes unsuitable for C-H amination.
Introduction

Catalytic C-H amination represents an appealing approach for preparation of nitrogen containing compounds without requiring typical functional group manipulations.\(^1\)-\(^5\) A majority of these protocols are proposed to proceed through metal-nitrene species \([\text{M}]=\text{NR}^{'\text{6}}\) which may directly react with a C-H bond in substrates R-H to give amines R-NHR\(^{\prime}\). Commonly, isolable or \textit{in-situ} prepared nitrene precursors such as iminiodinanes PhI=NR based on electron-deficient sulfonylamines H\(_2\)NSO\(_2\)R or carbamates H\(_2\)NC(O)OR have been used with dirhodium\(^7\)-\(^11\) or ruthenium catalysts.\(^12\)-\(^18\) Nonetheless, the quest for more earth abundant, economical C-H functionalization catalysts motivates the investigation of first-row transition metal systems based on Mn,\(^19\) Fe,\(^20\)-\(^22\) Co,\(^23\)-\(^28\) and Cu.\(^29\)-\(^35\)

Only in a few cases, however, may discrete metal-nitrene species be isolated and subjected to detailed analysis. Che \textit{et al.} isolated and kinetically studied the novel (porph)Ru(=NSO\(_2\)R\(^\prime\))\(_2\) featuring trans-[M]=NSO\(_2\)R\(^\prime\) moieties.\(^13\),\(^15\) Based on the primary KIE’s of 4 – 11 observed in reactions with benzylic C-H bonds in substrates R-H, these reactions were suggested to proceed via H-atom abstraction (HAA) / radical recombination (RR) pathways to give the C-H amination products RNH(SO\(_2\)R\(^\prime\)). Cenini and co-workers crystallographically characterized the related electron-poor derivative (porph)Ru(=NAr\(^F\))\(_2\) (Ar\(^F\) = 3,5-(CF\(_3\))\(_2\)C\(_6\)H\(_3\)).\(^36\) Isolation of the bis(amide) (porph)Ru(N(1-cyclohexenyl)Ar\(^F\))\(_2\) which has added two equiv. of the cyclohexenyl radical to (porph)Ru(=NAr\(^F\))\(_2\) in the C-H amination of cyclohexene suggested a similar HAA / RR mechanism. These stepwise C-H amination pathways should be contrasted with an asynchronous concerted mechanism identified using stereochemical probes via putative [Rh\(_2\)]=NTs species (Scheme 2.1).\(^8\)
Previously, Warren and co-workers described the isolation of dicopper nitrenes \([\text{Cu}_2(\mu-\text{NR})]\) (R = aryl, Ad) obtained from the reaction of copper(I) \(\beta\)-diketiminates with organoazides \(\text{N}_3\text{R}\).\(^{29,37}\) For instance, the reaction of \(\{\text{Cl}_2\text{NN}\}\text{Cu}_2(\mu-\text{benzene})\) (1) with the organoazide \(\text{N}_3\text{Ad}\) (Ad = 1-adamantyl) yielded dicopper nitrene \(\{\text{Cl}_2\text{NN}\}\text{Cu}_2(\mu-\text{NAd})\) (2) (\(\{\text{Cl}_2\text{NN}\} = 2,4\text{-bis}(2,6\text{-dichloro})\text{phenylimido})\text{pentyl}\)). This species formally inserts the NAd group into \(sp^3\)-hybridized C-H bonds under stoichiometric and catalytic conditions (Scheme 2.2).\(^{29}\) Furthermore, this is the first example of an isolated copper nitrene species that participates in intermolecular nitrene transfer to C-H substrates.

Despite considerable interest, no terminal copper nitrene complex has been isolated to allow for clear mechanistic studies.\(^{32}\) The dicopper nitrenes \(\{\text{Cl}_2\text{NN}\}\text{Cu}_2(\mu-\text{NAd}),\) \(\{\text{Me}_3\text{NN}\}\text{Cu}_2(\mu-\text{NAd})\) and \(\{\text{Me}_3\text{NN}\}\text{Cu}_2(\mu-\text{NAr})\) (Ar = 3,5-Me_2C_6H_3) represent the only species characterized by X-ray (Figure 2.1). Solution studies suggested the possibility of
dissociation of a β-diketimino copper(I) fragment from \([\text{Cu}]_2(\mu-\text{NAr})\) (Figure 2.1) during the formation of an unsymmetrical species \(\text{[Cu]}(\mu-\text{NAr})[\text{Cu}']\) in the presence of an additional β-diketiminate-like species \([\text{Cu}]'\).\(^{37}\)

**Scheme 2.2.** Copper nitrene-based C-H amination.

![Scheme 2.2](image)

**Figure 2.1.** Previously investigated copper nitrenes.
Since the first observation of C-H amination and alkene aziridination with sulfonyl azides in the presence of copper, copper sulfonylnitrene species have attracted significant interest (Figure 2.1). Calculations on Nicholas’s cationic bis(imine) copper system showed that $\kappa^2$-N,O-NTs copper species represent the most likely intermediates for the C-H amination. The close separation of calculated triplet (ground) and multi-configurational singlet (excited) states leads to a bifurcation of reaction pathways: the former is predicted to react through stepwise HAA / RR while the later should react in a concerted fashion. Quite recently, Lewis acid adduct of a cationic copper-tosynitrene supported by tridentate amine isolated at low temperature have been reported. Substantiated by XAS and resonance Raman (rR) studies, DFT studies point to a $\kappa^2$-N,O-NTs binding mode in which the nitrene N-donor engages a Lewis acid such as Sc(OTf)$_3$. Reactivity studies reveal that this species aminates $sp^3$ C-H bonds in substrates such as toluene and even cyclohexane in modest yields (21-35%).

Direct, asynchronous, insertion of a metal-nitrene into a C-H bond and H-atom/radical rebound (HAA/RR) represent two opposing pathways considered for C-H functionalization with metal nitrenes (Scheme 2.1). While putative [Rh]$_2$=NSO$_2$R intermediates have been probed with radical clock substrates to give evidence for a concerted pathway, related copper-based systems employing diimine ligands provide evidence for contributions from both pathways. Moreover, the identification of an HAA / RR pathway for $\beta$-diketiminato [Cu]=NR species would specifically implicate three-coordinate copper(II) amides [Cu$^{II}$]-NHR’ as active intermediates. Recent synthetic and kinetic studies have revealed such [Cu$^{II}$]-NHR’ species to be active in stoichiometric C-H functionalization themselves, capable of both HAA of benzylic substrates R-H as well as capture of the resulting radical R• to give the functionalized amines R-NHR’.
Herein we report mechanistic investigations into stoichiometric and catalytic C-H amination via dicopper nitrenes that points to the importance of dissociation of a β-diketiminato fragment [CuI] from [Cu]2(-NR’) species to generate terminal nitrenes [Cu]=NR’ that directly react with C-H substrates R-H. Use of stereochemical probes provides insight into the nature of the C-H → C-N transformation. Examination of reactions with 1° and 2° alkyl azides N3CHRR’ (R, R’ = H or alkyl) reveal that dicopper nitrenes [Cu]2(-NCHR2) may be isolated, but rapidly convert to [CuI](NH=CR2) species in arene solvents where dissociation of a β-diketiminato copper(I) fragment [CuI] is favored.

Results and Discussion

2.2.a. Synthesis and Characterization of [[Cl2NN]Cu]2(µ-NtBu) (3)

Stirring the copper(I) precursor [[Cl2NN]Cu]2(µ-benzene) (1) with the 3° organoazide N3tBu in pentane gives [[Cl2NN]Cu]2(µ-NtBu) (3) as green crystals in 46 % yield (Scheme 2.3). The X-ray structure of 3 shows a bridging nitrene unit similar in form to the N-adamantyl variant 2 (Figure 2.2). The nearly C2-symmetric tert-butylnitrene complex 3 exhibits Cu-Nnitrene distances of 1.808(3) and 1.815(3) Å nearly identical to those in 2 (1.810(2) Å). The Cu···Cu separation of 2.9147(6) Å in 3 is somewhat shorter than found in 2 (2.969(1) Å) likely due to the slightly smaller steric impact of the tBu group compared to Ad. 1H and 13C{1H} NMR spectra of 3 reveal only one type each of N-aryl p-H and m-H environments, even down to -70 °C in toluene-d8, indicating facile rotation about the Cu-Nnitrene bonds at the expense of any Cu···Cu interaction.

Scheme 2.3. Synthesis of dicopper nitrene 3.
2.2.b. Kinetic Investigation of [Cu]$_2$(μ-N$^t$Bu) Reactivity with Ethylbenzene

We performed a series of kinetic experiments that support the dissociation of a [Cl$_2$NN]Cu fragment from 3 to generate the terminal nitrene [Cl$_2$NN]Cu=N$^t$Bu responsible for C-H amination reactivity (Scheme 2.4). The progress of the stoichiometric reaction of 3 ([3]$_0$ ~ 0.5 mM) with varying equivalents of ethylbenzene was monitored through loss of the intense optical band of 3 at $\lambda_{\text{max}} = 714$ nm ($\varepsilon = 3960$ M$^{-1}$cm$^{-1}$) using the method of initial rates (Figure 2.4.A). The initial rate of decay of 3 in benzene at 40 °C increases with added ethylbenzene (1000 - 10000 equiv), but exhibits saturation at higher ethylbenzene concentrations (Figure 2.4.B). This behavior is inconsistent with direct reaction between dicopper nitrene 3 and ethylbenzene. This also indicates a pre-equilibrium step involving [Cl$_2$NN]Cu dissociation from the 3 to form [Cl$_2$NN]Cu=N$^t$Bu prior to the rate-determining C-H functionalization step (Scheme 2.4).

Scheme 2.4. Proposed mechanistic steps for the stoichiometric reaction of 3 with C-H substrate, with rate law for consumption of 3 assuming steady state conditions for the terminal nitrene [Cu]=N$^t$Bu ([Cu] = [Cl$_2$NN]Cu).

$$
[Cu]_2(\mu-N^tBu) \xrightleftharpoons[k_{-1}]{k_1} [Cu]=N^tBu + [Cu]
$$

$$
[Cu]=N^tBu + R-H \xrightarrow[k_2]{\text{RA}} [Cu](HN(R)^tBu)
$$

rate = $k_{\text{obs}}[[Cu]_2(\mu-N^tBu)]$

$$
k_{\text{obs}} = \frac{k_1k_2[RH]}{k_{-1}[[Cu]] + k_2[RH]} = \frac{1}{k_{\text{obs}}} = \frac{k_{-1}[[Cu]]}{k_1k_2[RH]} + \frac{1}{k_1}
$$
Figure 2.2. X-ray structure of \([\text{[Cl}_2\text{NN]Cu}_2(\mu-\text{NiBu})\text{]}\) (3). Selected bond distances (Å) and angles (°): Cu1-N1 1.962(3), Cu1-N2 1.928(3), Cu1-N5 1.808(3), Cu2-N3 1.954(3), Cu2-N4 1.932(3), Cu2-N5 1.815(3), Cu1-Cu2 2.9147(6), Cu1-N5-Cu2 107.09(13), N1-Cu1-N2 93.47(12), N3-Cu2-N4 94.06(11). All hydrogen atoms are omitted for clarity.
Figure 2.3. $^1$H NMR (400 MHz) spectra of \([\text{Cl}_2\text{NN}]\text{Cu}\)\(_2\)(\(\mu\)-NtBu) (3) at RT in benzene-\(d_6\) (A) and at -70 °C in toluene-\(d_8\) (B). * denotes solvent impurity.
Figure 2.4. Kinetic plots for the amination of ethylbenzene by \([\text{[Cl}_2\text{NNCu}}]_2(\mu-\text{N}^\text{tBu})\) (3) at 40.0 °C. (A) Plots of concentration of 3 vs time for each concentration of ethylbenzene give initial rates in M/s from the slope of the linear plots. Initial rates were measured employing a concentration range of 3 from ca. 0.50-0.45 mM. (B) Plot of initial rate vs. concentration of ethylbenzene showing the saturation dependence on ethylbenzene.
To more closely monitor the dissociation of [Cu] from 3 that enables C-H amination by [Cu]=N^iBu, we followed the stoichiometric reaction of 3 with ethylbenzene in the presence of varying concentrations of added [Cu]. An inverse dependence of the rate on both the concentration of [Cl_2NN]Cu and R-H is expected from the rate law derived from steady-state approximation of a mechanistic scenario that involves dissociation of [Cu] from [Cu]_2(µ-N^iBu) (k_1 / k_1) to give low concentrations of [Cu]=N^iBu that participates in C-H amination (k_2) (Schemes 2.4). Careful control of the concentration of ethylbenzene is essential to observe a clear dependence of the initial rate on added [Cu]. Employing an ethylbenzene concentration of 16.5 mM (50 equiv. / 3), kinetic analysis at 40 °C reveals an inverse dependence of initial rate of loss of 3 on the concentration of added [Cl_2NN]Cu (0 – 20 equiv. / 3). A plot of 1 / k_{obs} vs the concentration of added [Cl_2NN]Cu is linear whose y-intercept is the inverse of the rate constant k_1 = 1.1(3) × 10^{-4} s^{-1} for dissociation of [Cl_2NN]Cu from ([[Cl_2NN]Cu]_2(µ-N^iBu) (3) under these conditions (Figure 2.6). However, this value for k_1 should be regarded as an estimate value only, as the equilibrium step is highly affected by the presence of arene solvents like benzene and ethylbenzene. Irregardless of this, these data speak for the importance of the dissociation of the dicooper nitrene species into the terminal nitrene form prior to C-H functionalization.
Figure 2.5. Kinetic plots for the amination of ethylbenzene by \([\text{Cl}_2\text{NNCu}]_2(\mu-\text{N}^3\text{Bu})\) (3) at 40.0 °C with varying amounts of added \([\text{Cl}_2\text{NNCu}]\) ([Cu]). (A) Plots of [3] vs. time for each concentration of [Cu] give initial rates of decay of 3 in M/s from the slope of the linear plot. The initial concentration of 3 and ethylbenzene were 0.34 mM and 16.5 mM, respectively, in each case. (B) Plot of initial rate vs. concentration of monocopper [Cu] showing the inverse dependence on [Cu].
2.2. *Stereochemical Probes – Mechanism of C-H Functionalization*

We then turned our attention to the mechanism by which $[\text{Cl}_2\text{NN}]\text{Cu=N}^t\text{Bu}$ formally inserts the $N^t\text{Bu}$ moiety into C-H bonds. Concerted (likely asynchronous) and stepwise (HAA/RR) pathways represent two limiting mechanistic scenarios by which C-H substrates R-H could react with the key $[\text{Cl}_2\text{NN}]\text{Cu=N}^t\text{Bu}$ intermediate to give R-NH$^t\text{Bu}$ (Scheme 2.1). We employed two different types of mechanistic probes (1,4-dimethylcyclohexane and benzylic radical) R-H that each support a stepwise HAA / RR pathway by providing evidence for the intermediacy of the corresponding radical R• in the C-H amination of R-H by 3.

There are three different kinds of C-H bonds in 1,4-dimethylcyclohexane, two primary, four secondary and two tertiary sites. If the mechanism proceeds through a H-atom abstraction /
radical recombination (HAA/RR) stepwise process, we anticipate four possible products for each isomer: two resulting from net insertion into tertiary C-H bonds and two resulting from net insertion into secondary C-H bonds (Scheme 2.5). Based on their higher C-H bond strengths, we do not anticipate favorable insertion into primary C-H bonds. If the HAA/RR mechanism is operative, the products for insertion into the tertiary C-H bonds are the same originating from either the cis or trans isomer of 1,4-dimethylcyclohexane as a result of rapid inversion of the radical generated at the tertiary site. The secondary products that originate from either cis- or trans-1,4-dimethylcyclohexane, however, are all diastereomeric.

Reaction of cis- and trans-1,4-dimethylcyclohexane (20 equiv.) with N₃⁻Bu catalyzed by 5 mol% [[Cl₂NN]Cu]₂(benzene) (1) at 100 °C leads to the C-H amination of 3° and 2° C-H bonds in these substrates in combined yields of 58% and 50% for the cis- and trans-isomers, respectively (Scheme 2.5). Importantly, amination of the 3° C-H bond in either the cis- or trans-isomer leads to the same two products in essentially equal ratios (46:54 and 44:56, respectively). These findings clearly indicate the intermediacy of a 3° radical R• that leads to a diastereomeric mixture of 3° C-H amination products R-NH⁻Bu.

We also found that the amount of secondary inserted products depends on the relative accessibility of the distinct 2° C-H bonds in the cis- and trans- isomers (Scheme 2.6). Steric strain has an effect on the stability and the distribution of the secondary inserted products by consideration of the reaction of the [Cu]-NH⁻Bu intermediate with 2° radicals formed by HAA to complete C-N bond formation. For the cis-isomer, there is a 1,3-diaxial interaction that strongly disfavors the formation of one of two possible 2° C-H amination products whereas such severe stereochemical considerations are not present in the 2° radical derived from the trans-isomer that leads to the two 2° C-H amination products observed.
Scheme 2.5. Product distribution of the catalytic C-H amination of cis- and trans-1,4-dimethylocyclohexane with N$_3$tBu assuming a stepwise HAA / RR mechanism.

\[
\begin{align*}
\text{N=N=NBu} & + \text{R-H} & \xrightarrow{10 \text{ mol\% } [\text{Cu}]} & \text{R-NH^tBu} \\
& & \xrightarrow{100^\circ C, 48 \text{ h}} & \\
\end{align*}
\]

**Cis-1,4-dimethylocyclohexane**

A: \([\text{Cl}_2\text{NN}]\text{Cu}=\text{N}^t\text{Bu}\)  \[\xrightarrow{}\]  tertiary products  \[\xrightarrow{}\]  \(3^\circ\text{ cis}\)  \[\xrightarrow{}\]  \(3^\circ\text{ trans}\)

B: \([\text{Cl}_2\text{NN}]\text{Cu}^{11-}\text{NH}^t\text{Bu}, -[\text{Cu}^t]\)

**Trans-1,4-dimethylocyclohexane**

A: \([\text{Cl}_2\text{NN}]\text{Cu}=\text{N}^t\text{Bu}\)  \[\xrightarrow{}\]  tertiary products  \[\xrightarrow{}\]  \(3^\circ\text{ cis}\)  \[\xrightarrow{}\]  \(3^\circ\text{ trans}\)

B: \([\text{Cl}_2\text{NN}]\text{Cu}^{11-}\text{NH}^t\text{Bu}, -[\text{Cu}^t]\)

\(2^\circ\text{ cis, cis}\)  \[\xrightarrow{}\]  \(2^\circ\text{ trans, trans}\)
Steric considerations also factor in the distribution of the $3^\circ:2^\circ$ products. Functionalization of the $3^\circ$ C-H bond in the cis-substrate is more favorable than in the trans-substrate, giving a $3^\circ:2^\circ$ C-H amination product distribution of 75:25 and 25:75, respectively. This may be the result of greater steric interactions between the axial 4-methyl group in the

**Scheme 2.6.** Chair structures of the secondary radicals and Newman projections showing the steric effects on the approach of [Cu]=N^t^Bu to the 2° C-H bonds of the trans- and cis-1,4-dimethylcyclohexane for HAA.

From *trans*-isomer

From *cis*-isomer

Steric considerations also factor in the distribution of the $3^\circ:2^\circ$ products. Functionalization of the $3^\circ$ C-H bond in the *cis*-substrate is more favorable than in the *trans*-substrate, giving a $3^\circ:2^\circ$ C-H amination product distribution of 75:25 and 25:75, respectively. This may be the result of greater steric interactions between the axial 4-methyl group in the
**trans**-substrate and the \([\text{Cl}_2\text{NN}]\text{Cu}={\text{N}^\text{tBu}}\) intermediate as it approaches the somewhat weaker tertiary C-H bond (Scheme 2.7).

**Scheme 2.7.** Chair structures and Newman projections showing the steric effects on the approach of \([\text{Cu}]=\text{N}^\text{tBu}\) to the 3° C-H bonds of the **trans**- and **cis**-1,4-dimethylcyclohexane for HAA.

Use of a benzylic radical clock further supports a stepwise mechanism for C-H amination (Scheme 2.8). As shown in Scheme 2.8, if reaction is concerted, the cyclopropane ring is expected to be intact in the product; otherwise, if via stepwise, either product 1 or 2, depending on how fast the radical rebound is. HAA from the benzylic position of 1-benzyl-**trans**-2-phenylcyclopropane (4) results in a radical that quickly rearranges \((k = 3.6(5) \times 10^8 \text{ s}^{-1})^{42}\) to its ring-opened form. C-H amination of 1-benzyl-**trans**-2-phenylcyclopropane (1 equiv.) with excess \(\text{N}_3\text{tBu}\) at 100 °C employing a full equivalent of \([\text{Cu}]\) gives only one product, the ring-opened product in 80% yield (Scheme 2.9). \(^1\text{H}-\text{NMR}\) analysis of the HCl-salt of this product clearly shows the **trans**-configuration of the resulting C=C bond in the ring opened product \((J_{\text{HH}}\text{ for vinylic H} = 16 \text{ Hz})\).
**Scheme 2.8.** Expected products of C-H amination of the α-cyclopropylbenzylic radical clock by either a concerted (A, product 1) or a stepwise (B, products 1 and 2 possible) pathway.

**Scheme 2.9.** Experimental C-H amination of the α-cyclopropylbenzylic radical clock following a stepwise pathway.
2.2.d. Formation of Copper Imine Complexes from New Dicopper Alkynitrenes

In our examination of the range of alkylazides that may participate in C-H amination using our catalytic protocols, we used representative 1° and 2° organoazides N₃R to probe the possibility of new isolable dicopper 1° and 2° alkynitrene species. Dr. Yosra Badiei has isolated dark purple crystals of \{[Cl₂NN]Cu\}_₂(µ-NCH₂CH₂Ph) (5) from the reaction of 1 and the representative 1° organoazide N₃CH₂CH₂Ph (Scheme 2.10).⁴³ Similarly, addition of N₃Cy to 1 in pentane results in immediate coloration of the pentane solution from which dark blue green crystals of \{[Cl₂NN]Cu\}_₂(µ-N(c-C₆H₁₁)) (6) may be isolated (Scheme 2.10). X-ray structure of 6 is shown in Figure 2.6. The Cu-Nₙitrene distances in 6 (1.793(3) and 1.804(3) Å) are similar to those in 5 (1.782(3) and 1.793(3) Å)⁴³ and in 2²⁹ and 3. These Cu-N distances are shorter than the Cu-Nₐmide distance of 1.839(9) Å in the copper(II) amide compound [Cl₂NN]Cu-NHAd.⁴¹ The Cu-⁻⁻⁻⁻⁻⁻Cu contact of 2.8782(7) Å in 6, however, is further contracted to those found in 2²⁹ and 3 due to the lower steric demand of the smaller N-alkyl substituents, same as what is observed by Dr. Badiei for 5 (Cu-⁻⁻⁻⁻⁻⁻Cu 2.8673(6) Å).⁴³

Schema 2.10. Facile nitrene to imine transformation.

```
[Cu]₂(benzene) + N₃CHRR'   chlorobenzene or pentane
              1   - N₂
[Cu]₂(µ-NCHRR')   benzene
              5   a-H migration
R = H, R' = CH₂Ph  [Cu]=NCHRR' + [Cu](benzene)
R + R' = c-C₆H₁₁  6

R = H, R' = CH₂Ph  7
R + R' = c-C₆H₁₀  8
```
We found that these 1° and 2° alkylnitrene complexes 5 and 6 are more significantly thermally sensitive than 1 and 3. Rather than participating in C-H amination of substrates such as ethylbenzene, dissolution of either 5 or 6 in benzene at RT results in the rapid conversion to the copper(I) imine adducts [Cl₂NN]Cu(HN=CHCH₂Ph) (7) or [Cl₂NN]Cu(HN=c-C₆H₁₀) (8) along with release of [Cl₂NN]Cu (Scheme 2.10). α-H migration qualitatively takes place much more quickly in benzene than in solvents that do not coordinate well to the [Cl₂NN]Cu fragment such as ether or pentane. Thus, loss of [Cl₂NN]Cu from 5 and 6 to form the corresponding terminal 1° and 2° alkylnitrene complexes [Cl₂NN]Cu=NCHRR’ likely precedes α-H migration to give the imine adducts 7 and 8. Consistent with the rapid conversion of [Cl₂NN]Cu=NCHR’R’ intermediates to the corresponding imines [Cl₂NN]Cu(NH=CRR’), attempted C-H amination of ethylbenzene with either 5 or 6 did not provide any C-H functionalized product nor did attempted catalytic C-H amination of ethylbenzene with N₃CH₂CH₂Ph or N₃Cy in the presence of 1.

The X-ray structures of 7 and 8 (only 8 is shown in Figure 2.7) reveal trigonal coordination at Cu with Cu-Nimine distances of 1.885(5) and 1.914(2) Å. These compounds have short C=Nimine distances of 1.223(8) Å and 1.275(3) Å, respectively, compared to the C-Nitrene distances of 5 and 6 (1.434(4) and 1.435(5) Å, respectively). The aldimine N-H moieties give rise to high energy bands at 3283 and 3276 cm⁻¹ in the IR spectra of 7 and 8.
Figure 2.6. X-ray structure of \([\{\text{Cl}_2\text{NN}\}\text{Cu}]_2(\mu-\text{N}(\text{c-C}_6\text{H}_{11}))\) (6). Selected bond distances (Å) and angles (°): Cu1-N1 1.943(4), Cu1-N2 1.916(3), Cu1-N5 1.793(3), Cu2-N3 1.941(3), Cu2-N4 1.927(3), Cu2-N5 1.804(3), Cu1-Cu2 2.8782(7), Cu1-N5-Cu2 106.30(17), N1-Cu1-N2 94.41(65), N3-Cu2-N4 94.50(15). All hydrogen atoms, except α-C-H, are omitted for clarity.
Figure 2.7. Xray structure of [Cl₂NN]Cu(HN=(c-C₄H₁₀) (8). Selected bond distances (Å) and angles (°): Cu1-N1 1.9846(16), Cu1-N2 1.9345(16), Cu1-N3 1.9114(17), N3-C1 1.275(3), N1-Cu1-N2 96.37(7), N1-Cu1-N3 124.58(7), N2-Cu1-N3 139.01(7), Cu1-N3-C1 130.35(15). All hydrogen atoms, except the imine N-H, are omitted for clarity.
2.2.e. Implications on the Reactivity of Copper Nitrenes

Terminal copper nitrenes have long been considered as reactive intermediates in the nitrene group transfer reactions of alkene aziridination and C-H amination. Due to their high anticipated reactivity illustrated by reaction with unactivated 2° and 3° C-H bonds, challenges still remain in the isolation of these species. Nonetheless, the formation of “protected” form of the terminal nitrene allows for the isolation of dicopper nitrenes \([Cu]_2(\mu\text{-NR})\) that may dissociate a \([Cu]\) fragment to reveal low concentrations of the reactive terminal species \([Cu]=\text{NR}\). Importantly, this strategy also allows for the isolation of dicopper nitrenes for which the terminal species may be inherently unstable as we found for 1° and 2° species 5 and 6. This approach has also been applied to the isolation of cationic \(N\text{-tosyl}N\text{itrene}\) complexes which has an additional \(\kappa^2\text{-N,O}\) bonding mode accessible. For instance, Vedernikov and Caulton first described a purple complex of formulation \([\{\text{LCu}\}_2(\text{NTs})\}_2^{2+}\) upon reaction of PhI=NTs and their copper(I) catalyst.\(^{35,44}\) In a related chelating amine framework, formal substitution of a \([\text{LCu}]^+\) fragment for ScOTf\(_3\) resulted in \([\text{triamine}]\text{Cu}(\mu\text{-NTs)}\text{ScOTf}_3\) a formulation supported by spectroscopy and theory (Figure 2.1).\(^{40}\)

Our studies of C-H amination that proceed through the terminal copper alkynitrene \([\text{Cl}_2\text{NN}]\text{Cu}=\text{NR}\) clearly reveal that C-H amination takes place via a stepwise HAA / RR mechanism. A joint experimental / theory report by Nicholas, Houk, and colleagues that examined putative cationic \(\{(\text{diimine})\text{Cu(NTs)}\}_+\) intermediates provided evidence for competing direct insertion and HAA / RR pathways. For instance, reaction of a catalyst mixture prepared from the diimine ligand in Figure 2.1 and \([\text{Cu(NCMe)}_4]\text{PF}_6\) (10 mol%) with PhI=NTs in the presence of radical clock substrate 4 gave an 18% and 6% yield of the ring opened and ring closed C-H amination products.\(^{39}\)
Previous studies with the closely related \([\text{Cl}_2\text{NN}]\text{Cu} / \text{N}_3\text{Ad}\) catalytic system revealed a linear correlation between the \(\ln(\text{rate})\) of C-H amination of substrates R-H and the C-H bond strength.\(^2^9\) Normalizing for the number of equivalent reacting of C-H bonds, a C-H bond in cyclohexane (C-H BDE = 97 kcal/mol) reacts 480 times slower than a C-H bond in indane (C-H BDE = 85 kcal/mol) at 110 °C. A rate limiting HAA process was also suggested for Ray’s recently reported Lewis acid stabilized tosyl nitrene due to the linear correlation of \(\ln(\text{rate})\) vs. C-H bond strength.\(^4^0\) Furthermore, kinetic isotope measurements reveal similar KIEs for copper nitrene intermediates that engage in HAA reactions. The \([\text{Cl}_2\text{NN}]\text{Cu} / \text{N}_3\text{Ad}\) system gave KIEs of 5.3(2) and 6.6(1) for the C-H amination of ethylbenzene and cyclohexane at 110 °C, respectively.\(^2^9\) Importantly, stoichiometric C-H amination of ethylbenzene with \([\text{[Cl}_2\text{NN}]\text{Cu}]_2(\mu-\text{NAd})\) gave an identical KIE of 5.1(2) under related conditions. Nicholas observed a KIE of 4.6 in the C-H amination of cumene by the \{(diimine)\text{Cu}\}^+ / \text{PhI}=\text{NTs}\) system at RT\(^3^9\) while Ray reported a KIE of 5.1 in the HAA of dihydroanthracene at -90 °C.\(^4^0\) KIEs in the range of 4-12 have been reported for species such as (porph)\text{Ru}(=\text{NTs})_2\(^1^3,1^5\) and [Me\text{3NN}]\text{Ni}=\text{NAd}\(^4^5\) demonstrated to participate in HAA reactions, though higher KIE’s that deviate significantly from the value for classical H-atom transfer (6.5)\(^4^6\) have been observed via Fe(III)-imide intermediates by Betley (13-24).\(^2^0\)

Clear evidence for a HAA / RR pathway for reaction of \([\text{Cl}_2\text{NN}]\text{Cu}=\text{NR}’\) with R-H indicates that \([\text{Cl}_2\text{NN}]\text{Cu-}\text{NHR}’\) species serve as intermediates in C-H amination. Previously, we have shown that two equivalents of \([\text{Cl}_2\text{NN}]\text{Cu-NHAd}\) engage in stoichiometric C-H amination of ethylbenzene by a HAA / RR sequence.\(^4^1\) Thus is of interest to compare the intrinsic HAA reactivity of the terminal copper nitrene \([\text{Cl}_2\text{NN}]\text{Cu}=\text{NR}’\) and copper(II) amide \([\text{Cl}_2\text{NN}]\text{Cu-NHR}’\) (R’ = Ad, tBu) species. A rate constant of \(2.2(2) \times 10^{-5} \text{M}^{-1}\text{s}^{-1}\) could be
measured for HAA of ethylbenzene by \([\text{Cl}_2\text{NN}]\text{Cu-NHAd}\) (Scheme 2.11).\(^{41}\)

**Scheme 2.11.** Roles for \([\text{Cl}_2\text{NN}]\text{Cu}=\text{NR'}\) and \([\text{Cl}_2\text{NN}]\text{Cu}=\text{NR'}\) in C-H amination.

\[
\begin{align*}
\text{[Cu]=NHR'} + \begin{array}{c}
\text{H} \\
\end{array} & \rightarrow \begin{array}{c}
\text{H} \\
\end{array} + [\text{Cu}^{\text{II}}]-\text{NHR'} \\
\text{[Cu}^{\text{II}}]-\text{NHR'} + \begin{array}{c}
\text{H} \\
\end{array} & \rightarrow \begin{array}{c}
\text{H} \\
\end{array} + [\text{Cu}^{\text{I}}](\text{NH}_2\text{R'}) \\
\text{[Cu}^{\text{II}}]-\text{NHAd} + \begin{array}{c}
\text{H} \\
\end{array} & \rightarrow \begin{array}{c}
\text{H} \\
\end{array} + [\text{Cu}^{\text{I}}]
\end{align*}
\]

*HAA by copper nitrenes and copper(II) amides*

*RR by copper(II) amides*

While we are unfortunately unable to directly compare the C-H bond reactivity of \([\text{Cl}_2\text{NN}]\text{Cu}=\text{NR'}\) (\(R' = \text{Ad}\) or \(^1\text{Bu}\)) species, it is clear that it is much higher. Analysis of the experimental data and the rate law derived from steady state analysis (Scheme 2.4 and Table 2.3) suggests the relationship \(k_{\text{HAA}} \approx 6 \times 10^{-6} / K_{\text{eq}}\). While we do not have an experimental value for \(K_{\text{eq}}\) corresponding to dissociation of \([\text{Cl}_2\text{NN}]\text{Cu}\) from \(\{[\text{Cl}_2\text{NN}]\text{Cu}\}_2(\mu-\text{NAd})\) (\(3\)) in benzene (Scheme 2.4), \(K_{\text{eq}}\) is lower than \(10^{-2}\) based on NMR analysis. No new nitrene species could be seen in the RT NMR spectrum of \(3\) in benzene-\(d_6\). Based on calculations that accompanied the initial report of \(1^{,29,47}\), dissociation of a [\(\text{Cu}^{\text{I}}\)] fragment from \(1\) as \([\text{Cl}_2\text{NN}]\text{Cu}\)(benzene) corresponds to a \(\Delta G = +5.8\) kcal/mol at 298 K. Taking into account the concentration of neat benzene, an equilibrium constant \(K_{\text{eq}} \approx 1 \times 10^{-3}\) may be crudely estimated at 40 °C. Using this estimate of \(K_{\text{eq}}\) for dissociation of [\(\text{Cu}^{\text{I}}\)] from \([\text{Cu} ]_2(\mu-\text{N}^1\text{Bu})\), we find that HAA of ethylbenzene
by [Cl₂NN]Cu=NᵗBu should possess a bimolecular rate constant in the vicinity of ca. $6 \times 10^{-3} \text{ M}^{-1}\text{s}^{-1}$ at 40 °C.

These data speak to the very high HAA reactivity of the terminal nitrene species [Cl₂NN]Cu=NR’ (R’ = Ad, tBu) species which is at least two orders of magnitude greater than that of the [Cl₂NN]Cu-NHAd and the closely related nickel-imide [Me₃NN]Ni=NAd ($k_{\text{HAA}} = 2.4(2) \times 10^{-5} \text{ M}^{-1}\text{s}^{-1}$ for ethylbenzene at 35 °C). The origin of the high reactivity of terminal alkynitrene species [Cl₂NN]Cu=NR is the high N-H bond strength in the copper(II) amide [Cl₂NN]Cu-NHR’ calculated to be 98.4 kcal/mol for [Cl₂NN]Cu-NHAd. In comparison, the N-H BDEs in [Cl₂NN]Cu(NH₂Ad) and [Me₃NN]Ni-N(H)Ad are calculated to be 68 and 85.2 kcal/mol, respectively.

Unfortunately, the high reactivity of terminal copper nitrene species also facilitates rapid α-H migration reactions via [Cl₂NN]Cu=NCHRR’ intermediates to give imine adducts [Cl₂NN]Cu(HN=CRR’). Such rearrangements in copper-alkynitrene complexes are reminiscent of α-H migration processes observed in free singlet alkynitrenes. For instance, photolysis of the alkylazide CH₃N₃ results in formation of HN=CH₂ via singlet [CH₃N]. A related β-H migration takes place from an Ir(III) benzylazide complex [Ir](N₃CH₂Ph) with loss of N₂ to give the corresponding [Ir](NH=CHPh) species, but no Ir-nitrene intermediate was observed.

**Conclusion**

Through a series of kinetic experiments we have shown that the dicopper nitrene dissociates to form the terminal nitrene which is the reactive intermediate for C-H amination. Mechanism for the reaction is stepwise via HAA / RR, based on scrambling results in the stereochemical experiments. The β-diketiminato copper nitrenes {[Cl₂NN]Cu}₂(μ-NR’) (R’ = Ad, tBu) represent sparse members of isolated and/or well characterized late first row transition
metal imides/nitrenes that show high reactivity towards C-H amination of strong \( sp^3 \) C-H bonds. Zhang provided EPR evidence supporting the presence of porphyrin Co(III)-nitrene radical intermediates capable of HAA/RR with 2° benzylic C-H substrates.\(^{27}\) A high spin dipyrrromethene Fe\(^{III}\)-imido \([\text{Fe}]=\text{NAr’}(\text{Ar’} = 4-\text{tBuC}_6\text{H}_4)\) isolated by Betley and co-workers directly aminates toluene.\(^{20}\) Warren group recently reported that the \( \beta \)-diketiminato nickel(III)-imide \([\text{Me}_3\text{NN}]\text{Ni}=\text{NAd}\) undergoes HAA with benzylic R-H substrates indane, ethylbenzene, and toluene to form the nickel-amide \([\text{Me}_3\text{NN}]\text{Ni-NHAd}\) and hydrocarbyl radical \( \text{R•} \).\(^{45}\) Attack of the nickel-imide by \( \text{R•} \) led to formation of the nickel(II) amides \([\text{Me}_2\text{NN}]\text{Ni-N}(\text{R})\text{Ad}\), though the C-H amination product \( \text{HN}(\text{R})\text{Ad} \) is observed in the reaction of \([\text{Me}_3\text{NN}]\text{Ni}=\text{NAd}\) with indane. Hillhouse et al. has isolated a low-coordinate nickel imido complex with an especially bulky NHC ligand, \((\text{IPr*})\text{Ni}=\text{N(dmp)}\) (dmp = 2,6-dimesitylphenyl).\(^{51}\) This nickel imido complex reacts with ethene, forming the vinylamine \((\text{dmp})\text{NH(CH=CH}_2\)\). The high reactivity of these copper nitrene also dictate the rapid rearrangement of 1° and 2° copper nitrenes to corresponding copper imines, setting up limitations to the applicability of these types of nitrenes in C-H amination.

Since the rate of C-H amination via HAA/RR is strongly coupled to the loss of a \([\text{Cu}^1] \) fragment from dicopper nitrenes \([\text{Cu}]_2(\mu-\text{NR’})\), synthetic studies that focus on the use of especially bulky \( \beta \)-diketiminato ligands and/or nitrene substituents that discourage the formation of dinuclear species should be expected to yield a significant rate enhancement. Coupled with the calculated strength of the N-H bond in \([\text{Cl}_2\text{NN}]\text{Cu-NHAd}\) (98.4 kcal/mol) formed via HAA of a substrate R-H via terminal \([\text{Cl}_2\text{NN}]\text{Cu}=\text{NAd}\),\(^{45}\) such approaches may place the catalytic functionalization of methane (C-H BDE = 105 kcal/mol)\(^{52}\) via \( \beta \)-diketiminato \([\text{Cu}]=\text{NR’}\) species within reach.
Experimental Details

2.4.a. General Procedures and Instrumentation

All experiments were carried out in a dry nitrogen atmosphere using an MBraun glovebox and/or standard Schlenk techniques, unless otherwise stated. 4A molecular sieves were activated in vacuo at 180 ºC for 24 h. Dry benzene, dichloromethane and tetrahydrofuran (THF) were purchased from Aldrich and were stored over activated 4A molecular sieves under nitrogen. Diethyl ether was first sparged with nitrogen and then dried by passage through activated alumina columns. Pentane was first washed with conc. HNO₃/H₂SO₄ to remove olefins, stored over CaCl₂ and then passed through activated alumina columns. All deuterated solvents were obtained from Cambridge Isotopes Laboratories, Inc., sparged with nitrogen, dried over activated 4A molecular sieves and stored under nitrogen.

¹H and ¹³C NMR spectra were recorded on Varian 400 MHz spectrometer (400 and 100.4 MHz, respectively). All NMR spectra were recorded at room temperature unless otherwise noted and were indirectly referenced to TMS using residual solvent signals as internal standards. GC-MS spectra were recorded on a Varian Saturn 2100T, elemental analyses were performed on a Perkin-Elmer PE2400 microanalyzer in our laboratories, and UV-Vis spectra were recorded on a Cary 50 spectrophotometer.

All reagents were obtained commercially unless otherwise noted and typically stored over activated 4A molecular sieves. {[Cl₂NN]Cu}₂(μ-benzene) (I)²⁹ was prepared by literature methods or may be obtained from Strem Chemicals (#29-7050).

2.4.b. General Precautions on Synthesis and Handling of Azides

Caution! While some organoazides can explosively decompose upon heating, exposure to high fluxes of light, or exposure to some metal complexes and some metal surfaces, we did not
experience any such uncontrolled reactivity in this work. All catalytic reactions with azides at elevated temperatures were performed in pressure vessels behind a Plexiglass shield.

Following literature procedures, $N_3^1$Bu$^{53}$ and $N_3^1$Cy$^{54}$ were prepared by reaction of NaN$_3$ with either tBuOH or CyBr under appropriate conditions. N$_3$CH$_2$CH$_2$Ph was prepared via modification of published procedures involving tosylation of PhCH$_2$CH$_2$OH$^{55}$ followed by reaction of PhCH$_2$CH$_2$OTs with NaN$_3$.$^{56}$

2.4.c. Preparation of Copper Compounds (3-8)

{[Cl$_2$NN]Cu)$_2$(µ-N$^t$Bu) (3). To slurry of 1 (0.173 g, 0.177 mmol) in 30 mL pentane was added a solution of N$_3^t$Bu (0.143 g, 1.44 mmol) in 20 mL pentane. This yellowish suspension was stirred for 24 h at RT; after ~10 min, it turned into a yellow-green slurry. The mixture was passed through a short Celite stick (ca. 1 cm$^3$), and the solvent was immediately removed in vacuo. The dark green residue was taken into ~10 mL pentane, filtered through a short Celite stick (ca. 1 cm$^3$), concentrated in vacuo to ~ 3 mL, and allowed to stand overnight at -35 ºC. Dark green blocks of the product formed (0.079 g, 46%) that were suitable for X-ray diffraction.  

$^1$H NMR (400 MHz, benzene-$d_6$, RT): δ 6.99 (d, 8, Ar-$m$-H), 6.42 (t, 4, Ar-$p$-H), 5.15 (s, 2, backbone –CH), 1.64 (s, 12, backbone –CH$_3$), 0.75 (s, 9, tBu –CH$_3$); $^{13}$C{$^1$H} NMR (100 MHz, benzene-$d_6$): δ 164.85, 147.31, 128.51, 128.27, 125.70, 100.11, 73.96, 29.95, 23.43. UV-Vis: $\lambda_{\text{max}}$ (benzene) = 714 nm (3960 cm$^{-1}$M$^{-1}$) with other prominent optical bands centered at 459 and 598 nm (Figure 2.8). Anal. Calcd. For C$_{38}H_{35}$Cl$_8$N$_5$Cu$_2$: C, 46.93; H, 3.63; N, 7.20. Found: C, 47.33; H, 3.86; N, 6.69.
N_3Cy (0.170 g, 1.36 mmol) in 5 mL pentane was added to a stirring slurry of 1 (0.259 g, 0.264 mmol) in 10 mL pentane. The initially yellow color of the slurry turned greenish blue in 2 min with effervescence of N\textsubscript{2}(g). The mixture was stirred for 10 min at room temperature, immediately filtered through a short Celite stick (ca. 1 cm\textsuperscript{3}) and the solvent was removed in vacuo. The resulting dark blue-green residue was extracted with cold pentane (~ 1.5 mL, -35 °C), passed through a short Celite stick (ca. 1 cm\textsuperscript{3}) and allowed to stand overnight at -35 °C. Dark blue crystals formed that were suitable for X-ray diffraction. Room temperature benzene-\textit{d}_6 solutions of this compound convert quickly (<5 min) to [Cl\textsubscript{2}NN]Cu(NH=\textit{c}-C\textsubscript{6}H\textsubscript{10}) (8) and [Cl\textsubscript{2}NN]Cu(benzene) as monitored by \textit{1}H NMR spectroscopy, undergoing α-H migration qualitatively faster than 5.

[Cl\textsubscript{2}NN]Cu(NH=\textit{c}-C\textsubscript{6}H\textsubscript{10}) (8). N\textsubscript{3}Cy (0.166 g, 1.33 mmol) in 5 mL ether was added to a stirring slurry of 1 (0.245 g, 0.205 mmol) in 10 mL ether. The color of the mixture turned greenish blue in 2 min with effervescence of N\textsubscript{2}(g). The mixture was left to stir for 24 h at RT upon which its color turned back to the initial yellow color. The mixture was filtered through Celite and concentrated in vacuo to ca. 2 mL and allowed to stand overnight at -35 °C. Yellow
crystals that crashed out of solution were collected and dried to afford 0.135 g (49\%) that were suitable for X-ray diffraction. $^1{H}$ NMR (400 MHz, benzene-$d_6$): $\delta$ 7.38 (s, 1, $NH$ imine), 7.10 (d, 4, Ar-$m$-H), 6.37 (t, 2, Ar-$p$-H), 5.03 (s, 1, backbone-CH), 2.02 (t, 2, $\alpha$-CH$_2$ from $=C$), 1.88 (s, 6, backbone-CH$_3$), 1.14 (d, 2, $\beta$-CH$_2$ from $=C$), 0.99 (t, 2, $\alpha$-CH$_2$ from $=C$), 0.87 (q, 2, $\gamma$-CH$_2$ from $=C$), 0.81 (d, 2, $\beta$-CH$_2$ from $=C$); $^{13}{C}$[$^1{H}$] NMR (100 MHz, benzene-$d_6$): $\delta$ 183.42 ($=CH$ imine), 163.80, 149.03, 130.61, 128.50, 122.85, 95.21, 39.41, 38.84, 27.14, 26.91, 25.06, 23.57. IR, thin film: 3276 cm$^{-1}$ (N-H). Anal. Calcd. For C$_{23}$H$_{24}$Cl$_4$N$_3$Cu: C, 50.43; H, 4.42; N, 7.67. Found: C, 50.65; H, 4.43; N, 7.40.

$\{[Cl_2NN]Cu\}_2(\mu$-NCH$_2$CH$_2$Ph) (5) and $[Cl_2NN]Cu(NH=CHCH$_2$Ph)$ (7) were first prepared and characterized by Dr. Yosra Badiei.$^{43}$ For the purpose of completeness in reporting, some data were borrowed from her thesis and presented in this chapter as well. For experiments involving these compounds, synthesis is followed from what is reported by Dr. Badiei.$^{43}$ From freshly prepared 7, IR thin film 3283 cm$^{-1}$ (N-H). Anal. Calcd. For C$_{25}$H$_{22}$Cl$_4$N$_3$Cu: C, 52.70; H, 3.89; N, 7.37. Found: C, 52.57; H, 3.66; N, 7.07.

2.4.d. Kinetic Measurement by UV-Vis Spectroscopy

Solutions for kinetic analysis by UV-Vis spectroscopy were prepared using freshly prepared and crystallized 3. A known amount of 3 was dissolved in RT benzene to a known volume using a volumetric flask. This sample was used for UV-Vis analysis and stored frozen at -35 °C until needed. A known portion of this stock solution (unfrozen) was added with appropriate amount of ethylbenzene and $\{[Cl_2NN]Cu\}_2$(benzene), followed by dilution to 10.0 mL with benzene at RT. The decreasing concentration of 3 at 40.0 °C was quantified by UV-Vis spectroscopy employing an 18s scan interval, by considering the decrease in absorbance at $\lambda_{max} = 714$ nm. The method of initial rates was used for kinetic analyses to minimize the effect of
[Cl$_2$NN]Cu generation in C-H amination by $\{[\text{Cl}_2\text{NN}][\text{Cu}]_2(\mu-\text{N}^t\text{Bu})\}$ which leads to a deceleration of effective rates.

**Dependence on Ethylbenzene.** The dependence on ethylbenzene was determined by monitoring the initial rate of disappearance of 3 ($\lambda = 714 \text{ nm}$) by UV-Vis employing benzene solutions of 3 of known concentration with varying equivalents of ethylbenzene. A stock solution was prepared by dissolving 3 (0.031 g, 0.032 mmol, 3.188 mM) in 10 mL benzene. Four aliquots of this stock solution (1.500 mL, 0.0048 mol) were taken. To each portion was added different amount of ethylbenzene: 0.585 mL (1000 equiv), 1.170 mL (2000 equiv), 2.925 mL (5000 equiv) and 5.855 mL (10000 equiv). Each portion was diluted to 10 mL with benzene and an aliquot (3 mL) was used for UV-Vis analysis sample. The decreasing concentration of 3 at 40.0 °C was quantified by UV-Vis spectroscopy employing an 18 s scan interval.

Plots of concentration of 3 vs. time gave relatively straight lines with initial rates inferred from the slopes of the [3] vs. time data collected in Table 2.1. A plot of these initial rates against the concentration of ethylbenzene shows that there is saturation dependence on ethylbenzene.

**Mechanistic Interpretation of the Dependence of Rate on Ethylbenzene.** Our observed kinetics are consistent with a preliminary equilibrium between dissociation of $\{[\text{Cl}_2\text{NN}][\text{Cu}]_2(\mu-\text{N}^t\text{Bu})\}$ into a terminal [Cl$_2$NN]Cu=N$^t$Bu and [Cl$_2$NN]Cu, and association of the latter two to form the dicopper nitrene. This mechanistic scheme in which the terminal nitrene is the active species for the amination predicts saturation kinetics on the concentration of ethylbenzene [RH]. At low [RH] ($k_{-1}[[\text{Cu}]] + k_2[\text{RH}] \approx k_{-1}[[\text{Cu}]]$), the rate is first order in [RH]. At very high [RH], $k_2[\text{RH}]$ predominates, removing the net dependence on the rate of decay of 3 on [RH].
Table 2.1. Observed initial rates of decay of \( \{[\text{Cl}_2\text{NN}\text{Cu}]_2(\mu-\text{N}^2\text{Bu}) \} \) in the C-H amination of ethylbenzene at 40.0 °C with varying equivalents of ethylbenzene. Initial rates were measured employing concentration of \( 3 \) in the range of 0.50-0.45 mM.

<table>
<thead>
<tr>
<th>Ethylbenzene Equiv</th>
<th>[ethylbenzene] (M)</th>
<th>Initial Rate (M/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000</td>
<td>0.4846</td>
<td>1.52 \times 10^{-7}</td>
</tr>
<tr>
<td>2000</td>
<td>0.9431</td>
<td>2.43 \times 10^{-7}</td>
</tr>
<tr>
<td>5000</td>
<td>2.321</td>
<td>3.35 \times 10^{-7}</td>
</tr>
<tr>
<td>10000</td>
<td>4.636</td>
<td>3.50 \times 10^{-7}</td>
</tr>
</tbody>
</table>

**Dependence of rate on [Cu] ([Cu] = [Cl\text{2NN}Cu]).** Employing the initial rates method, the dependence on the rate of decay of \( 3 \) on added [Cu] in the presence of 50 equiv. ethylbenzene with respect to \( 3 \) was determined by UV-vis analysis. A stock solution of \( 3 \) was prepared by dissolving freshly synthesized \( 3 \) (0.032 g, 0.033 mmol) in benzene in a 10 mL volumetric flask. A stock solution of [Cu] was prepared by dissolving \( \{[\text{Cl}_2\text{NN}\text{Cu}]_2(\text{benzene}) \} \) (0.540 g, 0.551 mmol, 0.1103 M) in benzene using a 10 mL volumetric flask. These solutions were kept cold (-35 °C) until needed. Each UV-Vis sample solution was made by mixing 1.00 mL of stock solution of \( 3 \), 50 equiv ethylbenzene (20.2 \( \mu \)L, 0.165 mmol) and varying equivalents (0, 1, 2, 5, 10, and 20) of [Cu] (29.8 \( \mu \)L, 59.7 \( \mu \)L, 149 \( \mu \)L, 298 \( \mu \)L, and 597 \( \mu \)L of [Cu] stock solution, respectively). Each sample was diluted with benzene to 10 mL and an aliquot (~3 mL) was taken for UV-Vis analysis at 40.0 °C employing an 18 s scan interval.

For these sample solutions, plots of concentration of \( 3 \) against time were obtained. The slope of each line was taken as the initial rate in M/s, summarized in Table 2.2.
Table 2.2. Observed initial rates of decay of $\{[\text{Cl}_2\text{NN}]\text{Cu}\}_2(\mu-\text{N}^t\text{Bu})$ (3) at 40.0 °C in the C-H amination of 50 equiv. ethylbenzene (16.5 mM) with varying equivalents of $[\text{Cl}_2\text{NN}]\text{Cu}$. The initial concentration of 3 was 0.34 mM in each case.

<table>
<thead>
<tr>
<th>Equiv of $[\text{Cl}_2\text{NN}]\text{Cu}$</th>
<th>Concentration of $[\text{Cl}_2\text{NN}]\text{Cu}$ (M)</th>
<th>Initial Rates, (M/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>4.73 x 10^{-8}</td>
</tr>
<tr>
<td>1</td>
<td>3.29 x 10^{-4}</td>
<td>2.87 x 10^{-8}</td>
</tr>
<tr>
<td>2</td>
<td>6.58 x 10^{-4}</td>
<td>2.11 x 10^{-8}</td>
</tr>
<tr>
<td>5</td>
<td>1.65 x 10^{-3}</td>
<td>1.23 x 10^{-8}</td>
</tr>
<tr>
<td>10</td>
<td>3.29 x 10^{-3}</td>
<td>6.41 x 10^{-9}</td>
</tr>
<tr>
<td>20</td>
<td>6.58 x 10^{-3}</td>
<td>4.28 x 10^{-9}</td>
</tr>
</tbody>
</table>

By employing 50 equiv. ethylbenzene and added monocopper [Cu], the concentration of these species in the reaction mixture were considered constant over time. Thus the rate law simplifies to rate = $k_{\text{obs}}$ [3]. To obtain $k_{\text{obs}}$ relating to the mechanism shown in Scheme 2.4, each of the initial rates obtained at different [Cu] concentrations was divided by the initial concentration of $\{[\text{Cl}_2\text{NN}]\text{Cu}\}_2(\mu-\text{N}^t\text{Bu})$ (3) (Table 2.3). A plot 1/$k_{\text{obs}}$ vs. [Cu] concentration gave a straight line with slope $k_1/(k_1k_2[RH])$ and y-intercept 1/$k_1$. From these data the first order rate constant for the dissociation of $[\text{Cl}_2\text{NN}]\text{Cu}$ from the dicopper nitrene $\{[\text{Cl}_2\text{NN}]\text{Cu}\}_2(\mu-\text{N}^t\text{Bu})$ is approximated as $k_1 = 1.1(3) \times 10^{-4}$ s$^{-1}$.

To approximate the value of $k_2$, or the rate constant for HAA, we substituted values for monocopper $[\text{Cl}_2\text{NN}]\text{Cu}$ and ethylbenzene concentrations into equation for rate law in Scheme 2.4. Taking entry 3 of Table 2.3 ($[[\text{Cl}_2\text{NN}]\text{Cu}] = 6.58 \times 10^{-4}$ and [ethylbenzene] = 0.0165 M; and $k_{\text{obs}} = 6.21 \times 10^{-5}$ s$^{-1}$), value of $k_2$ is $(6 \times 10^{-6}$ M$^{-1}$s$^{-1})/K_{eq}$. 

99
Table 2.3. Tabulation of $k_{obs}$ (s$^{-1}$) for amination of ethylbenzene by \{[Cl$_2$NN]Cu\}_2(\mu-N^tBu) (3) at 40.0 °C with varying equivalents of added [Cl$_2$NN]Cu.

<table>
<thead>
<tr>
<th>Equiv added [Cl$_2$NN]Cu</th>
<th>Concentration of [Cl$_2$NN]Cu (M)</th>
<th>$k_{obs}$ (s$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>$1.39 \times 10^{-4}$</td>
</tr>
<tr>
<td>1</td>
<td>$3.29 \times 10^{-4}$</td>
<td>$8.45 \times 10^{-5}$</td>
</tr>
<tr>
<td>2</td>
<td>$6.58 \times 10^{-4}$</td>
<td>$6.21 \times 10^{-3}$</td>
</tr>
<tr>
<td>5</td>
<td>$1.65 \times 10^{-3}$</td>
<td>$3.67 \times 10^{-3}$</td>
</tr>
<tr>
<td>10</td>
<td>$3.29 \times 10^{-3}$</td>
<td>$1.89 \times 10^{-3}$</td>
</tr>
<tr>
<td>20</td>
<td>$6.58 \times 10^{-3}$</td>
<td>$1.26 \times 10^{-3}$</td>
</tr>
</tbody>
</table>

$$\frac{1}{k_{obs}} = \frac{k_1[[Cu]]}{k_1k_2[RH]} + \frac{1}{k_1} \quad \text{where} \quad k_1/k_{-1} = K_{eq}$$

$$\frac{1}{6.21 \times 10^{-5}} = \frac{6.58 \times 10^{-4}}{0.0165} \quad \frac{1}{K_{eq}k_2} + \frac{1}{k_1}$$

$$k_2 = \frac{6 \times 10^{-6}}{K_{eq}}$$

Figure 2.9. Approximation of $k_2$ using entry of Table 2.3.

Double Reciprocal Plot under Ethylbenzene-Rich Conditions

A double reciprocal plot was also generated employing data from our ethylbenzene rich conditions outlined in Table 2.1 ([ethylbenzene] = 0.48 - 4.6 M). For each run, $k_{obs}$ was obtained by dividing each initial rate indicated in Table 2.1 by the initial concentration of \{[Cl$_2$NN]Cu\}_2(\mu-N^tBu) (3). A plot of $1/k_{obs}$ vs. $1 /$ [ethylbenzene] gave a straight line with y-intercept $1/k_1$ (Figure 2.10) from which the first order rate constant for the dissociation of [Cl$_2$NN]Cu from the dicopper nitrene 3 under these conditions is calculated as $k_1 = 1.0(1) \times 10^{-3}$.
s\(^{-1}\) (Scheme 2.4). The straight line generated provides further support for the mechanistic interpretation outlined in Scheme 2.4. Under ethylbenzene-rich conditions, this value is about 10 times greater than the \(k_1\) calculated from the dependence of rates on the concentration of \([\text{Cl}_2\text{NN}]\text{Cu}\) (Figure 2.5, \(k_1 = 1.1(3) \times 10^{-4} \text{ s}^{-1}\)) which employed a constant concentration of ethylbenzene of 16.5 mM. Thus, the nature of the solvent may influence the rate of dissociation of a \([\text{Cl}_2\text{NN}]\text{Cu}\) fragment from \([\text{Cl}_2\text{NN}]\text{Cu}\)\(_2\)(\(\mu\)-\(\text{N}^t\text{Bu}\)) to give the terminal nitrene \([\text{Cl}_2\text{NN}]\text{Cu}=\text{N}^t\text{Bu}\).

### 2.4.e. Qualitative Rates of Catalytic C-H Amination vs. Temperature

Two portions of a \(\text{N}^3\text{Bu}\) solution in ethylbenzene (1.00 mL, 0.89 M, 0.89 mmol) were dosed with an aliquot of 2 in ethylbenzene (1.00 mL, 0.025 M, 0.025 mmol), and further diluted with ethylbenze to a total volume of 15.0 mL. These were heated until reaction reached to about

![Figure 2.10](image.png)

**Figure 2.10.** Plot of \(1/k_{\text{obs}}\) vs. \(1/\text{[ethylbenzene]}\) at 40 °C. The inverse of the y-intercept is taken as \(k_1\ (1.0(1) \times 10^{-3} \text{ s}^{-1})\), the rate constant for the dissociation of dicopper nitrene to terminal nitrene under conditions of high concentration of ethylbenzene.
90% completion, at 40 °C for 5 d and 100 °C for 20 h, as indicated from change in color greenish to yellow. The reaction mixtures were cooled, exposed to air for several hours and passed through Celite to remove oxidized Cu. Each reaction was sampled and analyzed by GC/MS in triplicate. The C-H amination yield of PhCH(NH\text{tBu})CH₃ was obtained by comparing the integrations to a separate standard of 1:1 α-methyl-N-(tert-butyl)-benzenemethanamine : 1,2,4,5-tetrachlorobenzene. The yields at 40 °C and 100 °C are 93% and 91%, respectively. Under these conditions, we observe TOF values of 0.16 and 0.83 hr⁻¹ at 40 °C and 100 °C, respectively.

**Synthesis of Authentic Sample of α-methyl-N-(tert-butyl)-benzenemethanamine**

A solution of N₃\text{tBu} (0.099 g, 0.100 mmol) in ethylbenzene (10.00 mL) was mixed with a solution of 2 in ethylbenzene (5.00 mL, 0.025 M, 0.025 mmol) into pressure vessel and heated at 100 °C for 24 h. The reaction mixture was cooled, exposed to air for several hours and passed through Celite to remove oxidized Cu. The solvent was removed in vacuo and the residue was purified through silica flash chromatography, using hexane: ethyl acetate (gradient concentration, flow rate 5 mL/mon) as eluent. The product was analyzed by GC/MS to find pure product with m/z 178 in EI mode. $^1$H NMR (400 MHz, chloroform-$d_1$): $\delta$ 7.38 (d, 2, Ar-o-H), 7.28 (m, 2, Ar-m-H), 7.19 (t, 1, Ar-p-H), 3.96 (q, 1, benzylic -CH), 1.32 (d, 3, -CH₃), 1.02 (s, 9, -C(CH₃)₃).

**2.4.f. Stereochemical Analysis of the C-H Insertion Products**

In order to establish whether the C-H amination reaction via copper alkynitrene species proceeds through a concerted or a stepwise (radical) C-H insertion process, the stereoselectivity of the [Cl₂NN]Cu catalyzed reactions of N₃\text{tBu} with the substrates 1,4-dimethylcyclohexane and a benzylic radical clock were examined.
Catalytic Amination of cis- and trans-1,4-dimethylcyclohexane with \( \text{N}_3\text{Bu} \). Two portions of \( \text{N}_3\text{Bu} \) (0.198 g, 2.00 mmol) were dosed, one mixed with cis-1,4-dimethylcyclohexane (6.00 mL, 41.8 mmol) and the other with the trans-isomer (6.00 mL, 40.6 mmol). A solution of \( \{[\text{Cl}_2\text{NN}]\text{Cu}\}_2\text{(benzene)} \) (1.00 mL, 0.025 M, 0.025 mmol – 2.5 mol% relative to \( \text{N}_3\text{Bu} = 5 \) mol% [Cu] relative to \( \text{N}_3\text{Bu} \)) in benzene was added into each of the aliquot of the azide-substrate solution (3.00 mL). These reaction mixtures were heated for 48 h at 100 °C in a sealed, thick walled reaction vessel. The color of the solution changed from light yellow to dark green. The mixtures were quenched by exposing to air for several hours, filtered through Celite stick and analyzed via GC/MS in CH\(_2\)Cl\(_2\). GC/MS indicated that there are no other products except for the aminated products. The solvent was removed \textit{in vacuo} from each reaction mixture, the residue was taken as the crude yield for the reaction, 55% (0.105 g) for the cis- and 50% (0.0915 g) from the trans-isomer. Amination at both tertiary and secondary C-H bonds were observed, with selectivity of 3°:2° 75:25 and 25:75 for cis- and trans-isomer respectively. Tertiary products were obtained in the same distribution (44:56 for trans-isomer and 46:64 for cis-isomer), irrespective of substrate used.

**Product Distribution of the Catalytic Amination of trans-1,4-dimethylcyclohexane with \( \text{N}_3\text{Bu} \).** The GC/MS(EI) profile of the C-H amination reaction mixture of trans-1,4-dimethylcyclohexane with \( \text{N}_3\text{Bu} \) is shown in Figure 2.11 (left). Peaks marked as 1B and 1D are taken as the tertiary products, while 1A and 1C are assigned as the secondary products. Peaks 1B and 1C are clearly separate, though not completely resolved. The EI-MS of products 1B and 1D are consistent with facile loss of a methyl group (- m/z 15) from the molecular ion (m/z = 183) that
limits its observation by EI, whereas this molecular ion is observed for secondary products 1A and 1C. The protonated molecular ion (M+1: m/z = 184) is apparent in the CI-MS spectra of each species 1A–1D. Confirmation of the components 1B and 1D as tertiary C-H amination products is made by comparison of products at the same retention times in the amination of cis-1,4-dimethylcyclohexane with identical MS spectra (Figures 2.11 – left and Figure 2.12).

Product Distribution of the Catalytic Amination of cis-1,4-dimethylcyclohexane with N₃Bu. The GC/MS(EI) profile of the C-H amination reaction mixture of cis-1,4-dimethylcyclohexane with N₃Bu is shown in Figure 2.11 (right). There are only three C-H amination products observed; one of the two possible secondary insertion products is not observed. Peaks marked as 2A and 2C are taken as the tertiary products, while 2B is assigned as a secondary product. The EI-MS of products 2A and 2C are consistent with facile loss of a methyl group (- m/z 15) from the molecular ion (m/z = 183) that limits its observation by EI, whereas this molecular ion is observed for the secondary product 2B. The protonated molecular ion (M+1: m/z = 184) is apparent in the CI-MS spectra of each species 2A–2C. Confirmation of the components 2A and 2C as tertiary C-H amination products is made by comparison of products at the same retention times in the amination of trans-1,4-dimethylcyclohexane with identical MS spectra (Figure 2.11 – right and Figure 2.12).
Table 2.4. Product analysis from the catalytic amination of cis- and trans-1,4-dimethylcyclohexane with N\textsubscript{3}tBu. Labels refer to C-H amination product peaks in Figure 2.10.

<table>
<thead>
<tr>
<th>Trans-1,4-dimethylcyclohexane</th>
<th>Cis-1,4-dimethylcyclohexane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Label</td>
<td>Retention time (min)</td>
</tr>
<tr>
<td>1A</td>
<td>7.483</td>
</tr>
<tr>
<td>1B</td>
<td>7.623</td>
</tr>
<tr>
<td>1C</td>
<td>7.708</td>
</tr>
<tr>
<td>1D</td>
<td>9.762</td>
</tr>
</tbody>
</table>

Figure 2.11. GC/MS-EI mode profile of the reaction mixture from the catalytic amination of trans-1,4-dimethylcyclohexane (LEFT) and cis-1,4-dimethylcyclohexane (RIGHT) with N\textsubscript{3}tBu; Top – GC showing the inserted products, as indicated by flags; Bottom - MS of each highlighted GC component peak.

GC instrumentation: Varian Saturn 2100T GC/MS; 30 m HP-5 (5% phenyl dimethylpolysiloxane) column; ultrapure He gas as carrier gas at a flow rate of 1.2 mL/min; starting temperature at 100 °C, hold for 3 min, ending temperature at 101 °C with a ramp rate of 0.1 °C/min.
C-H amination of a mixture of cis- and trans-1,4-dimethylcyclohexane with N\textsubscript{3}Bu. To further confirm that the assigned 3° inserted products from the trans-isomer are indeed the same as the ones from the cis-isomer, we carried out a catalytic C-H amination run (same conditions as above) employing a mixture of the cis and trans isomers. GC/MS analysis of the product mixture was done three times, and each set of data was plotted using MagicPlot Student free software (http://magicplot.com/, downloaded 17 September 2011). Gaussian curve fitting was done for each peak to determine the retention times (Table 2.5 and Figure 2.12). Five peaks (M1 – M5) are seen that correspond to the 5 individual C-H amination products of which two (M2 and M5) are in common, indicating them as the 3° amination products.

**Table 2.5.** Retention times of the C-H insertion products in a mixture of cis- and trans-1,4-dimethylcyclohexane along with their assignments from comparison with product mixtures from separate reactions with pure cis- and trans-1,4-dimethylcyclohexane (see Table 2.4).

<table>
<thead>
<tr>
<th>Retention times (min)</th>
<th>Peak M1</th>
<th>Peak M2</th>
<th>Peak M3</th>
<th>Peak M4</th>
<th>Peak M5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial 1</td>
<td>7.501</td>
<td>7.641</td>
<td>7.716</td>
<td>7.785</td>
<td>9.786</td>
</tr>
<tr>
<td>Trial 2</td>
<td>7.497</td>
<td>7.636</td>
<td>7.710</td>
<td>7.780</td>
<td>9.782</td>
</tr>
<tr>
<td>Trial 3</td>
<td>7.484</td>
<td>7.628</td>
<td>7.696</td>
<td>7.766</td>
<td>9.767</td>
</tr>
<tr>
<td>Average</td>
<td>7.494</td>
<td>7.635</td>
<td>7.707</td>
<td>7.777</td>
<td>9.778</td>
</tr>
</tbody>
</table>

Assignment 1A (2° from trans-isomer) 1B/2A (3°) 1C (2° from trans-isomer) 2B (2° from cis-isomer) 1D/2C (3°) cis-isomer

The products were not isolated, and the relative abundance of each inserted product is approximated through its direct response in the GC/MS-EI analysis. GC/MS analysis was done three times for each GC/MS sample to establish the reproducibility of the results. Each set of
data was plotted using MagicPlot Student software. Peak areas were determined by fitting a Gaussian curve for the peak. A summary of the peak areas is presented in Table 2.6.

Table 2.6. Relative abundance (unscaled) of the C-H insertion products from the catalytic amination of cis- and trans-1,4-dimethylcyclohexane with N₃Bu.

<table>
<thead>
<tr>
<th></th>
<th>Trans-1,4-dimethylcyclohexane</th>
<th>Cis-1,4-dimethylcyclohexane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial</td>
<td>Percentage of Component</td>
<td>Percentage of Component</td>
</tr>
<tr>
<td></td>
<td>1A (2°) 1B (3°) 1C (2°) 1D (3°)</td>
<td>2A (3°) 2B (2°) 2C (3°)</td>
</tr>
<tr>
<td>1st</td>
<td>11 11 64 14</td>
<td>34 25 41</td>
</tr>
<tr>
<td>2nd</td>
<td>11 11 64 14</td>
<td>34 25 41</td>
</tr>
<tr>
<td>3rd</td>
<td>11 11 64 14</td>
<td>34 25 41</td>
</tr>
<tr>
<td>Average</td>
<td>11 11 64 14</td>
<td>34 25 41</td>
</tr>
</tbody>
</table>

Figure 2.12. Gaussian fitted curves for the GC-MS(EI) plots of the inserted products from the catalytic amination of trans- and cis-1,4-dimethylcyclohexane with N₃Bu using MagicPlot Student software. LEFT: C-H amination products from trans-isomer, MIDDLE:C-H amination products from cis-isomer and RIGHT: C-H amination products of a mixture of cis- and trans-isomers. M2 and M5 (right) represent the superimposed 3° insertion products. Extremely small peaks marked by asterisks (M⁺ - 2) appear to be a result of subsequent oxidation products of the aminated species.
**Synthesis of 1-benzyl-** trans-2-pheno**lycyclopropane**

Trans-1,3-diphenylpropene was first prepared following a literature procedure involving the reaction of phenylacetaldehyde (20.032 g, 0.167 mol) and KOH (10.036 g, 0.179 mol) in 95% ethanol (80 mL). This mixture was refluxed for 4 h. After cooling, the reaction mixture was washed with brine and extracted with diethyl ether. The organic layer was washed with water, dried with anhydrous MgSO₄ and rotary evaporated to remove the solvent. The residue was purified by silica column chromatography using hexanes as eluent. Collected fractions were pooled and the solvent was removed in vacuo, resulting to a colorless, slightly oily liquid, in 11.678 g yield (72 %). GC/MS of the product showed two peaks of the same M⁺ value (m/z 194), in 2.7 % and 97.2 % ratio assigned as cis- and trans-isomers. The ¹H NMR in chloroform- d₉ is shown in Figure 2.13.

Using a modified cyclopropanation procedure, the benzylic radical clock was synthesized from trans-1,3-diphenylpropene. In an inert atmosphere, a cold (-35 °C) solution of trifluoroacetic acid (TFA, 1.200 mL, 0.0157 mol) in CH₂Cl₂ (20 mL) was added gradually by syringe into a cold solution of diethylzinc (16.0 mL, 0.0158 mol, 1.0 M in hexanes) in CH₂Cl₂ (20 mL). During addition, a gel-like mixture was formed which changed to a clear, homogeneous solution after stirring for 10 min. This solution was cooled at -35 °C for ~ 10 min. A cold solution CH₂I₂ (1.300 mL, 0.0161 mol) in CH₂Cl₂ (20 mL) was added dropwise to the cold ZnEt₂ / TFA solution. While the mixture was still colorless, evolution of some gas was observed. The mixture was stirred for ca. 10 min and then placed in a -35 °C freezer for 10 min. Finally, a cold solution of trans-1,3-diphenylpropene (3.062 g, 0.0158 mol) in CH₂Cl₂ (20 mL) was added dropwise to the cold solution containing the organozinc reagent. The resulting mixture was allowed to warm to RT and stirred for 24 h, eventually turning to slight yellow. After 24 h,
GC/MS-EI analysis of an aliquot showed that the reaction had not yet reached completion. Another full equivalent of the organozinc reagent generated from Et₂Zn, TFA and CH₂I₂ in CH₂Cl₂ was added and the mixture was heated at 30-40 °C for 36 h in a closed vessel. The reaction mixture was quenched aqueous HCl (1M, 50 mL) in an ice-bath. The organic layer was collected and the aqueous layer was extracted with diethyl ether (2 × 20 mL). The pooled organic layer was washed with saturated NaHCO₃, water and brine solution (each ca. 50 mL), and dried with anhydrous MgSO₄. The solvent was removed in vacuo and the residue was purified through silica column chromatography using hexanes as eluent. The product was isolated in 1.30 g yield (39 %).

Analysis by GC/MS-EI of this product indicated the desired trans-cyclopropane radical clock product (M⁺: m/z = 208, 97.2%) along with very small amounts of the cis-cyclopropane (M⁺: m/z = 208, 1.3 %) and unreacted propene starting material (M⁺: m/z = 208, 1.5 %). ¹H NMR analysis clearly indicated the formation of the desired product (Figure 2.13). This radical clock substrate was used for catalytic C-H amination experiments below without further purification.
Figure 2.13. $^1$H NMR spectra (400 MHz, chloroform-$d_1$, RT) of trans-1,3-diphenylpropene (top) and 1-benzyl-trans-2-phenylcyclopropane (bottom).
Catalytic Amination of a Benzylic Radical Clock.

A solution of 1-benzyl-trans-2-phenylcyclopropane (0.150 g, 0.720 mmol) and N₃Bu (0.357 g, 3.60 mmol) was added into a slurry of [{Cl₂NNCu}(benzene) (0.353 g, 0.360 mmol) in benzene (1.00 mL). The reaction was allowed to stir at 100 °C for 48 h in a sealed, thick walled reaction vessel. The color changed to dark green after only 2 min, then to dark brown towards the end of the reaction. After quenching the reaction by exposing it to air for several hours, the solution was filtered through Celite and the solvent was removed under vacuum. GC/MS analysis of the crude reaction mixture revealed only one C-H amination product of the radical clock (m/z = 280) along with unreacted radical clock along and a small amount of a product from the amination of the reactive trans-1,3-diphenylpropene impurity. The crude mixture was chromatographed on silica using 8:2 CH₂Cl₂: methanol as eluents. The third pooled fraction was collected and contains the aminated radical clock. The solvent was removed dried in vacuo resulting to a dark brown oily residue in 80% (0.1602 g) yield. Precipitating this with ethereal HCl resulted to an HCl salt whose ¹H NMR analysis is consistent with a ring-opened aminated product. ¹H NMR of the HCl salt (400 MHz, chloroform-d₁): δ 9.63 (m, 2, -NH·HCl), 7.72 (m, Ar-H), 7.40 (m, Ar-H), 7.34 (m, Ar-H), 7.14 (m, Ar-H), 7.07 (m, Ar-H), 6.59 (m, Ar-H), 6.32 (d, 1, vinylic H, JHH, Hz = 16), 5.65 (m, 1, vinylic H, JHH, Hz = 16), 4.27 (m, 1, benzylic -CH), 3.83 (m, 1, -CH₂), 3.20 (m, 1, -CH₂), 1.36 (s, 9, -Bu CH₃) (see Figure 2.15 for labelling and ¹H-¹H correlation spectrum).
Figure 2.14. GC/MS-EI mode profile of the reaction mixture from the catalytic amination of 1-benzyl-trans-2-phenylcyclopropane with N₃Bu. (Top) GC showing the inserted product. (Bottom) EI-MS of the highlighted GC component peak.
Figure 2.15. $^1$H NMR (top) and $^1$H-$^1$H COSY (bottom) NMR spectra (400 MHz, chloroform-$d_1$, RT) of the HCl-salt of the product from the amination of the radical clock 1-benzyl-trans-2-phenylcyclopropane with $N_3$Bu catalyzed by $\{[Cl_2NN]Cu\}_2(\mu$-benzene) (2) at 100 °C.
2.4.g. Rearrangement versus Amination: Catalytic Amination of Ethylbenzene using $N_3Cy$ and $N_3CH_2CH_2Ph$

In an attempt to test the potential of $1^\circ$ and $2^\circ$ alkylazides in catalytic amination, a catalytic reaction with ethylbenzene and $N_3Cy$ or $N_3CH_2CH_2Ph$ was setup. A solution of $N_3Cy$ (0.123 g, 0.983 mmol) in ethylbenzene (5.00 mL) or $N_3CH_2CH_2Ph$ (0.147 g, 0.997 mmol) in ethylbenzene (5.00 mL) was mixed with a solution of 2 in ethylbenzene (5.00 mL, 0.0101 M, 0.051 mmol). This slightly yellow green solution was further diluted with ethylbenzene (5.00 mL), and transferred into pressure vessel and heated at 100 °C for 24 h. The solution rapidly changed to yellow after ~10 min. After 24 h, the reaction mixture was exposed to air for several hours and passed through Celite to remove oxidized Cu. Analysis by GC/MS showed that there is no aminated products resulting from either azide, only the imine was observed.

Freshly prepared 5 (51 mg, 0.050 mmol) or 6 (42 mg, 0.042 mmol) was added to a solution of standard 1,2,4,5-tetrachlorobenzene (1 equiv / 5 or 6) in ethylbenzene (3.00 mL). These solutions were heated at 70 °C for 24h, upon which the solution turned from blue/purple to yellow quite rapidly, ~2 min. The colled solutions were quenched by exposing to air for several hours and filtered through Celite stick. Similarly, analysis by GC/MS showed that there is no aminated products resulting from either dicopper nitrene, only the imine was observed.
2.4.h. Crystallographic Details

Single crystals of \([\text{Cl}_2\text{NNCu}]_2(\mu-\text{N}^t\text{Bu}) \cdot \text{pentane}\ (3 \cdot \text{pentane}), [\text{Cl}_2\text{NNCu}]_2(\mu-\text{NCy}) \cdot \text{pentane}\ (6 \cdot \text{pentane})\) and \([\text{Cl}_2\text{NNCu}](\text{NH}=\text{c-C}_6\text{H}_{10})\) (8) were mounted under mineral oil or perfluoroalkyl ether oil on glass fibers and immediately placed in a cold nitrogen stream at 100(2) K (for 3, 6, and 8) on a Bruker SMART CCD system. Hemispheres of data were collected (0.3° ω-scans; 2θmax = 56°; monochromatic Mo Ka radiation, λ = 0.7107 Å) and integrated with Bruker SAINT program. Structure solutions were performed using the SHELXTL/PC suite\(^a\) and XSEED.\(^b\) Intensities were corrected for Lorentz and polarization effects and an empirical absorption correction was applied using Blessing’s method as incorporated into the program SADABS.\(^c\) Non-hydrogen atoms were refined with anisotropic thermal parameters and hydrogen atoms were included in idealized positions. The molecule of pentane associated with \([\text{Cl}_2\text{NNCu}]_2(\mu-\text{N}^t\text{Bu})\) (3) was mildly disordered and modeled over two sites in a 54 / 46 ratio.

References for X-ray structure refinement details

(a) SHELXTL-PC, Vers. 5.10; 1998, Bruker-Analytical X-ray Services, Madison, WI; G. M. Sheldrick, SHELX-97, Universität Göttingen, Göttingen, Germany.

(b) L. Barbour, XSEED, 1999.

### Table 2.7. Crystallographic data for compounds 3, 6, and 8.

<table>
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<tr>
<th>Compd.</th>
<th>([{\text{Cl}_2\text{NN}}\text{Cu}}_2(\mu\text{-N}^\text{t}Bu)) • pentane (3 • pentane)</th>
<th>([{\text{Cl}_2\text{NN}}\text{Cu}}_2(\mu\text{-NCy})) • pentane (6 • pentane)</th>
<th>([\text{Cl}_2\text{NN}]Cu(NH=c-C_6H_10)) (8)</th>
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<td>(\text{C}<em>{43.5}\text{H}</em>{43}\text{Cl}_8\text{Cu}_2\text{N}_5)</td>
<td>(\text{C}<em>{23}\text{H}</em>{24}\text{Cl}_4\text{CuN}_3)</td>
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<td>100(2)</td>
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<td>10.9720(10)</td>
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<td>(c) (Å)</td>
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<td>0.90 and -0.82</td>
<td>0.48 and -0.20</td>
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References


(43) Badiei, Y. M., Georgetown University, 2009.


CHAPTER 3

C-H Amination by Copper Arylnitrenes


Abstract

β-diketiminato dicopper arylnitrenes \([\text{Cl}_2\text{NN}]\text{Cu}\)\(_2(\mu-\text{NAr})\) were synthesized from the reaction the \([\text{Cl}_2\text{NN}]\text{Cu}\)\(_2(\mu-\text{benzene})\) and aryl azides (N\(_3\)Ar\(_{F6}\) and N\(_3\)Ar\(_{p-CN}\)), in addition to the previously isolated \([\text{Cl}_2\text{NN}]\text{Cu}\)\(_2(\mu-\text{NMes})\) by Dr. Yosra Badiei. Stoichiometric reaction of these discrete dicopper nitrenes with substrates featuring \(sp^2\) hybridized C-H bonds revealed that these species are less reactive towards C-H bonds than the dicopper alkylnitrenes \([\text{Cl}_2\text{NN}]\text{Cu}\)(\(\mu\)-NR) (R = \(\text{t-Bu}\) or \(1-\text{Ad}\)). Importantly, the nitrile moiety of dicopper arylnitrenes \([\text{Cl}_2\text{NN}]\text{Cu}\)\(_2(\mu-\text{NAr})\) decays to diazenes ArN=NAr, representing an important by-product observed in stoichiometric and catalytic reactions involving \([\text{Cu}]_2(\mu-\text{NAr})\) species. Kinetic studies of the stoichiometric reaction between \([\text{Cl}_2\text{NN}]\text{Cu}\)\(_2(\mu-\text{NMes})\) and ethylbenzene indicates that it is a complicated reaction, though it suggests a first order kinetics with respect to the dicopper nitrile. The rate of reaction is accelerated with the addition of pyridine. A mechanistic possibility where loss of a \([\text{Cl}_2\text{NN}]\text{Cu}\) fragment from \([\text{Cl}_2\text{NN}]\text{Cu}\)\(_2(\mu-\text{NMes})\) to give the terminal nitrile \([\text{Cl}_2\text{NN}]\text{Cu}=\text{NMes}\) that reacts with C-H bonds along with \([\text{Cl}_2\text{NN}]\text{Cu}(\text{py})\) is proposed, a more complex mechanism is also possible. Decomposition of these dicopper arylnitrenes \([\text{Cu}]_2(\mu-\text{NAr})\) in solvent lacking reactive C-H bonds like benzene gives the diazene ArN=NAr and anilines as the major products, especially for electron-poor arylnitrenes. When followed by UV-Vis spectroscopy, the decay of the dicopper arylnitrene does not give a clear \(1^{st}\) or \(2^{nd}\) order dependency on the dicopper nitrile. One proposed reason is that the copper arylnitrene may be a common intermediate for coupling resulting to diazene and HAA resulting to anilines. These again indicate the complicated nature of the mechanism that involves copper arylnitrenes. Catalytic reactions of arylazides N\(_3\)Ar with benzylic and allylic substrates R-H employing \([\text{Cl}_2\text{NN}]\text{Cu}\)\(_2(\mu-\text{benzene})\) as catalyst gave the C-H amination product R-NHAr
along with the corresponding aniline (H₂NAr) and diazene (ArN=NAr). When competing with C-H amination, diazene formation is more pronounced when electron-rich azides are employed.

**Introduction**

C-H amination is a rapidly developing field of research for the direct synthesis of amines enabling the direct conversion of a C-H bond to a C-N bond.²⁻⁶ Most protocols involving transition metal catalysis propose metal nitrene [M]=NR intermediates.⁵,⁷ Perhaps the most common nitrene precursor used are iminioiodinanes, either isolated or prepared *in situ* from sulfonyl amines or carbamates and PhI(OR)₂.⁸⁻¹² Organic azides N=N=NR are considered as practical and environmentally-friendly nitrene source, as they are readily available and easily synthesized, with molecular nitrogen as by-product.

We reported the use of the unactivated 1-adamantylazide (N₃Ad) in the catalytic amination of *sp*³-C-H bonds using \{{[Cl₂NN]Cu}_{2}(μ-benzene)\} (I) as catalyst.¹³ We also carefully explored the mechanism of the copper-catalyzed C-H amination using dicopper alkynitrenes \{{[Cl₂NN]Cu}_{2}(μ-NR)\} presented in Chapter 2.¹⁴ The mechanism involves dissociation of the dicopper alkynitrene to give the terminal copper nitrene [Cl₂NN]Cu=NR and [Cl₂NN]Cu. The terminal nitrene is the active hydrogen atom abstraction (HAA) agent (Scheme 3.1). A crucial finding is that terminal copper nitrenes [Cl₂NN]Cu=NCHR’R bearing α-H atoms on the nitrene substituent are subject to tautomerization to the copper(I) imine [Cl₂NN]Cu(NH=CR’R). This unfortunately limits the potential of using a wide variety of alkylazides into our catalytic protocol.

Thus, we focus our attention on other azides N=N=NR that would lead to nitrene intermediates [Cu]=NR not subject to this rearrangement. Arylazides N₃Ar should lead to [Cu]=NAr intermediates not subject to this tautomerization reaction. Moreover, arylazides N₃Ar
are easily synthesized from the corresponding anilines $\text{H}_2\text{NAr}$ through diazotization.\textsuperscript{15} Their use allows for the direct introduction of $N$-substituted aryl groups into a molecule via C-H bonds. Cenini \textit{et al.} reported the use of aryl azides in the amination of allylic and benzylic C-H bonds using Co(II)\textsuperscript{16-20} and Ru(II)\textsuperscript{16,18,21-23} porphyrin complexes as catalysts (Schemes 1.15 – Chapter 1).

\textbf{Scheme 3.1.} Mechanism for C-H amination using dicopper alkynitrenes ($R' = \text{Ad}$ and \textsuperscript{1}Bu).

\[
\begin{align*}
\text{i)} & \quad [\text{Cu}]_2(\mu-\text{NR}') \quad \xrightleftharpoons[k_1]{k_{-1}} \quad [\text{Cu}]=\text{NR}' + [\text{Cu}]_2(\mu-\text{NAr}) \\
\text{dicopper} & \quad \text{aryl nitrene} \quad \text{terminal} \\
& \quad \text{copper nitrene} \\
\text{ii)} & \quad [\text{Cu}]=\text{NR}' + \text{R-H} \quad \xrightarrow[k_{\text{HAA}}]{\text{Cu}^{\text{II}}-\text{NHR}'} \quad \text{[Cu]}^{\text{II}}-\text{NHR}' + \text{R} \cdot \text{amide} \\
\end{align*}
\]

Herein we report the isolation of dicopper arylnitrene species $\{[\text{Cl}_2\text{NN}]\text{Cu})(\mu-\text{NAr})$ from the reaction of the $\beta$-diketiminato copper(I) complex $\{[\text{Cl}_2\text{NN}]\text{Cu}\}_2(\mu-\text{benzene})$ (1) with a small family of arylazides $\text{N}_3\text{Ar}$. The reactivity of these dicopper nitrenes towards $sp^3$ C-H bonds was investigated along with decomposition pathways that involve bimolecular coupling of $[\text{Cu}]=\text{NAr}$ intermediates to give diazenes $\text{ArN}=\text{NAr}$.

\textbf{Results and Discussion}

\textbf{3.2.a. Synthesis of New Dicopper Arylnitrenes}

Following the successful synthesis of $\{[\text{Cl}_2\text{NN}]\text{Cu}\}_2(\mu-\text{NMes})$ (2) (Mes = 2,4,6-trimethylphenyl or mesityl) by Dr. Yosra Badiei,\textsuperscript{24} two new dicopper arylnitrenes were synthesized from reaction of $\{[\text{Cl}_2\text{NN}]\text{Cu}\}_2(\mu-\text{benzene})$ (1) with the more electron-deficient aryl azides $\text{N}_3\text{Ar}^{\text{F6}}$ and $\text{N}_3\text{Ar}^{p-\text{CN}}$ ($\text{Ar}^{\text{F6}} = 3,5\text{-bis(trifluoromethyl)phenyl}$, $\text{Ar}^{p-\text{CN}} = p\text{-cyanophenyl}$).
Reaction of 1 with N$_3$Ar$^{F6}$ in pentane yielded the dark blue / purple crystals of [{[Cl$_2$NN]Cu$_2$}(µ-NAr$^{F6}$)] (3) in 77% yield (Scheme 3.2.A). In the solid state, there are actually two molecules of 3 in an asymmetric unit, along with two molecules of azide N$_3$Ar$^{F6}$ that co-crystallize. X-ray structures of the two molecules of 3 (named as 3a and 3b) are shown separately in Figures 3.1.a and 3.1.b. The two molecules are very similar in structure and
metrical parameters, showing the familiar bridging nitrene unit between the two copper centers present in previous structurally characterized examples\textsuperscript{13,14} (see Chapter 2). The Cu⋯Cu distances for 3a and 3b (2.8212(14) and 2.8204(15) Å, respectively) are shorter than those of \{[Cl\textsubscript{2}NN]Cu\}\textsubscript{2}(μ-NAd) or \{[Cl\textsubscript{2}NN]Cu\}\textsubscript{2}(μ-N\textsuperscript{t}Bu) (2.969(1) and 2.9147(6) Å, respectively), much closer to that of the dicopper aryl nitrene counterpart \{[Cl\textsubscript{2}NN]Cu\}\textsubscript{2}(μ-NMes) (2.830(4) Å) and the previously characterized \{[Me\textsubscript{3}NN]Cu\}\textsubscript{2}(μ-NAr') (Ar' = 3,5-Me\textsubscript{2}C\textsubscript{6}H\textsubscript{3}) (2.911(1) Å).\textsuperscript{25} The molecule 3A has symmetric Cu-N\textsubscript{nitrene} (1.802(7) Å) distances, while 3B has more asymmetric Cu-N\textsubscript{nitrene} (1.791(7) and 1.808(7) Å) distances. These values are more similar to \{[Me\textsubscript{3}NN]Cu\}\textsubscript{2}(μ-NAr') and shorter than those reported for \{[Cl\textsubscript{2}NN]Cu\}\textsubscript{2}(μ-NAd) or \{[Cl\textsubscript{2}NN]Cu\}\textsubscript{2}(μ-N\textsuperscript{t}Bu). Molecules 3A and 3B have smaller Cu-N\textsubscript{nitrene}-Cu angle of 103.0(3) and 103.2(3)° than any of the three reported dicopper nitrenes.

Dark purple crystals of \{[Cl\textsubscript{2}NN]Cu\}\textsubscript{2}(μ-NAr\textsuperscript{p-CN})Cu[Cl\textsubscript{2}NN] (4) were isolated from the reaction of 1 with N\textsubscript{3}Ar\textsuperscript{p-CN} in chlorobenzene / pentane in 68 % yield (Scheme 3.2.B). The X-ray structure of 4 is shown in Figure 3.2, showing a similar bridging nitrene unit between the two copper centers. The Cu⋯Cu distance for 4 (2.9877(7) Å) is comparable to that of \{[Cl\textsubscript{2}NN]Cu\}\textsubscript{2}(μ-NAd) or \{[Cl\textsubscript{2}NN]Cu\}\textsubscript{2}(μ-N\textsuperscript{t}Bu) (2.969(1) and 2.9147(6) Å, respectively) and definitely longer than that of 2 and 3A or 3B. The cyano group of the NAr\textsuperscript{p-CN} moiety is also able to bind [Cl\textsubscript{2}NN]Cu in the solid state, with Cu3-N6 distance of 1.855(3) Å. The presence of this extra [Cl\textsubscript{2}NN]Cu may have been the reason why the Cu⋯Cu contact in 4 is longer than the other dicopper aryl nitrene; steric hindrance of the aryl groups of the β-diketiminate ligands of the mononuclear [Cl\textsubscript{2}NN]Cu with that of the bridging nitrene moiety may cause the a widening of the Cu-N\textsubscript{nitrene}-Cu vector (111.07(15)°), which is more similar to those of the dicopper alkyl nitrenes than 2, 3A, 3B or {[Me\textsubscript{3}NN]Cu}\textsubscript{2}(μ-NAr').
In solution, 3 is highly symmetric molecule exhibiting only one set of aryl *meta*- and *para*-hydrogens for the β-diketiminate ligands, as can be seen from its H NMR spectrum in benzene-d$_6$ (Figure 3.3). This spectrum demonstrates $C_{2v}$-symmetry in solution, higher than the approximate $C_2$-symmetry of the molecule shown in the solid state, indicating that there is a full rotation about the Cu-N$_{nitrene}$ vector, losing the Cu···Cu interaction seen in the solid state. The resonance of the backbone C-H (δ 4.84 ppm) appears at the more upfield region as compared to that for 2 (δ 5.08 ppm). Compound 4 also exhibit an approximate $C_2$-symmetry, only one set of aryl *meta*- and *para*-hydrogens for the β-diketiminate ligands for the dinuclear portion. The other copper(I) β-diketiminate complex bonded through the cyano group of the nitrene seems to be labile and dissociates from the rest of the molecule as the resonances accounted for these hydrogens are very similar to the resonances reported for $[\text{Cl}_2\text{NN}]\text{Cu}$ in benzene-d$_6$.

### 3.2.b. Stoichiometric Reactions of the Dicopper Arylnitrenes with C-H Substrates

The previously isolated dicopper alkylnitrene $\{[\text{Cl}_2\text{NN}]\text{Cu}\}_2(\mu\text{-NAd})$ has been shown to facilitate C-H amination of benzylic and $sp^3$ substrates like indane, toluene and cyclohexane.$^{13}$ The dicopper arylnitrene $\{[\text{Me}_3\text{NN}]\text{Cu}\}_2(\mu\text{-NAr'})$ is reported to do nitrene group transfer to isocyanide CN$'^t$Bu and trimethylphosphine PMe$_3$ to form carbodiimide Ar$'$N=C=N$'^t$Bu and phosphoimide Ar$'$N=PMe$_3$. But in the presence of styrene, $\{[\text{Me}_3\text{NN}]\text{Cu}\}_2(\mu\text{-NAr'})$ did not afford the aziridination product, but rather the diazene Ar$'$N=NAr$'$ and the hydrazine Ar$'$NH-NHAr$'$. With these in mind, we went on to try these new dicopper arylnitrene compounds in stoichiometric C-H amination with benzylic and $sp^3$ C-H substrates.
**Figure 3.1.a.** X-ray structure of molecule A of \([\text{Cl}_2\text{NN}]\text{Cu}_2(\mu-\text{NArF}_6)\) (3a). Selected bond distances (Å) and angles (°): Cu1-Cu2 2.8212(14), Cu1-N1 1.930(7), Cu1-N2 1.886(7), Cu2-N3 1.937(7), Cu2-N4 1.898(7), C1-N5 1.802(7), Cu2-N5 1.802(7), N1-Cu1-N2 95.6(3), N3-Cu2-N4 95.9(3), Cu1-N5-Cu2 103.0(3). All hydrogen atoms are omitted for clarity.
Figure 3.1.b. X-ray structure of molecule B of \{[\text{Cl}_2\text{NN}]\text{Cu}_2(\mu-\text{NArF})\} (3b). Selected bond distances (Å) and angles (°): Cu3-Cu4 2.8204(15), Cu3-N6 1.895(7), Cu3-N7 1.934(7), Cu4-N8 1.907(7), Cu4-N9 1.935(7), C3-N10 1.791(7), Cu4-N10 1.808(7), N6-Cu3-N7 95.4(3), N8-Cu4-N9 96.0(3), Cu3-N10-Cu4 103.2(3). All hydrogen atoms are omitted for clarity.
Figure 3.2. X-ray structure of $\text{[Cl}_2\text{NNCu}]_2(\mu\text{-NAr}^{p\text{-CN}})\text{[Cl}_2\text{NNCu}]$ (4). Selected bond distances (Å) and angles (°): Cu1-Cu2 2.9877(7), Cu1-N1 1.924(3), Cu1-N2 1.906(3), Cu2-N3 1.898(3), Cu2-N4 1.933(3), Cu1-N5 1.814(3), Cu2-N5 1.810(3), Cu3-N6 1.855(3), Cu3-N7 1.905(5), Cu3-N8 1.982(3), N6-C1 1.152(3), N1-Cu1-N2 95.76(12), N3-Cu2-N4 96.32(14), Cu1-N5-Cu2 111.07(15), N7-Cu3-N8 97.38(13), Cu3-N6-C1 166.7(3). All hydrogen atoms are omitted for clarity.
Figure 3.3. $^1$H NMR (400 MHz, RT, benzene-$d_6$) spectrum of $\{[\text{Cl}_2\text{NN}]\text{Cu}\}_2(\mu$-\text{ArF}_6$)$ (3).
Scheme 3.4. $^1$H NMR (400 MHz, RT, benzene-$d_6$) spectrum of $\{[$Cl$_2$NN]Cu$_2$(µ-NAr$^{p-CN}$)Cu[Cl$_2$NN]$\} (4).$
Solutions of 2, 3 and 4 in neat ethylbenzene, indane and cyclohexane (0.01 M in concentration) were heated at 80 °C for 24 h (Table 3.1). The benzylic amination product along with the corresponding aniline (H₂NAr) and diazene (ArN=NAr) were observed in most cases. For indane, the benzylic amination product is only observed in quantifiable amounts with 2; with 3 and 4, benzylic amination product is detected in GC/MS but only diazene is quantified by ¹H NMR. Heating the solutions at lower temperatures (40 or 60 °C) did not change the product distribution of the reaction mixture, it just took longer time for the reaction to be complete (48 h or longer), as indicated by the change of color from purplish/bluish color of the [Cu]₂(μ-NAr)

Table 3.1. ¹H NMR yields of stoichiometric reaction of dicopper arylnitrenes with ethylbenzene and indane.

<table>
<thead>
<tr>
<th>[Cu]₂(μ-NAr)</th>
<th>¹H NMR Yield, %</th>
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<tr>
<td></td>
<td>product</td>
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<tr>
<td>2</td>
<td>19</td>
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<tr>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
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</table>

BDE = 87 kcal/mol

<table>
<thead>
<tr>
<th>[Cu]₂(μ-NAr)</th>
<th>¹H NMR Yield, %</th>
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<tbody>
<tr>
<td></td>
<td>very minute</td>
</tr>
<tr>
<td>2</td>
<td>71</td>
</tr>
<tr>
<td>3</td>
<td>very minute</td>
</tr>
<tr>
<td>4</td>
<td>very minute</td>
</tr>
</tbody>
</table>

BDE = 85.9 kcal/mol
species to yellowish brown.

These dicopper arylnitrenes are less efficient as nitrene group transfer agents as compared to their dicopper alkynitrene counterparts.\textsuperscript{13,14} Considering the same mechanism for C-H amination as dicopper alkynitrene\textsuperscript{14} (Chapter 2), the dicopper arylnitrene \{[Cl\textsubscript{2}NN]Cu\}_\textsubscript{2}(\mu-NAr) is thought to dissociate in solution to give low concentrations of the terminal nitrene [Cl\textsubscript{2}NN]Cu=NAr along with [Cl\textsubscript{2}NN]Cu(solvent) (Scheme 3.3). We rationalize the product profiles above (Table 3.1) by proposing that the terminal nitrene can either: (a) perform HAA on the C-H substrate to give [Cu]-NHAr and R• or (b) couple to form diazene ArN=NAr. It is also possible that the diazene formation may come from the coupling of copper(II) anilides, forming hydrazine, which further oxidizes to diazene (Scheme 3.3.C). In a recent report by the Warren group about the C-H amination of \textit{sp\textsuperscript{3}} benzylic, benzylic and unactivated C-H substrates using anilines, with 1 as catalyst and di-tert-butyl peroxide as oxidant, this is the mechanism by which they proposed diazene is derived.\textsuperscript{26} This includes further complications in the reactivity of these copper arylnitrenes.

In general, the product distribution in the stoichiometric reaction of these dicopper arylnitrenes depends on how fast the terminal copper arylnitrene can be intercepted by a C-H substrate. If this HAA step is slow, coupling of dicopper arylnitrenes may occur. Still, comparison of the rates of HAA and coupling (eqn 1 of Scheme 3.3), HAA step is favored by ramping up the amount of C-H substrate, diluting the reaction mixture. In stoichiometric reactions, the reaction mixture is considered as concentrated (more concentrated than in catalytic conditions), coupling of the terminal copper arylnitrenes is more favored. The lower amount of diazene formed from the reaction of 2 may have arisen from the steric provided by the \textit{ortho}-methyl groups, lessening the chance for the two terminal copper nitrenes from coupling.
Scheme 3.3. Two possible reactions for terminal copper aryl nitrene.

\[ [\text{Cu}]_2(\mu-\text{NAr}) \xrightarrow{\kappa_1} [\text{Cu}]=\text{NAr} + [\text{Cu}] \]

\[ \text{dicopper} \quad \text{aryl nitrene} \quad \text{terminal} \quad \text{copper nitrene} \]

\[ [\text{Cu}] = [\text{Cl}_2\text{NN}]\text{Cu} \]

A. C-H Functionalization

i) \[ [\text{Cu}]=\text{NAr} + \text{R-}\text{H} \xrightarrow{k_{\text{HAA}}} [\text{Cu}^{\text{II}}]-\text{NHar} + \text{R} \bullet \]

\[ \text{copper(II)} \quad \text{amide} \]

ii) \[ [\text{Cu}^{\text{II}}]-\text{NHar} + \text{R} \bullet \xrightarrow{k_{\text{RR}}} [\text{Cu}](\text{NH}(\text{R})\text{Ar}) \]

B. Cu-Nitrene Coupling

iii) \[ [\text{Cu}]=\text{NAr} + [\text{Cu}]=\text{NAr} \xrightarrow{k_{\text{coupling}}} \]

\[ \text{diazene-bound copper} \]

C. Cu\textsuperscript{II}-Anilide Coupling

iii) \[ [\text{Cu}^{\text{II}}]-\text{NHar} + [\text{Cu}^{\text{II}}]-\text{NHar} \xrightarrow{k'_{\text{coupling}}} \]

iv. \[ \text{ArHN-NHar} \xrightarrow{[\text{Ox}]} \text{ArN=NAr} \]

Comparison of Rates

\[ \frac{\text{rate HAA}}{\text{rate coupling}} = \frac{k_{\text{HAA}} [([\text{Cu}]=\text{NAr}) [\text{RH}]}{k_{\text{coupling}} [[\text{Cu}]=\text{NAr}]^2} \]

\[ \frac{\text{rate HAA}}{\text{rate coupling}} = \frac{k_{\text{HAA}} [\text{RH}]}{k_{\text{coupling}} [([\text{Cu}]=\text{NAr})]} \quad \text{(eqn 1)} \]

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3.2.c. Catalytic Reaction with Ethylbenzene

Catalytic reactions of these three aryl azides (N$_3$Mes, N$_3$Ar$^{F6}$, and N$_3$Ar$^{p-CN}$) were run using ethylbenzene as the representative benzylic C-H (benzylic C-H BDE = 87 kcal/mol)\(^1\) at 80 °C for 24 hours and 2 mol% catalytic loading of 1. Same as with the above stoichiometric reactions, GC/MS analysis of the reaction mixtures were messier than those of using alkylazides,\(^{13}\) with the most identifiable fractions consisted of the benzylic amination product, aniline and diazene. \(^{1}\)H NMR yields of the reaction products are presented in Table 3.2. Conversion is better achieved with the reaction of electron-poor aryl azides N$_3$Ar$^{F6}$ and N$_3$Ar$^{p-CN}$, at about 80-90%. It also seems that selectivity for nitrene insertion over coupling is greater for electron deficient copper arylnitrene. Our observed trends are consistent with those of Cenini et al. with their Ru\(^{21}\)- and Co\(^{17}\)-porphyrin-catalyzed reactions of toluene and similar benzylic C-H substrates. Amination with more electron-poor aryl azides gave better results, although formation of diazene is still a competitive reaction.

Table 3.2. \(^1\)H NMR yields of catalytic reaction of aryl azides with ethylbenzene.

<table>
<thead>
<tr>
<th>N$_3$Ar$^X$, aryl azide</th>
<th>N$_3$Ar$^X$ (2) mol% 1, 80 °C, 24 h, (-)N$_2$ (\rightarrow) product</th>
<th>(^1)H NMR Yield, %</th>
<th>aniline</th>
<th>diazene</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) N$_3$Mes</td>
<td>24</td>
<td>2</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>2) N$_3$Ar$^{F6}$</td>
<td>74</td>
<td>6</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>3) N$_3$Ar$^{p-CN}$</td>
<td>48</td>
<td>17</td>
<td>14</td>
<td></td>
</tr>
</tbody>
</table>
If the HAA step is the rate-determining step in the mechanism, it is postulated that the driving force for the reaction of these copper nitrenes is the strength of the N-H bond of the copper(II) anilide \([\text{Cl}_2\text{NN}]\text{Cu}^{II}\text{-NHAr}\) formed after HAA of the terminal copper arylnitrene (Scheme 3.3). Generally, electron rich groups on the anilines weaken the N-H bonds while electron deficient groups increase N-H BDE, when compared to that aniline (Table 3.3). We expect that this trend correlates to the N-H bond strength of the corresponding copper(II) anilide \([\text{Cl}_2\text{NN}]\text{Cu}^{II}\text{-NHAr}\). Copper arylnitrenes \([\text{Cl}_2\text{NN}]\text{Cu}^=\text{NAr}\) with electron-poor substituted phenyl group have more driving force because of the stronger N-H bond of the \([\text{Cl}_2\text{NN}]\text{Cu}^{II}\text{-NHAr}\).

**Table 3.3.** N-H bond strengths of some representative anilines.\(^1\)

<table>
<thead>
<tr>
<th>(X)</th>
<th>N-H BDE, kcal/mol</th>
<th>(X)</th>
<th>N-H BDE, kcal/mol</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) H</td>
<td>92.2</td>
<td>5) 4-OME</td>
<td>87.2</td>
</tr>
<tr>
<td>2) 2-Me</td>
<td>90.6</td>
<td>6) 2,4-Me(_2)</td>
<td>88.0</td>
</tr>
<tr>
<td>3) 4-Me</td>
<td>90.0</td>
<td>7) 3,5-(CF(_3))(_2)</td>
<td>97.2</td>
</tr>
<tr>
<td>4) 4-CN</td>
<td>95.2</td>
<td>8) 2,4,6-Cl(_3)</td>
<td>95.5</td>
</tr>
</tbody>
</table>

Combining the catalytic and stoichiometric results, we postulate that the selectivity for C-H bond functionalization over diazene formation of these terminal copper arylnitrenes is generally kinetically controlled. From Scheme 3.3 equation 1, diazene formation is promoted if the concentration of the terminal copper arylnitrene is high, as in the case of stoichiometric reactions. We expect that the concentration of \([\text{Cl}_2\text{NN}]\text{Cu}=\text{NAr}\) in a catalytic reaction is very low, it selects to react with the C-H substrate as it is present in greater concentration, than coupling.
3.2.d. Mechanistic Insight into C-H Amination of Ethylbenzene with $\{[\text{Cl}_2\text{NN}]\text{Cu}\}_2(\mu\text{-NMes})$

Given the competing formation of diazene, the mechanism of C-H amination through these dicopper aryl nitrenes warrants a more detailed investigation. Since reaction of $\{[\text{Cl}_2\text{NN}]\text{Cu}\}_2(\mu\text{-NMes})$ (2) gave the least amount of diazene by-product, it seems to be the relatively more well-behaved as compared to other dicopper aryl nitrenes. Thus, we followed the stoichiometric reaction of 2 (0.116 mM) with neat ethylbenzene at 60 °C via UV-Vis spectroscopy, monitoring the change in the strong absorbance at 553 nm ($\varepsilon = 17200 \text{ M}^{-1}\text{cm}^{-1}$) (Figure 3.3.A). In neat ethylbenzene, kinetic analysis via 1st order integrated rate law shows a plot that generally curved at the latter stages of the analysis, indicating the possible buildup of

![Scheme 3.4](image)

### Scheme 3.4. C-H functionalization using dicopper aryl nitrene.

i) $[\text{Cu}]_2(\mu\text{-NAr})_{\text{dicopper arylnitrene}} \xrightarrow{k_1} [\text{Cu}]=\text{NAr}_{\text{terminal copper nitrene}} + [\text{Cu}]$

ii) $[\text{Cu}]=\text{NAr} + \text{R}-\text{H} \xrightarrow{k_{\text{HAA}}} [\text{Cu}^{\text{II}}]-\text{NHAr} + \text{R}^*$

iii) $[\text{Cu}^{\text{II}}]-\text{NHAr} + \text{R}^* \xrightarrow{k_{\text{RR}}} [\text{Cu}](\text{NH}(\text{R})\text{Ar})$

iv) $[\text{Cu}] + \text{py} \rightarrow [\text{Cu}]($py$)$

**Pseudo-1st order rate law without py**

\[
\text{rate} = \frac{k_1 k_2 [\text{RH}]}{k_{-1} [[\text{Cu}]] + k_2 [\text{RH}]}[[\text{Cu}]_2(\mu\text{-NAr})]
\]

\[
\text{rate} = k_{\text{obs}} [[\text{Cu}]_2(\mu\text{-NAr})]
\]

$[\text{Cu}] = [\text{Cl}_2\text{NN}]\text{Cu}$

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the [Cl₂NN]Cu from the dissociation and slowing down the rate. This dicopper arynitrene 2 has a half-life of ca. 20 h and a pseudo-1st order rate constant of \(8.0 \times 10^{-4} \text{s}^{-1}\) in ethylbenzene (Figure 3.3.B). When the UV-Vis study of the decomposition of 2 (0.100 mM) in ethylbenzene in the presence of 1000 equiv pyridine (py) was done at 60 °C, the plot is now less curved, though it is still evident at the latter stages (Figure 3.4.B). Significantly, the rate was increased, with a half-life ca. 3 h and a pseudo first order rate constant of \(3.9 \times 10^{-3} \text{s}^{-1}\). Considering that dicopper arynitrene can dissociate to [Cl₂NN]Cu=NAr and [Cl₂NN]Cu, added pyridine might have formed a complex with [Cl₂NN]Cu as it is formed, upsetting the equilibrium and pushing the dissociation to the terminal copper nitrene (Scheme 3.4, step iv). We are able to crystallize [Cl₂NN]Cu(py) (5) from the reaction of 1 and pyridine in ether/pentane (Scheme 3.5, Figure 3.5 for X-ray structure).²⁷ GC/MS analyses of the reaction mixtures after UV-Vis studies showed that the C-H functionalization is accompanied by diazene formation, although the amount of diazene formed decreased in the presence of py. This indicates that the reaction monitored is more complex than just C-H amination of ethylbenzene.

**Scheme 3.5.** Synthesis of [Cl₂NN]Cu(py) (5).
Figure 3.3. Stoichiometric reaction of \([\text{Cl}_2\text{NNCu}]_2(\mu\text{-NMes})\) (2) in ethylbenzene at 60 °C: A) UV-Vis profile over time, scans every 30 min; B) integrated 1st rate law plot \(\ln \left[ (A-A_{\text{inf}}) / (A_0-A_{\text{inf}}) \right] \) against time.
A.) UV-Vis profile of $\{[\text{Cl}_{2}\text{NN}]\text{Cu}\}_{2}(\mu-\text{NMes})\) (2) in ethylbenzene + 1000 equiv py

B.) Kinetic analysis for the reaction of $\{[\text{Cl}_{2}\text{NN}]\text{Cu}\}_{2}(\mu-\text{NMes})\) (2) in ethylbenzene + 1000 equiv py

Figure 3.4. Stoichiometric reaction of $\{[\text{Cl}_{2}\text{NN}]\text{Cu}\}_{2}(\mu-\text{NMes})\) (2) + 1000 equiv pyridine in ethylbenzene at 60 °C: A) UV-Vis profile over time, scans every 5 min; B) integrated 1$^{\text{st}}$ rate law plot $\ln \left(\frac{(A-A_{\text{inf}})}{(A_{0}-A_{\text{inf}})}\right)$ against time.
Figure 3.5. X-ray structure of [Cl₂NN]Cu(py) (5). Selected bond distances (Å) and angles (°): Cu-N1 1.970(2), Cu-N2 1.916(2), Cu-N3 1.918(2), N1-Cu-N2 97.70(9), N1-Cu-N3 141.87(10), N2-Cu-N3 120.39(9). All hydrogen atoms are omitted for clarity.
3.2.e. Allylic Substrates for C-H Amination

Allylic C-H bonds are weaker than ordinary saturated C-H bonds because of their lower BDEs (mostly in the range of 80-85 kcal/mol).\textsuperscript{1} Thus, these bonds are slightly activated and functionalization at these allylic positions gives access to an amine group next to a double bond. These make olefins an interesting substrate for C-H amination. But because of the unsaturation site in olefins, nitrene addition across the double bond with these substrates gives aziridines, which typically competes with allylic C-H amination.

Table 3.4. $^1$H NMR yields of catalytic reaction of aryl azides with cyclohexene.

<table>
<thead>
<tr>
<th>Aryl azide</th>
<th>$^1$H NMR Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>product</td>
</tr>
<tr>
<td>$N_3$Mes</td>
<td>12</td>
</tr>
<tr>
<td>$N_3$Ar$^F6$</td>
<td>78</td>
</tr>
</tbody>
</table>

To compare the electronic effect of the substituent on the nitrene, reactions of aryl azides $N_3$Mes and $N_3$Ar$^F6$ with 5 equiv cyclohexene (BDE 81.9 kcal/mol)\textsuperscript{1} were run in benzene at 80 °C for 24 h at a 2.5 mol % loading of 1. GC/MS and $^1$H NMR analyses of the reaction mixture showed formation of the allylic amination product and diazene (Table 3.4). Aziridine is not considered as product based on the fragmentation seen in GC/MS and on the chemical shifts of
the mixture. It was also observed from the $^1\text{H}$ NMR spectra that 20 % of $\text{N}_3\text{Mes}$ and 13 % of $\text{N}_3\text{Ar}$ remained. These results suggest that cyclohexene may have been coordinating to the Cu(I) catalyst via its C=C $\pi$-bond, impeding activation of the weakly Lewis basic organoazide $\text{N}_3\text{Ar}$. This has also been observed in the C-H amination of cyclohexene using the $^4\text{BuOO}^4\text{Bu} / \text{aniline}$ protocol.$^{26}$

To qualitatively determine the strength of binding of olefins to $[\text{Cl}_2\text{NN}]\text{Cu}$ in the prototypical arene solvent benzene, solution studies of the competition between allylbenzene and cyclohexene suggested the formation of an olefin adduct with 1. Through the addition of 1.5 equiv of each olefin to 1 equiv 1 in benzene-$d_6$, it is clear that each olefin binds more strongly to 1 than benzene (Scheme 3.5). Both olefins showed a significant upfield shift resonance ($\delta$ 4.23 ppm for allylbenzene and $\delta$ 4.41 ppm for cyclohexene). Nevertheless, these results suggest that there is a significant competition between the coordination of the olefin and the coordination of the azide for activation.

Scheme 3.6. Equilibrium between $\beta$-diketiminato copper(I) cyclohexene and allylbenzene adduct.

![Scheme 3.6](image)

Indeed, when 2 equiv of cyclohexene was added to a stirring slurry of 1 in ether/pentane gave light yellow granular crystals of adduct $[\text{Cl}_2\text{NN}]\text{Cu}(\eta^2\text{-cyclohexene})$ (6) in 34 % yield
The X-ray structure of 6 shows a coplanar arrangement of the double bond of the cyclohexene and the ligand backbone with a distorted square geometry around Cu (with angles N1-Cu-N2 96.91(7)°, N1-Cu-C1 112.14(8)°, N2-Cu-C2 111.22° and C1-Cu-C2 39.66, Σ angles 390°). This is similar to the arrangement of the previously reported β-diketiminato copper(I)-olefin adducts (with styrene and ethylene). As with the styrene adduct, there is a significant back bonding interaction from the d¹⁰ copper center and the π* molecular of the cyclohexene, as shown by the lengthening of the C=C double of the cyclohexene adduct (1.377(3) Å) as compared to the reported bond length for free cyclohexene (1.335(3) Å). The ¹H NMR spectrum in benzene-d₆ of 6 shows a complete coordination of the olefin because of the upfield shift for the resonances of the vinylic Hs for the 6 at δ4.42 ppm compared to that of pure cyclohexene at δ 5.69 ppm. Also, the β-diketiminato backbone ligand peak for the cyclohexene adduct 6 at δ 5.03 ppm is different from that of naked copper complex [Cl₂NN]Cu (δ 4.84 ppm). Also the

**Scheme 3.7.** Synthesis of [Cl₂NN]Cu(η²-cyclohexene) (6).
Figure 3.6. X-ray structure of [Cl₂NN]Cu(η²-cyclohexene) (6). Major conformer of cyclohexene ring shown that involves disorder about two sets of positions for C4A, C5A (57 % occupancy). Selected bond distances (Å) and angles (°): Cu-N1 1.9327(16), Cu-N2 1.9384(16), Cu-C1 2.023(2), Cu-C2 2.027(2), C1-C2 1.377(3), N1-Cu-N2 96.91(7), N1-Cu-C1 112.14(8), N2-Cu-C2 111.22(8), C1-Cu-C2 39.66(8). All hydrogen atoms are omitted for clarity.
3.2.f. Decomposition of Dicopper Arylnitrene in Benzene

Diazene formation is a competitive reaction from the stoichiometric and catalytic reactions of the dicopper arylnitrenes \([\{\text{Cl}_2\text{NN}\}\text{Cu}\}_2(\mu-\text{NAr})\). When solutions of these dicopper arylnitrenes in benzene were heated at 80 °C for 24 h, we found that the reaction decomposition products are mostly the diazene ArN=NAr and aniline H$_2$NAr. $^1$H NMR yields were determined and are summarized in Scheme 3.8. There is about 10 % of the dicopper arylnitrenes that remained after reactions. Diazenes are instead in high yield for the 3 and 4, about 30 % for both case (maximum yield is 50 %). Also in the case of 4, the amount of aniline formed is unusually high. At this moment, the source of the H-atoms in the formation of anilines is unknown, although this aniline is proposed to come from the double HAA, HAA of the copper arylnitrene and then second HAA of the copper(II) anilide. Since sp$^2$ C-H bond of benzene (BDE = 112.9 kcal/mol)$^1$ is strong, we do not expect that HAA on this bond will occur. We did not observe any

Scheme 3.8. Decomposition of dicopper arylnitrenes in benzene.

\[
\begin{align*}
\{\text{Cl}_2\text{NN}\}\text{Cu}_2(\mu-\text{NMes}) & \quad \text{benzene} \quad 80 \, ^\circ\text{C}, \quad 24 \, \text{h} \\
2 & \quad \text{NH}_2\text{Mes} \quad + \quad \text{MesN=NMes} \\
& \quad 6.5 \, \% \quad + \quad 3.5 \, \% \\
\{\text{Cl}_2\text{NN}\}\text{Cu}_2(\mu-\text{NAr}^{F6}) & \quad \text{benzene} \quad 80 \, ^\circ\text{C}, \quad 24 \, \text{h} \\
3 & \quad \text{NH}_2\text{Ar}^{F6} \quad + \quad \text{Ar}^{F6}\text{N=NAr}^{F6} \\
& \quad 8.8 \, \% \quad + \quad 32.3 \, \% \\
\{\text{Cl}_2\text{NN}\}\text{Cu}_2(\mu-\text{NAr}^{p-CN}) & \quad \text{benzene} \quad 80 \, ^\circ\text{C}, \quad 24 \, \text{h} \\
4 & \quad \text{NH}_2\text{Ar}^{p-CN} \quad + \quad \text{Ar}^{p-CN}\text{N=NAr}^{p-CN} \\
& \quad 63 \, \% \quad + \quad 31.6 \, \%
\end{align*}
\]
C-H amination product of benzene coming from radical rebound of copper(II) anilide and the phenyl radical nor biphenyl which comes from coupling of two phenyl radicals.

To gain further insight on how the diazene is formed from the dicopper aryl nitrene, we studied the decomposition of these dicopper aryl nitrenes in benzene. The specific compounds are \([\text{Cl}_2\text{NN} \text{Cu}]_2(\mu-\text{Nmes})\) (2) and \([\text{Cl}_2\text{NN} \text{Cu}]_2(\mu-\text{NAr}^{\text{F6}})\) (3) which possess different steric and electronic properties. These decomposition reactions were performed at 80 °C and monitored via UV-Vis spectroscopy.

For \([\text{Cl}_2\text{NN} \text{Cu}]_2(\mu-\text{Nmes})\) (2), the decrease in absorbance at 553 nm correlated to the change in [2], as monitored every 0.6 s for 150 s. There is no new observable copper species in the region \(\lambda = 400-800\) nm formed as the reaction progresses, suggesting formation of the optically silent copper(I) species \([\text{Cl}_2\text{NN} \text{Cu}]\) as a product (Figure 3.17). For each sample solution, plot of change in absorbance against time gives the initial rate as the slope in M/s (Figure 3.7.A). The natural logarithm of these initial rates is plotted against the natural logarithm of concentration of the dicopper aryl nitrenes to give the order of the reaction with respect to the dicopper aryl nitrene as the slope of the line (Figure 3.7.B). The slope of the line is found to be non-integral 0.82. Similarly, varying concentrations of \([\text{Cl}_2\text{NN} \text{Cu}]_2(\mu-\text{NAr}^{\text{F6}})\) (3) were prepared and analyzed through UV-Vis spectroscopy. For this dicopper aryl nitrene, there is a new copper species forming whose \(\lambda_{\text{max}}\) is centered at 679 nm, with isosbestic point at 628 nm (Figure 3.18). This new species maybe the copper(I) diazene adduct (Figure 3.9), though it was not isolated. Treatment of data is same above. The slope of the line is found to be a non-integral value of 0.85 (Figure 3.8.B). This non-integral value for slope of the ln/ln plot for both the dicopper aryl nitrenes again suggests the presence of competing mechanisms for consumption of dicopper aryl nitrenes.
We believe that the equilibrium between the dicopper arylnitrene and terminal arylnitrene and \([\text{Cl}_2\text{NN}]\text{Cu}\) is an important factor in the decomposition of these dicopper nitrenes, we run another set of samples for UV-Vis analysis, but now with constant concentration of \([\text{Cl}_2\text{NN}]\text{Cu}\) added into 2 and 3. With a constant concentration of \([\text{Cl}_2\text{NN}]\text{Cu}\) kept constant even the start of the reaction, this will make its build-up kinetically irrelevant especially at the later stage of the reaction. In the presence of constant concentration of \([\text{Cl}_2\text{NN}]\text{Cu}\) (1.5-3.0 equiv with respect to 2), the order of the reaction with respect to 2 is found to be 1.2 (Figure 3.8.B). While in the presence of added \([\text{Cl}_2\text{NN}]\text{Cu}\) (1.4-2.0 equiv with respect to 3), order of reaction with respect to 3 is 1.43 (Figure 3.6.B). Again, this non-integral value of order indicates that more complicated mechanistic steps are involved for copper arylnitrenes, which may indicate that this species is a common intermediate for different possible mechanistic outcomes, two of which may be the diazene and aniline. Also, the amount of \([\text{Cl}_2\text{NN}]\text{Cu}\) added (1.4-3 equiv) may not be enough to sufficiently buffer the amount of \([\text{Cl}_2\text{NN}]\text{Cu}\) formed at the later stage of the reaction.

**Figure 3.9.** Possible structure of the copper-diazene complex.
Figure 3.7. Kinetic analysis of the decomposition of \([\text{Cl}_2\text{NN}]\text{Cu}_2(\mu\text{-NMes})\) (2) (0.206-0.0670 mM) in benzene at 80 °C: A) plot of absorbance against time, where the slope of the line is initial rate; B) plot of natural logarithms of initial rate and [2].

A.) Plot of concentration against time

B.) Plot of natural logarithm of concentration against natural logarithm of initial rate
Figure 3.8. Kinetic analysis of the decomposition of $\left(\text{Cl}_2\text{NN}\right)\text{Cu}(\mu-\text{NAr}^{\text{F6}})$ (3) (0.163-0.584 mM) in benzene at 80 °C: A) plot of absorbance against time, where the slope of the line is initial rate; B) plot of natural logarithms of initial rate and [3].
Figure 3.10. Kinetic analysis of the decomposition of \([\text{Cl}_2\text{NN}]\text{Cu}_2(\mu\text{-NMes}) (2)\) (0.031-0.067 mM) + constant concentration of \([\text{Cl}_2\text{NN}]\text{Cu}\) (0.097 mM) in benzene at 80 °C: A) plot of absorbance against time, where the slope of the line is initial rate; B) plot of natural logarithms of initial rate and \([2]\).
Figure 3.11. Kinetic analysis of the decomposition of $\{[\text{Cl}_2\text{NN}]\text{Cu}\}_2(\mu-\text{NAr}^F)\text{ (3)}$ (0.487-0.715 mM) + constant concentration of $[\text{Cl}_2\text{NN}]\text{Cu}$ (0.968 mM) in benzene at 80 °C: A) plot of absorbance against time, where the slope of the line is initial rate; B) plot of natural logarithms of initial rate and [3].
3.2.g. Exploring Other Copper(I) Complexes as Catalysts

Two additional copper(I) complexes were tried as catalysts for the C-H amination of ethylbenzene with aryl azides $\text{N}_3\text{Mes}$ and $\text{N}_3\text{Ar}^\text{F6}$. $\{[\text{Cl}_2\text{NNCF}_3]\text{Cu}\}_2(\mu\text{-benzene})$ (developed by Dr. Stefan Wiese)$^{30}$ and a bis(oxazoline) copper(I) complex formed from the addition of $[\text{IndaBOX}]\text{H}$ to $\text{Cu}^\text{i}O^\text{i}\text{Bu}$ (in situ) (Figure 3.12). We hypothesized changing the electronic structure of the catalyst may result to a more active copper nitrene intermediates. Che and co-workers showed that Ru complexes with fluorine-substituted porphyrin ligands catalyzed nitrogen atom transfer reactions to saturated C-H bonds.$^{31}$ High catalytic turnovers were achieved, with PhI=NTs or PhI(OAc)/NH$_2$R ($R = \text{Ts}, \text{Ns}, \text{SO}_2\text{Me}$) even for conditions where the organic substrate is limiting. Bis(oxazoline) ligands like $[\text{IndaBOX}]\text{H}$ provide a defined arrangement of around metal complexes, with constraint pockets. This may improve on the diazene formation and also have access to the stronger primary C-H bond of ethylbenzene.

![Figure 3.12](image_url)

**Figure 3.12.** Structures of $[\text{Cl}_2\text{NNCF}_3]\text{Cu}$ and $[\text{IndaBOX}]\text{Cu}$ catalysts.
Using these new catalysts, reactions of the aryl azides with ethylbenzene were performed at 80 °C for 24 h with yields summarized in Table 3.4. Unfortunately, there is no clear trend observed. With \([\text{Cl}_2\text{NN}_\text{CF}_3]\text{Cu}\), conversion and yields for reaction are almost the same as those obtained using 1 as catalyst. As for \([\text{IndaBOX}]\text{Cu}\) the yields were markedly lower, likely due to poor conversion of the organoazide. Perhaps due to the crowded nature of the complex, the steric hindrance may have prevented efficient activation of the organoazide. Alternatively, the \textit{in situ} formation of this species could be inefficient. For instance, four coordinate bis(ligand) copper(II) complexes of related bis(oxazolines) have been synthesized.\(^{32,33}\)

The dicopper arylnitrene \(\{[\text{Cl}_2\text{NN}_\text{CF}_3]\text{Cu}\}_2(\mu-\text{NAr}^{\text{F6}})\) (7) was isolated in low yield from the reaction of \([\text{Cl}_2\text{NN}_\text{CF}_3]\text{Cu}(\text{NCMe})\) and \(\text{N}_3\text{Ar}^{\text{F6}}\) (Scheme 3.7). The X-ray structure of 7 is shown in Figure 3.12, with the familiar bridging nitrene moiety between two copper centers (Cu···Cu 2.8878(5) Å). But this copper compound is relatively more thermally sensitive as compared to 3. We noticed that in the sample used for X-ray diffraction analysis, majority of the crystals on the slide are colored orange, which is found to be the diazene \(\text{Ar}^{\text{F6}}\text{N}═\text{NAr}^{\text{F6}}\) when mounted on the diffractometer. Only a small amount of purplish solids were observed that correspond to the dicopper arylnitrene 7. Unfortunately, we did not get much of 7, so we did not do any stochiometric reaction with it, although this can be envisioned as an intermediate in the reaction of \(\text{N}_3\text{ArF6}\) and \(\{[\text{Cl}_2\text{NN}_\text{CF}_3]\text{Cu}\}_2(\mu-\text{benzene})\).
Table 3.4. $^1$H NMR yields of catalytic reaction of aryl azides with ethylbenzene using different catalysts.

<table>
<thead>
<tr>
<th>Aryl azide $\text{N}_3\text{Ar}$</th>
<th>product yield, %</th>
<th>$\text{NHAr}$ yield, %</th>
<th>$\text{N}_2\text{Ar}$ yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>$[\text{Cl}_2\text{NNCF}_3]\text{Cu}$</td>
<td>N$_3$Mes 12</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>N$_3$Ar$^{F6}$ 78</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>$[\text{IndBOX}]\text{Cu}$</td>
<td>N$_3$Mes 3</td>
<td>61</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>N$_3$Ar$^{F6}$ 3</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

For $[\text{Cl}_2\text{NNCF}_3]\text{Cu}$: 0.045 M azide  
For $[\text{IndBOX}]\text{Cu}$: 0.067 M azide

Scheme 3.9. Synthesis of $\{[\text{Cl}_2\text{NNCF}_3]\text{Cu}\}_2(\mu-$NAr$^{F6})$ (7).
Figure 3.13. X-ray structure of \( \{[\text{Cl}_2\text{NCF}_3]\text{Cu}\}_2(\mu-\text{NAr}^6) \) (7). Selected bond distances (Å) and angles (°): Cu1-Cu2 2.8878(5), Cu1-N1 1.930(2), Cu1-N2 1.892(2), Cu2-N3 1.941(2), Cu2-N4 1.900(2), C1-N5 1.797(2), Cu2-N5 1.802(2), N1-Cu1-N2 97.33(10), N3-Cu2-N4 97.07(10), Cu1-N5-Cu2 106.72(12). All hydrogen atoms are omitted for clarity.
Conclusion

We have surveyed the applicability of several aryl azides in C-H amination of allylic and benzylic $sp^3$ C-H bonds with $[\text{Cl}_2\text{NN}]\text{Cu}$ as catalyst, which generally gives the C-H amination product along with aniline and diazene as major by-products. The reaction is affected by the nature of the nitrene group, with electron-poor substituents promoting the amination. The terminal copper nitrene species $[\text{Cl}_2\text{NN}]\text{Cu}=$NAr with electron-poor substituent on the nitrene group is more active towards HAA, possibly because of the stronger N-H bond of the resulting copper(II) anilide $[\text{Cl}_2\text{NN}]\text{Cu}-\text{NHAr}$. Further exploration with isolated discrete dicopper aryl nitrene species showed that the diazene formation is favored at more concentrated conditions, suggesting that it is more of a kinetic control rather than thermodynamics. Pseudo 1$^{\text{st}}$ order plot for the stoichiometric reaction of 2 in neat ethylbenzene shows distinct curvature at the latter stage, indicating a more complex mechanism. The rate was enhanced in the presence of pyridine, possibly because py binds to $[\text{Cl}_2\text{NN}]\text{Cu}$ produced upon the dissociation of 2 to stabilize the terminal copper nitrene $[\text{Cl}_2\text{NN}]\text{Cu}=$NMes against recombination with $[\text{Cl}_2\text{NN}]\text{Cu}$ to revert to 2. Decomposition of these dicopper aryl nitrenes in presumably non-reacting substrate like benzene results to diazene formation and a little aniline, though where hydrogen comes from is uncertain at the moment. The rate this decomposition in benzene is found to be dependent on several factors, as it is a rather very complicated mechanism. The rate of dissociation of the dicopper aryl nitrene and the rate of coupling may have factored in, to name a few mechanistic possibilities for the copper aryl nitrene. Preliminary attempts in using other copper(I) complexes as catalyst did not yield markedly better or more general results, as comparable or lower conversion and yield were gathered with two related copper(I) complexes that were explored.
Experimental Details

3.4.a. General Procedures and Instrumentation

Same as in previous chapter – see section 2.4.a.

Synthesis of $\{[\text{Cl}_2\text{NN}_{\text{CF}_3}\text{Cu}]_2(\mu\text{-benzene})\}^3$ was from Dr. Stefan Wiese’s thesis. Using a procedure described from the literature, the ligand $[\text{IndaBOX}]\text{H}^{34}$ was prepared from the condensation of $(1S,2R)$-1-amino-2-indanol and diethylmalonimidate dihydrochloride in THF while Cu'O'Bu$^{13}$ was synthesized from the reaction of KO'Bu and CuI in THF.

3.4.b. General Precautions on Synthesis and Handling of Azides

For general precautions on the synthesis and handling of azides – see section 2.4.b. The azides $\text{N}_3\text{Ar}^{p\text{-CN}}$, $\text{N}_3\text{Mes}$, $\text{N}_3\text{Ar}^{\text{F}6}$ were synthesized according to literature procedure, through diazotization of the corresponding anilines followed by substitution of the azido group. Generally, the electron rich azide was derived using $^1\text{BuONO}$ for diazotization and $\text{N}_3\text{TMS}$ as azide source, while the electron poor azide was synthesized using $\text{NaNO}_2$ for diazotization followed by $\text{NaN}_3$ as azide source, in CF$_3$COOH as medium.$^{35}$

3.3.c. Synthesis of Copper Complexes (2-7)

$\{[\text{Cl}_2\text{NN}]\text{Cu}]_2(\mu\text{-NMes})$ (2) was first prepared and characterized by Dr. Yosra Badiei.$^{24}$ For experiments involving 2, synthesis is followed from what is reported.

$\{[\text{Cl}_2\text{NN}]\text{Cu}]_2(\mu\text{-NAr}^{\text{F}6})$ (3). To a solution of $\{[\text{Cl}_2\text{NN}]\text{Cu}]_2(\mu\text{-benzene})$ (1) (0.156 g, 0.159 mmol) in fluorobenzene (5.00 mL) was added a solution of 3,5-bis(trifluoromethyl)phenyl azide ($\text{N}_3\text{Ar}^{3,5-(\text{CF}_3)2}$, 0.211 g, 0.796 mmol) in fluorobenzene (2 mL). This yellowish solution turned to dark green to black after ~2 min and was allowed to stir at RT for 1 h. The solvent was
removed in vacuo and the residue was taken up in pentane (10 mL). The mixture was filtered through a Celite stick, concentrated in vacuo to ~ 3 mL, placed in freezer at -35 °C. Dark purple crystals formed (0.338 g, 40 %) that were suitable for X-ray diffraction. $^1$H NMR (400 MHz, benzene-$d_6$, RT): δ 8.28 (s, 2, Ar-ω-H of NAr$_6^F$), 7.73 (s, 1, Ar-ω-H of NAr$_6^F$), 6.80 (d, 8, Ar-κ-

Figure 3.14. Beer’s law plot for $\{[\text{Cl}_2\text{NN}]\text{Cu}\}_2(\mu\text{-NAr}_6^F)$ (3).

H), 6.24 (t, 4, Ar-ω-H), 4.84 (s, 2, backbone –CH), 1.49 (s, 12, backbone –CH$_3$). $^{13}$C{$^1$H} NMR (100 MHz, benzene-$d_6$): 224.09, 164.51, 143.73, 132.06, 128.51, 128.27, 127.88, 125.40, 110.77, 98.71, 22.98. UV-Vis $\lambda_{\text{max}}$ (benzene) = 492 nm (3384 M$^{-1}$s$^{-1}$) and 663 nm (3691 M$^{-1}$s$^{-1}$) with a shoulder centered at 575 nm (3320 M$^{-1}$s$^{-1}$). Anal. Calcd. for C$_{42}$H$_{29}$Cl$_3$Cu$_2$F$_7$N$_5$: 44.79 C, 2.59 H, 6.21 N. Found: 45.04 C, 2.81 H, 6.04 N.

$\{[\text{Cl}_2\text{NN}]\text{Cu}\}_2(\mu\text{-NAr}_6^{p-CN})(\text{Cu}[\text{Cl}_2\text{NN}])$ (4). A sample of 1-azido-4-cyanobenzene (N$_3$Ar$^{p-CN}$, 0.056 g, 0.389 mmol) was added to a solution of $\{[\text{Cl}_2\text{NN}]\text{Cu}\}_2(\mu$-benzene) (1) (0.381 g, 0.395 mmol) in chlorobenzene (10.0 mL). The reaction turned dark purple immediately with N$_2$ bubbles effervescing out of the solution. The reaction was stirred at RT for 1 h, after which it was filtered through Celite stick. The resulting solution was concentrated to ~ 2 mL, layered with cold pentane (2 mL) and allowed to recrystallize at – 35 °C. Dark purple crystals were collected in 68% yield (0.395 g, with 1 as limiting - 1.5 equiv 1: 1 equiv N$_3$Ar$^{p-CN}$) and
were suitable for X-ray diffraction. $^1$H NMR (400 MHz, benzene-$d_6$, RT): $\delta$ 7.67 (d, 2, Ar-$o$-H of NAr$^p$-CN ortho to nitrene N), 7.11 (d, 4, Ar-$p$-H of mononuclear [Cu], overlapped with solvent), 6.76 (d, 8, Ar-$p$-H of the dinuclear [Cu], overlapped with solvent), 6.45 (t, 2, Ar-$p$-H of the mononuclear [Cu]), 6.29 (d, 2, Ar-$m$-H of NAr$^p$-CN meta to nitrene N), 6.16 (t, 4, Ar-$p$-H of dinuclear [Cu]), 4.95 (s, 2, backbone $-CH$ of dinuclear [Cu]), 4.86 (s, 1, backbone $-CH$ of mononuclear [Cu]), 1.74 (s, 6, backbone $-CH_3$ of mononuclear [Cu]), 1.58 (s, 12, backbone $-CH_3$ of dinuclear [Cu]). UV-Vis $\lambda_{max}$ (benzene) = 505 nm (13341 M$^{-1}$s$^{-1}$), 578 nm (13621 M$^{-1}$s$^{-1}$) and 663 nm (14517 M$^{-1}$s$^{-1}$). Anal. Calcd. for C$_{58}$H$_{43}$Cl$_{12}$Cu$_3$N$_8$: 47.45 C, 2.95 H, 7.63 N. Found: 47.48 C, 3.10 H, 8.18 N.

An alternate procedure involves 1-azido-4-cyano-benzene (0.101 g, 0.701 mmol) in ether (2.00 mL) was added to a slurry of 1 (0.331 g, 0.343 mmol) in ether (10.0 mL), and the reaction mixture was stirred overnight at RT. The solution was filtered through Celite stick and concentrated to ~ 3 mL. The solution was layered with ~1 mL pentane and placed in freezer at -35 °C. Unfortunately, crystals formed even after a week are not suitable for X-ray crystallography. The dark purple residue was collected by decantation and dried in vacuo in 16 % yield (0.075 g). $^1$H NMR (400 MHz, benzene-$d_6$, RT): $\delta$ 7.68 (d, 2, Ar-$o$-H of NAr$^p$-CN ortho
For the reactions of 4 described below, 4 is synthesized from chlorobenzene / pentane and not from ether / pentane; and for calculations, the compound is treated as trinuclear rather than dinuclear.

\([\text{Cl}_2\text{NN}]\text{Cu(py)}\) (5). In a glovebox, pyridine (200.0 µL, 2.473 mmol) was added into a stirring slurry of \([\text{Cl}_2\text{NN}]\text{Cu}\)\(_2\) (benzene) (0.567 g, 0.579 mmol) in ether (15 mL), resulting to a yellow-orange mixture. After stirring overnight, the mixture was passed through a Celite filter stick and rotary evaporated to dryness. The residue was washed with ether (~3 mL) and dried under vacuo to afford 0.462 g (75%) of bright yellow crystals. A saturated ether solution (~2 mL) of the adduct with a few drops of added pyridine was layered with pentane (~1 mL) and allowed to stand overnight at -35 °C. Very bright yellow crystals formed that were suitable for X-ray diffraction. \(^1\text{H} \text{NMR (400 MHz, benzene-}\text{d}_6\)): δ 8.01 (d, 2, o-H of py ring), 7.04 (d, 3, m-H of Ph ring), 6.56 (t, 1, p-H of py ring), 6.34 (t, 2, p-H of Ph ring), 6.22 (t, 2, m-H of py ring), 5.03 (s, 1, backbone-CH), 1.87 (s, 6, backbone-CH\(_3\)); \(^{13}\text{C} \{^{1}\text{H}\} \text{NMR (benzene-}\text{d}_6\): δ 164.39, 149.89, 148.71, 135.84, 130.85, 128.72 (overlaps with solvent peak), 124.89, 123.31, 95.45, 23.85. Anal. Calcd. For \(\text{C}_{22}\text{H}_{18}\text{Cl}_{4}\text{N}_{3}\text{Cu}\): C, 49.88; H, 3.42; N, 7.93. Found: C, 47.76; H, 3.37; N, 7.53. (Repeated attempts to achieve satisfactory elemental analysis were hindered by facile loss of pyridine from 5.)

\([\text{Cl}_2\text{NN}]\text{Cu(}\eta^2\text{-cyclohexene)}\) (6). In a glovebox, cyclohexene (152.0 µL, 1.500 mmol) was added into a stirring slurry of \([\text{Cl}_2\text{NN}]\text{Cu}\)\(_2\) (benzene) (0.300 g, 0.306 mmol) in pentane (5-mL), resulting to a yellowish mixture. After 10 minutes of stirring, the mixture was passed
through a Celite filter stick and concentrated under vacuo to ~2 mL. The light yellow-orange solution was allowed to stand overnight at -35°C. Very light yellow crystals formed to afford 0.110 g (34%) that were suitable for X-ray diffraction. $^1$H NMR (400 MHz, benzene-$d_6$): δ 7.06 (d, 4, $m$-H of Ph ring), 6.42 (t, 2, $p$-H of Ph ring), 5.03 (s, 1, backbone-CH), 4.42 (s, 2, vinylic $H$ of cyclohexene), 1.77 (s, 6, backbone-CH$_3$), 1.55 (dd, 4, $\alpha$-CH$_2$ from the double bond of cyclohexene), 1.17 (m, 4, $\beta$-CH$_2$ from the double bond of cyclohexene); $^{13}$C($^1$H) NMR (benzene-$d_6$): δ 165.20, 148.34, 131.51, 128.94 (overlaps with solvent peak), 124.84, 96.38, 92.38, 25.42, 23.91, 23.86. Anal. Calcd. For C$_{23}$H$_{23}$Cl$_4$N$_2$Cu: C, 51.85; H, 4.35; N, 5.26. Found: C, 51.68; H, 4.34; N, 5.20.

$\{[\text{Cl}_2\text{NNCF}_3]\text{Cu}\}_2(\mu-\text{NaNF}_6)\ (7)$. $[\text{Cl}_2\text{NNCF}_3]\text{Cu(NCMe)}$ was first prepared by stirring $\{[\text{Cl}_2\text{NNCF}_3]\text{Cu}\}_2(\mu$-benzene) in MeCN overnight; afterwards the solvent was removed in vacuo. The residue was washed with pentane (10 mL, 2×) and dried in vacuo; this residue was used as prepared. To a slurry of $[\text{Cl}_2\text{NNCF}_3]\text{Cu(NCMe)}$ (0.150 g, 0.275 mmol) in ether (10.0 mL) was added a solution of $\text{N}_3\text{ArF}_6$ (0.150 g, 0.588 mmol) in ether (5.0 mL). This mixture was stirred at RT for 30 min, after which the solvent was removed in vacuo. The residue was taken in pentane (15 mL) and passed through Celite stick. The solution was concentrated to ~ 3 mL, and placed in freezer at -35 °C. Samples of the crystals taken from this mixture showed that there are at least two kinds of crystals present, mostly orange crystals and a couple of dark purple ones. The orange crystal was mounted on the diffractometer, which turned out to be the diazene ($\text{ArF}_6\text{N}=\text{NArF}_6$). The dark purple crystal was mounted on the diffractometer was dicopper nitrene 7. Unfortunately, not much of 7 was isolated (~ 20 mg) and no further characterization was done.
3.4.d. Stoichiometric Reactions of Dicopper Arylnitrenes with sp$^3$ C-H Substrates

Freshly prepared dicopper nitrenes 2 (0.031 g, 0.030 mmol), 3 (0.034 g, 0.030 mmol) and 4 (0.044 g, 0.030 mmol) were each dissolved in the following solvents: cyclohexane, ethylbenzene and indane (3.00 mL, 0.01 M). These reaction mixtures were heated at 80 °C for 24 h, the reaction mixture changed its color from blue/purple to brown. The reactions were quenched by exposing to air for several hours, passed through Celite stick into a vial with 1 equiv 1,2,4,5-tetrachlorobenzene (with respect to NAr moiety) and the solvent was removed \textit{in vacuo}. The residue was taken up in chloroform-$d_1$ for $^1$H NMR analysis and an aliquot from this solution was taken for GC/MS analysis. $^1$H NMR spectra of these reaction mixtures were compared with those reported in literature and from authentic samples.$^{26}$

GC/MS analysis of reaction mixtures involving cyclohexane showed the only formation of the corresponding diazenes without any C-H amination products. For ethylbenzene, amination products, anilines and diazenes were identified from GC/MS analysis and quantified from NMR spectra. And lastly from the indane reactions, inserted products, anilines and diazenes were also identified, but only in the case of 2 that the inserted products and anilines were quantified from the $^1$H NMR spectra. $^1$H NMR spectra of the reactions of 3 and 4 indicate reaction mixtures are mostly diazenes.

\textbf{Preparation of Authentic Samples.} Authentic samples of inserted products and diazenes were prepared according to literature.$^{26}$ Inserted products were prepared from the reaction of corresponding anilines (NH$_2$Mes, NH$_2$Ar$^{F6}$ and NH$_2$Ar$^{p-CN}$) and C-H substrates (ethylbenzene, indane, cyclohexane) using di-\textit{t}ert-butyl peroxide as oxidant and 1 as catalyst. Diazene were prepared from the oxidation of anilines in household bleach.$^{37}$ $^1$H NMR (400 Hz, chloroform-$d_1$)
of MesN=NMes: $\delta$ 6.95 (s, 4, Ar-$m$-H), 2.40 (s, 12, Ar-$o$-CH$_3$), 2.32 (s, 12, Ar-$p$-CH$_3$); $^1$H NMR (400 Hz, chloroform-$d_1$) of Ar$^{Fe}$N=N Ar$^{Fe}$: $\delta$ 8.45 (s, 4, Ar-$o$-H), $\delta$ 8.07 (s, 2, Ar-$p$-H); $^1$H NMR (400 Hz, chloroform-$d_1$) of Ar$^{p-CN}$N=NAr$^{p-CN}$: $\delta$ 8.02 (d, 4, Ar-$o$-H), $\delta$ 7.83 (d, 4, Ar-$m$-H).

3.4.e. General Procedure for Catalytic Reactions Using Arylazides and 1 as Catalyst

**Ethylbenzene.** A stock solution of 1 (0.036 g, 0.037 mmol, 7.47 $\times$ 10$^{-3}$ M) was dissolved in ethylbenzene (5.0 mL). A sample of this catalyst stock solution (0.50 mL, 2 mol% with respect to azide) was added into the azide (0.200 mmol) solution in ethylbenzene (5.0 mL). This reaction mixture was heated at 80 °C for 24 h. The reactions were quenched by exposing to air for several hours, filtered through Celite stick into a vial with an aliquot of 1,2,4,5-tetrachlorobenzene in flourobenzene (1.0 mL, 0.20 M). A sample of the reaction mixtures was taken for GC/MS analysis (in CH$_2$Cl$_2$), and the rest was dried in vacuo. The residue was taken in chloroform-$d_1$ for $^1$H NMR (400 MHz) analysis.

**Cyclohexene.** A stock solution of 1 (0.25 g, 0.26 mmol) in benzene was prepared. To prepare the reaction mixture, an aliquot of the azide (0.200 mmol) solution in benzene (1.0 mL), cyclohexene in benzene (2.0 mL, 0.5 M), 1,2,4,5-tetrachlorobenzene in benzene (1.0 mL, 0.2 M) and stock solution of 1 (1.0 mL, 2.5 mol% with respect to azide) were mixed together in a pressure vessel charged with a stir bar. These solutions were heated at 80 °C for 24 h, afterwards exposed to air to oxidize Cu$^1$ to CuO. The mixture was passed through Celite stick and sample was prepared for GC/MS (in pentane). The mixture was evaporated and the residue was taken in chloroform-$d_1$ for $^1$H NMR (400 MHz) analysis. The spectra were compared with those reported by Dr. Ray Gephart for product analysis. \(^{26}\)
**1H NMR Analysis of Binding of Olefins to 1.** In an NMR tube, 1.5 equiv allylbenzene (39.8 µL, 0.30 mmol), 1.5 equiv cyclohexene (30.4 µL, 0.30 mmol) and 1 equiv 1 (0.179 g, 0.19 mmol) were mixed with benzene-$d_6$ (1.0 mL). The mixture was shaken vigorously for ~1 min. The 1H NMR spectrum of reaction mixture is shown in Figure 3.16. It seems that the olefins bind more strongly than benzene as resonances for 1 is not observed. An equilibrium constant is

$$K_{eq} = \frac{[\text{allylbenzene}][\text{cyclohexene}][\text{1}]}{[\text{benzene}][\text{allylbenzene}][\text{cyclohexene}]} = \frac{(4.55)(2.77/2)}{(1.00)(2.24/2)} = 7.66$$

**Figure 3.16.** 1H NMR (400 MHz, benzene-$d_6$) analysis of binding of allylbenzene and cyclohexene to 1 and approximation of equilibrium constant.
approximated from comparison of the integrations of the resonances assigned for the copper-olefin complexes and those for alkenes (Figure 3.16).

3.4.f. Catalytic Reactions of Ethylbenzene and Arylazides Using Other Copper(I) Complexes as Catalysts

\{[\text{Cl}_2\text{NNCF}_3\text{Cu}]_2(\mu-\text{benzene})\}. A stock solution of the catalyst (0.055 g, 0.05 mmmol) in ethylbenzene (20.0 mL) was prepared. A sample of an azide solution (0.50 mmol) in ethylbenzene (5.0 mL), a solution of 1,2,4,5-tetrachlorobenzene in benzene (1.0 mL, 0.5 M) and a solution of 1 (5.0 mL, 2.5 mol% with respect to azide). These mixtures were heated at 80 °C for 24 h. The reaction mixtures were exposed to air for several hours, filtered through Celite stick. An aliquot of the reaction mixture was prepared for GC/MS analysis (in pentane); and the solvent from the rest of the mixture was removed in vacuo, the residue was taken in chloroform-\text{d}_1 for \textsuperscript{1}H NMR (400 MHz) analysis.

\textbf{[IndaBOX]Cu}. A stock solution of the catalyst was prepared by mixing [IndaBOX]H (0.052 g, 0.16 mmmol) and CuO\textsuperscript{t}Bu (0.021 g, 0.15 mmol) in ethylbenzene (18.0 mL). The reaction mixture was prepared by mixing azide solution (1 mmol) in ethylbenzene (5.0 mL), 1,2,4,5-tetrachlorobenzene in ethylbenzene (4.0 mL, 0.25 M) and an aliquot of the catalyst stock solution (6.00 mL). These mixtures were heated at 80°C for 24 h. The reaction mixtures were exposed to air for several hours, filtered through Celite stick. An aliquot of the reaction mixture was prepared for GC/MS analysis (in pentane); and the solvent from the rest of the mixture was removed in vacuo, the residue was taken in chloroform-\text{d}_1 for \textsuperscript{1}H NMR (400 MHz) analysis.
3.4.g. Kinetic Analysis of the Decomposition of 2 in Ethylbenzene at 60 °C

Freshly prepared 2 (0.003 g, 0.003 mmol) was dissolved in ethylbenzene in a 25-mL volumetric flask. This stock solution (1.16 × 10⁻⁴ M) was kept at -35 °C until needed.

An aliquot (3.00 mL) of this stock solution was transferred into a Schlenk UV-Vis quartz cuvette. The reaction was run at 60 °C and the decreasing concentration of 2 was quantified at a 30 min interval for up to three half-lives.

Another aliquot (4.31 mL) of the stock solution was transferred into a Schlenk UV-Vis quartz cuvette. Into this solution, 1000 equiv pyridine was added (0.040 mL, 0.50 mmol) and further diluted with ethylbenzene (0.65 mL) leading to a final concentration of 1.0 × 10⁻⁴ M for 2. The decreasing concentration of 2 from this solution was measured at 5 min interval for up to three half-lives.

3.4.h. UV-Vis Analyses of the Decomposition of 2 and 3 in Benzene at 80 °C

Stock solutions in benzene were prepared from freshly prepared 2 (0.008 g, 0.08 mmol, 3.093 × 10⁻⁴ M) in benzene (20 mL) and 3 (0.011 g, 0.010 mmol, 9.748 × 10⁻⁴ M) in benzene (10 mL) and stored at -35 °C until further use. Stock solution of 1 (0.028 g, 0.029 mmol, 2.905 × 10⁻⁴ M) was prepared in benzene in volumetric flask (10 mL) and stored at -35 °C until further use. The decomposition reaction was run at 80 °C, at an interval of 0.60 s for duration of 150 s.

Without added [Cl₂NN]Cu. For decomposition of 2, five solutions were prepared by taking the desired volume of stock solution of 2 and diluted to 3.0 mL with benzene (Table 3.5). Similarly, five solutions of stock solution of 3 were taken and diluted to 3.0 mL with benzene (Table 3.5). The disappearance of 2 or 3 was quantified via UV-Vis analysis at 80 °C every 0.60 s.
With added [Cl$_2$NN]Cu. Since the dicopper arylnitrene is presumed to dissociate to form the terminal copper arylnitrene and [Cl$_2$NN]Cu, another sets of UV-Vis reactions were run, with a certain amount of [Cl$_2$NN]Cu. For decomposition of 2, four solutions were prepared by mixing the desired volume of stock solution of 2, 0.05 mL stock solution of 1 and diluted to 3.0 mL with benzene (Table 3.5). Similarly, four solutions of stock solution of 3 were taken, added with 0.50 mL stock solution of 1 and diluted to 3.0 mL with benzene (Table 3.5). The disappearance of 2 or 3 was quantified via UV-Vis analysis at 80 °C every 0.60 s.

| Table 3.5. Kinetic analysis of decomposition of 2 and 3 in benzene at 80 °C |
|---|---|
| **For decomposition of 2 without [Cu]** | **For decomposition of 3 without [Cu]** |
| Volume, mL | [2], mM | Initial Rate, $\times 10^{-3}$ M/s | Volume, mL | [3], mM | Initial Rate, $\times 10^{-3}$ M/s |
| 0.65 | 0.067 | 2.12 | 1.8 | 0.584 | 6.63 |
| 0.5 | 0.0516 | 2.06 | 1.5 | 0.487 | 6 |
| 0.4 | 0.0412 | 1.55 | 1 | 0.325 | 5.52 |
| 0.3 | 0.0309 | 1.29 | 0.8 | 0.26 | 3.72 |
| 0.2 | 0.0206 | 0.839 | 0.5 | 0.163 | 2.23 |
| **For decomposition of 2 with [Cu]** | **For decomposition of 3 with [Cu]** |
| Volume, mL | [2], mM | Initial Rate, $\times 10^{-3}$ M/s | Volume, mL | [3], mM | Initial Rate, $\times 10^{-3}$ M/s |
| 0.65 | 0.067 | 4.37 | 2 | 0.715 | 6.63 |
| 0.5 | 0.0516 | 3.85 | 1.9 | 0.617 | 6 |
| 0.4 | 0.0412 | 2.33 | 1.8 | 0.584 | 5.52 |
| 0.3 | 0.0309 | 1.85 | 1.5 | 0.487 | 3.72 |

For each solution, the absorbance is plotted against time, from which the slope is taken as the initial rate of the reaction for that said solution in M/s (Table 3.5). From these, the natural logarithm of the initial rates (in M/s) are plotted against the natural logarithms of the concentration of 2 or 3 (in M). From these plots, the order of the reaction with respect to the dicopper arylnitrenes is determined.
Decomposition of 2 and 3 in Benzene. Freshly prepared 2 and 3 (0.300 mmol) were dissolved in benzene (3.0 mL) and heated at 80 °C for 24 h. The reaction mixtures were exposed to air for several hours, filtered through Celite stick, into which 1 equiv 1,2,4,5-tetrachlorobenzene in fluorobenzene (with respect to NAr). A sample for GC/MS was prepared in CH$_2$Cl$_2$, and the rest was dried *in vacuo*. The residue was taken in CHCl$_3$-$d_1$ for $^1$H NMR (400 MHz) analysis.

3.4.i. Crystallographic Details

Single crystals of [[Cl$_2$NN]Cu]$_2$(μ-NAr$^{F6}$) (3), [[Cl$_2$NN]Cu]$_2$(μ-NAr$^{p-CN}$)[[Cl$_2$NN]Cu] (4), [Cl$_2$NN]Cu(py) (5), [Cl$_2$NN]Cu(η$^2$-cyclohexene) (6) and [[Cl$_2$NN$_{CF3}$]Cu]$_2$(μ-NAr$^{F6}$) • ½ pentane (7 • ½ pentane) were mounted under mineral oil or perfluoroalkyl ether oil on glass fibers and immediately placed in a cold nitrogen stream at 100(2) K (for 3-6) and at 248(2) K for 7) on a Bruker SMART CCD system. Hemispheres or full spheres of data were collected, as necessary (0.3° or 0.5° ω-scans; 2θ$_{max}$ = 56°; monochromatic Mo Kα radiation, λ = 0.7107 Å) and integrated with Bruker SAINT program. Structure solutions were performed using the SHELXTL/PC suite and XSEED. Intensities were corrected for Lorentz and polarization effects and an empirical absorption correction was applied using Blessing’s method as incorporated into the program SADABS. Non-hydrogen atoms were refined with anisotropic thermal parameters and hydrogen atoms were included in idealized positions. The cyclohexene ring of [Cl$_2$NN]Cu(η$^2$-cyclohexene) (6) was mildly disordered and modeled in two sites in a 57 / 43 ratio.

References for X-ray structure refinement details

(a) SHELXTL-PC, Vers. 5.10; 1998, Bruker-Analytical X-ray Services, Madison, WI; G. M. Sheldrick, SHELX-97, Universität Göttingen, Göttingen, Germany.
(b) L. Barbour, XSEED, 1999.


**Table 3.6.** Crystallographic data for compounds 3-7.

<table>
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<th>Compd.</th>
<th>([{\text{Cl}_2\text{NN}\text{Cu}}_2(\mu-\text{NAr}^{+}_F)} (3))</th>
<th>([{\text{Cl}_2\text{NN}\text{Cu}}_2(\mu-\text{NAr}^{+}_CN)\text{][Cl}_2\text{NN}]\text{Cu}} (4))</th>
<th>([\text{Cl}_2\text{NN}\text{Cu}(\text{py})} (5))</th>
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<td>formula</td>
<td>(\text{C}<em>{100}\text{H}</em>{63}\text{Cl}<em>{16}\text{Cu}<em>4\text{F}</em>{24}\text{N}</em>{16})</td>
<td>(\text{C}<em>{65}\text{H}</em>{46}\text{Cl}_{12}\text{Cu}_3\text{N}_8)</td>
<td>(\text{C}<em>{22}\text{H}</em>{18}\text{Cl}_4\text{Cu}_3\text{N}_3)</td>
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<td>Mol. Wt.</td>
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<td>1555.12</td>
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<tr>
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<td>1.21-28.28</td>
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<td>59841</td>
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<tr>
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Largest diff. peak and hole e\(^{-} \cdot \) Å\(^3\)) | 5.28 and -0.89 | 0.98 and -1.03 | 1.18 and -0.57 |
Continuation of Table 3.6. Crystallographic data for compounds 3-7.

<table>
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<tr>
<th>Compd.</th>
<th>[Cl$_2$NN]Cu($\eta^2$-cyclohexene) (6)</th>
<th>[{[Cl$<em>2$NN$</em>{CF3}$]Cu$<em>2$(µ-NAr$</em>{F6}$) • ½ pentane (7 • ½ pentane)</th>
</tr>
</thead>
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<tr>
<td>formula</td>
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</tr>
<tr>
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<td>0.43 and -0.42</td>
<td>2.25 and -1.36</td>
</tr>
</tbody>
</table>
References

(24) Badiei, Y. M., Georgetown University, 2009.
(30) Wiese, S., Georgetown University, 2011.
CHAPTER 4

Copper Nitrenes: C-H Selectivity and Reprogramming for C-H Functionalization
Abstract

The reactivity of β-diketiminato copper nitrene [Cl$_2$NN]Cu=NR (R = tBu, Ad) intermediates with strong, unactivated $sp^3$ C-H bonds was investigated. Using substrates such as pentane, 2,3-dimethylbutane and 2,4-dimethylpentane, the trend in C-H bond selectivity observed is $3^\circ > 2^\circ > 1^\circ$. We observed that if a weaker, more reactive C-H bond is sterically unaccessible, amination can occur at a stronger C-H bond; amination at $1^\circ$ C-H site was favored over amination at the $2^\circ$ C-H site of 2,4-dimethylpentane. Changing the catalyst structure suggests that the preference for the stronger secondary, but less sterically hindered C-H bonds in pentane (secondary C-H at C-2) may be improved with introduction of bulkier and more electron-deficient β-diketiminato ligands. This C-H amination behavior may be “reprogrammed” for more general C-H functionalization via [Cu]=NR and [Cu$^{II}$]-FG intermediates. Copper nitrenes [Cu]=NR can be used as the metal-based H-atom abstraction (HAA) agent with C-H substrates R-H to give [Cu$^{II}$]-NHR and R•; the radical R• may be captured by [Cu$^{II}$]-FG to give R-FG and [Cu$I$]. For instance, stoichiometric reaction of {[Cl$_2$NN]Cu}$_2$(µ-N$^t$Bu) and [Cl$_2$NN]Cu$^{II}$-NHAr$_{Cl^3}$ with neat ethylbenzene gives PhCH(NHAr$_{Cl^3}$)CH$_3$ at 80 °C and 24 h in 80 % yield. This experiment suggest that the terminal copper nitrene [Cl$_2$NN]Cu=NNtBu can effectively engage in HAA with ethylbenzene and subsequently [Cl$_2$NN]Cu$^{II}$-NHAr$_{Cl^3}$ can efficiently capture the carboradical formed to result to the inserted product PhCH(NHAr$_{Cl^3}$)CH$_3$; [Cl$_2$NN]Cu$^{II}$-NHAr$_{Cl^3}$ does not undergo facile HAA with ethylbenzene under these conditions. Catalytic reactions of N$_3$Ad and NH$_2$Ar$_{Cl^3}$ in neat ethylbenzene give PhCH(NHAr$_{Cl^3}$)CH$_3$ in low yields, possibly because of the concentration of [Cl$_2$NN]Cu$^{II}$-NHAr$_{Cl^3}$ to capture the carboradical in the reaction mixture is not sufficient enough to effect complete conversion. Other oxidants like PhI=O and N$_3$Ts can be used, though yields are low. Functionalization with substrates H-FG
such as H-CH$_2$NO$_2$ and Ac-OPh is possible, though these unoptimized systems suffer from low yields of C-H functionalized products. Nonetheless, these results allow us to think of new pathways to implement [Cl$_2$NN]Cu=NR intermediates in catalytic C-H functionalization.

Introduction

The direct formation of C-N bonds from C-H bonds can offer an efficient preparation of nitrogen-based value-added products. Two of the major challenges of C-H amination are

Scheme 4.1. Some strategies developed to address the selectivity challenges in C-H amination.

1. Benzyllic

   H-NHR
   
   R'H + H-oxidant
   
   Oxidant

2. Allylic

   H-NHR
   
   R'R + H-oxidant
   
   Oxidant

3. Adjacent to Heteroatom

   X = OR, NHR, C(O)R

   Intramolecular

   R'
   
   NH
   
   R
   
   Oxidant
   
   H-oxidant

   Oxidant
   
   H-oxidant
chemoselectivity and regioselectivity. The abundance of C-H bonds in organic substrates presents a complication as to which type and what position of the C-H bond is to be functionalized. For many intermolecular C-H amination methodologies under development, most of the C-H bonds functionalized are slightly activated (nearby a heteroatom or π-system), although there are few examples where unactivated hydrocarbons like cyclohexane may be aminated. In contrast, catalytic intramolecular C-H amination can favor five- or six-membered transition states that control the site of C-H functionalization.

In this Chapter, we extend the use of our catalyst \( \{\text{Cl}_2\text{NN}[\text{Cu}]_2(\mu-\text{benzene}) \} \) (1) to aminate C-H bonds with higher C-H bond strength using organic azides as nitrene source. For instance, in the C-H amination of cis and trans-1,4-dimethylcyclohexane, we observed C-H amination at both the 3° and 2° C-H bonds, indicating that functionalization of stronger 2° C-H bonds can take place in the presence of weaker, yet more sterically hindered 3° C-H bonds. This suggested the possibility of tuning the copper catalyst structure to analyze the electronic and steric effects on C-H amination. We exploit the strength of copper nitrenes as HAA agent, and explore on it application into general C-H functionalization protocol.

**Results and Discussion**

**4.2.a. Chemoselectivity and Regioselectivity of C-H Amination**

With our success in the C-H amination of \( sp^3 \) secondary and benzylic substrates like ethylbenzene (BDE = 87 kcal/mol) or even cyclohexane (BDE = 97.6 kcal/mol) with \( \text{N}_3\text{Ad} \) using 1 as catalyst, we examined the reaction of pentane (BDEs = 99 and 100 kcal/mol) with \( \text{N}_3\text{Bu} \) at 100 °C for 24 h (Scheme 4.2). Analysis of the reaction mixture by GC/MS and \(^1\text{H}\) NMR spectroscopy showed that there are three products, indicating that all types of C-H bonds in
pentane were functionalized. The overall yield is 68% with the 2° C-H bond at C-2 representing the major site of C-H amination (49 % yield). We observed a distribution, corrected for the number statistically available hydrogens, as 4 % for amination at C-1, 60 % at C-2 and 36 % at C-3. These results were comparable to those reported by Peréz and colleagues for their PhI=NTs and TpXAg system. In their system, they reported overall amination yields about 15-65%, with preference for C-H amination at the secondary C-2 C-H bond (50-60% of total C-H functionalized products).

Scheme 4.2. Reaction of N₃⁺Bu in neat pentane at 100 °C using 2.5 mol% I as catalyst.

Two additional substrates were examined: 2,3-dimethylbutane and 2,4-dimethylpentane. These substrates were heated at 100 °C with N₃⁺Bu and 2.5 mol% I as catalyst for 48 h to ensure that reaction is complete (Scheme 4.2). For 2,3-dimethylbutane, the system is relatively more reactive towards the 3° C-H than the stronger 1° C-H bonds, though it is present in greater quantity (12 primary C-H bonds vs 2 tertiary C-H bonds) (Scheme 4.3A). We obtained a 46 % GC/MS yield (51 % ¹H NMR yield) for amination product at the 3° C-H site, with a statistical distribution of 98 % (corrected for the number of hydrogens). In 2,4-dimethylpentane, there are
three types of C-H bonds present: 12 primary C-H, 2 secondary C-H and 2 tertiary C-H bonds. GC/MS analysis of the reaction mixture for the 2,4-dimethylpentane substrate showed that the tertiary C-H bonds are more favored to be aminated, in 35 % GC/MS yield (37 % $^1$H NMR yield) (Scheme 4.3.B). We observed an overall yield of 42 %, about 97 % statistical distribution of which is amination at the tertiary C-H site. The primary C-H bonds (7 % GC/MS yield, 3 % statistical distribution) were functionalized as well, over the secondary C-H bonds possibly because of the steric inaccessibility of the secondary C-H bonds.

**Scheme 4.3.** Reaction of $\text{N}_3^t\text{Bu}$ in neat 2,3-dimethylbutane and 2,4-dimethylpentane at 100 °C using 2.5 mol% 1 as catalyst.

A. 2,3-dimethylbutane

\[
\text{\begin{center}
\includegraphics[scale=0.4]{Scheme43A.png}
\end{center}}
\]

B. 2,4-dimethylpentane

\[
\text{\begin{center}
\includegraphics[scale=0.4]{Scheme43B.png}
\end{center}}
\]

* $^1$H NMR Yield
4.2.b. Copper Nitrene and Copper(II) Amide as HAA Agents

For our copper(I) β-diketiminate catalyst (1), two protocols have been developed for C-H bond amination. The first one involves azides as the N-H substrates, which is shown to proceed via a stepwise hydrogen atom abstraction (HAA) / radical capture (RC) with terminal copper nitrene as intermediate (Chapter 2, Scheme 4.4.A). The second one involves an amine and an external oxidant di-tert-butyl peroxide (tBuOOtBu, DTBP) which is also shown to proceed through a stepwise HAA / RC mechanism which includes a copper(II) amide as intermediate (Scheme 4.4.B).

To compare the relative reactivity of [Cu]=NAd and [Cu]II-NHAd intermediates for HAA reactions with C-H substrates, reactions of {[Cl2NN]Cu}2(µ-NAd) (2) (isolated and prepared in situ from N3Ad and 1) and [Cl2NN]CuII-NHAd (3) with neat pentane were carried out (Table 4.1). GC/MS of the reactions mixtures showed that C-H aminated products for pentane were observed from the reactions with copper nitrene; in contrast only 1-adamantylamine is observed as product from the reaction with copper(II) amide. These results speak for the very high HAA reactivity of copper nitrenes over copper(II) amides. The difference in HAA reactivity of copper nitrene and copper(II) amide can be explained by the strength of the N-H bond formed after HAA. Calculations by Cundari and colleagues indicate that the BDE of the N-H bond of resulting copper species after HAA, for copper(II) amide [Cl2NN]CuII-NHAd BDE is 98.4 kcal/mol while for copper(I) amine [Cl2NN]CuI(HNAd) BDE is 68 kcal/mol (Scheme 4.5).
**Scheme 4.4.** Mechanism for C-H amination using β-diketiminato copper nitrene and β-diketiminato copper(II) amide.

**A. Copper Nitrene**

\[
\begin{align*}
1 & + \text{N}_3\text{Ad} \rightarrow \{[\text{Cl}_2\text{NN}]\text{Cu}\}_2(\mu\text{-NAd}) + \text{N}_2 \\
\text{dicopper nitrene}
\end{align*}
\]

\[
\{[\text{Cl}_2\text{NN}]\text{Cu}\}_2(\mu\text{-NAd}) \rightarrow [\text{Cl}_2\text{NN}]\text{Cu}\equiv\text{NAd} + [\text{Cl}_2\text{NN}]\text{Cu}
\]

\[
\begin{align*}
[\text{Cl}_2\text{NN}]\text{Cu}\equiv\text{NAd} + R'^{-}\text{H} & \rightarrow [\text{Cl}_2\text{NN}]\text{Cu}^{\text{II}}\text{-NHAd} + R'^{-}\text{•} & \text{HAA} \\
\text{copper nitrene} & & \text{copper(II) amide}
\end{align*}
\]

\[
[\text{Cl}_2\text{NN}]\text{Cu}^{\text{II}}\text{-NHAd} + R'^{-}\text{•} \rightarrow [\text{Cl}_2\text{NN}]\text{Cu}^{\text{I}} + R'^{-}\text{-NHAd} & \text{RC}
\]

**B. Copper(II) Amide**

\[
\begin{align*}
1 & + \text{tBuO-O}^{\text{tBu}} \rightarrow 2 [\text{Cl}_2\text{NN}]\text{Cu}^{\text{II}}\text{-O}^{\text{tBu}} \\
\text{copper tert-butoxide}
\end{align*}
\]

\[
[\text{Cl}_2\text{NN}]\text{Cu}^{\text{II}}\text{-O}^{\text{tBu}} + \text{NH}_2\text{Ad} \rightarrow [\text{Cl}_2\text{NN}]\text{Cu}^{\text{II}}\text{-NHAd} + \text{tBuOH}
\]

\[
\begin{align*}
[\text{Cl}_2\text{NN}]\text{Cu}^{\text{II}}\text{-NHAd} + R'^{-}\text{H} & \rightarrow [\text{Cl}_2\text{NN}]\text{Cu}^{\text{I}}(\text{NH}_2\text{Ad}) + R'^{-}\text{•} & \text{HAA} \\
\text{copper(II) amide} & & \text{copper(I) amine}
\end{align*}
\]

\[
[\text{Cl}_2\text{NN}]\text{Cu}^{\text{II}}\text{-NHAd} + R'^{-}\text{•} \rightarrow [\text{Cl}_2\text{NN}]\text{Cu}^{\text{I}} + R'^{-}\text{-NHAd} & \text{RC}
\]

**Scheme 4.5.** Comparison of BDE of copper species from after HAA of copper nitrene and copper(II) amide.

\[
[\text{Cl}_2\text{NN}]\text{Cu}=\text{NAd} + R'^{-}\text{H} \rightarrow [\text{Cl}_2\text{NN}]\text{Cu}^{\text{II}}\text{-NHAd} & \text{BDE} = 98.4 \text{ kcal/mol}
\]

\[
[\text{Cl}_2\text{NN}]\text{Cu}^{\text{II}}\text{-NHAd} + R'^{-}\text{H} \rightarrow [\text{Cl}_2\text{NN}]\text{Cu}^{\text{I}}(\text{NH}(\text{R})\text{Ad}) & \text{BDE} = 68 \text{ kcal/mol}
\]
Surprisingly, the reaction with NH₂Ad/DTBP, where 3 is generated in situ, yielded a more selective product distribution for the secondary C₂ site (88% vs 60% for copper nitrene). This suggests that for reaction involving stronger C-H bonds, there may be a different HAA agent, other than the copper(II) amide. It a recent report from the Warren group, they showed through a series of kinetic and theoretical analyses the etherification of cyclohexane with DTBP using 1 as catalyst.¹ They proposed a mechanism that involves activation of the copper(I) catalyst by DTBP to form [Cl₂NN]Cu^{II}-O^⁻Bu (4) and ³BuO• (Scheme 4.6). Stoichiometric reaction of 4 with neat cyclohexane showed no formation of the ether, but tert-butyl cyclohexyl ether is obtained when cyclohexane is reacted with DTBP with 5-10 mol% of 1 at RT. This suggests that 4 is not the HAA agent, but rather ³BuO•. With this, it can be similarly proposed

Table 4.1. ¹H NMR yields of the pentane reaction using different copper-based HAA agent.

<table>
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<tr>
<th>Source of HAA Agent</th>
<th>Temperature, °C</th>
<th>¹H NMR Yield, %</th>
<th>Selectivity per C-H Bond, %</th>
<th>C1: C2: C3</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) N₃Ad, 1 (in situ)</td>
<td>110</td>
<td>4  59  17</td>
<td>3: 61: 36</td>
<td></td>
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<tr>
<td>(2) [Cl₂NN]Cu²(µ-NAd) (2)</td>
<td>80</td>
<td>6  29  7</td>
<td>10: 60: 30</td>
<td></td>
</tr>
<tr>
<td>(3) [Cl₂NN]Cu^{II}-NHAd (3)</td>
<td>80</td>
<td>GC/MS shows no product, just NH₂Ad</td>
<td>n/a</td>
<td></td>
</tr>
<tr>
<td>(4) NH₂Ad, DTBP, 1 (in situ)</td>
<td>90</td>
<td>5  48  2</td>
<td>6: 88: 6</td>
<td></td>
</tr>
</tbody>
</table>
that in the reaction of pentane and NH$_2$Ad / DTBP, $^t$BuO• abstracts an H atom from pentane, then 2 captures the resulting radical to form the amination product (Scheme 4.7). This mechanistic possibility for C-H amination (and other forms of C-H functionalization) is currently being pursued by the Warren group.$^{19}$

**Scheme 4.6.** Proposed mechanism for C-H etherification.$^1$

a) \[ [\text{Cl}_2\text{NN}]\text{Cu} + ^t\text{BuO}-\text{O}^t\text{Bu} \rightarrow [\text{Cl}_2\text{NN}]\text{Cu}^{\text{II}}-\text{O}^t\text{Bu} (4) + ^t\text{BuO}• \text{tert-butoxy radical} \]

b) $^t$BuO• + \[ \text{H} \rightarrow \text{H}• + ^t\text{BuOH} \text{HAA} \]

c) \[ [\text{Cl}_2\text{NN}]\text{Cu}^{\text{II}}-\text{O}^t\text{Bu} + \text{H•} \rightarrow [\text{Cl}_2\text{NN}]\text{Cu} + \text{H}•-\text{O}^t\text{Bu} \text{RC} \]

**Scheme 4.7.** Proposed mechanism for C-H amination of pentane using NH$_2$Ad / DTBP.

\[ [\text{Cl}_2\text{NN}]\text{Cu} + ^t\text{BuO}-\text{O}^t\text{Bu} \rightarrow [\text{Cl}_2\text{NN}]\text{Cu}^{\text{II}}-\text{O}^t\text{Bu} + ^t\text{BuO}• \text{HAA} \]

\[ ^t\text{BuO}• + \text{H} \rightarrow \text{H}• + ^t\text{BuOH} \text{HAA} \]

\[ [\text{Cl}_2\text{NN}]\text{Cu}^{\text{II}}-\text{O}^t\text{Bu} + \text{NH}_2\text{Ad} \rightarrow [\text{Cl}_2\text{NN}]\text{Cu}^{\text{II}}-\text{NHAd} + ^t\text{BuOH} \text{acid-base} \]

\[ \text{H•} + [\text{Cl}_2\text{NN}]\text{Cu}^{\text{II}}-\text{NHAd} \rightarrow \text{H•} + [\text{Cl}_2\text{NN}]\text{Cu} \text{RC} \]
4.2.c. Modifications on Copper Catalyst

To help improve the selectivity of the C-H functionalization reaction, a variety of electronic and structural changes on β-diketiminate ligand structure have been examined. Along with \( \{[\text{Cl}_2\text{NN}_{\text{CF}_3}]\text{Cu}\}_2(\mu-\text{benzene}) \) complex developed by Dr. Stefan Wiese, Grace Jang in the Warren group is currently developing a series of β-diketiminato copper(I) complexes as possible C-H functionalization catalysts (Figure 4.1). Herein these copper complexes were tested as

![Structures of copper(I) complexes](image)

**Figure 4.1.** Structures of the copper(I) complexes (= [Cu]) examined as catalysts in the C-H amination of pentane.
possible catalysts for C-H amination using the organoazide protocol.

Reactions in pentane were run at 110 °C using N₃Ad as the nitrene source and 5 mol% of one of the copper(I) β-diketiminato catalysts ([Cu]); yields are collected in Table 4.2. All of these reactions mixtures turned to green after some time, except for the reaction with [Cl₂NNCF₃]Cu which turned orange-yellow. For the reactions with catalyst Generally, the reactions were stopped after the mixture turned to yellow or brownish yellow. These results are preliminary and not yet optimized under more stringent, uniform conditions. Nonetheless, we observed that amination takes place at the C-1, C-2, C-3 for most of the catalysts used. The use of N-aryl groups with bulky o-substituents (Ph or tBu) slightly improved the preference for amination at the C-2 position. Using [tBuNNCF₃]Cu (entry 4) and [PhNNCF₃]Cu (entry 5) showed a statistical distribution of about 86 % and 82% respectively for aminated product at the C-2 position. In fact, this selectivity is quite similar to that found in C-H amination with NH₂Ad / DTBP catalyzed by [Cl₂NN]Cu. Using [PhFNNCH₃]Cu as catalyst hardly improve the distribution for the aminated product at C-2 position (statistical distribution 68 %) when compared to the 1st generation catalyst [Cl₂NNCH₃]Cu (statistical distribution 64 %). Interestingly, ortho-substitution of the N-aryl group of the ligand is important, as with [2,4-Cl₂NN]Cu(NCMe) as catalyst conversion (12 %) is still poor even after 48 h of heating, when compared to that gathered from [Cl₂NNCH₃]Cu (73 %). One of the major downside in this reaction is the necessity to heat the reaction mixture at high temperature (110 °C), which may be addressed in the future by use of a microwave reactor.¹²
Table 4.2. C-H amination of pentane using $\text{N}_3\text{Ad}$ as nitrene source with various β-diketiminato copper(I) complexes as catalysts.

![Chemical reaction diagram]

<table>
<thead>
<tr>
<th>[Cu] complex</th>
<th>$^1\text{H}$ NMR Yield, %</th>
<th>Statistical Distribution, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1-Ad</td>
<td>2-Ad</td>
</tr>
<tr>
<td>(1) [2,4-Cl$_2$NN]Cu(NCMe)$_2$</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>(2) [PhFNN$_\text{CF}_3$]Cu$^*$</td>
<td>1</td>
<td>36</td>
</tr>
<tr>
<td>(3) [PhFNN$_\text{CH}_3$]Cu$^2$</td>
<td>3</td>
<td>49</td>
</tr>
<tr>
<td>(4) [$^1\text{BuNN}_\text{CF}_3$]Cu$^*$</td>
<td>n/a</td>
<td>11</td>
</tr>
<tr>
<td>(5) [PhNN$_\text{CF}_3$]Cu$^1$</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>(6) [Cl$<em>2$NN$</em>\text{CH}_3$]Cu$^2$</td>
<td>&lt; 1</td>
<td>56</td>
</tr>
<tr>
<td>(7) [Cl$<em>2$NN$</em>\text{CF}_3$]Cu$^1$</td>
<td>&lt; 1</td>
<td>32</td>
</tr>
<tr>
<td>(8) Control$^*$</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

$^1$Heated for 24 h; $^2$Heated for 48 h

*some amount of $\text{N}_3\text{Ad}$ remained
4.2.d. Reprogramming of the C-H Amination Reaction

In 2012, Groves and co-workers reported the use of a manganese porphyrin complex as catalyst for fluorination of unactivated $sp^3$ C-H bonds in organic substrates (Scheme 4.4).\textsuperscript{21} The reaction proceeds through an oxomanganese(V) intermediate that does HAA from C-H substrates R-H, forming the hydroxomanganese(IV) complex and the corresponding C-based radical R•. From this hydroxomanganese(IV) complex, a ligand exchange occurs to give the a related difluoro complex that engages the radical R• to form the R-F product.

Scheme 4.8. Fluorination of C-H substrates using a manganese porphyrin catalyst.
As shown in Scheme 4.4, the copper nitrene in our β-diketiminate copper system operates via HAA of the copper nitrene, followed by RC of the copper(II) amide species. Inspired by the mechanism proposed by Groves et al.,\textsuperscript{21} we began to examine how we can reprogram C-H amination into a protocol general to C-H functionalization using this copper nitrene (Scheme 4.8). Because of the high HAA activity of copper nitrenes, we plan to employ copper nitrene intermediates [Cu]=NAd for HAA. A key variation in this general C-H functionalization is the introduction of new copper(II) species [Cl\textsubscript{2}NN]Cu\textsuperscript{II}-FG that can do RC of the carboradical formed from HAA (Scheme 4.8.3). Access to these [Cl\textsubscript{2}NN]Cu\textsuperscript{II}-FG species may be through acid-base exchange of [Cl\textsubscript{2}NN]Cu\textsuperscript{II}-NHAd and H-FG (Scheme 4.8.2). This mechanistic proposal is similar to that put forth by Groves et al.\textsuperscript{21} the main difference is how the reactive intermediate for RC is generated. In their proposal, the species [Mn](OH)(F) is formed by H-atom abstraction by [Mn](=O)(F).\textsuperscript{21} Then [Mn](OH)(F) does fluoride anion exchange with AgF to form AgOH and [Mn](F)\textsubscript{2} – the species responsible for RC.\textsuperscript{21} In this mechanism, functionalization is quite limited to fluorination. In our proposal, the reactive species for RC is generated from the reaction of H-FG and the copper(II) amide, no additional metal salt is needed. The major challenge will be finding suitable β-diketiminato copper(II) species, [Cl\textsubscript{2}NN]Cu\textsuperscript{II}-FG (FG = functional group), that can efficiently recombine with the carboradical to develop this method into a more diverse

**Scheme 4.9.** General mechanism proposed for C-H functionalization using copper nitrene.

1. \([\text{Cl}_2\text{NN}]\text{Cu}=\text{NR} + \text{R}’-\text{H} \rightarrow \text{Cl}_2\text{NN}\text{Cu}^{\text{II}}-\text{NHAd} + \text{R}’\cdot\text{H}\)  
   \(\text{copper nitrene}\)  
   \(\text{copper(II) amide}\)

2. \([\text{Cl}_2\text{NN}]\text{Cu}^{\text{II}}-\text{NHR} + \text{H-FG} \rightarrow \text{Cl}_2\text{NN}\text{Cu}^{\text{II}}-\text{FG} + \text{NH}_2\text{R}\)  
   \(\text{acid-base exchange}\)

3. \([\text{Cl}_2\text{NN}]\text{Cu}^{\text{II}}-\text{FG} + \text{R}’\cdot \rightarrow \text{Cl}_2\text{NN}\text{Cu}^{\text{I}} + \text{R}’-\text{FG}\)  
   \(\text{RR}\)
C-H functionalization.

To test this hypothesis, two available β-diketiminato copper(II) species \([\text{Cl}_2\text{NN}]\text{Cu}^{\text{II}}-\text{O}^{\text{Bu}}\) (4) and \([\text{Cl}_2\text{NN}]\text{Cu}^{\text{II}}-\text{NHAr}^{\text{Cl}_3}\) (5) were used as representative \([\text{Cl}_2\text{NN}]^{\text{II}}-\text{FG}\) species. Importantly, these species do not exhibit significant stoichiometric C-H functionalization chemistry on their own (Figure 4.2).\(^{19}\) For instance, reaction of 4 with neat cyclohexane was shown not to give any etherification products.\(^{1}\) DFT calculations done by Dr. Timothy H. Warren on the electronic energy difference associated for HAA of ethylbenzene with 4 (\(\Delta E_{\text{HAA}} = +19.3\) kcal/mol; neglects zero point and entropic contributions) suggests that 4 does not engage HAA with ethylbenzene. Grace Jang of the Warren group is currently working on the isolation and investigation of the role of copper(II) anilides \([\text{Cl}_2\text{NN}]\text{Cu}^{\text{II}}-\text{NHAr}\) in C-H amination. She found that stoichiometric reaction of 5 in ethylbenzene gave only about 10% of the C-H amination product.\(^{19}\)

\[
\begin{align*}
\text{[Cl}_2\text{NN]}\text{Cu}^{\text{II}}\text{-O}^{\text{Bu}} &\quad \text{(4)} \\
\text{[Cl}_2\text{NN]}\text{Cu}^{\text{II}}\text{-NHAr}^{\text{Cl}_3} &\quad \text{(5)}
\end{align*}
\]

**Figure 4.2.** Structures of the β-diketiminato copper(II) species examined for reprogramming reactions.
Stoichiometric reactions of \([\{[\text{Cl}_2\text{NN}]\text{Cu}\}_2(\mu-\text{N}^t\text{Bu})\} (6)\) were performed with equimolar amounts of 4 and 5 in ethylbenzene at 80 °C for 24 h. The GC/MS and \(^1\text{H}\) NMR analyses of the reaction of 4 and 6 showed that aminated product of ethylbenzene (PhCH(NH^t\text{Bu})CH_3) was formed in 98 % \(^1\text{H}\) NMR yield, instead of ether product (PhCH(O^t\text{Bu})CH_3) (Scheme 4.10). On the other hand, GC/MS and \(^1\text{H}\) NMR analyses of the reaction of 5 and 6 indicates that majority of the inserted product is (PhCH(NH\text{Ar}^\text{Cl}_3)CH_3) in about 80 % yield (Scheme 4.11).

Scheme 4.10. Stoichiometric reaction of \([\{[\text{Cl}_2\text{NN}]\text{Cu}\}_2(\mu-\text{N}^t\text{Bu})\) and \([\text{Cl}_2\text{NN}]\text{Cu}^{\text{II}}\)O^t\text{Bu} in ethylbenzene.

\[\begin{align*}
\{[\text{Cl}_2\text{NN}]\text{Cu}\}_2(\mu-\text{N}^t\text{Bu}) & \quad \text{H} & \quad \text{NH}^t\text{Bu} & \quad \text{O}^t\text{Bu} \\
+ & \quad \text{[Cl}_2\text{NN]}\text{Cu}^{\text{II}}\text{-O}^t\text{Bu} & \quad \text{24 h, 80 °C} & \quad \rightarrow \\
& \quad \text{> 98 %} & \quad \text{not observed} \\
\end{align*}\]

The difference in the reactivity of \([\text{Cl}_2\text{NN}]\text{Cu}^{\text{II}}\)-FG may be accounted to the difference in their electronic structures (Figure 4.3). The orbital diagram shows a 2-center, 3-electron \(\pi\)-interaction between the Cu\(^{\text{II}}\) \(d_{yz}\) orbital and the filled lone pair of the \(sp^2\)-hybridized FG donor atom. This interaction accounts for the significant radical character on the donor atom of FG. The lower effective nuclear charge on N makes the lone pair of this donor atom higher in energy.
than that of O, closer to the energy of the Cu d orbital and corresponding Cu-N π* orbital. This imparts more significant radical character on N of [Cl₂NN]Cu^II-NHR than on O of [Cl₂NN]Cu^II-O^tBu. In fact [Cl₂NN]Cu^II-NHAd (3) has a spin density of 0.49 e⁻ at N.¹⁶ This explains why [Cl₂NN]Cu^II-NH^tBu captures the carboradical better than [Cl₂NN]Cu^II-O^tBu.¹⁶

**Scheme 4.11.** Stoichiometric reaction of [{Cl₂NN}Cu]₂(µ-N^tBu) and [Cl₂NN]Cu^II-NHArCl³ in ethylbenzene.

![Scheme 4.11](image)

The alkyl group of the copper(II) amide is more electron-rich and increases the energy of the pₓ orbital of N as compared to the electron-deficient aryl group of the copper(II) anilide. To compare with 3, Grace Jang reports that the calculated spin density on the N for 5 is 0.25 e⁻.¹⁹ This clearly indicates that there is a greater potential for the copper(II) amide like [Cl₂NN]Cu^II-NHR to do RC than copper(II) anilide. But because copper nitrene is only present in very low concentration in solution, and copper(II) amide [Cl₂NN]Cu^II-NH^tBu is derived from the HAA reaction of copper nitrene, this means that the concentration of copper(II) amide in the reaction...
mixture is also very low. The higher concentration of $[\text{Cl}_2\text{NN}]\text{Cu}^\text{II}-\text{NHAr}^{\text{Cl}_3}$ (5) over $[\text{Cl}_2\text{NN}]\text{Cu}^\text{II}-\text{NH}^t\text{Bu}$ in the reaction mixture, the copper(II) anilide 5 is more readily available for radical capture.

![Figure 4.3](image)

**Figure 4.3.** Depiction of the electronic structure of $[\text{Cl}_2\text{NN}]\text{Cu}^\text{II}$-FG.

**Scheme 4.12.** Acid-base exchange of $[\text{Cl}_2\text{NN}]\text{Cu}^\text{II}-\text{O}^t\text{Bu}$ and $[\text{Cl}_2\text{NN}]\text{Cu}^\text{II}-\text{NHR}$ with H-FG to generate $[\text{Cl}_2\text{NN}]\text{Cu}^\text{II}$-FG.

*Generation of $[\text{Cl}_2\text{NN}]\text{Cu}^\text{II}$-FG from $[\text{Cl}_2\text{NN}]\text{Cu}^\text{II}-\text{O}^t\text{Bu}$*

$[\text{Cl}_2\text{NN}]\text{Cu}^\text{II}-\text{O}^t\text{Bu} + \text{NH}_2\text{Ad} \rightarrow [\text{Cl}_2\text{NN}]\text{Cu}^\text{II}-\text{NHAd} + \text{HO}^t\text{Bu}$

$[\text{Cl}_2\text{NN}]\text{Cu}^\text{II}-\text{O}^t\text{Bu} + \text{NH}_2\text{Ar} \rightarrow [\text{Cl}_2\text{NN}]\text{Cu}^\text{II}-\text{NHAr} + \text{HO}^t\text{Bu}$

*Generation of $[\text{Cl}_2\text{NN}]\text{Cu}^\text{II}$-FG from $[\text{Cl}_2\text{NN}]\text{Cu}^\text{II}-\text{NHR}$*

$[\text{Cl}_2\text{NN}]\text{Cu}^\text{II}-\text{NHAd} + \text{H-FG} \rightarrow [\text{Cl}_2\text{NN}]\text{Cu}^\text{II}$-FG + HNHA

H-FG = H-NHAr
An attempt was made to employ this protocol in a catalytic manner. A challenge that is recognized is generating and keeping a good concentration of \([\text{Cl}_2\text{NN}]\text{Cu}^{\text{II}}-\text{FG}\) in solution to effectively compete with copper(II) amide \([\text{Cl}_2\text{NN}]\text{Cu}^{\text{II}}-\text{NHR}\), although this species is only present in minimal amount in solution. We propose that \([\text{Cl}_2\text{NN}]\text{Cu}^{\text{II}}-\text{FG}\) is generated from the acid-base exchange of \([\text{Cl}_2\text{NN}]\text{Cu}^{\text{II}}-\text{NHR}\) and H-FG, similar to the acid-base exchange of \([\text{Cl}_2\text{NN}]\text{Cu}^{\text{II}}-\text{OtBu}\) and NH$_2$R or NH$_2$Ar described for the copper(II) amide protocol (Scheme 4.12).\(^{16,17}\) To promote a high concentration of \([\text{Cl}_2\text{NN}]\text{Cu}^{\text{II}}-\text{FG}\), a small amount DTBP may be added into the reaction mixture, to generate a small amount of \([\text{Cl}_2\text{NN}]\text{Cu}^{\text{II}}-\text{OtBu}\) to preactivate H-FG to produce \([\text{Cl}_2\text{NN}]\text{Cu}^{\text{II}}-\text{FG}\).

Reaction of 1 equiv N$_3$Ad and 4 equiv NH$_2$Ar$^{\text{Cl}_3}$ was performed in neat ethylbenzene (with or without catalytic amount of DTBP) at 110 °C for 24 h (Scheme 4.13). GC/MS analysis of the reaction mixtures showed although C-H amination with aniline occurred in ca. 25% yield, a significant amount of N$_3$Ad remained. In contrast, Dr. Ray Gephart showed that as high as 99%

**Scheme 4.12.** Catalytic reprogramming of C-H amination by \([\text{Cl}_2\text{NN}]\text{Cu}=\text{NAd}\) and NH$_2$Ar$^{\text{Cl}_3}$ with ethylbenzene as substrate.

(1)

1 equiv N$_3$Ad + 4 equiv NH$_2$Ar$^{\text{Cl}_3}$

\[\begin{array}{c}
\text{H} \\
\text{neat}
\end{array} \xrightarrow{5 \text{ mol\% 1}} \begin{array}{c}
\text{H} \\
\text{24 h, 100 °C} \\
\text{25 \% yield 21 \%}
\end{array}
\]

(2)

1 equiv N$_3$Ad + 4 equiv NH$_2$Ar$^{\text{Cl}_3}$

\[\begin{array}{c}
\text{H} \\
\text{neat}
\end{array} \xrightarrow{5 \text{ mol\% 1}} \begin{array}{c}
\text{H} \\
\text{24 h, 100 °C} \\
\text{20 \% yield 18 \%} \\
\text{+ 2.5 mol\% tBuOOtBu}
\end{array}
\]

All yields are $^1$H NMR yield in CDCl$_3$. 192
% C-H amination yield can be derived from the reaction of 1 equiv NH$_2$Ar$^{Cl3}$ and 1.2 equiv $^1$BuOO$^1$Bu in neat ethylbenzene catalyzed by as low as 1 mol% 1.\textsuperscript{17} GC/MS analysis indicated ca. 40% unreacted N$_3$Ad based on integrated area against that for 1,2,4,5-terachlorobenzene standard. Unfortunately, this may account for the lower yield for C-H amination. Clearly conversion is a problem for this protocol. A possible explanation for low activation of N$_3$Ad may because the copper catalyst 1 is tied up already with the aniline. Also, reaction may have needed longer time for activation of the azide to occur in significant amount. On the brighter side, GC/MS analysis showed no C-H functionalized product PhCH(NHAd)CH$_3$ derived from the adamantylamide intermediate.

In line with these reprogramming reactions, we also looked into changing the nature of the HAA agent (Scheme 4.14) by using other other oxidants like PhI=O (iodosylbenzene) and N$_3$Ts (tosyl azide). We proposed that reaction of these oxidants with [Cl$_2$NN]Cu give metal oxo

\textbf{Scheme 4.14.} Proposed general catalytic cycle for reprogramming of C-H functionalization using metal-oxo or metal-nitrene as metal-based HAA agent.

\[ E = O, \text{NR from PhI=O or N}_3\text{R} \]
[Cl₂NN]Cu=O and metal nitrene [Cl₂NN]Cu=NTs as the HAA agent. Reaction of 1 equiv of PhIO and 4 equiv NH₂ArCl₃ in neat ethylbenzene with 10 mol% 1 and catalytic amount amount of DTBP yielded only about 8% of the C-H functionalization product PhCH(NHArCl₃)CH₃ (Scheme 4.15.A). GC/MS showed a very small amount of acetophenone is formed, which is the oxidized form of the C-H hydroxylation product of ethylbenzene. This hydroxylation product could come from RC of [Cl₂NN]Cu²⁺-OH (Scheme 4.14). As this is an interesting result and certainly needs more improvement, we account the low conversion on the poor solubility of PhIO in ethylbenzene. On the other hand, reaction of 1 equiv N₃Ts and 4 equiv NH₂ArCl₃ in neat ethylbenzene at 80 °C for 24 h, with 10 mol% 1 and 2.5 mol% DTBP gave a 40 % yield of PhCH(NHArCl₃)CH₃ (Scheme 4.15.B). GC/MS of the reaction mixture showed a small amount of PhCH(NHTs)CH₃ about 8 %.

**Scheme 4.15.** Catalytic reprogramming of C-H amination using PhIO and N₃Ts and NH₂ArCl₃.

(1)  
1 equiv PhIO +  
4 equiv NHArCl₃  
[neat]  
\[ \text{H} \]  
[5 mol% 1]  
24 h, 80 °C  
+ 2.5 mol% \(^{1}\text{BuOO}^{1}\text{Bu} \]  
[8 % yield]  
 reacted with  
[PhC]  
[\text{H}]  
+ PhI  
+ PhI

(2)  
1 equiv N₃Ts +  
4 equiv NHArCl₃  
[neat]  
\[ \text{H} \]  
[5 mol% 1]  
24 h, 80 °C  
+ 2.5 mol% \(^{1}\text{BuOO}^{1}\text{Bu} \]  
[40 % yield]  
 reacted with  
[PhC]  
[\text{H}]  
+ NH₂Ts  
40 %
We then explored use of other substrates like \textit{tert}-butyl alcohol, methanol, nitromethane (NO$_2$CH$_3$) and phenyl acetate (PhOAc) to access the applicability of our reprogramming setup. Reaction of 1 equiv of N$_3$Ad or N$_3$Ts and 4 equiv H-FG in neat ethylbenzene with 10 mol\% 1 and catalytic amount of DTBP, heated at 110 for N$_3$Ad reaction or 80 for N$_3$Ts reaction. Alcohols are not good H-FG substrates, yields for inserted products are only about <1\%. Acid-base exchange between [Cl$_2$NN]Cu$_{\text{II}}$-NHR’ (R’ = Ad, Ts) and RO-H is not that facile, probably because NH$_2$R’ and ROH have comparable pKa. On the other hand, reactions with NO$_2$CH$_3$ and PhOAc yielded, small amount of functionalized products (PhCH(FG)CH$_3$) (Table 4.3). For nitromethane, the C-H bonds are appreciably acidic because of the nitro group, and the acid-base reaction of the copper(II) amide and H-CH$_2$NO$_2$ gives the copper(II) nitromethanoate (Scheme 4.16.A). This species has been recently isolated and characterized by colleague Dan Seidenberg, he is currently working on the intermediacy of this species in C-H functionalization.

The use of phenyl acetate in this reprogramming protocol suggests copper(II) amide can do group exchange with an ester to form copper(II) phenolate and the organic amide RN(H)C(O)CH$_3$ (Scheme 4.16.B). This reaction is similar to nucleophilic acyl substitution of carboxylic acid derivatives. Although the isolation of the copper(II) phenolate is still quite elusive, Nick Sapiezynski showed that phenyl acetate and other substituted phenyl acetate can be used as substrates to functionalize benzylic C-H bond of ethylbenzene with 1 as catalyst. GC/MS analyses of these reaction mixtures showed inserted products derived from [Cl$_2$NN]Cu$_{\text{II}}$-NHR’, especially those derived from N$_3$Ad PhCH(NHAd)Me. For N$_3$Ts reactions, major side product is the tosylamide, which may derived from double HAA, first by copper tosylnitrene, then by copper(II) tosylamide. As preliminary as these results were, these results give exciting possibility for application of copper nitrenes in C-H functionalization, which warrants further exploration in the future.
Table 4.3. Catalytic reprogramming of C-H functionalization using N$_3$Ad and N$_3$Ts and NO$_2$CH$_3$ and PhOAc as substrates.

![Chemical structure and reaction scheme]

<table>
<thead>
<tr>
<th>FG substrates</th>
<th>product</th>
<th>side product</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO$_2$CH$_2$-H</td>
<td>3 - PhCH(NHAd)Me</td>
<td>3 - PhCH(NHAd)Me</td>
</tr>
<tr>
<td>PhOAc</td>
<td>12 - PhCH(NHAd)Me</td>
<td>34 - PhCH(NHAd)Me</td>
</tr>
<tr>
<td>NO$_2$CH$_2$-H</td>
<td>6 - NH$_2$Ts; 32 - PhCH(NHTs)Me</td>
<td>45 - NH$_2$Ts; 32 - PhCH(NHTs)Me</td>
</tr>
<tr>
<td>PhOAc</td>
<td>9 - NH$_2$Ts; 7 - PhCH(NHTs)Me</td>
<td>60 - NH$_2$Ts; 7 - PhCH(NHTs)Me</td>
</tr>
</tbody>
</table>

$^1$H NMR yield, %

Scheme 4.16. Proposed generation of [Cl$_2$NN]Cu$^{II}$-FG using CH$_3$NO$_2$ and PhOAc.

**A. Nitromethane**

[Cl$_2$NN]Cu=NR + R'-H $\rightarrow$ [Cl$_2$NN]Cu$^{II}$-NHR

[Cl$_2$NN]Cu$^{II}$-NHR + H-CH$_2$NO$_2$ $\rightarrow$ [Cl$_2$NN]Cu$^{II}$-[C$\equiv$CH$_2$] + NH$_2$R

Copper(II) nitromethanoate

**B. Phenyl acetic acid**

[Cl$_2$NN]Cu=NR + R'-H $\rightarrow$ [Cl$_2$NN]Cu$^{II}$-NHR

[Cl$_2$NN]Cu$^{II}$-NHR + PhOC(O)CH$_3$ $\rightarrow$ [Cl$_2$NN]Cu$^{II}$-OPh + NH$_2$R

Copper(II) phenolate
Conclusion

Catalytic reaction of $N_3^1Bu$ and pentane using 1 as catalyst showed that C-H amination can be achieved on the secondary C-H bonds and even the stronger primary C-H bonds of pentane, with selectivity for the secondary and less hindered C-H bonds. Further reaction with substrates like 2,3-dimethylbutane and 2,4-dimethylpentane indicates that the copper alkylnitrene has a preference for tertiary $>\$ secondary $>\$ primary C-H bonds, although the steric accessibility of the reacting C-H bond influences this selectivity. Modifications in the $\beta$-diketiminate ligand structure can impart better selectivity in C-H amination for the less sterically hindered secondary C-H bonds of pentane by using bulkier, more electron-poor catalysts. We also showed that copper nitrene $[Cl_2NN]Cu=NA^d$ is more reactive as HAA agent compared with copper(II) amide $[Cl_2NN]Cu^{\text{II}}-NA^d$, as a consequence of the BDE of the N-H bond of the resulting copper species after HAA. Furthermore, stoichiometric reaction of copper alkylnitrene $[Cl_2NN]Cu^{\text{II}}-NH^tBu$ with $[Cl_2NN]Cu^{\text{II}}-NAr^{Cl^3}$ showed that the copper alkylnitrene can be used as external HAA agent to provide the carboradical, which is captured by the $[Cl_2NN]Cu^{\text{II}}-NAr^{Cl^3}$, resulting to anilino-substituted substrate instead of alkylamino-substituted. Unfortunately, transferring this into a catalytic protocol is less straightforward, as the conversion of the azide to the copper nitrene is not complete and the RC agent $[Cl_2NN]Cu^{\text{II}}-FG$ is harder to generate in situ. Use of other oxidants like PhIO and $N_3Ts$ may be used, though PhIO has solubility issues. Nonetheless, we are able to apply this protocol on C-H functionalization with NO$_2$CH$_3$ and PhOAc with $N_3Ad$ and $N_3Ts$ as nitrene precursors.
Experimental Details

4.4.a. General Procedures and Instrumentation

Same as in previous chapters – see section 2.4.a.

For general precautions on the synthesis and handling of azides – see section 2.4.b. The azides used were synthesized according to literature procedure N₃Bu,₂⁴ N₃Ts,₂⁵ while N₃Ad was purchased from Sigma-Aldrich and was used as received. Iodosylbenzene was prepared from hydrolysis of iodobenzene diacetate in sodium hydroxide solution.²⁶

Preparations of {[Cl₂NN]Cu₂(µ-NAd)}₁² (2), [Cl₂NN]Cu⁺⁻NHAd₁⁶ (3), [Cl₂NN]Cu⁺⁻O'Bu₁⁶ (4) and {[Cl₂NN]Cu₂(µ-N'Bu)}₁³ (6) are followed from literature and {[Cl₂NNCF₃]}₂(µ-benzene)²⁰ from the procedure described in the thesis of Dr. Stefan Wiese, while [Cl₂NN]Cu⁺⁻NHArCl₃ (5)¹⁹ is followed from the synthetic protocol developed by Grace Jang in the Warren Group. All the other copper(I) β-diketiminato complexes described in section 4.2.c were prepared and graciously shared by Grace Jang.

4.4.b. General Protocol for Catalytic C-H Amination Using N₃Bu

Three portions of N₃Bu (0.099 g, 1.00 mmol each) were dosed, one mixed with pentane (15 mL), the next with 2,3-dimethylbutane (10 mL) and the last one with 2,4-dimethylpentane (10 mL). Into each was added an aliquot of the solution of 1 in benzene (1.00 mL, 0.025 mmol, 2.5 mol% with respect to N₃Bu). The reaction mixtures were heated at 100 °C for 24 h (for the pentane reaction) and 48 h (for 2,3-dimethylbutane and 2,4-dimethylpentane). For all cases, the reaction mixtures turned to green after about 30 minutes, and turned to yellowish brown by the time the reaction was stopped. The reaction mixtures were exposed to air for several hours to
oxidize the copper catalyst, passed through Celite stick into a vial containing 1,2,4,5-tetrachlorobenzene in fluorobenzene (1.00 mL, 1.0 M, 1.00 mmol). An aliquot of this resulting mixture was analyzed through GC/MS (in CH₂Cl₂) and ¹H NMR spectroscopy (in chloroform-d₁, 400 MHz).

For the pentane reaction, there are three peaks with m/z 143; yield is determined from the ¹H NMR spectrum, Figure 4.4. Assignments: δ 2.68 ppm, m, 0.49, 1H, CH₃CH(NHᵗBu)CH₂CH₂CH₃; δ 2.52 ppm, t, 0.10, 2H, CH₂(NHᵗBu)CH₂CH₂CH₂CH₃; δ 2.36 ppm, m, 0.14, 1H, CH₃CH₂CH(NHᵗBu)CH₂CH₃.

**Figure 4.4.** ¹H NMR spectrum (400 MHz, chloroform-d₁) of the pentane reaction using N₃ᵗBu and 1 as catalyst.
From the GC/MS of reaction mixture of 2,3-dimethylbutane, Figure 4.5, two inserted products (1A and 2A) were observed (M⁺ = 157), present in 42% and 4% (integrated areas with respect to that of 1,2,4,5-tetrachlorobenzene, labeled 3A). Product 1A is assigned as aminated product at the tertiary C-H bond of 2,3-dimethylbutane, because of the distinct fragment from α-cleavage in amine. Only this product from the amination of the tertiary C-H bond is detected in ¹H NMR spectrum (Figure 4.6): δ 1.64 ppm, m, 0.51, 1H, (CH₃)₂CHC(NH₃Bu)(CH₃); δ 1.19 ppm, s, 4.20, 9H, (CH₃)₂CHC(NH'Bu)(CH₃); δ 1.10 ppm, s, 1.10, 6H, (CH₃)₂CHC(NH'Bu)(CH₃); δ 0.89 ppm, d, 2.86, 6H, (CH₃)₂CHC(NH'Bu)(CH₃).

Figure 4.5. GC/MS spectrum of the reaction mixture of 2,3-dimethylbutane and N₃'Bu and 1 as catalyst.
Figure 4.6. $^1$H NMR spectrum (400 MHz, chloroform-$d_1$) of the reaction of 2,3-dimethylbutane and $N_3^t$Bu and 1 as catalyst.

Scheme 4.15. Fragmentation pattern to account for the fragment m/z 114 for the $(\text{CH}_3)_2\text{HC}(\text{NH}^t\text{Bu})(\text{CH}_3)_2$ and $(\text{CH}_3)_2\text{CHCH}_2\text{C}(\text{NH}^t\text{Bu})(\text{CH}_3)_2$.

From 2,3-dimethylbutane

\[ \text{NH}^t\text{Bu} \xrightarrow{\alpha\text{-cleavage}} \text{N}^t\text{Bu} + \cdot \]

m/z 114

From 2,4-dimethylpentane

\[ \text{NH}^t\text{Bu} \xrightarrow{\alpha\text{-cleavage}} \text{N}^t\text{Bu} + \cdot \]

m/z 114
For the reaction of 2,4-dimethylpentane and N$_3$Bu, two aminated products were observed instead of the expected three. GC/MS analysis showed that peak 1A is the aminated product at the tertiary position, while peak 2A is the aminated product at the primary position (Figure 4.7). This assignment is made based on the fragment m/z 114, which is the result of α-cleavage (Scheme 4.9). Based on the integrated areas of the peaks and compared against that of 1,2,4,5-tetrachlorobenzene (3A), yield for product (CH$_3$)$_2$CHCH$_2$C(NH$^t$Bu)(CH$_3$)$_2$ (1A) is 35 %, while (CH$_3$)$_2$CHCH$_2$CH(CH$_2$NH$^t$Bu)(CH$_3$) (2A) is 7 %. Only the tertiary inserted product is observed from the $^1$H NMR (Figure 4.8): δ 1.70 ppm, m, 0.37, 1H, (CH$_3$)$_2$CHCH$_2$C(NH$^t$Bu)(CH$_3$)$_2$; δ 1.19

![Figure 4.7. GC/MS spectrum of the reaction mixture of 2,4-dimethylpentane and N$_3$Bu and 1 as catalyst.](image)
ppm, d, 0.65, 2H, (CH₃)₂CHCH₂C(NHᵗBu)(CH₃)₂; δ 1.15 ppm, s, 2.27, 9H, (CH₃)₂CHCH₂C(NHᵗBu)(CH₃)₂; δ 1.13 ppm, s, 1.73, 6H, (CH₃)₂CHCH₂C(NHᵗBu)(CH₃)₂; δ 0.91 ppm, d, 1.67, 6H, (CH₃)₂CHCH₂C(NHᵗBu)(CH₃)₂.

Figure 4.8. ¹H NMR spectrum (400 MHz, chloroform-d₁) of the reaction 2,4-dimethylpentane and N₃ᵗBu and 1 as catalyst.

4.4.c. Copper Nitrene vs. Copper(II) Amide as HAA Agent

In separate pressure vessels, freshly prepared \([\text{Cl}_2\text{NNCu}]_2(\mu-\text{NAd})\) (2) and \([\text{Cl}_2\text{NNCu}^{\text{II}}-\text{NHAd}]\) (3) were mixed with pentane (15 mL) and heated at 80 °C for 24 h. In another pressure vessel, N₃Ad (1 mmol, 0.177 g) was mixed with 1 in benzene (1.00 mL, 0.025 mmol, 2.5 mol% with respect to N₃Ad) and pentane (15 mL), and heated to 110 °C for 48 h.
Another setup was made by mixing pentane (15 mL) with NH₂Ad (1 mmol, 0.152 g), iBuOOiBu (1.2 mmol, 0.250 mL) and 1 in benzene (1.00 mL, 0.025 mmol, 2.5 mol% with respect to NH₂Ad), which was heated at 90 °C for 24 h. All reaction mixtures changed from green to yellowish mixture after being heated for the designated time. The reaction mixtures were quenched by exposing to air, filter through Celite stick into a vial with an aliquot of 1,2,4,5-tetrabenzene in fluorobenzene (1 equiv with respect to NAd for 2 and 3 or N₃Ad). An aliquot was taken for GC/MS (in CH₂Cl₂) and ¹H NMR (in chloroform-d₁, 400 MHz) analyses. GC/MS analyses showed that there are three amination products for the reaction with 2 and N₃Ad, while only NH₂Ad was seen for the reaction of 3. Yields for the reaction of 2 and N₃Ad were determined from the ¹H NMR spectrum (representative spectrum is shown in Figure 4.9, for the

![Figure 4.9. ¹H NMR spectrum (400 MHz, chloroform-d₁) of the reaction of pentane and N₃Ad and 1 as catalyst.](image-url)
reaction with N$_3$Ad). Assignments: δ 2.76 ppm, m, 1H, CH$_3$CH(NHAd)CH$_2$CH$_2$CH$_3$; δ 2.51 ppm, t, 2H, CH$_2$(NHAd)CH$_2$CH$_2$CH$_2$CH$_3$; δ 2.44 ppm, m, 0.11, 1H, CH$_3$CH$_2$CH(NHAd)CH$_2$CH$_3$.

4.4.d. Reaction of N$_3$Ad and Pentane Using a Variety of β-Diketiminato Copper(I) Complexes

In separate pressure tubes, an aliquot of N$_3$Ad in pentane (1.00 mL, 0.50 mmol) was mixed with a portion of the β-diketiminato copper(I) complex, listed in Figure 4.1, in benzene (0.50 mL, 0.025 mmol, 5 mol% with respect to N$_3$Ad as [Cu]) and diluted with pentane (6.5 mL). A control was setup separately by mixing an aliquot of N$_3$Ad in pentane (1.00 mL, 0.50 mmol) and pentane (7.0 mL). All reaction mixtures were heated to 110 °C for 24 or 48 h accordingly as detailed in Table 4.2. Afterwards, the reaction mixtures were exposed to air and passed through Celite stick into a vial with 1 equiv 1,2,4,5-tetrachlorobenzene (with respect to N$_3$Ad). A sample of each reaction mixture was taken for GC/MS (in CH$_2$Cl$_2$) and $^1$H NMR (in chloroform-$d_1$, 400 MHz) analyses.

4.4.e. Stoichiometric Reaction of [{Cl$_2$NN}Cu]$_2$(μ-N$^t$Bu) with [Cl$_2$NN]Cu$^{II}$-FG

Freshly prepared compounds [Cl$_2$NN]Cu$^{II}$-O$^t$Bu (4) (0.016 g, 0.031 mmol) and [Cl$_2$NN]Cu$^{II}$-NHAr$^{Cl}$ (5) (0.020 g, 0.031 mmol) were mixed each with freshly prepared [{Cl$_2$NN}Cu]$_2$(μ-N$^t$Bu) (6) (0.030 g, 0.031 mmol) and dosed with ethylbenzene (3.0 mL). All mixtures were heated at 80 °C for 24 h. The reaction mixtures were quenched by exposing to air and passed through Celite stick into a vial containing 1 equiv 1,2,4,5-tetrachlorobenzene (with respect to N$^t$Bu). A sample of each reaction mixture was taken for GC/MS (in CH$_2$Cl$_2$) and $^1$H NMR (in CHCl$_3$-$d_1$, 400 MHz) analyses. Comparison of the GC/MS and $^1$H NMR spectra of the reaction of 4 and 6 in ethylbenzene and the catalytic reaction of N$_3$Bu in ethylbenzene using 1 as
catalyst indicate that the inserted product is PhCH(NH\text{tBu})CH_3 (chapter 2). In contrast, analysis of the reaction of 5 and 6 in ethylbenzene showed that the inserted observed is PhCH(NHAr\text{Cl}_3)CH_3. \textsuperscript{1}H NMR spectrum of the reaction mixture is shown in Figure 4.10 and compared to the reported chemical shifts\textsuperscript{17} for PhCH(NHAr\text{Cl}_3)CH_3, giving the yield as 81 % based on δ 5.02 ppm, 1H, 0.81, PhCH(NHAr\text{Cl}_3)CH_3.

4.4.f. Catalytic Reprogramming Reactions Using 1 as Catalyst

Into separate pressure vessels, a portion of H-FG (NH\text{2Ar}\text{Cl}_3, NO_2CH_3, PhOAc) in ethylbenzene (1.00 mL, 1.00 mmol) was mixed an aliquot of 1 in ethylbenzene (1.00 mL, 0.0125 mmol, 5 mol% with respect to N\text{3Ad}) and diluted with ethylbenzene (0.75 mL). Di-\text{\text{-}tert-}butyl peroxide (2.0 µL, 2.5 mol% with respect to N\text{3Ad}) was added to all reaction mixture except for one of the NH\text{2Ar}\text{Cl}_3 setups. Then a portion of the N\text{3Ad} solution in ethylbenzene (1.00 mL, 0.25 mmol) was added. These mixtures were heated at 110 °C for 24 h. The reaction mixtures were quenched by exposing to air and passed through Celite stick into a vial containing 1 equiv 1,2,4,5-tetrachlorobenzene. A sample of each reaction mixture was taken for GC/MS (in CH_2Cl_2) and \textsuperscript{1}H NMR (in CHCl_3-\text{d}_1, 400 MHz) analyses.

Into separate pressure vessels, a portion of FG-substrates (NH\text{2Ar}\text{Cl}_3, NO_2CH_3, PhOAc) in ethylbenzene (1.00 mL, 1.00 mmol) was mixed an aliquot of 1 in ethylbenzene (1.00 mL, 0.0125 mmol, 5 mol% with respect to N\text{3Ts}) and diluted with ethylbenzene (0.75 mL). Di-\text{\text{-}tert-}butyl peroxide (2.0 µL, 2.5 mol% with respect to N\text{3Ts}) was added, followed by a portion of the N\text{3Ts} solution in ethylbenzene (1.00 mL, 0.25 mmol) was added. These mixtures were heated at 80 °C for 24 h. The reaction mixtures were quenched by exposing to air and passed through
Celite stick into a vial containing 1 equiv 1,2,4,5-tetrachlorobenzene. A sample of each reaction mixture was taken for GC/MS (in CH₂Cl₂) and ¹H NMR (in chloroform-ᵈ₁, 400 MHz) analyses.

Into separate pressure vessels, a portion of H-FG (NH₂Ar廒, NO₂CH₃, PhOAc) in ethylbenzene (1.00 mL, 1.00 mmol) was mixed with an aliquot of 1 in ethylbenzene (1.00 mL, 0.0125 mmol, 5 mol% with respect to PhIOAc) and diluted with ethylbenzene (0.75 mL). Di-tert-butyl peroxide (2.0 µL, 2.5 mol% with respect to PhIOAc), PhIOAc powder (0.055-0.057 g, 0.25 mmol), and ethylbenzene (1.00 mL) were added. These mixtures were heated at 80 °C for 24 h, after which these were quenched by exposing to air and passed through Celite stick into a vial containing 1 equiv 1,2,4,5-tetrachlorobenzene. A sample of each reaction mixture was taken for GC/MS (in CH₂Cl₂) and ¹H NMR (in chloroform-ᵈ₁, 400 MHz) analyses.

Figure 4.10. ¹H NMR spectrum (400 MHz, chloroform-ᵈ₁) of the stoichiometric reaction of 4 and 6 in ethylbenzene.
References


(20) Wiese, S., Georgetown University, 2011.


CHAPTER 5

Synthesis and Exploratory Reactivity of Linked β-Diketiminato Copper Complexes
Abstract

The reaction of O₂ and copper(I) complexes represents a vigorous area of research to provide insight into enzymes capable of activating O₂ and to extend this reactivity to synthetic systems. β-diketiminato ligands are widely used as ligands for copper(I) complexes as synthetic analogues of copper-based enzymes. We introduce new sets of β-diketiminato ligands bearing an ortho-linked aniline as a bridge between two β-diketiminate moieties capable of coordinating metal centers. Such families of linked ligands allows for the study of copper-based enzymes whose activity is proposed to be via the cooperation of two Cu centers. Previous versions of non-linked β-diketiminate ligands lead to formation of mononuclear four-coordinate dicopper di-oxo complexes. New copper(I) complexes of these linked ligands [iPr₂NN-C₂-Cu₂](CN₂.Me₂Ph)_2 and [iPr₂NN-C₂-Cu₂](2-pic)_2 have been prepared bearing isocyanide and 2-picoline ligands to complete trigonal coordination at each non-interacting copper center. Addition of O₂ into [iPr₂NN-C₂-Cu₂](CN₂.Me₂Ph)_2 showed no reaction, while into [iPr₂NN-C₂-Cu₂](2-pic)_2 resulted to a new copper species, currently characterized only by its λ max at 426 nm, which is proposed to be a monooxo-bridged dicopper(II) complex [Cu₂](μ-O). This copper species is also generated when [iPr₂NN-C₂][Cu²-OtBu]₂ is reacted with H₂O. This report provides new opportunities for study of copper-enzymes, as well as exploration of reactions possibly can be mediated by a cooperative Cu system.
Introduction

Selective functionalization of methane remains one of the most intriguing challenges in C-H bond functionalization. This molecule is considered as the most inert among alkanes, attributed to highly energy-intensive homolytic and heterolytic cleavage of the C-H bond (BDE of 105.0(1) kcal/mol,\(^1\) pKa ~ 50-51).\(^2\)-\(^4\) These attributes make methane a particularly recalcitrant substrate for redox and acid-base chemistry.\(^3\),\(^4\)

Methane is present in copious amounts on planet Earth and can be found as the major component (around 70-98%)\(^5\) in natural gas, byproduct of the coal mining\(^6\) and in methane clathrates in arctic seabeds.\(^2\),\(^7\) In the United States alone, the methane (as wet natural gas) proven reserve is estimated at 348.8 trillion cubic feet in 2011.\(^8\) Roughly 25% of electricity generation in the United States comes from the combustion of natural gas.\(^8\),\(^9\) With the increasing global energy demand of the growing population, along with the depleting oil reserves (especially those from Middle Eastern countries), it is more reasonable to shift the focus on energy source on natural gas, due to both economical and environmental considerations.\(^4\),\(^10\)

Methane is a very volatile and flammable gas making its distribution from the major pipelines to the end users difficult and extremely dangerous. This limits it as a truly globally traded energy resource.\(^4\) Costly technologies being practiced in gas industries is the compression of gas at ca 80 bars for trans-continental pipeline distribution and refrigeration to produce liquefied natural gas for trans-oceanic transport aboard ships.\(^2\) There are serious safety concerns for the loading and unloading of liquefied methane at ports near populated areas. These transport issues translate to growing interest in the conversion of methane to methanol as liquid fuel.
Methanol is a versatile molecule and serves as the main C\textsubscript{1} feedstock in the industrial preparation of many chemicals and commodities (Figure 5.1).\textsuperscript{11} It can be converted to dimethyl ether,\textsuperscript{12} a component of diesel, and to biodiesel by transesterification of triglycerides.\textsuperscript{11} It can also be converted to small olefins, ethylene and propylene, which then serve as raw material to prepare longer alkanes, alkenes, polymers, among others. Oxidation of methane to formaldehyde and acetic acid provides the building blocks for many O-based compounds, especially butanediol, vinyl acetate and terephthalic acid, which are generally used in polymer synthesis.\textsuperscript{11}

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{methanol.png}
\caption{Some applications of methanol as a fuel and C\textsubscript{1} feedstock.}
\end{figure}

As a transportation fuel, methanol is used as an M85 blend of 85% methanol and 15% gasoline for the flexible fuel vehicles developed by Ford in the 1980s.\textsuperscript{13,14} Methanol has high octane rating and burns more cleanly producing less toxic emission, resulting in better performance and lower greenhouse gas levels than gasoline. Methanol is also being considered as fuel for fuel cells based on the the direct methanol fuel cell developed by Olah and colleagues from the Jet Propulsion Laboratory.\textsuperscript{12} This fuel cell provides a more efficient way generate electricity from the oxidation of methanol to carbon dioxide and water, at lower controlled temperature conditions. Methanol is regarded as an ideal hydrogen reservoir for these
electrochemical cells, having greater density of hydrogen atoms as compared to other possible liquid fuels stable at normal conditions. There is a great deal of promise in developing large-scale and portable types of this fuel cell; this is a very active research area in the energy sector.\textsuperscript{12,14,15}

\textbf{5.1.a. Industrial Conversion of Methane to Methanol}

The existing methanol manufacture from natural gas is generally a two-step process involving (a) conversion of methane feedstock to a mixture of H\textsubscript{2}, CO and CO\textsubscript{2} or the synthesis gas (syngas) and (b) catalytic production of methanol from the syngas (Scheme 5.1).\textsuperscript{2,5,13,16} The conversion of methane to syngas is a high temperature ‘reforming’ step, achieved either by steam reforming or autothermal reforming. In steam reforming, conversion of methane to CO and H\textsubscript{2} is highly endothermic step, facilitated by a nickel-based catalyst, and is typically done at very high temperatures and pressures. Carbon dioxide is sometimes formed when there is a water-gas shift reaction of CO and H\textsubscript{2}O. Autothermal reforming slightly overcomes the huge energy expenditure of the steam reforming by partially oxidizing methane, typically with molecular O\textsubscript{2}, at considerably higher temperatures.\textsuperscript{17} On the other hand, the conversion of syngas to methanol is an exothermic step, which is typically catalyzed by a copper-zinc oxide on alumina support at moderate temperatures.

The requirement for high temperatures and pressures makes the current technology for methane to methanol conversion practiced in the industry highly undesirable. Nevertheless, this technology will remain as the means to produce methanol, because of the necessity for this molecule in chemical production. This directs the need to search for more economically viable and environmentally friendly alternatives.
5.1.b. Nature’s Way of Producing Methanol from Methane

Nature provides inspiration for a path towards discovery of efficient processes for the conversion of methane to methanol. Methanotrophs are bacteria found in sewage sludge, rice paddies, landfills, that utilize methane as carbon and energy source, selectively transforming it methanol under ambient conditions. In these bacteria, the ‘reactor’ is the metalloenzyme methane monooxygenase (MMO), present in two forms, the soluble MMO (sMMO) and the particulate MMO (pMMO). The sMMO form is a diiron-three protein site present in the bacterial cytoplasm and is expressed under low copper concentration conditions. Being the more isolable form although less prevalent, many isolation and characterization studies have been on the
sMMO form. On the basis of stereochemical studies, in combination with theoretical calculations, the mechanism of methanol formation from methane is best described to be at the carboxylate bridged diiron (Scheme 5.2). 20 A bis(μ-oxo)diiron(IV) site is formed from the activation of O₂ (A), followed by the stepwise activation of the C-H bond of methane: hydrogen atom abstraction (HAA) results to the carboradical and diiron(μ-oxo)(μ-hydroxo) (B) and radical capture (RC) of the carboradical and the hydroxo, facilitated by the intake of the solvent molecule (H₂O) resulting to the diiron(μ-oxo)(μ-aqua) complex (C).

**Scheme 5.2.** Hydroxylation of methane through the carboxylate-bridged diiron active site of sMMO.

The particulate form of methane monoxygenase (pMMO) is the more common membrane-bound form, which is activated in a copper-saturated environment. 20 Only quite recently Rosenzweig and colleagues determined an X-ray structure of this pMMO from *Metylococcus capsulatus* (Bath), consisting of a trimeric polypeptide units (pmoA, pmoB and pmoC) approximately 105 Å long and 90 Å in diameter. 21 This has three distinct metal centers
shown in Figure 5.2.A, two centers contain copper and the other one is proposed to have iron. An interesting metal site is found in the soluble domain of pmoB, there is a dicopper site with a 2.5 - 2.7 Å Cu···Cu distance coordinated to His 33, His 137, His 139 (Figure 5.2.B and C). Both His 137 and His 139 bind one of the Cu center through their side chain N atoms. The other Cu site is coordinated to His 33, through the side chain N atom and the N-terminal amino nitrogen. They subsequently offered compelling support that the dinuclear copper site [(His)$_2$Cu$^1$- Cu$^1$(HisCH$_2$CHRNH$_2$)]$^{2+}$ is indeed the active site of pMMO. Propylene epoxidation and methane oxidation activities were restored when the apo pMMO was titrated with 2-3 equivalents of copper ions and not with iron ions, indicating that the active site is more likely the soluble pmoB. They also presented that activity is restored for the recombinant fragment of the soluble pmoB where the dicopper site is undisrupted.

5.1.c. Production of Methanol from Methane on Zeolite Frameworks

Schoonheydt and co-workers reported the selective conversion of methane to methanol ($\geq$ 98%) on O$_2$-activated copper-exchanged zeolite Cu-ZSM-5 at relatively modest temperatures (100 – 175 °C) after it was activated by O$_2$. They found that the characteristic peak at 441 nm (22,700 cm$^{-1}$) for the O$_2$-activated Cu-ZSM-5 disappears as methane is introduced. In conjunction with the Solomon group, Schoonheydt described resonance Raman spectroscopic studies coupled with DFT studies on the methane oxidation of the O$_2$-activated Cu-ZSM-5 that strongly correlates to a [Cu$^\text{II}$]$_2$(µ-O) (A) core as the reactive site (Scheme 5.3). Further theoretical studies support a stepwise process for the oxidation of methane, with the formation of [Cu$^{1.5}$]$_2$(µ-OH) core (B). The strong O-H bond of the [Cu$^{1.5}$]$_2$(µ-OH) core upon hydrogen atom abstraction greatly drives the oxidation reaction, This HAA step is the rate limiting step with an experimental activation energy of 15.7 ± 0.5 kcal/mol.
Figure 5.2. Structure of pMMO: PDB 1YEW, with a blow-up of the proposed dicopper active site.
**5.1.d. Reactivity of β-Diketimino Copper(I) Complexes with Oxygen**

Undoubtedly, both in nature and synthetic models, copper plays an integral role in the activation of dioxygen and its resulting reactivity towards C-H substrates.\(^{26-28}\) There has been a variety of synthetic copper/O\(_2\) complexes identified or proposed as biomimics (Figure 5.3).\(^{22,25,26,29,30}\) Different Cu:O\(_2\) stoichiometry and geometry can be derived from using different ligands.\(^{26}\) Copper(I) β-diketiminate complexes have been used extensively to serve as synthetic models for copper-based enzymes.\(^{31,32}\) Generally, dioxygen activation of copper(I) β-diketiminato complexes leads to either side-on monocopper(III) peroxo complexes \(^{33,34}\) with extremely sterically hindered ligand motifs (R\(^1\), R\(^2\) = \(^t\)Bu, R\(^3\) = \(^i\)Pr), while smaller ligands (R\(^1\), R\(^2\) = Me, \(^t\)Bu, CF\(_3\) for R\(^3\) = Me; R\(^1\), R\(^2\) = H for R\(^3\) = \(^i\)Pr) give bis(µ-hydroxo)dicopper(II) complexes\(^{35,36}\) via H-atom abstraction reactions of reactive dicopper bis(µ-oxo) intermediates.

**Scheme 5.3.** Oxidation of methane on the O\(_2\)-activated Cu-ZSM-5.
Sofi Bahgat from the Warren group has isolated a similar bis(µ-oxo)dicopper(III)
from the reaction of [{Cl₂NN}Cu]₂(µ-benzene) and O₂ which features a diamond core.

Scheme 5.4. Some well-characterized copper-O₂ structures for the β-diketiminate ligands.

(Scheme 5.3). Sofi Bahgat from the Warren group has isolated a similar bis(µ-oxo)dicopper(III)
from the reaction of [{Cl₂NN}Cu]₂(µ-benzene) and O₂ which features a diamond core.
structure.\textsuperscript{37} To date, there is no structurally characterized (by X-ray crystallography) copper complex with $[\text{Cu}]_2(\mu$-O) core, though in some ligand systems, this has been proposed as the structure of the spectroscopically characterized intermediate.\textsuperscript{38-42}

5.1.e. Linked Ligand Copper Systems

Another way to possibly generate the $[\text{Cu}]_2(\mu$-O) core is to use a ligand system where two mononucleating ligands are tethered. Although most of the tethered copper(I) complexes have been geared towards characterizing $\text{trans-}\mu$-1,2-peroxodicopper(II) complexes (Figure

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure5.png}
\caption{Previous examples of tethered ligands used to observe the $[\text{Cu}]_2(\mu$-O) core.}
\end{figure}
Reglier et al. reported the presence of a \([\text{Cu}_2(\mu-O)]\) core from the reaction of 2 equivalents of the copper complex of Bpi (Figure 5.4) and \(\text{O}_2\) in \(\text{CH}_2\text{Cl}_2\).\(^{43}\) They based their conclusions on the stoichiometry of \(\text{O}_2\) needed for a four-electron reduction, as well as the stoichiometry of \(\text{PPh}_3\) needed to produce an equivalent of \(\text{O}=\text{PPh}_3\). More recently, Limberg and co-workers observed the formation of new copper species from the reaction of \([\text{Me}_2\text{C}_6\text{H}_3\text{Xanthdim}](\text{Cu(NCCH}_3))_2\) and \(\text{O}_2\) at 640 nm at -80 °C.\(^{30}\) This species does oxidative coupling of 2,4-di-\(\text{tert}\)-butylphenolate. They account this species as the \([\text{Cu}_2(\mu-O)]\) based on the comparison of the spectral data with few known examples, including that of \([(\text{Bpi})\text{Cu}_2](\mu-O)\).

Just a few months ago, Limberg et al. reported another linked ligand copper system, \([\text{FurNeu}(\text{Cu(NCCH}_3))_2]\), which allows access to a \([\text{Cu}_2(\mu-O)]\) upon its reaction with \(\text{O}_2\) or \(\text{PhI}=\text{O}\).\(^{29}\) This species has absorption peaks at 644 nm – similar to that reported for their xanthene-based Cu system,\(^{30}\) and around 450 nm – similar to that reported for Cu-ZSM-5.\(^{24,25}\) Reactivity of this \([\text{Cu}_2(\mu-O)]\) core towards oxo-atom transfer to \(\text{PPh}_3\) is quite less efficient, while yield of its coupling reaction of 2,4-di-\(\text{tert}\)-butylphenol is better than their previous result.\(^{30}\)

Although, they are not able to structurally isolate \([\text{Cu}_2(\mu-O)]\), they are able to isolate a chloro-bridged dicopper complex, \([\text{FurNeu}[\text{Cu}_2](\mu-\text{Cl})]\), with a Cu⋯Cu distance of 3.199(1) Å and Cu1-Cl-Cu2 angle of 88.883(16)°.
5.1.f. Project Objectives

The close electronic similarity of the imido (NR$_2^-$) and oxo (O$_2^-$) ligands prompted us to target the synthesis of related dicopper oxo species [Cu]$_2$(μ-O) related to [Cu]$_2$(μ-NR) species that our group has previously prepared and study using β-diketiminate ligands.$^{44-46}$ Since reaction of copper(I) β-diketiminate complexes typically gives {[[β-dik]Cu]$_2$(μ-O)$_2$ (β-dik = β-diketiminate) species, a special approach is required to prevent the formation of this entity. Tolman found that simple addition of O-atom donors such as py→O or Me$_3$N→O to copper(I) β-diketimimates led to formation of either [[β-dik]Cu(O←amine) or {[[β-dik]Cu]$_2$(μ-O)$_2$ species. No {[[β-dik]Cu]$_2$(μ-O) species could be identified, even with a 2 : 1 ratio of [β-dik]Cu and amine→O reagents.$^{47}$ Identifying that the mononucleating version of the β-diketiminate ligands leads to the formation of the coplanar diamond [Cu]$_2$(μ-O)$_2$ structure (Scheme 5.4), we aim to develop series of β-diketiminate copper complexes, with a linked ligand motif shown in Figure 5.5. We rationalize that having one side of the β-diketiminate ligand linked by a common aniline,

![Diagram](image.png)

**Figure 5.5.** General structure of the linked β-diketiminate ligands used in this project.
this provides steric bulk on the ligand which we hope can prevent the formation of a coplanar [Cu]_2(µ-O)_2.

In this Chapter, we report our attempts in developing series of linked β-diketiminato ligands and the preparation of Cu(I) and Cu(II) complexes of these ligands. Preliminary reactivity studies of the copper(I) linked ligand complex on the activation of small molecules like O_2, di-tert-butyl peroxide and azides are explored.

Results and Discussion

5.2.a. Synthesis of Linked β-Diketiminate Ligands

The linked ligands are generally synthesized in two steps: (a) preparation of the ketoimine “X₂-half ligand” CH₃C(=N(2,6-X₂C₆H₃))CH₂C(O)CH₃ and (b) condensation of the half ligand and the linker. The half ligand is prepared by refluxing the aniline with 20 equiv of 2,4-pentanedione (as solvent) under acid catalysis (Scheme 5.5.a). The half ligand with electron rich anilines CH₃C(=N(2,6-Me₂C₆H₃))CH₂C(O)CH₃ and CH₃C(=N(2,6-iPr₂C₆H₃))CH₂C(O)CH₃ are generally collected as very viscous oil in ~ 99 % yield, after removing the excess 2,4-pentanedione in vacuo; while the CH₃C(=N(2,6-Cl₂C₆H₃))CH₂C(O)CH₃ half ligand is recrystallized from ethanol in 65% yield.

The typical Dean-Stark condensation route used for the synthesis of N-aryl β-diketiminate ligands proved to be useful in the synthesis of the H₂[iPr₂NN-C₂] linked ligand (Scheme 5.5.b.1). This ligand can be prepared in 35 % yield and a 11g scale. For the other half ligand and linker combinations, β-diketiminate with N-aryl o-iPr or o-Me groups, H[iPr₂NN] and H[Me₂NN], were obtained instead. The ketoimine formation is an equilibrium reaction, and with traces of water in the reaction mixture, hydration of some of the half ligand may have occurred,
with the reformed aniline condensing with the half ligand. To avoid this unfavorable equilibrium, another synthetic route was considered, where the half ligand is alkylated first with Meerwein’s reagent (triethylloxonium tetrafluoroborate, \([\text{Et}_2\text{O}]^+\text{[BF}_4^-\]) (Scheme 5.5.b.2).\(^5\) This makes the carbonyl C more susceptible to nucleophilic attack by the linker. Through this route, the linked ligands \(\text{H}_2[\text{iPr}_2\text{NN}-\text{O}], \text{H}_2[\text{Me}_2\text{NN}-\text{O}]\) and \(\text{H}_2[\text{Cl}_2\text{NN-C}_2]\) were prepared in considerable yields (Table 5.1). These Meerwein reactions were done in smaller scale (~ 3 g yield of linked ligand), although Harder et al. reported that such reaction can also be done in larger scale (~ 20 g).

<table>
<thead>
<tr>
<th>Linked Ligand</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{H}_2[\text{iPr}_2\text{NN-C}_2])</td>
<td>35</td>
</tr>
<tr>
<td>(\text{H}_2[\text{Me}_2\text{NN-O}])</td>
<td>20</td>
</tr>
<tr>
<td>(\text{H}_2[\text{Cl}_2\text{NN-C}_2])</td>
<td>12</td>
</tr>
</tbody>
</table>

Table 5.1. Summary of the yields of the linked \(\beta\)-diketiminate ligands
Scheme 5.5. Linked ligand synthesis.

a.) Half Ligand Synthesis

\[
\text{C}_{6}H_{5}\text{CO} \quad + \quad \begin{array}{c}
\text{C}_{6}H_{5}\text{NH} \\
\text{O}
\end{array}
\xrightarrow{\text{catalytic } p\text{-TsOH}} \quad \begin{array}{c}
\text{C}_{6}H_{5}\text{NH} \\
\text{N}
\end{array}
\]

\[X = \text{iPr, Cl, Me}\]

b.1.) Linked Ligand Synthesis via Dean-Stark Condensation

\[
\begin{array}{c}
\text{C}_{6}H_{5}\text{NH} \\
\text{O}
\end{array} \quad + \quad \begin{array}{c}
\text{C}_{6}H_{5}\text{NH} \\
\text{N}
\end{array}
\xrightarrow{p\text{-TsOH}} \quad \begin{array}{c}
\text{C}_{6}H_{5}\text{NH} \\
\text{N}
\end{array}
\]

\[X = \text{iPr}\]

b.2.) Linked Ligand Synthesis via Meerwein Reaction

\[
\begin{array}{c}
\text{C}_{6}H_{5}\text{NH} \\
\text{O}
\end{array} \quad + \quad \begin{array}{c}
\text{C}_{6}H_{5}\text{NH} \\
\text{N}
\end{array}
\xrightarrow{[\text{Et}_2\text{O}][\text{BF}_4]} \quad \begin{array}{c}
\text{C}_{6}H_{5}\text{NH} \\
\text{N}
\end{array}
\]

\[X = \text{iPr, Cl, Me}\]

\[\{\text{~}X\text{~}\} = \text{ OCH}_2\text{O, CH}_2\text{CH}_2}\]

\[\text{H}_2[\text{iPr}_2\text{NN-C}_2]\]

\[29\%\]
5.2.b. Copper Complexes of Linked β-Diketiminate \( H_2[Cl_2\text{NN}-C_2] \) and \( H_2[Me_2\text{NN}-O] \) Ligands

Following the route typically used for the synthesis of \([Cl_2\text{NN}][Cu]_2(\mu-\text{benzene})\),\(^{45}\) the neutral \( H_2[Cl_2\text{NN}-C_2] \) linked ligand underwent reaction with 2.2 equivalents of \( CuO^tBu \) in THF in the presence of 10 equiv. benzene or acetonitrile at RT (Scheme 5.6.a). The reaction mixture initially turned darker yellow, which later changed to blue green solution with some brown residue. Blue green crystals were isolated from the ether in 20% yield. X-ray studies showed that the crystal is a copper(II) complex of the \([Cl_2\text{NN}-C_2] \) linked ligand \( \kappa^4-[Cl_2\text{NN}-C_2][Cu]^{II} \) (1), there are two molecules of 1 (1A and 1B) in an asymmetric unit (Figure 5.6.A and B). Both molecules show the two β-diketiminate portions wrapped up a Cu(II) ion in a distorted tetrahedral geometry with a dihedral angle in the range of 64-67° and an average Cu-N distances of 1.9826(18) Å. The copper(I) complex may have been formed, but because of the close proximity of the two copper(I) sites, disproportionation may have occurred resulting to the formation of \( Cu^0 \) as the brown powder and 1. This prompted us to use stronger σ-donors as ancillary ligands to stabilize the \( Cu^I \) complex.

Similar attempts of using several Cu(I) salts (CuCl, CuOTf, \([Cu(\text{MeCN})_4]PF_6\)) with the dilithium salt \( Li_2[Me_2\text{NN}-O] \) of the linked ligand in THF led to formation of blue solution with brown residue, even with 10 equiv MeCN. Following the synthesis described for the preparation of \([Cl_2\text{NN}][Cu]_2(\mu-\text{Cl})_2\),\(^{51}\) reaction of the dilithium salt \( Li_2[Me_2\text{NN}-O] \), 2.2 equiv of CuCl in THF led to a blue green solution, and blue green crystals of \( \kappa^4-[Me_2\text{NN}-O][Cu]^{II} \) (2) were isolated after recrystallization from ether in 43% yield (Scheme 5.6.b). The X-ray structure of 2 is similar to 1 where the linked ligand is in twisted tetrahedral form around a Cu(II) ion, forming a dihedral angle of 57.9° and 68.8° with an average Cu-N distances of 1.9832(19) Å (Figure 5.7). This indicates that bigger ortho-\( N \)-aryl substituents on the aniline may provide the bulkiness needed to
prevent this twisting of the ligand. The UV-Vis spectrum of 2 in CH₂Cl₂ shows a λ_{max} = 632 nm (estimated ε = 1136 M⁻¹s⁻¹) and a shoulder band centered around 440 nm (Figure 5.8). Isotopic X-band electron paramagnetic (EPR) spectrum of 2 in benzene at RT shows a very broad one-line spectrum (Figure 5.9). Simulation allows assignment of g_{iso} = 2.111, A_{iso}^{(63/63)Cu} = 94 MHz and A_{iso}^{(14N)} = 30 MHz for the 4 N donors of the linked β-diketiminate ligand.

**Scheme 5.6.** Isolation of mononuclear Cu^{II} complexes of the linked ligand:

<table>
<thead>
<tr>
<th></th>
<th>a) [Cl₂NN-C₂]Cu^{II} (1)</th>
<th>b) [Me₂NN-O]Cu^{II} (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a)</td>
<td>[Cl₂NN-C₂] + 2.2 equiv Cu^{I}Bu</td>
<td>THF, crystallized in ether</td>
</tr>
<tr>
<td></td>
<td>THF, crystallized in ether</td>
<td>Cu^{I}, -2 equiv 'BuOH</td>
</tr>
<tr>
<td>b)</td>
<td>Li₂[Me₂NN-O] + 2.2 equiv CuCl₂</td>
<td>THF, crystallized in ether</td>
</tr>
<tr>
<td></td>
<td>THF, crystallized in ether</td>
<td>CuCl₂, -2 equiv LiCl</td>
</tr>
</tbody>
</table>

Ar = X
L = Y

a: 1, [Cl₂NN-C₂]Cu(II), X = Cl, Y = CH₂CH₂
b: 2, [Me₂NN-O]Cu(II), X = Me, Y = OCH₂O
Figure 5.6.A. X-ray structure of 1st molecule of κ⁴-[Cl₂NN-C₂]Cu²⁺ (1A). Selected bond distances (Å) and angles (°): Cu1-N1 1.9838(19), Cu1-N2 1.9838(19), Cu1-N3 1.9838(19), Cu1-N4 1.9838(19), N1-Cu1-N2 93.54(8), N3-Cu1-N4 93.55(8); dihedral angles (°): 64.4 and 67.0. All hydrogen atoms are omitted for clarity.
Figure 5.6.B. X-ray structure of 2nd molecule of κ^4-[Cl_2NN-C_2]Cu^{II} (1B). Selected bond distances (Å) and angles (°): Cu2-N5 1.9810(18), Cu2-N6 1.9814(18), Cu2-N7 1.9870(18), Cu2-N8 1.9784(18), N5-Cu2-N6 93.38(7), N7-Cu2-N8 93.59(7); dihedral angles (°): 65.4 and 67.4. All hydrogen atoms are omitted for clarity.
Figure 5.7. X-ray structure of κ₄-[Me₂NN-O]Cu^{II} (2). Selected bond distances (Å) and angles (°): Cu1-N1 2.018(2), Cu1-N2 1.967(2), Cu1-N3 1.955(2), Cu1-N4 1.997(2), N1-Cu1-N2 94.61(9), N3-Cu1-N4 92.44(9); dihedral angles (°): 56.9 and 68.8. All hydrogen atoms are omitted for clarity.
Figure 5.8. UV-Vis spectrum of 2 (1.36 mM) in CH$_2$Cl$_2$ at RT.

$$\lambda_{\text{max}} = 632 \text{ nm}$$

Figure 5.9. Isotopic X-band EPR spectrum of 2 (1.00 mM) in CH$_2$Cl$_2$ at RT: 8.984495 GHz, ModWidth = 0.1 mT, Power = 0.09850 mW, time constant = 0.1 s; Simulation (Gaussian lineshape with 38 G line broadening gives $g_{\text{iso}} = 2.111$, $A(^{63}\text{Cu}) = 94$ MHz, $A(^{14}\text{N}) = 30$ MHz for 4 equivalent N atoms (unresolved).
5.2.c. Synthesis and Reactivity of Isocyanide Copper(I) Complexes of Bulkier Linked Ligand

Simply reacting the dilithium salt Li\(_2\)[\(\text{Pr}_2\text{NN}-\text{C}_2\)] and 2 equiv. Cu\(^{\text{I}}\)O\(^{\text{t}}\)Bu, with 10 equivalents MeCN in THF did not give a copper(I) complex, but instead resulted to the same blue green solution with brown powder. Attempts in crystallizing this Cu(II) complex did not lead to any success. This result is consistent with the need of using a better ligand for the copper(I) \(\beta\)-diketiminato center than the weakly binding MeCN.

Reaction of H\(_2\)[\(\text{Pr}_2\text{NN-0}\)] with 2.2 equiv. Cu\(^{\text{I}}\)O\(^{\text{t}}\)Bu and 2.2 equiv. \(\text{tert}\)-butyl isocyanide (CN\(^{\text{t}}\)Bu) in THF gave light yellow crystals of \([\text{Pr}_2\text{NN-O-Cu}](\text{CN}^{\text{t}}\text{Bu})_2\) (3) as recovered from pentane 15 % (Scheme 5.7.a). Similarly, reaction of H\(_2\)[\(\text{Pr}_2\text{NN-C}_2\)], 2.2 equiv. Cu\(^{\text{I}}\)O\(^{\text{t}}\)Bu and 2.2 equiv. \(2,6\)-dimethylphenyl isocyanide (CNGAr) in THF, gave light yellow crystals of \([\text{Pr}_2\text{NN-C}_2-Cu](\text{CN}^{\text{t}}\text{Bu})_2\) (4) from fluorobenzene in 53% yield (Scheme 5.7.b). X-ray structures of 3 and 4 are shown in Figures 5.10 and 5.11, respectively. Both 3 and 4 show a trigonal planar arrangement around the Cu center (\(\Sigma\) angle about Cu1 = 360.0(14)\(^{\circ}\) and Cu2 = 359.5(16)\(^{\circ}\) for 3, \(\Sigma\) angle about Cu = 359.9(9)\(^{\circ}\) for 4), with the linked ligand in an ‘open’ form with non-interacting Cu centers. Compound 4 is a symmetric molecule because of inversion center and only a half of the molecule was present in the asymmetric unit. These compounds are similar in structure to those previously reported for mononuclear \([\text{Pr}_2\text{NN}]\text{Cu}(\text{CN}^{\text{t}}\text{Bu})\)\(^{52}\) and \([\text{Me}_3\text{NN}]\text{Cu}(\text{CN}^{\text{t}}\text{Bu})\)\(^{53}\). The Cu-C_isocyanide bond distance for 3 and 4 (1.825(4) and 1.837(8) Å for 3; 1.822(3) Å for 4) are slightly longer than those for \([\text{Pr}_2\text{NN}]\text{Cu}(\text{CN}^{\text{t}}\text{Bu})\)\(^{52}\) (1.817(2) Å) and \([\text{Me}_3\text{NN}]\text{Cu}(\text{CN}^{\text{t}}\text{Bu})\)\(^{53}\) (1.814(2) Å). This suggests that the \(\pi\)-backbonding for the dinuclear copper isocyanide complexes is weaker than for the mononuclear analogs, most likely because of the added sterics of the linker.
Despite the seemingly highly symmetric nature of compound 4, $^1$H NMR spectrum of 4 in benzene-$d_6$ shows that it is highly asymmetric in solution (Figure 5.12). The presence of two backbone-CH resonances ($\delta$ 4.96 and 5.13 ppm), as well as the complicated resonances for backbone --CH(CH$_3$)$_2$ and --CH(CH$_3$)$_2$ indicates that there may be fluxional processes occurring in solution. We think that in solution, rotation about the C-O bond of the -OCH$_2$O- part of the

**Scheme 5.7.** Synthesis of isocyanide copper(I) complexes of the linked ligand:
(a) [iPr$_2$NN-O-Cu$_2$](CN$i^t$Bu)$_2$, (b) [iPr$_2$NN-C$_2$-Cu$_2$](CNAr)$_2$.

a) [iPr$_2$NN-O-Cu$_2$](CN$i^t$Bu)$_2$

\[
[i\text{Pr}_2\text{NN-O}] + 2.2 \text{ equiv Cu$i^t$Bu} + 2.2 \text{ equiv NC} \xrightarrow{\text{THF}} \text{crystallized from ether} \]

b) [iPr$_2$NN-C$_2$-Cu$_2$](CNAr)$_2$

\[
[i\text{Pr}_2\text{NN-C$_2$}] + 2.2 \text{ equiv Cu$i^t$Bu} + 2.2 \text{ equiv NC} \xrightarrow{\text{THF}} \text{crystallized from fluorobenzene} \]

Ar = 2,6-dimethylphenyl
linker orients at one point the Cu-CNAr are parallel but pointing opposite (Scheme 5.8). At other time, the two Cu-CNAr bonds are parallel with the aryls rings of CNAr facing each other. This will also give the two backbone C-H resonances.

**Scheme 5.8.** Different orientations of the Cu-CNAr that result bond from the rotation about the C-O bond of the -OCH2O- part of the linker.
Figure 5.10. X-ray structure of \([\text{Pr}_2\text{NN-O-Cu}_2]\)(\text{CN}^t\text{Bu})_2 (3). Selected bond distances (Å) and angles (°): Cu1-N1 1.954(3), Cu1-N2 1.919(3), Cu1-C1 1.825(4), C1-N5 1.148(5), Cu1-N3 1.976(3), Cu1-N4 1.906(3), Cu2-C2 1.837(5), C2-N6 1.145(6), N1-Cu1-N2 98.31(12), N3-Cu2-N4 96.16(13), Cu1-C1-N5 172.0(4), Cu2-C2-N6 170.5(4). All hydrogen atoms are omitted for clarity.
Figure 5.11. X-ray structure of [\textsuperscript{1}Pr\textsubscript{2}NN-C\textsubscript{2}-Cu\textsubscript{2}](CNAr)\textsubscript{2} (4). Selected bond distances (Å) and angles (°): Cu-N1 1.9249(19), Cu-N2 1.9547(19), Cu-C 1.822(3), C-N3 1.152(3), N1-Cu1-N2 97.62(8), Cu-C-N3 175.1(2). All hydrogen atoms are omitted for clarity.
Figure 5.12. $^1$H NMR (400 MHz, benzene-$d_6$) spectrum of 4.

Figure 5.13. UV-Vis spectra of the reaction of $[^3]$Pr$_2$NN-C$_2$-Cu$_2$(CNAr)$_2$ (4) following addition of 20 equiv O$_2$ at –40 °C and warming up to 0 °C.
The potential of 4 in the activation of molecular O\textsubscript{2} is examined through low-temperature UV-Vis spectroscopy. Twenty equivalents of O\textsubscript{2} is added to an ether solution of 4 at -40 °C. There is no apparent change in the UV-Vis profile of 4 (Figure 5.13) even after the solution is warmed up to 0 °C, suggesting that there is no reaction between 4 and O\textsubscript{2}. This seems that the isocyanide binds slightly stronger, and molecular O\textsubscript{2} cannot compete for binding, hence no activation.

**5.2.d. Synthesis of 2-Picoline Copper(I) Complex of the H\textsubscript{2}[\textit{i}Pr\textsubscript{2}NN-C\textsubscript{2}] Ligand**

To access a copper(I) complex with a relatively labile ancillary ligand, we performed the reaction of the dilithium salt Li\textsubscript{2}[\textit{i}Pr\textsubscript{2}NN-C\textsubscript{2}] and 1.1 equiv. of [Cu(\mu-I)(2-pic)]\textsubscript{2} (2-pic = 2-picoline or 2-methylpyridine)\textsuperscript{48} in THF gave a dark yellow solution (Scheme 5.8). Bright yellow crystals of [\textit{i}Pr\textsubscript{2}NN-C\textsubscript{2}-Cu\textsubscript{2}](2-pic)\textsubscript{2} (5) were obtained from ether in 61 % yield by crystallization at -40 °C. The X-ray structure of 5 (Figure 5.14) is similar to those previously reported β-diketiminato copper(I) pyridine or derivatives [Me\textsubscript{2}NN]Cu(2,4-lutidine),\textsuperscript{48} [\textit{i}Pr\textsubscript{2}MeNN]Cu(2,4-lutidine)\textsuperscript{48} and [Cl\textsubscript{2}NN]Cu(pyridine).\textsuperscript{54} Compound 5 has trigonal planar geometry around Cu (Σ angles about Cu, 359.92 and 359.8°), with Cu-N\textsubscript{picoline} distances of 1.921(5) and 1.943(5) Å, similar to previously reported β-diketiminato copper(I) pyridine or derivatives. Although 5 is also in its ‘open’ form, its Cu-N\textsubscript{picoline} vectors are pointed almost parallel to one another giving a Cu···Cu distance of 7.254 Å. In comparison to the Cu-C\textsubscript{isocyanide} bond of 3 and 4, in which for both, these bonds are pointed opposite each other, with the two Cu(I) centers far apart from one another. This parallel arrangement may be of importance in activation of small molecules like O\textsubscript{2}.
Figure 5.14. X-ray structure of [Pr₂NN-C₂-Cu₂](2-pic)_2 (5). Selected bond distances (Å) and angles (°): Cu1-N1 1.014(5), Cu1-N2 1.969(4), Cu1-N5 1.921(5), Cu2-N3 1.931(4), Cu2-N4 1.966(5), Cu2-N6 1.943(5), N1-Cu1-N2 99.66(19), N3-Cu2-N4 97.4(2). All hydrogen atoms are omitted for clarity.
**Scheme 5.8.** Synthesis of the 2-picoline complex \([\text{^{i}Pr_2NN-C}_2\text{-Cu_2}](2\text{-pic})_2\) (5).

\[
\text{Li}_2[\text{^{i}Pr_2NN-C}_2] + 1.1 \text{ equiv } [\text{Cu(\mu-\text{l})(2-pic)}]_2 \xrightarrow{\text{THF}} \text{crystallized from ether}
\]

**Figure 5.15.** $^1$H NMR (400 MHz, acetonitrile-$d_3$) spectrum of 5.
Similar to those observed from $^1$H NMR spectrum of 4, $^1$H NMR spectrum of 5 in acetonitrile-$d_3$ shows that in solution (Figure 5.15), the fluxional rotation process operates, resulting in unsymmetric structures in solution (Scheme 5.8 – change CNAr to 2-picoline). The backbone-CH resonances appear at δ 4.70 and 4.72 ppm.

**5.2.e. Reactivity of $[^{iPr}_2NN-C_2$-$Cu_2](2pic)_2$ with Dioxygen, Di-tert-butylperoxide and Azides**

Reaction of 5 with 1 equivalent O$_2$ in ether, at -80 °C is monitored by low temperature UV-Vis spectroscopy (Figure 5.16). Interestingly, a new copper species formed with a λ$_{\text{max}}$ of 426 nm (estimated ε = 4030 M$^{-1}$s$^{-1}$). This spectral feature is similar to the one reported by Schoonheydt and Solomon for the O$_2$-activated Cu-ZSM-5 λ$_{\text{max}}$ = 441 nm, which suggests that the structure might be [Cu]$_2$(μ-O) (Figure 5.17).$^{25}$ Although this λ$_{\text{max}}$ is different from the reported by Limberg et al. λ$_{\text{max}}$ = 644 nm for the {[Xanthdim]Cu}(μ-O) and {[Ferneu]Cu}(μ-O) systems,$^{29,30}$ this is still different from the dicopper(II) bis(μ-O) reported for Cu(I) β-diketiminate systems.$^{26}$ This species is quite stable at -80 °C for up to approximately 2-3 h, although started to degrade at -40 °C. Attempts in isolating this species are still undergoing right now.

Reaction of 5 and 1 equiv of O$_2$ in ether at -80 °C resulted to greenish brown solution. Although a low-temperature EPR study was not done, EPR spectrum of the solution at RT showed a very broad peak (Figure 5.18). Simulation allows assignment of $g_{\text{iso}} = 2.11$, $A_{\text{iso}}$ ($^{63/65}$Cu) = 115 for 1 Cu and $A_{\text{iso}}$ ($^{14}$N) = 30 for the 2 N donors of the linked β-diketiminate ligand. This simulation assignment indicates that the only one Cu center is involved, which may mean that the two Cu centers may not be in cooperation. Resonance Raman spectrum of the reaction of 5 and 1 equiv of O$_2$ in ether at excitation wavelength = 458 nm shows three bands at
~400, ~533 and ~796 cm\(^{-1}\) (Figure 5.19). Further assignment is pending upon analysis of samples prepared with \(^{18}\)O\(_2\) by resonance Raman spectroscopy.

**Figure 5.16.** UV-Vis spectra of the reaction of \([\text{\textit{i}}\text{Pr}_2\text{NN-C}_2\text{-Cu}_2]\)\(_2\) (2-pic)_2 \((5) (0.265 \text{ mM})\) with 1 equiv O\(_2\) in ether at -80 °C.

\[
\begin{align*}
\text{trans-}\mu-1,2\text{-peroxo} & & \mu-\eta^1:\eta^2\text{-peroxo} & & \mu-\eta^1:\eta^2\text{-peroxo} & & \text{Schoonheydt} & & \text{Limberg} \\
\lambda_{\text{max}}, & & & & & & \text{2009} & & \text{2011, 2013} \\
\text{nm} & & & & & & 510, 600 & & 360, 520 & & 300, 400 & & 441 & & 644
\end{align*}
\]

**Figure 5.17.** Summary of the \(\lambda_{\text{max}}\) of known 2:1 Cu: O\(_2\) complexes and [Cu]\(_2\)(\(\mu\)-oxo) cores.
Figure 5.18. Isotopic X-band EPR spectrum of reaction of 5 and 1 equiv of O$_2$ (1.00 mM) in ether at RT: 8.906626 GHz, ModWidth = 0.5 mT, Power = 2.0000 mW, time constant = 0.03 s; Simulation (Gaussian lineshape with 33 G line broadening gives $g_{iso} = 2.11$, $A^{(63}\text{Cu}) = 115$ MHz, $A^{(14}\text{N}) = 30$ MHz for 2 equivalent N atoms (unresolved).

Figure 5.19. Resonance Raman spectrum of 5 (20 mM, black line) and its reaction (red line) with excess O$_2$ in ether: $\lambda_{ex} = 458$ nm, bands observed 400, 533, 796 cm$^{-1}$. 
Following the reported synthesis for \([\text{Cl}_2\text{NN}]\text{Cu}^{\text{II}}\cdot\text{O'Bu},^5\text{I}\) 5 equiv di-tert-butyl peroxide \((\text{tBuOO'tBu}, \text{DTBP})\) was added to a cold slurry of 5 in pentane. This bright yellow slurry rapidly changed to dark red brown solution. Dark red brown crystals of \([\text{iPr}_2\text{NN-C}_2][\text{Cu}^{\text{II}}\cdot\text{O'Bu}]_2\) (6) were recovered from the saturated pentane solution at -35 °C in 46 % yield. The X-ray structure of 6 shows a symmetric molecule (Figure 5.20), with the familiar trigonal planar arrangement around each Cu center and the linked ligand in its ‘open’ form. Compound 6 has a comparable Cu-O bond distance of 1.771(4) Å as compared to 1.785(2) Å for \([\text{Cl}_2\text{NN}]\text{Cu}^{\text{II}}\cdot\text{O'Bu},^5\text{I}\)

Compound 6 may open a new route for generating other copper(II) complexes of the linked ligand. Room-temperature isotropic EPR spectrum of 6 in toluene showed a very broad peak (Figure 5.21). Simulation allows assignment of $g_{\text{iso}} = 2.101$, $A_{\text{iso}}\left(^{63/65}\text{Cu}\right) = 95$ and $A_{\text{iso}}\left(^{14}\text{N}\right) = 30$ for the 2 N donors of the linked β-diketiminate ligand. The $g_{\text{iso}}$ for 6 is rather smaller than the reported $g_{\text{iso}} (= 2.11(1))$ for \([\text{Cl}_2\text{NN}]\text{Cu}^{\text{II}}\cdot\text{O'Bu},^5\text{I}\) but $A_{\text{iso}}\left(^{63/65}\text{Cu}\right)$ for 6 is very similar, which is consistent with having a trigonal planar geometry geometry around Cu.

Reaction of compound 6 with an equivalent of H$_2$O in ether/THF at -80 °C showed a growth of new Cu species (Figure 5.21). The peak associated for 6 ($\lambda_{\text{max}} = 470$ nm, estimated $\varepsilon = 4884$ M$^{-1}$s$^{-1}$) disappeared and a new peak formed around 421 nm, which is very similar to that peak associated with \([\text{Cu}_2]\left(\mu-\text{O}\right)\) core when 5 is reacted with O$_2$. The baseline for the spectrum of the reaction of 5 and H$_2$O is higher than that of the copper complex, probably because there was a change in solvent. Nonetheless, we envisioned that this reaction proceeds via acid-base ligand exchange of –O'Bu and H$_2$O (Scheme 5.9).
Figure 5.20. X-ray structure of $[^{1}Pr_{2}NN\cdot C_{2}][Cu^{II}\cdot O^{'Bu}]_{2}$ (6). Selected bond distances (Å) and angles (°): Cu-N1 1.881(4), Cu-N2 1.882(4), Cu-O 1.771(4), N1-Cu1-N2 94.72(18), N1-Cu-O 132.7(2); N2-Cu-O 132.0(0). All hydrogen atoms are omitted for clarity.
Figure 5.21. Isotopic X-band EPR spectrum of reaction of $[\text{iPr}_2\text{NN-C}_2][\text{Cu}^{II}\text{-O}^{\text{Bu}}]_2$ (6) (1.00 mM) in toluene at RT: 8.898939 GHz, ModWidth = 0.1 mT, Power = 0.99800 mW, time constant = 0.03 s; Simulation (Gaussian lineshape with 42 G line broadening gives $g_{\text{iso}} = 2.101$, $A^{(63}\text{Cu}) = 95$ MHz, $A^{(14}\text{N}) = 30$ MHz for 2 equivalent N atoms

Figure 5.22. UV-Vis spectra of the reaction of $[\text{iPr}_2\text{NN-C}_2][\text{Cu}^{II}\text{-O}^{\text{Bu}}]_2$ (6) and 1 equivalent H$_2$O at –80 °C in ether/THF.
In line with these oxo-transfer reactions, we also explored on the reaction of \([^{1} \text{Pr}_2 \text{NN-C}_2 \text{Cu}_2](2\text{-pic})_2 \text{(5)}\) with some organic azides we have used in our previous studies. In general, when excess arylazides \(N_3\text{Ph}\) (phenyl), \(N_3\text{Mes}\) (mesityl), \(N_3\text{Ts}\) (tosyl) were reacted with 5 in THF or toluene or chlorobenzene, instead of the familiar purple or dark blue colored solution of the \{[\text{Cl}_2\text{NN}]\text{Cu}(\mu-\text{NAr})\} (see Chapter 3), a brownish/orangish solution was observed. We did not get any suitable crystals from any of these reaction. When excess \(N_3\text{Ar}^{\text{F6}}\) is reacted with 5 in toluene at RT, the yellowish solution changed to an orange brown solution. Dark orange crystals were recovered from a saturated ether solution. Though quality is still low, Xray studies show that it is an Cu-azide adduct,\([^{1} \text{Pr}_2 \text{NN-C}_2-\text{Cu}_2](\text{N}=\text{N}=\text{NAr}^{\text{F6}})_2\) instead of the dicopper nitrene (Figure 5.23). Activation of the azide through the copper center may have been so slow, probably because the larger isopropyl groups on the ligand.

**Scheme 5.9.** Proposed reaction pathway for the formation of \([\text{Cu}_2](\mu-\text{O})\) from the reaction of \([^{1} \text{Pr}_2 \text{NN-C}_2][\text{Cu}^{\text{II}}\text{-O}^{\text{Bu}}]_2 \text{(6)}\) and \(\text{H}_2\text{O}\).
Figure 5.23. X-ray structure of \([\text{[Pr}_2\text{NN-C}_2\text{-Cu}_2]\text{(N=N=NAr}^{F_6})_2\) (7). Selected bond distances (Å) and angles (°): Cu1-Cu2 2.625(3), Cu1-N5 2.001(8), Cu1-N2 2.128(9), Cu1-N8 1.947(9), Cu1-N3 2.102(8), Cu2-N10 1.917(8), Cu2-N4 1.915(8), N5-N6 1.298(11), N6-N7 1.300(11), N8-N9 2.625(3), N9-N10 1.335(11), N5-N6-N7 115.8(8), N8-N9-N10 114.0(8), N5-Cu1-N8 132.5(4), N2-Cu1-N5 112.9(3), N3-Cu1-N2 121.8(3), N3-Cu1-N8 133.9(3), N4-Cu2-N10 163.2(4). All hydrogen atoms are omitted for clarity.
Conclusion

Linked β-diketiminate ligands were prepared via Dean-Stark condensation or Meerwein reagent in moderate yields. With the appropriate bulkiness on the aniline, as well as strong additional σ-donors, Cu(I) complexes of the linked ligands \([i^3\text{Pr}_2\text{NN}-\text{O-Cu}_2](\text{CN}^\text{tBu})_2\) (3), \([i^3\text{Pr}_2\text{NN}-\text{C}_2-\text{Cu}_2](\text{CN}^{2,6-\text{Me}_2\text{Ph}})_2\) (4) and \([i^3\text{Pr}_2\text{NN}-\text{C}_2-\text{Cu}_2](2\text{-pic})_2\) (5) were synthesized. Because of the stronger π-backbonding possibly experiencing by the isocyanide complexes than the 2-picoline complex, aside from having the two centers almost parallel from each other for the case of 5, there was no reaction between 4 and O₂. Reaction of 5 and O₂ resulted to a new copper species, whose absorption wavelength peak is similar to the one reported by Schoonheydt et al. for the O₂-activated Cu-ZSM-5\(^{25}\) as the monooxo-bridged dicopper \([\text{Cu}_2(\text{µ-O})]\). Interestingly, reaction of \([i^3\text{Pr}_2\text{NN}-\text{C}_2][\text{Cu}^{\text{II}}-\text{O}'\text{Bu}]_2\) (6), prepared from the reaction of 5 and \(i^3\text{BuOO}'\text{Bu}\), with H₂O gave a new species whose \(\lambda_{\text{max}}\) is similar to that of the species derived from 5 and O₂.

We believe that these linked Cu(I/II) complexes opens many possibilities on exploring reactions that may not be accessible with the mononuclear Cu(I/II) complexes. Synthesis and characterization of the intermediate \([\text{Cu}_2]_2(\text{µ-O})\) may still entail a lot more low-temperature experimentation, the promise that it brings on C-H functionalization is still great. It is also possible that the use of diisopropyl groups on the anilines of the ligands may have been so bulky for easy access to the copper centers when the activating oxygen or other small molecule, as was seen from the reaction with arylazides. Mono-substituted anilines may be used instead of the disubstituted ones, like ortho-tert-butylaniline, ortho-phenylaniline. To further prevent the twisting of the linker anilines, 2,2’-diaminobiphenyls may used which may still provide the necessary bulkiness, but will prevent the unnecessary twisting of the linker giving rise to a wider range of conformations in solution.
Experimental Details

5.4.a. General Procedures and Instrumentation

Same as in previous chapters – see section 2.4.a.

5.4.b. Synthesis of the Linked β-Diketiminato Ligands

General Procedure for the Synthesis of Half Ligands. The half ligands were synthesized following the revised method in literature. With a Dean-Stark apparatus, 1 equiv of aniline was refluxed with catalytic amount of \( p \)-toluenesulfonic acid dihydrate (\( p \)-TsOH\( \cdot \)H\(_2\)O, 5 mol% with respect to aniline) in neat (20 equiv) 2,4-pentanediene for 6-10 h. When cooled, the solvent was dried in vacuo until a very viscous residue was obtained. For the cases of [Me\(_2\)NN]-half and [iPr\(_2\)NN]-half, these brownish viscous oils were used as is, without further purification. For [Cl\(_2\)NN]-half, this residue was taken in ethanol and allowed to recrystallize overnight resulting to light brownish solids. Typical scale and yield for the synthesis, along with \(^1\)H NMR resonances for each half ligand are summarized below:

[Me\(_2\)NN]-half. 10 mL (0.081 mol) 2,6-dimethylaniline, 167 mL (1.6 mol) 2,4-pentanediene, 0.85 g (4.5 mmol) \( p \)-TsOH\( \cdot \)2H\(_2\)O, typically taken as 100 % yield after rotary evaporation; \(^1\)H NMR (400 MHz, chloroform-\( d_1 \)): \(^1\)H NMR (400 MHz, CHCl\(_3\)-\( d_1 \)): \( \delta \) 11.91 (s, 1, enamine \(-\text{NH} \)), 7.08 (m, 3, Ar-\( H \)), 5.18 (s, 1, backbone –CH\(_2\)), 2.17 (s, 6, Ar-o-\( CH_3 \)), 2.08 (s, 3, backbone –CH\(_3\)), 1.60 (s, 3, backbone –CH\(_3\)).

[iPr\(_2\)NN]-half. 16 mL (0.084 mol) 2,6-diisopropylaniline, 175 mL (1.71 mol) 2,4-pentanediene, 0.84 g (4.2 mmol) \( p \)-TsOH\( \cdot \)H\(_2\)O, typically taken as 100 % yield after rotary evaporation; \(^1\)H NMR (400 MHz, chloroform-\( d_1 \)): \( \delta \) 12.04 (s, 1, enamine \(-\text{NH} \)), 7.26 (d, 2, Ar-\( m-\)
H), 7.14 (t, 1, Ar-p-H), 5.18 (s, 1, backbone –CH), 3.00 (m, 2, Ar-o-CH(CH₃)₂), 2.09 (s, 3, backbone –CH₃), 1.60 (s, 3, backbone –CH₃), 1.18 (d, 6, Ar-o-CH(CH₃)₂), 1.12 (d, 6, Ar-o-CH(CH₃)₂).

[Cl₂NN]-half. 10 g (0.62 mol) 2,6-dichloroaniline, 130 mL (1.24 mol) 2,4-pentanedione, 0.6 g (3.15 mmol) p-TsOH•H₂O, after recrystallization light brownish crystals/powder 65 % yield (15.14 g); ¹H NMR (400 MHz, chloroform-d₁): δ 12.03 (s, 1, enamine -NH), 7.36 (d, 2, Ar-m-H), 7.16 (t, 1, Ar-p-H), 5.29 (s, 1, backbone –CH), 2.11 (s, 3, backbone –CH₃), 1.72 (s, 3, backbone –CH₃).

Synthesis of the Linker Aniline. The C₂-linker (2,2’-ethylenedianiline) was purchased from TCI America and was used as is without further purification. The O-linker was prepared following a revised literature procedure from a two-step synthesis involving a) S_N² reaction of 2-nitrophenol and diiodomethane⁵⁵ giving bis(2-nitrophenoxy)methane and b) reduction of nitro group to amino group to afford the O-linker 2,2’-(methyleneoxy)bis(phenylamine).⁵⁶

A mixture of 2 equiv 2-nitrophenol (5.044 g, 0.036 mol), 2 equiv K₂CO₃ (4.562 g, 0.033 mol) and 1 equiv CH₂I₂ (1.4 mL, 0.017 mol) in DMSO (25 mL) was refluxed under air for overnight, resulting to a very dark orange mixture. When cooled, the mixture was dumped into icy H₂O (300 mL) and stirred for 30 min to several hours. The dirty white/light brown residue was filtered, washed with cold H₂O (100 mL), cold ethanol (100 mL) and then cold ether (100 mL). Upon drying in vacuo, the light yellow powder was gathered in 88 % yield (4.45 g, 0.015 mol) as bis(2-nitrophenoxy)methane. ¹H NMR (400 MHz, chloroform-d₁): δ 7.83 (d, 2, Ar-H ortho to the nitro group), 7.58 (t, 2, Ar-H meta to nitro group), 7.49 (d, 2, Ar-H ortho to the ether group), 7.16 (t, 2, Ar-H meta to ether group), 5.91 (s, 2, methylene -CH₂).
Under nitrogen, into a mixture of bis(2-nitrophenoxy)methane (4.068 g, 0.014 mol), dry Pd/C (10% w/w) (0.086 g) in ethanol (100 mL) was added 7 equiv H$_2$NNH$_2$•H$_2$O (65%) (7.00 mL, 0.098 mol) using a syringe. The mixture was stirred at RT for ~15 min, then refluxed under N$_2$ for 5 h to overnight. When cooled, the mixture was filtered through Celite, the filtrate was collected and dried under vacuo giving dirty white powder which is taken as the O-linker 2,2’-(methylenedioxy)bis(phenylamine) in 95% yield (3.07 g). $^1$H NMR (400 MHz, chloroform-$d_1$): δ 7.09 (d, 2, Ar-H ortho to the amino group), 6.58 (t, 2, Ar-H meta to amino group), 6.71 (t overlapped with d, 4, Ar-H ortho and meta to the ether group), 5.91 (s, 2, methylene -CH$_2$), 3.81 (br s, 4, -NH$_2$).

There are two ways used to tether the half ligands and the linker anilines: a) by Dean-Stark condensation and b) by Meerwein reaction.$^{50}$ From experience, Dean-Stark condensation worked with the synthesis of H$_2$[iPr$_2$NN-C$_2$], while H$_2$[iPr$_2$NN-O], H$_2$[Me$_2$NN-C$_2$] and H$_2$[Cl$_2$NN-C$_2$] were prepared following the Meerwein reaction.

**Synthesis of H$_2$[iPr$_2$NN-C$_2$].** Using a Dean-Stark apparatus, the mixture of 2 equiv [iPr$_2$NN]-half (22.0 g, 0.085 mol), 1 equiv C$_2$ linker aniline (9.00 g, 0.042 mol), 2 equiv p-TsOH•H$_2$O (16.17 g, 0.085 mol) in toluene (100 mL) was refluxed for 48 h. The solids formed upon cooling were collected and taken up in equal parts saturated NaHCO$_3$(aq): CH$_2$Cl$_2$ (600 mL) and stirred for 3 h. The CH$_2$Cl$_2$ layer was collected, dried with anhydrous MgSO$_4$ and concentrated to ~150 mL in vacuo. The solution was layered with ethanol (100 mL) and placed at -18°C overnight to afford light yellow powder. This product was collected, and a second crop was gathered from re-freezing the mother liquor if necessary. The yield was 35% (11 g). $^1$H NMR (400 MHz, chloroform-$d_1$): δ 12.29 (s, 2, enamine –N-H-N), 7.07 (m, 10, Ar-H of N-C$_2$-anilino substituent overlapped with Ar-m-H of N-$^1$Pr$_2$-anilino substituent), 6.93 (d, 2, Ar-m-H of N-C$_2$-anilino substituent).
substituent), 6.81 (t, 2, Ar-<i>p</i>-H of <i>N</i>-<sup>1</sup>P<sub>2</sub>-anilino substituent), 4.88 (s, 1, backbone –<i>CH</i>), 3.02 (hept, 4, Ar-<i)o</i>-<i>CH</i>(<i>CH</i><sub>3</sub>)<sub>2</sub>), 2.71 (s, 4, -<i>CH</i><sub>2</sub><i>CH</i>–2-), 1.82 (s, 6, backbone –<i>CH</i><sub>3</sub>), 1.68 (s, 6, backbone –<i>CH</i><sub>3</sub>), 1.14 (d, 12, Ar-<i)o</i>-<i>CH</i>(<i>CH</i><sub>3</sub>)<sub>2</sub>), 0.95 (d, 12, Ar-<i)o</i>-<i>CH</i>(<i>CH</i><sub>3</sub>)<sub>2</sub>).

**General Procedure for the Meerwein Reaction.** The Meerwein reagent [Et<sub>3</sub>O][BF<sub>4</sub>] was purchased from Sigma Aldrich as a solution in CH<sub>2</sub>Cl<sub>2</sub> or prepared as crystalline white or sticky residue following literature procedure. This solid sample of the Meerwein reagent was kept at -35 °C until needed. In the glovebox, one equiv of half ligand in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was mixed with 1.2 equiv of [Et<sub>3</sub>O][BF<sub>4</sub>] in CH<sub>2</sub>Cl<sub>2</sub> (5 mL), and stirred at RT for 24 h. The next day, 1.2 equiv of NEt<sub>3</sub> was added and the mixture was stirred at RT for additional 2 h. Into this mixture, 0.5 equiv of the linker aniline and equivolume of CH<sub>2</sub>Cl<sub>2</sub>/NEt<sub>3</sub> were added. The resulting mixture was stirred at RT between 3-5 d. The next steps of the workup may be done under air. The mixture was dried in vacuo, the residue was taken up in minimum volume of CH<sub>2</sub>Cl<sub>2</sub>/methanol solution or just methanol, and placed at -18 °C for at least 24 h. Typical scale and yields gathered for the synthesis, along with <sup>1</sup>H NMR (400 MHz) resonances for the linked ligands prepared through this Meerwein reaction are summarized below:

**H<sub>2</sub>[<sup>1</sup>P<sub>2</sub>NN-O].** 2.159 g (8.32 mmol) [<sup>1</sup>P<sub>2</sub>NN]-half, 2.033 g (10.6 mmol) Meerwein reagent, 0.958 (4.16 mmol) O-linker; dark brown solids 20 % (0.600 g); <sup>1</sup>H NMR (400 MHz, chloroform-<i>d</i><sub>1</sub>): δ 12.44 (s, 2, enamine –N–<i>H</i>–N), 7.09 (s, 6, Ar-<i>H</i> of <i>N</i>-<sup>1</sup>P<sub>2</sub>-anilino substituent), 6.96 (two overlapped d, 4, Ar-<i)o</i>-<i>H</i> of N-O-anilino substituent), 6.83 (t, 2, Ar-<i>m</i>-<i>H</i> of N-O-anilino substituent), 6.52 (t, 2, Ar-<i>m</i>-<i>H</i> of N-O-anilino substituent), 5.48 (s, 2, -OCH<sub>2</sub>O-) 4.87 (s, 2, backbone –<i>CH</i>), 2.98 (m, 4, Ar-<i)o</i>-<i>CH</i>(<i>CH</i><sub>3</sub>)<sub>2</sub>), 1.97 (s, 6, backbone –<i>CH</i><sub>3</sub>), 1.68 (s, 6, backbone –CH<sub>3</sub>), 1.16 (d, 12, Ar-<i)o</i>-<i>CH</i>(<i>CH</i><sub>3</sub>)<sub>2</sub>), 1.04 (d, 12, Ar-<i)o</i>-<i>CH</i>(<i>CH</i><sub>3</sub>)<sub>2</sub>).
\textbf{H}_2[\textbf{Me}_2\textbf{NN-C}_2]. \ 2.069 \text{ g (10.18 mmol) [Me}_2\text{NN]-half, 2.830 \text{ g (15.0 mmol) Meerwein reagent, 1.179 \text{ g (5.12 mmol) O-linker; light yellow brown solids 50% (1.525 g); } ^1\text{H NMR (400 MHz, chloroform-d}_1\text{): } \delta 12.58 \text{ (s, 2, enamine –N-H-N), 7.02 \text{ (d, 6, Ar-H of N-Me}_2\text{-anilino substituent), 6.8 \text{ (two overlapped d, 4, Ar-o-H of N-O-anilino substituent), 6.46 \text{ (t, 2, Ar-m-H of N-O-anilino substituent), 6.46 \text{ (t, 2, Ar-m-H of N-O-anilino substituent), 5.49 \text{ (s, 2, -OCH}_2\text{O-), 4.87 \text{ (s, 2, backbone –CH), 2.10 \text{ (s, 12, Ar-o-CH}_3\text{), 2.04 \text{ (s, 6, backbone –CH}_3\text{), 1.66 \text{ (s, 6, backbone –CH}_3\text{), 1.16 \text{ (d, 12, Ar-o-CH(CH}_3\text{)}_2\text{), 1.04 \text{ (d, 12, Ar-o-CH(CH}_3\text{)}_2\text{).}}]}

\textbf{H}_2[\textbf{Cl}_2\text{NN-C}_2]. \ 2.044 \text{ g (8.37 mmol) [Cl}_2\text{NN]-half, 1.934 \text{ g (10.18 mmol) Meerwein reagent, 0.967 \text{ (4.56 mmol) C}_2\text{-linker; bright yellow crystals 12% (0.309 g); } ^1\text{H NMR (400 MHz, chloroform-d}_1\text{): } \delta 12.13 \text{ (s, 2, enamine –N-H-N), 7.21 \text{ (d, 4, Ar-m-H of N-C}_2\text{-anilino substituent), 7.09 \text{ (m, 6, Ar-H of N-iPr}_2\text{-anilino substituent), 7.00 \text{ (t, 2, Ar-m-H of N-C}_2\text{-anilino substituent), 6.81 \text{ (t, 2, Ar-m-H of N-C}_2\text{-anilino substituent), 4.91 \text{ (s, 2, backbone –CH), 2.86 \text{ (s, 4, -CH}_2\text{CH}_2\text{)}, 1.87 \text{ (s, 6, backbone –CH}_3\text{), 1.77 \text{ (s, 6, backbone –CH}_3\text{).}}]

\textit{5.4.c. Preparation of Copper Complexes (1-7)}

\kappa^4[-\textbf{Cl}_2\text{NN-C}_2]\textbf{Cu(II) (1).} \ A cold solution of \textbf{H}_2[\textbf{Me}_2\text{NN-C}_2] \ (0.094 \text{ g, 0.140 mmol) in THF (10 mL) was mixed with cold solution of Cu\textsuperscript{II}O\textsuperscript{Bu}\textsuperscript{58} \ (0.041 \text{ g, 0.300 mmol) in THF (10 mL). After stirring for 5-10 min, benzene (1.5 mL) was added and the solution was stirred for 3 h, during which a change of color from yellow solution to greenish brown mixture within just minutes. The brown residue was filtered off through Celite, and the greenish filtrate was dried in \textit{vacuo}. The residue was taken in ether (3 mL) and passed through Celite stick and placed at -35 \textdegree C. Green crystals were collected in 20% yield (20 mg) that were suitable for X-ray diffraction analysis.
κ⁴-[Me₂NN-O]Cu(II) (2). Lithium salt of H₂[Me₂NN-O] was prepared by treating the cold solution of H₂[Me₂NN-O] (0.241 g, 0.401 mmol) in THF (10 mL) with nBuLi (1.6 M in hexanes, 0.60 mL, 0.944 mmol) using a syringe. The mixture was stirred for 30 min, then anhydrous CuCl₂ (0.124 g, 0.858 mmol) was added as solids. The green colored mixture was stirred overnight. The solvent was removed in vacuo, and the residue was taken in ether (15 mL). The ether mixture was passed through Celite, concentrated to about 3 mL and placed at -35 °C. Blue green crystals that were suitable for X-ray crystallography were collected in 88 % (0.235 g). Alternate route for synthesis is just by adding 1.2 equiv of CuCl₂.

[\textit{i}Pr₂NN-O-Cu₂](CN^tBu)₂ (3). Into a solution of H₂[\textit{i}Pr₂NN-O] (0.090 g, 0.130 mmol) in THF (10 mL) was added a solution of Cu\textit{i}O^tBu⁵⁸ (0.041 g, 0.300 mmol) in THF (10 mL). After stirring at RT for 5-10 min, the dark brown solution was placed in freezer for ~ 3 min, then tert-butylisocyanide (CN^tBu, 34 µL, 0.300 mmol) in THF (3 mL). The mixture was stirred at RT for 1 h and dried under vacuo. This residue was taken in fluorobenzene (3 mL), filtered through Celite stick and layered with pentane (1 mL). The clear light amber colored solution was cooled at -35 °C, from which light yellow brown crystals of [\textit{i}Pr₂NN-C₂-O](CN^tBu)₂ (3) that suitable for X-ray diffraction was collected in 15% yield (20 mg).

[\textit{i}Pr₂NN-\textit{C₂}-Cu₂](CNAr)₂ (4). A solution of H₂[\textit{i}Pr₂NN-C₂] (0.076 g, 0.109 mmol) in THF (10 mL) was mixed with a solution of Cu\textit{i}O^tBu⁵⁸ (0.032 g, 0.234 mmol) in THF (10 mL), and stirred for 5-10 min. The dark brown solution was placed in freezer for ~ 3 min; afterwards, into this cold solution, 2,6-dimethylphenylisocyanide (CNAr, 0.036 g, 0.275 mmol) was added. The mixture was stirred at RT for 1 h, then dried in vacuo. The residue was taken up in fluorobenzene (3 mL), filtered through Celite stick and places in freezer at -35 °C. Very light
yellow crystals of $[^1\text{Pr}_2\text{NN}-\text{C}_2-\text{Cu}_2](\text{CNAr})_2$ (4) were gathered at 53 % yield (62 mg) that suitable for X-ray diffraction analysis.

$[^1\text{Pr}_2\text{NN}-\text{C}_2-\text{Cu}_2](2\text{pic})_2$ (5). Lithium salt of $\text{H}_2[^1\text{Pr}_2\text{NN-C}_2]$ was first prepared by mixing a cold solution of $\text{H}_2[^1\text{Pr}_2\text{NN-C}_2]$ in pentane and 2.2 equiv of $n\text{BuLi}$ in hexanes, the solution was stirred overnight. Afterwards, the solution was concentrated in vacuo for about ½ its original volume and equivolume of ether was added. This precipitated out $\text{Li}_2[^1\text{Pr}_2\text{NN-C}_2]$, which was collected, dried in vacuo and use without additional purification. The CuI-2-picoline complex $[\text{Cu}(\mu-\text{I})(2-\text{pic})]_2$ was prepared by stirring a mixture of 2.2 equiv CuI in THF and 2.2 equiv 2-picoline (equivalence is calculated based on the amount of $\text{Li}_2[^1\text{Pr}_2\text{NN-C}_2]$ to be used = 1.1 equiv $[\text{Cu}(\mu-\text{I})(2-\text{pic})]_2$) overnight at RT, which changed to whitish slurry from yellowish solution. This slurry was used as prepared without isolation.

Into the pre-prepared $[\text{Cu}(\mu-\text{I})(2-\text{pic})]_2$ (CuI: 0.881 g, 4.62 mmol + 2-pic: 0.460 mL, 4.65 mmol) slurry in (THF) 15 mL, solid $\text{Li}_2[^1\text{Pr}_2\text{NN-C}_2]$ (1.45 g, 2.1 mmol) was added, and the mixture was stirred at RT for 3 h. This turned to yellowish brown solution immediately. The solution was dried in vacuo, the residue that resulted was taken up in ether (10 mL × 3), and passed through Celite. The ether solution was concentrated in vacuo to about 5-10 mL, placed at -35 °C. Bright yellow crystals of $[^1\text{Pr}_2\text{NN-C}_2-\text{Cu}_2](2\text{pic})_2$ (5) were gathered in 63 % yield (1.3 g) that suitable for X-ray diffraction analysis.

$[^1\text{Pr}_2\text{NN-C}_2][\text{Cu}^{\text{II}}-\text{O}^\text{tBu}]_2$ (6). Into a cold slurry of $[^1\text{Pr}_2\text{NN-C}_2-\text{Cu}_2](2\text{pic})_2$ (5) (0.247 g, 0.228 mmol) in pentane (10 mL) was added di-tert-butyl peroxide (DTBP, $^\text{'BuOO}^\text{tBu}$, 0.200 mL, 1.09 mmol) which turned immediately to dark reddish brown. The mixture was shaken vigorously for ~ 10 min, then filtered through Celite stick. The filtrate was concentrated to about
3 mL and placed at -35 °C immediately. Reddish brown crystals of [iPr₂NN-C₂][Cu-O¹Bu]₂ (6) were afforded at 46 % yield (0.108 g) that were suitable for X-ray analysis.

\[ [iPr₂NN-C₂-Cu₂](N=N=NArF₆)₂ \] (7). Cold solution of \([iPr₂NN-C₂-Cu₂](2pic)₂ \) (5) (0.167 g, 0.166 mmol) in chlorobenzene (5 mL) was mixed with cold solution of 3,5-bis(trifluoromethyl)phenylazide (N₃ArF₆, 0.085 g, 0.333 mmol) in chlorobenzene (2 mL), and the mixture was stirred for 3 h (-35 °C to RT). The solution was dried in vacuo and the residue was taken up in pentane (10-15 mL). The pentane solution collected after filtration through Celite was concentrated in vacuo and placed at -35 °C. Brownish crystals of \([iPr₂NN-C₂-Cu₂](N=N=NArF₆)₂ \) (7) were collected that are suitable for X-ray analysis in 10 % (20 mg) yield.

After letting an acetonitrile-\(d₃\) solution of 5 stand for few days, yellow crystals were afforded and X-ray diffraction analysis indicated that it is \([iPr₂NN-C₂-Cu₂](NCMe)₂ \) (8) (Figure 5.24). Although this compound crystallizes with two molecules of 8, but because of the presence of inversion center in the molecule only half of each molecule is contained in an asymmetric unit. Only one molecule is shown in Figure 5.24.

5.4.d. Low Temperature UV-Vis Experiments

Freshly crystallized 4, 5, 6 were dissolved in appropriate solvent and stored at –35 °C until further needed.

**Reaction of 4 with Dioxygen.** A solution of \([iPr₂NN-C₂-Cu₂](CNAr) \) (4) (0.014 g, 0.013 mmol, 2.59 mM) was dissolved in toluene (10 mL). An aliquot (3.00 mL, 7.77 µmol) was taken and placed in a Schlenk UV-Vis cuvette and thermostatted at –40 °C in a UV-Vis spectrophotometer. Twenty equivalents O₂ (3.8 mL) was added using a syringe slowly and the spectrum was scanned. The instrument was warmed up to 0 °C, and another scan was done.
**Reaction of 5 with Dioxygen.** A stock solution of \([\text{\textsuperscript{1}Pr}_2\text{NN-C}_2-\text{Cu}_2]_2\) (5) (0.025 g, 0.025 mmol, 2.65 mM) was prepared in ether (10 mL). From this stock solution, an aliquot (1 mL) was taken to make a more dilute solution (conc1, 0.265 mM). Three millimeters of this conc1 (dilute) solution of 5 (3.00 mL, 0.795 mmol) was taken and placed in a Schlenk UV-Vis cuvette and thermostatted at –80 °C in a UV-Vis spectrophotometer. One equivalent O₂ (19 mL) was added using a syringe slowly and the spectrum was scanned.

**Reaction of 6 with H₂O.** A stock solution of \([\text{\textsuperscript{1}Pr}_2\text{NN-C}_2][\text{Cu}^{II}-\text{O}^\text{Bu}_2]_2\) (6) (0.022 g, 0.021 mmol, 2.11 mM) was prepared in ether (10 mL). From this stock solution, a new more dilute solution was prepared from an aliquot (1 mL) of the stock solution and further dilution to 10 mL with ether, making conc2 (0.0211 mM). An aliquot of this conc2 solution of 6 (3.00 mL, 0.063 mmol) was taken and placed in a Schlenk UV-Vis cuvette and thermostatted at –80 °C in a UV-Vis spectrophotometer. On the other hand, anhydrous THF (10 mL) was pumped out from the box in a vial stoppered with a septum, and into this, 0.02 mL deionized H₂O (from a sample that was sparged with N₂ for at least 30 min) using a syringe, and shaken vigorously. An aliquot of the H₂O/THF solution (0.60 mL, 1 equiv) was added into the UV-Vis sample using a syringe slowly and the spectrum was scanned.
Figure 5.23. X-ray structure of \( [\text{Pr}_2\text{NN-C}_2\text{-Cu}_2]\)(\text{NCMe})_2 \) (8). Selected bond distances (Å) and angles (°): Cu-N1 1.987(3), Cu-N2 1.890(3), Cu-N3 1.870(4), N3-C 1.138(5), N1-Cu1-N2 98.55(13), Cu-N3-C 159.3(4). All hydrogen atoms are omitted for clarity.
5.4.e. EPR Spectroscopy

The EPR measurements were performed in air-tight quartz tubes. Solution EPR spectra were recorded on a JEOL continuous wave spectrometer JES-FA200 equipped with an X-band Gunn oscillator bridge and a cylindrical mode cavity. Spectral simulation was performed using the program QCMP 136 by Prof. Dr. Frank Neese from the Quantum Chemistry Program Exchange as used by Neese et al. in J. Am. Chem. Soc. 1996, 118, 8692-8699. The fittings were performed by the “chi by eye” approach. Collinear g and A tensors were used.

5.4.f. Resonance Raman Spectroscopy

A stock solution of 5 was prepared by dissolving [(^3)Pr2NN-C2-Cu2](2pic)2 (5) (0.216 g, 0.215 mmol, 0.0216 mM) in ether (10 mL). A sample for rRaman spectroscopy was prepared by taking an aliquot (0.5 mL, 0.011 mmol) in an NMR tube and cooled to – 78 °C (dry ice/acetone). While under flowing N2, 20 equiv O2 (5.28 mL) was added using a syringe. After several seconds, the sample was evacuated and sealed. The sample was kept under liquid N2 temperature and sent to Stanford University for the instrumentation and analysis.
5.4.g. Crystallographic Details

Single crystals of \(\kappa^4-[\text{Cl}_2\text{NN-C}_2]\text{Cu(II)}\) (1 • ether), \(\kappa^d-[\text{Me}_2\text{NN-O}]\text{Cu(II)}\) (2), \([\text{Pr}_2\text{NN-O-Cu}_2](\text{CN}^\text{Bu})_2\) (3 • pentane), \([\text{Pr}_2\text{NN-C}_2-\text{Cu}_2](\text{CNAr})_2\) (½ 4 • 3 fluorobenzene), \([\text{Pr}_2\text{NN-C}_2-\text{Cu}_2](2\text{pic})_2\) (5 • ether), \([\text{Pr}_2\text{NN-C}_2][\text{Cu}^\text{II}-\text{O}^\text{Bu}]_2\) (½ 6 • 2 DTBP), \([\text{Pr}_2\text{NN-C}_2-\text{Cu}_2](\text{N=N=NArF}^\text{6})_2\) (7 • toluene), \([\text{Pr}_2\text{NN-C}_2-\text{Cu}_2](\text{NCMe})_2\) (8 • NCMe) were mounted under mineral oil or perfluoroalkyl ether oil on glass fibers and immediately placed in a cold nitrogen stream at 100(2) K on a Bruker SMART CCD system. Hemispheres or full spheres of data were collected, as necessary (0.3° or 0.5° ω-scans; 2θmax = 56°; monochromatic Mo Ka radiation, \(\lambda = 0.7107 \text{ Å}\)) and integrated with Bruker SAINT program. Structure solutions were performed using the SHELXTL/PC suite\(^a\) and XSEED\(^b\). Intensities were corrected for Lorentz and polarization effects and an empirical absorption correction was applied using Blessing’s method as incorporated into the program SADABS.\(^c\) Non-hydrogen atoms were refined with anisotropic thermal parameters and hydrogen atoms were included in idealized positions.

References for X-ray structure refinement details

(a) SHELXTL-PC, Vers. 5.10; 1998, Bruker-Analytical X-ray Services, Madison, WI; G. M. Sheldrick, SHELX-97, Universität Göttingen, Göttingen, Germany.

(b) L. Barbour, XSEED, 1999.

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Continuation of Table 5.2. Crystallographic data for compounds 1-8.

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