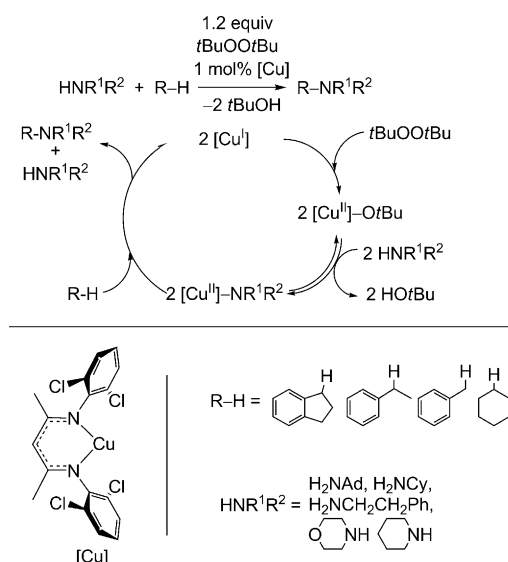


*Raymond T. Gephart III, Daria L. Huang, Mae Joanne B. Aguila, Graham Schmidt, Andi Shahu, and Timothy H. Warren**

We recently showed that the β -diketiminato copper(I) complex $[(\text{Cl}_2\text{NNCu})_2(\mu\text{-benzene})]$ (**1**) catalyzes the amination of $\text{C}_{\text{sp}^3}\text{-H}$ bonds of ethylbenzene, indane, and even the completely unactivated substrate cyclohexane with the primary alkylamines 1-adamantylamine, cyclohexylamine, and phenethylamine employing $t\text{BuOO}t\text{Bu}$ as an oxidant (Scheme 1).^[9b] Emphasizing the non-nitrene nature of this protocol,

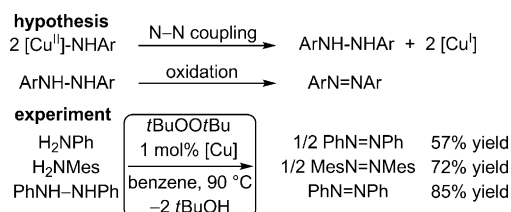


Aiming to extend our C–H amination protocol to aromatic amines H_2NAr , we were quite concerned that our system would instead catalyze their oxidation to diazenes $\text{ArN}=\text{NAr}$. Although first reported in 1955,^[15] the use of copper(I) halides in pyridine for the aerobic oxidation of anilines into azobenzenes recently has been rediscovered as a versatile method for the synthesis of aromatic diazenes.^[16] Indeed, early mechanistic studies suggested copper(II) anilides $\text{Cu}^{\text{II}}\text{--NHAr}$ as key intermediates which are subject to bimolecular N–N coupling to give the hydrazines ArNH--NHAr en route to diazenes $\text{ArN}=\text{NAr}$ (Scheme 2).^[15b,c]

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Scheme 2. Oxidation of anilines and hydrazines by [Cu]/ $t\text{BuOO}t\text{Bu}$ catalyst system gives diazenes.

the C–H amination product with a concomitant reduction in the diazene MesN=NMes (Figure 1; see Table S1 and Figures S1 and S2 in the Supporting Information).

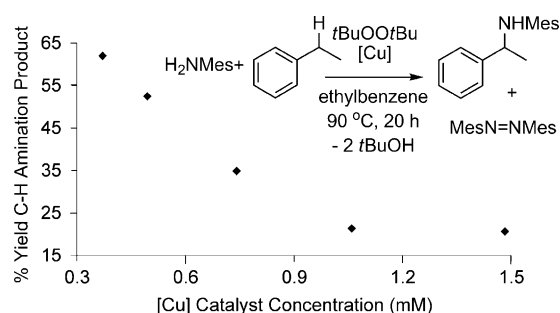


Figure 1. Dependence of product yield on catalyst concentration in the C–H amination of ethylbenzene by H_2NMes .

Based on the dramatic effect that the catalyst concentration has on diazene formation, we hypothesize that a bimolecular reaction occurs between two copper(II) anilido intermediates, $[\text{Cu}^{\text{II}}]\text{-NHMe}$ (formed by reaction of $[\text{Cu}^{\text{II}}]\text{-O}t\text{Bu}$ with H_2NMes ; see Scheme 1), to give MesNH-NHMe which may be subsequently oxidized to MesN=NMe (Scheme 2). Consistent with this hypothesis, PhNH-NHPh is oxidized to PhN=NPh under catalytic conditions (100% conversion, 85% diazene yield; Scheme 2). The reaction of H_2NPh or H_2NMes with $t\text{BuOO}t\text{Bu}$ in the presence of the catalyst [Cu] but in the absence of a $\text{C}_{\text{sp}^3}\text{-H}$ substrate leads to complete consumption of the primary aromatic amine, thus forming PhN=NPh and MesN=NMe in 57 and 72% yield, respectively.

We then examined the dependence of the substrate C–H bond strength on the selectivity for C–H amination versus diazene formation when employing H_2NMes and $t\text{BuOO}t\text{Bu}$ with 1 mol% [Cu] at 90 °C (Table 1). The neat substrates cyclohexane (40% yield), toluene (18%), ethylbenzene (60%), indane (85%), and 1,2,3,4-tetrahydronaphthalene (95%) give C–H amination product yields that generally increase with decreasing C–H bond strength.

A key insight into diazene formation is revealed by monitoring the selectivity for C–H amination with a series of p -substituted anilines $p\text{-XC}_6\text{H}_4\text{NH}_2$ in neat ethylbenzene (Figure 2). Electron-withdrawing groups greatly enhance selectivity for C–H amination over diazene formation: the particularly electron-poor p -cyano derivative gives a yield of 95%. This trend follows both the Hammett–Brown σ^+

Table 1: C–H amination of hydrocarbons with H_2NMes .^[a]

$\text{H}_2\text{NMes} + \text{R-H} \xrightarrow[90\text{ }^\circ\text{C, 24 h}]{1.2\text{ equiv } t\text{BuOO}t\text{Bu, 1 mol\% [Cu]}} \text{R-NHMe}$			
Entry	R–H	C–H BDE ^[b] [kcal mol ^{−1}]	Yield [%]
1		83	95
2		85	85
3		87	60
4		90	18
5		97	40

[a] Reaction conditions: 1 mmol H_2NMes , 1.2 mmol $t\text{BuOO}t\text{Bu}$, 20 mL neat substrate, 1 mol% [Cu], 90 °C, 24 h; ¹H NMR yields. [b] C–H BDEs from Ref. [17].

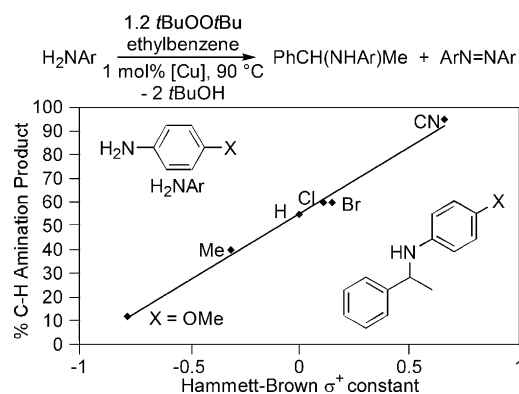
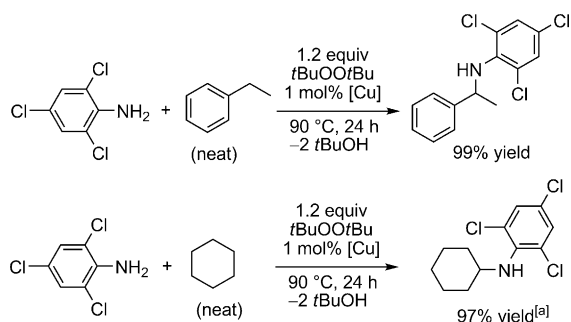


Figure 2. C–H amination product yields with a series of p -substituted anilines H_2NAr in neat ethylbenzene.

parameter ($R^2 = 0.99$) as well as the N–H bond strength for the parent aniline ($R^2 = 0.93$; see Figure S4 in the Supporting Information). Anilines possessing electron-withdrawing substituents are particularly resistant toward diazene formation. For instance, attempted oxidation of 2,4,6- $\text{Cl}_3\text{C}_6\text{H}_2\text{NH}_2$ with $t\text{BuOO}t\text{Bu}$ in benzene with 1 mol% [Cu] gives less than 5% of the corresponding diazene after 24 hours at 90 °C.

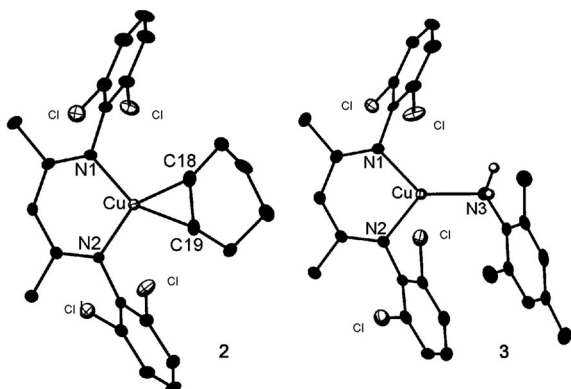
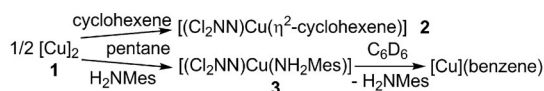
The reluctance of 2,4,6- $\text{Cl}_3\text{C}_6\text{H}_2\text{NH}_2$ to undergo oxidation to the corresponding diazene under our catalytic conditions identifies it as an excellent amine for the functionalization of challenging C–H substrates. In neat ethylbenzene and cyclohexane, C–H amination with 2,4,6- $\text{Cl}_3\text{C}_6\text{H}_2\text{NH}_2$ gives the corresponding N-alkyl-substituted anilines in 99 and 97% yield, respectively (Scheme 3). Thus, anilines possessing electron-withdrawing groups are especially effective in the functionalization of completely unactivated $\text{C}_{\text{sp}^3}\text{-H}$ bonds.



Scheme 3. C–H amination of hydrocarbons with $\text{H}_2\text{NAr}^{\text{Cl}}$. Yields determined by ^1H NMR spectroscopy. [a] Isolated in 95% yield.

These observations reveal a combination of factors required to achieve high C–H amination yields with modest C–H substrate loadings: a) low catalyst concentrations to prevent bimolecular N–N coupling, b) anilines with electron-poor substituents, and c) substrates with somewhat lower C–H bond strengths.

We examined a broader range of anilines with cyclohexene which possesses a C–H bond of modest strength (C–H BDE $\approx 82 \text{ kcal mol}^{-1}$).^[17] We were initially surprised at the low conversions of anilines (1 mmol scale) in C–H amination when performed in neat cyclohexene ca. 20 mL). Since alkenes may bind to copper(I) complexes,^[18] we considered inhibition by coordination of cyclohexene to the $[(\text{Cl}_2\text{NN})\text{Cu}]$ catalyst. Indeed, the cyclohexene adduct $[(\text{Cl}_2\text{NN})\text{Cu}(\eta^2\text{-cyclohexene})]$ (**2**) readily forms upon addition of cyclohexene to **1** in $[\text{D}_6]$ benzene (Scheme 4; see Figures S9 and S11 in the Supporting Information). Thus, cyclohexene binds more strongly to the $[\text{Cu}^{\text{I}}]$ center than benzene and may adversely affect catalyst performance by impeding the oxidation of $[\text{Cu}^{\text{I}}]$ by $t\text{BuOO}t\text{Bu}$ (Scheme 1). In contrast, $[(\text{Cl}_2\text{NN})\text{Cu}(\text{NH}_2\text{Mes})]$ (**3**), isolated by addition of H_2NMes to **1** in



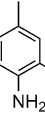
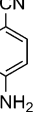
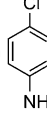
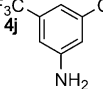
Scheme 4. X-ray structures of **2** and **3** illustrate coordination of cyclohexene and H_2NMes to the $[(\text{Cl}_2\text{NN})\text{Cu}]$ catalyst.^[23] The thermal ellipsoids are shown at 50% probability. See full crystallographic details in the Supporting Information.

pentane, readily loses H_2NMes in $[\text{D}_6]$ benzene, thus indicating that aniline substrates and products do not likely inhibit catalytic C–H amination (Scheme 4; Figures S10 and S12).

A subtle change in the catalytic reaction conditions allows the isolation of cyclohexene C–H amination products in up to 97% yield (Table 2). The use of 10 equivalents of cyclohexene, 1 equivalent of the aniline **4**, and 1.2 equivalents of

Table 2: C–H amination of cyclohexene with aniline derivatives.^[a]

Reaction scheme showing the conversion of an amine (R-NH-Ar) and 10 equivalents of cyclohexene to a product (R-N-Ar) using 1.2 equivalents of *t*BuOO*t*Bu, 1 mol% [Cu], at 90 °C for 24 h, with 2 equivalents of *t*BuOH as a byproduct.

4a		36%	4g		21% (32 %) ^[b]	4m		75%
4b		47%	4h		80%	4n		33%
4c		23%	4i		97%	4o		18%
4d		65%	4j		78%	4p		33%
4e		32% (41%) ^[b]	4k		91%	4q		33%
4f		31% (40%) ^[b]	4l		77%	4r		64%

[a] Reaction conditions: 1 mmol aniline, 1.2 mmol $t\text{BuOO}t\text{Bu}$, 10 mmol cyclohexene, 1 mol% $[\text{Cu}]$, 90 °C. Aniline structures are shown and the yields are those of the isolated products. [b] Used 5 mol% $[\text{Cu}]$ and yield was determined by ^1H NMR spectroscopy.

$t\text{BuOO}t\text{Bu}$ with 1 mol% $[\text{Cu}]$ catalyst under essentially solventless conditions enables C–H amination with a wide range of anilines. Both electron-rich and electron-poor anilines participate in C–H amination, though the presence of electron-withdrawing groups typically enhances the product yield.

When considering anilines with electron-releasing methyl substituents, those that provide modest steric hindrance to the N atom (**4b** and **4d**) result in higher yields. Anilines with larger *o*-alkyl substituents (**4e–g**), however, gave lower yields because of limited conversion of the aniline substrates, perhaps reflecting a sluggishness in the formation or C–H amination reactivity of the putative $[\text{Cu}^{\text{II}}]\text{-NHAr}$ intermediates. Increasing the catalyst loading to 5 mol% modestly increased the amination yields to 41, 40, and 32% (^1H NMR)

for *o*-Et-, *o*-*i*Pr-, and *o*-*t*Bu-substituted anilines, respectively (**4e–g**). In the case of the *o*-Et and *o*-*i*Pr derivatives, the conversion of aniline substantially increased, but so too did the formation of the corresponding diazene. Little diazene was observed for the *o*-*t*Bu-substituted aniline (**4g**); conversion of this sterically demanding aniline was a concern at both low (1 mol %) and high (5 mol %) catalyst loadings.

Anilines possessing electron-withdrawing groups provide excellent C–H amination yields (**4h–m**). Notably, catalysis was not inhibited by 2-aminopyridine which is known to form a variety of coordination compounds through κ^2 -*N,N* binding to metals in its anionic form.^[19] In contrast, no C–H amination product with 4-nitroaniline was observed, perhaps as a result of interaction of the nitro group with the metal center.^[20]

To demonstrate this catalysis proceeds through a non-nitrene-based mechanism, we surveyed a small range of *N*-alkyl-substituted anilines (**4o–r**). Paralleled in the series of primary aromatic amines, the presence of an electron-withdrawing group enhances the yield (**4r**). Oxidation of these secondary aromatic amines to the corresponding imines may compete with C–H amination as previously observed in the amination of cyclohexane with morpholine using this catalyst system.^[9b]

In conclusion, we present the first general use of anilines in the C–H amination of a range of substrates with C_{sp}³–H bonds. Previous related, though isolated, examples involve polyfluorinated arenes possessing acidic C_{sp}²–H bonds with electron-poor anilines^[21] or sterically hindered bromoarenes which undergo C–H functionalization of an *o*-*t*Bu group under attempted Buchwald–Hartwig cross-coupling with anilines.^[22]

The copper(I) catalyst [(Cl₂NN)Cu]₂(benzene)] in conjunction with the mild oxidant *t*BuOO*t*Bu enables the direct use of a variety of commercially available anilines in C–H amination. Even strong, unactivated C_{sp}³–H bonds may be efficiently functionalized by using low catalyst loadings and electron-poor anilines which suppress diazene formation. We rationalize these findings to result from the competition between the involvement of putative [Cu^{II}]-NHAr intermediates in C–H functionalization vs. their undesired bimolecular coupling which appears to be disfavored for electron-poor anilines. Future studies target the isolation of discrete copper(II) anilides [(Cl₂NN)Cu-NHAr] and an examination of their reactivity patterns to lay a concrete mechanistic foundation for this unique C–H amination system that tolerates both alkyl and arylamines.

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- [23] CCDC 876017 (**2**) and CCDC 876018 (**3**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.