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Copper–Nitrene Complexes in Catalytic C–H Amination**

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The direct catalytic transformation of typically inert carbon–hydrogen bonds into carbon–oxygen, carbon–nitrogen, and carbon–carbon bonds represents a significant challenge in organic synthesis and the chemical industry.[1] Ideally, such reactions would not require the presence of a functional group that is discarded later in the course of the chemical transformation, but would proceed with atom and energy efficiency and be of minimal environmental impact.

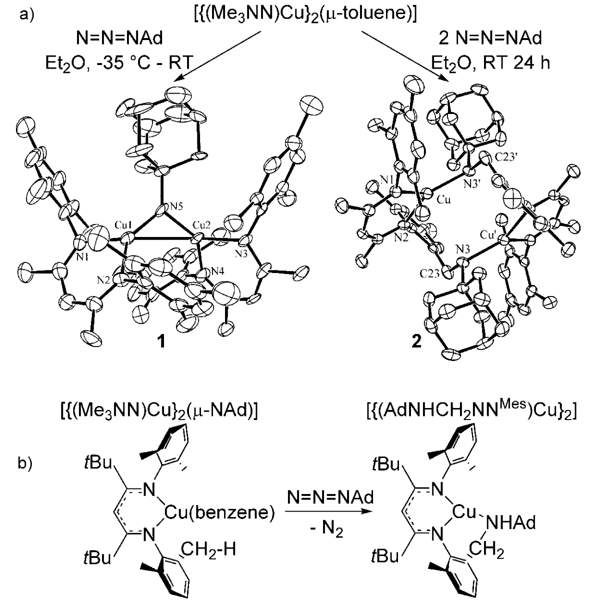
Chemical species capable of directly promoting this transformation often contain multiple bonds between late transition metals to oxygen, nitrogen, or carbon centers.[2] Nature provides inspiration with enzymes such as cytochrome P-450, which is efficient at inserting an oxygen atom into hydrocarbon C–H bonds through an iron–oxo intermediate ([Fe]=O).[3] The use of iminoiodanes (PhI=NR) has led to the generation of related metal–nitrene intermediates ([M]=NR), which in certain cases, exhibit stoichiometric reactivity with carbon–hydrogen bonds to give amines.[4]

Several catalytic protocols based on Rh,[5] Ru,[6] Ag,[7] Au,[8] Cu,[9] and other metals for the amination of benzylic or allylic C–H bonds with iminoiodanes bearing electron-deficient N substituents represent useful methodologies for the transformation of C–H into C–N bonds.[2,10,11] In these catalytic cases, metal–nitrene species are inferred, but their high reactivity makes their characterization as the active intermediates difficult. This lack of characterization is unfortunate, as a fundamental understanding of metal–nitrene species that mediate catalytic C–N bond formation would aid the development of more general systems for C–H bond functionalization.

In this context, we recently isolated a dicopper complex [{(Me$_3$NN)Cu}$_2$(μ-NAr)] (Ar = 3,5-dimethylphenyl) in which a nitrene is bound between two β-diketiminate copper fragments.[12] Solution studies supported the intermediacy of terminal copper–nitrene [Cu] = [(Me$_3$NN)Cu] through the dissociation of a β-diketiminate copper fragment from [{(Me$_3$NN)Cu}$_2$(μ-NAr)]. The terminal nitrene could not be directly observed owing to an unfavorable dissociation constant [Eq. (1); [Cu] = [(Me$_3$NN)Cu].

$$[[\mathrm{Cu}]_2(\mu\text{-NAr})] \xrightarrow{\text{benzene}} [\mathrm{Cu}]{=}\mathrm{NAr} + [[\mathrm{Cu}](\text{benzene})] \qquad (1)$$

In an attempt to encourage the dissociation of one copper β-diketiminato fragment, [(Me$_3$NN)Cu], by using the steric bulk of the nitrene substituent, we carried out the reaction of 1-adamantylazide (N$_3$Ad) with [{(Me$_3$NN)Cu}$_2$(μ-toluene)] in diethyl ether (Scheme 1 a). Immediate crystallization of the reaction mixture allowed the isolation of green [{(Me$_3$NN)Cu}$_2$(μ-NAd)] (**1**). Single crystal X-ray crystallographic data for **1** (Cu-N$_{\text{nitrene}}$ = 1.785(6), 1.821(5) Å; Cu···Cu = 2.901(2) Å) are quite similar to that found in [{(Me$_3$NN)Cu}$_2$(μ-NAr)].[12] Solutions of **1** are more thermally sensitive than those of its arylnitrene counterpart as the color of the solution changed from green to red during recrystallization attempts. This red substance can be isolated in 80%



Scheme 1. a) Synthesis and X-ray crystallographic structures of **1** and **2**. b) Intramolecular C–H amination with a bulky β-diketiminate ligand.

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yield from the reaction between [{(Me$_3$NN)Cu}$_2$(μ-toluene)] and 2 equivalents of N$_3$Ad in diethyl ether at room temperature for 24 hours (Scheme 1 a).[13]

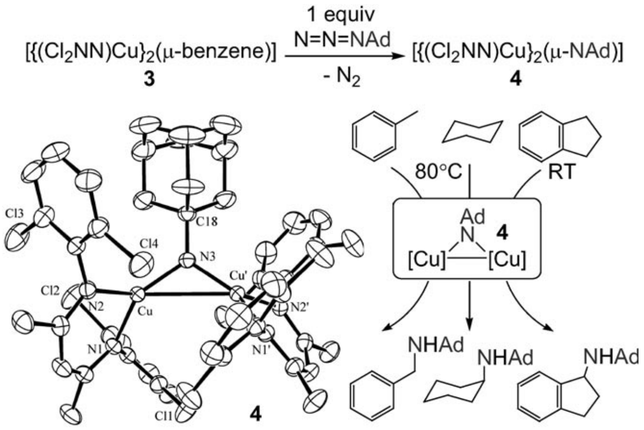
The X-ray crystal structure of the red, dimeric product **2** clearly shows coordination of the secondary amine functionality, ArCH$_2$NHAd, to each copper center (Cu-N = 2.040(4) Å). The amine results from the intramolecular insertion of an adamantylnitrene functionality into a C–H bond of one β-diketiminate *ortho*-methyl group. ^{1}H NMR spectra of **2** in [D$_6$]benzene show two inequivalent benzylic CH_2NHAd resonances, and IR spectroscopy indicates the presence of a new N–H bond ($\nu_{NH} = 3218\ cm^{-1}$). This mode of nitrene insertion into β-diketiminate *N*-aryl *o*-methyl substituents appears to be general. Reaction of [(Me$_2$NN$_{tBu}$)Cu-(benzene)], which contains backbone *tert*-butyl groups instead of methyl groups and two 2,6-Me$_2$C$_6$H$_3$ groups as *N*-aryl substituents, leads to a similar intramolecular nitrene insertion to give a monomeric product (Scheme 1 b).

We reasoned that the use of chemically inert substituents at the *ortho*-aryl position of the β-diketiminate N groups could thwart intramolecular nitrene insertion and enable the functionalization of more synthetically useful, exogenous C–H bonds. [{(Cl$_2$NN)Cu}$_2$(μ-benzene)] (**3**), having Cl substituents in the *ortho* positions of the β-diketiminate *N*-aryl groups, can be prepared in 94 % yield from the reaction of the free diimine [H(Cl$_2$NN)][14] and CuO*t*Bu in benzene. Reaction of [{(Cl$_2$NN)Cu}$_2$(μ-benzene)] with N$_3$Ad in chlorobenzene results in the isolation of [{(Cl$_2$NN)Cu}$_2$(μ-NAd)] (**4**) as a green crystalline material in 63 % yield. X-ray crystallographic analysis shows **4** to be similar in structure to [{(Me$_3$NN)Cu}$_2$(μ-NAr)] and **1**, possessing an NAd ligand symmetrically bridged between two Cu centers which are related through C_2-symmetry (Cu-N$_{nitrene}$ 1.810(2) Å; Cu···Cu: 2.969(1) Å; Scheme 2).

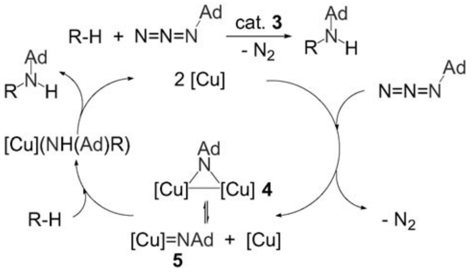
Benzene solutions of dicopper nitrene **4** exhibit diamagnetic ^{1}H and ^{13}C NMR spectra with a backbone C–H ^{1}H NMR resonance at δ 5.14 ppm. Solutions of **4** in benzene exhibit an intense green color owing to a low-energy charge-transfer band at $\lambda_{max} = 717$ nm ($\varepsilon = 5870\ M^{-1}cm^{-1}$) with a shoulder at $\lambda = 589$ nm. At room temperature, benzene solutions of **4** (ca. 0.1 mM) exhibit a half-life of approximately 3 hours. Heating **4** in [D$_6$]benzene at 80 °C for 4 hours gives H$_2$NAd in 95 % yield as identified by GC/MS methods.

Dissolution of dicopper nitrene **4** into several hydrocarbons containing sp^3 C–H bonds, however, results in clean transfer of the NAd moiety into these C–H bonds.[15] For instance, heating samples of **4** in neat toluene or cyclohexane at 80 °C for 3–4 hours results in quantitative nitrene transfer to provide the secondary amines PhCH$_2$NHAd and CyNHAd, respectively. For indane, a hydrocarbon with weaker benzylic C–H bonds, this reaction takes place at room temperature with a qualitatively comparable rate. This result suggests that nitrene C–H insertion, rather than dissociation of a [(Cl$_2$NN)Cu] fragment from **4**, may be rate limiting (Scheme 2 and Scheme 3).

This intermolecular C–H functionalization reaction may be carried out under catalytic conditions employing N$_3$Ad with 2.5 mol % [{(Cl$_2$NN)Cu}$_2$(benzene)] (**3**) in neat hydrocarbons at 110 °C (Table 1).[15] The yields of the isolated products of 90 % or higher were achieved with toluene, ethylbenzene, and indane. Cyclohexane, with its very strong C–H bond (95.5 kcal mol^{-1}), required 48 hours to reach high conversion; this reaction time could be significantly shortened by employing microwave heating ($T = 120$ °C, 1.5 h). By using benzene as the solvent, the catalytic amination of 1 equivalent of the substrate with 2.5 mol % **3** gives yields from 31–82 %. In addition, clean nitrene insertion into the sp^2-hybridized aldehyde C–H bond occurs to give 91 % yield of the amide (1 equivalent of benzaldehyde, 5 mol % **3**, at 80°, 16 hours in benzene). In some cases, the catalyst loadings may be reduced to 0.05 mol %, such as in the amination of ethylbenzene (5 equiv) with N$_3$Ad in benzene at 110 °C (90 % yield; 900 turnovers/Cu). A proposed mechanism for the catalytic C–H amination, based on our observations resulting from the use of stoichiometric amounts of reagents, is shown in Scheme 3.



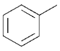
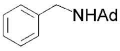
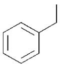
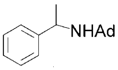
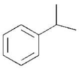
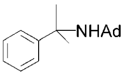
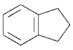
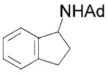
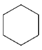
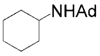
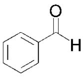
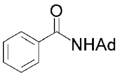
Scheme 2. Synthesis of dicopper nitrene **4** and its stoichiometric amination of C–H bonds.



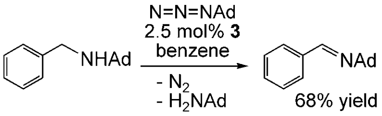
Scheme 3. Proposed catalytic cycle for C–H amination with N$_3$Ad catalyzed by [{(Cl$_2$NN)Cu}$_2$(μ-benzene)] (**3**).

The decreased yield for the toluene amination is principally because of the formation of imine PhCH=NAd that results from the oxidation of the primary product (PhCH$_2$NHAd). For instance, PhCH$_2$NHAd reacts with 1 equivalent of N$_3$Ad in the presence of 2.5 mol % **3** to give PhCH=NAd in 68 % yield along with H$_2$NAd at 110 °C in benzene [Eq. (2)]. This enables the direct conversion of toluene into the corresponding benzylic imine under related catalytic conditions by the use of a N$_3$Ad/toluene ratio of 2:1, which gives PhCH=NAd in 60 % yield with benzene as the solvent [Eq. (3)]. We did not observe the subsequent oxidation of the amine derived from ethylbenzene or indane under similar catalytic conditions.

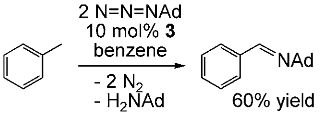
Table 1: Catalytic amination of C—H bonds with 1-adamantylazide (N_3Ad) employing 2.5 mol% [{$(Cl_2NN)Cu$}$_2$(μ-benzene)] (**3**).

Entry	Substrate	Product	Yield [%][a]	*t* [h]	Yield [%][d]
1			92	4	31
2			90	5	82 (85)[e]
3			80	24	50
4			93	1	80
5			90	48 (1.5)[c]	32 (40)[e]
6			91[b]	16	91

[a] All reactions were run in neat hydrocarbon substrate at 110°C and amines were isolated as hydrochloride salts. Reported yields are for isolated products. [b] 1 equivalent substrate in benzene, $T = 80$°C; isolated as amide. [c] Reaction carried out with microwave-assisted radiation, $T = 120$°C. [d] Reaction with 1 equivalent substrate and 1 equivalent azide in [D$_6$]benzene; yields determined by ^1H NMR methods. [e] Yields determined by using NMR methods employing 5 equivalents substrate in [D$_6$]benzene.



(2)



(3)

The connection between decreasing yields with decreasing substrate loadings for the other substrates employed is because of the competition between C—H amination and formation of the diazene AdN=NAd. A control experiment performed in benzene shows that **3** cleanly converts AdN_3 into AdN=NAd after 3 days at 110°C.

Competition experiments employing pairs of substrates (5 equiv each) at 110°C in benzene established that the strength of the C—H bond is a key factor that controls the relative rates of catalytic amination with N_3Ad (Figure 1). Furthermore, employing a 1:1 ratio of the substrate to its perdeutero analogue gives a kinetic isotope effect (KIE), k_H/k_D, of 5.3(2) for ethylbenzene and 6.6(1) for cyclohexane at 110°C. Notably, heating the isolated [{$(Cl_2NN)Cu$}$_2$(μ-NAd)] (**4**) in ethylbenzene isotopomers at 110°C gives the same KIE (5.1(2)) within experimental error. These values are on the low end of the range (4.8–11) observed in the stoichiometric CH insertion of ruthenium imides, which is thought to proceed by a hydrogen atom abstraction/rebound mechanism.[4]

Density functional theory (DFT) calculations were employed to address the putative terminal intermediate [$(Cl_2NN)Cu$=NAd] (**5**) (Scheme 3). Initial calculations at the DFT level support our experimental inability to directly observe this species owing to an unfavorable equilibrium constant for the dissociation of a [$(Cl_2NN)Cu$] fragment from dicopper nitrene **4** to give the terminal nitrene **5** ($\Delta G = +17.1$ kcal mol^{-1}; $\Delta H = +25.9$ kcal mol^{-1} at 1 atm and 298 K) [see Eq. (1)].

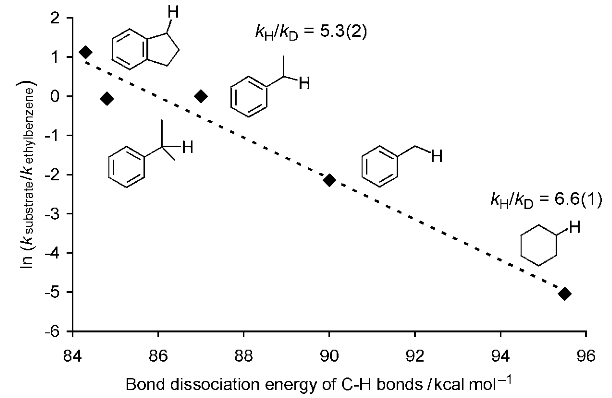


Figure 1. Catalytic rates of amination at 110°C relative to ethylbenzene [ln($k_{substrate}/k_{ethylbenzene}$)] versus C—H bond strength. All rates were normalized for the number of equivalent participating C—H bonds.

Several DFT studies of copper–nitrenes complexes have recently been published, indicating a triplet ground state.[16,17] In light of the research by Borden et al. on metal-free NPh[18] and theoretical studies by Cundari et al. on simpler copper–nitrene models,[19] we felt it prudent to a) employ complete active space self-consistent field (CASSCF)[20] multiconfiguration techniques instead of DFT methods, and b) model the full experimental models with CASSCF/MM hybrid methods. Several noteworthy results emanated from our computational analysis of [$(Cl_2NN)Cu$=NAd] (see Figure 2 and the Supporting Information). First, the ground state is a singlet, not a triplet as has been either assumed[17] or inferred[16] from previous DFT studies of copper–nitrene species having bidentate N-donor ligands.[21] Instead, it is predicted to be a singlet biradical on the basis of extensive CASSCF calculations[19] of both simple and elaborate models of the experimental intermediates reported herein. The singlet ground state of [$(Cl_2NN)Cu$=NAd] is calculated to be 18 kcal mol^{-1} below the triplet excited state. Second, the inability of DFT methods to correctly model the singlet ground state arises from the significant diradical nature of the copper–nitrene bond. The calculated natural orbital occupation numbers (NOONs) for the orbitals that define the Cu dπ—N$_{nitrene}$ pπ bond deviate significantly from 2.0 e$^-$ and 0.0 e$^-$. The NOONs for the singlet ground state of **5** are 1.5 e$^-$ and 0.5 e$^-$. This indicates a substantial contribution to the ground state CASSCF wavefunction from states involving $\pi_{CuN} \rightarrow \pi^*_{CuN}$ transitions. The pertinent natural orbitals are shown in Figure 2. Third, whereas the triplet excited state of [$(Cl_2NN)Cu$=NAd] has a more linearly coordinated nitrene ligand (Cu-N = 1.78 Å; Cu-N-C = 164°) the singlet ground state has bent nitrene coordination (Cu-N = 1.82 Å; Cu-N-C = 129°). Presumably, such a bent arrangement of the nitrene ligand will permit access of a wider array of hydrocarbon substrates at the copper–nitrene active intermediate.

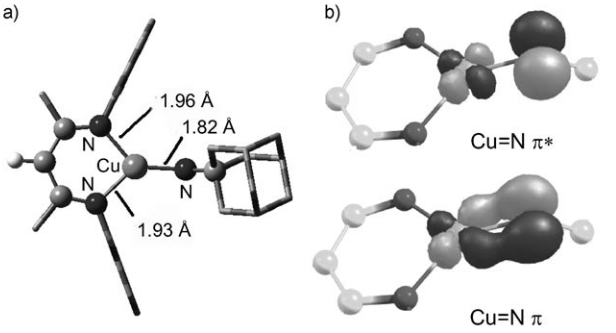


Figure 2. a) The calculated geometry and b) the CuN π and CuN π* natural orbitals for the singlet ground state of **5**. For both a) and b), balls represent atoms modeled with quantum (CASSCF) techniques and tubes depict atoms modeled with the MM3 force field. H atoms are omitted with the exception of the backbone H atoms in (a). Natural orbital occupation numbers are $1.5\,e^-$ for Cu=N (π) and $0.5\,e^-$ for Cu=N (π*).

The discrete dicopper nitrene intermediates, $[[Cu]_2(\mu\text{-NAd})]$, reported herein possess an unexpected potency towards nitrene insertion into C–H bonds. For the first time, nitrene precursors bearing aliphatic N substituents participate in catalytic amination of strong, unactivated sp^3 C–H bonds such as those in cyclohexane. In contrast to other catalytic systems, which employ electron-poor, heteroatom-rich N substituents such as sulfonyl or carbamate groups to achieve C–H bond insertion, the use of a tertiary organic azide allows direct formation of N-functionalized secondary organic amines. Whereas organic azides offer the possibility to directly introduce NR groups with organic N functionalities into C–H bonds[22] either intramolecularly[23] or intermolecularly,[24] they can suffer lower efficiencies as compared to their sulfonylnitrene intermediates.[10] Notably, the inexpensive copper catalyst[9,25] which is quite robust, allowing low catalyst loadings to give 900 turnovers/Cu in the amination of 5 equivalents of ethylbenzene with N$_3$Ad.

In terms of catalyst design, the *meta* stability of long sought copper–nitrene intermediates provides useful rates for catalytic C–H functionalization while also permitting characterization through experimental and computational methods. As such, this β-diketiminato copper-based system provides a credible starting point for the rational engineering of improved metal catalysts for hydrocarbon functionalization.

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Keywords: amination · C–H activation · copper · density functional calculations · nitrenes

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