Copper(II) Ketimides in sp^3 C-H Amination

Isuri U. Jayasooriya,[a] Abolghasem (Gus) Bakhoda,[a,b] Rachel Palmer,[a] Kristi Ng,[a] Nour L. Khachemoune,[a] Jeffery A. Bertke,[a] Timothy H. Warren [a]*

Commercialy available benzphenone imine ($HN{=}CPh_2$) reacts with β-diketiminato copper(II) *tert*-butoxide complexes [Cu^{II}]-O^{t}Bu to form isolable copper(II) ketimides [Cu^{II}]-N=CPh$_2$. Structural characterization of the three coordinate copper(II) ketimide [Me$_3$NN]Cu-N=CPh$_2$ reveals a short Cu-N$_{ketimide}$ distance (1.700(2) Å) with a nearly linear Cu-N-C linkage (178.9(2)°). Copper(II) ketimides [Cu^{II}]-N=CPh$_2$ readily capture alkyl radicals R• (PhCH(•)Me and Cy•) to form the corresponding R-N=CPh$_2$ products that competes with N-N coupling of copper(II) ketimides [Cu^{II}]-N=CPh$_2$ to form the azine Ph$_2$C=N-N=CPh$_2$. Copper(II) ketimides [Cu^{II}]-N=CAr$_2$ serve as intermediates in catalytic sp^3 C-H amination of substrates R-H with ketimines HN=CAr$_2$ and ^{t}BuOO^{t}Bu as oxidant to form *N*-alkyl ketimines R-N=CAr$_2$. This protocol enables the use of unactivated sp^3 C-H bonds to give R-N=CAr$_2$ products easily converted to primary amines R-NH$_2$ via simple acidic deprotection.

Introduction

Transition metal-catalysed sp^3 C-H amination protocols have gained an immense attention in the synthetic community over the past couple of decades.[1-4] A majority of these protocols proceed via metal-nitrene[2,5] [M]=NR' or metal-amide [M]-NR'R" intermediates.[1,6] Extensive studies on such intermediates and underlying mechanisms have paved the way towards more efficient sp^3 C-H amination protocols.[1]

Related metal-ketimide [M]-N=CR'R" intermediates, however, have received less attention in C-H amination chemistry. The strong metal-N$_{ketimide}$ interaction makes ketimides effective spectator ligands. For instance, ketimides stabilize high valent homoleptic Mn(IV)[7], Fe(IV)[8] and Co(IV)[9] complexes (Fig. 1a). In some cases, ketimides can also form via nickel and copper arylimido/nitrene intermediates [M]=NAr via C-C coupling at the *para*-position of the aryl nitrene ligand (Fig 1b). While this reactivity was initially uncovered with nickel β-diketiminato complexes,[10] reversible C-C bond formation/cleavage in related copper complexes provides access to free copper nitrenes [Cu]=NAr that participate in sp^3 C-H amination.[11, 12]

Fewer examples of ketimides exist, however, in which the ketimide ligand serves as a reactive intermediate in discrete transition metal complexes.[13] Metal ketimide intermediates have been proposed in several Pd-catalysed cross-coupling reactions of aryl (Fig. 1c)[14] and alkyl halides (Fig. 1d)[15] with benzophenone imine. Cu-catalysed photoredox cross-coupling reactions of redox-active alkyl esters (Fig. 1e)[16] and Cu-catalysed benzylic sp^3 C-H amination of with benzophenone imine (Fig. 1f)[17] are among other examples that may be mediated by metal-ketimide intermediates. Moreover, Stahl and colleagues have proposed copper(II) ketimides in the N-N oxidative coupling of imines Ar$_2$C=NH to azines Ar$_2$C=N-N=CAr$_2$ under aerobic or electrocatalytic conditions (Fig. 1g).[18, 19]

Herein we describe discrete first-row transition metal-ketimide complexes intimately involved in C-H amination

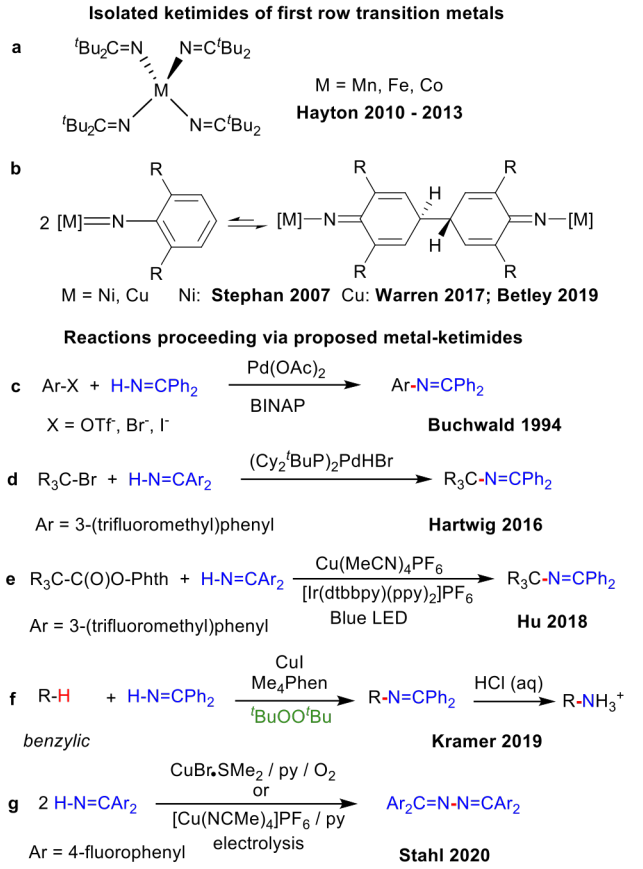


Fig. 1. Transition metal ketimide complexes.

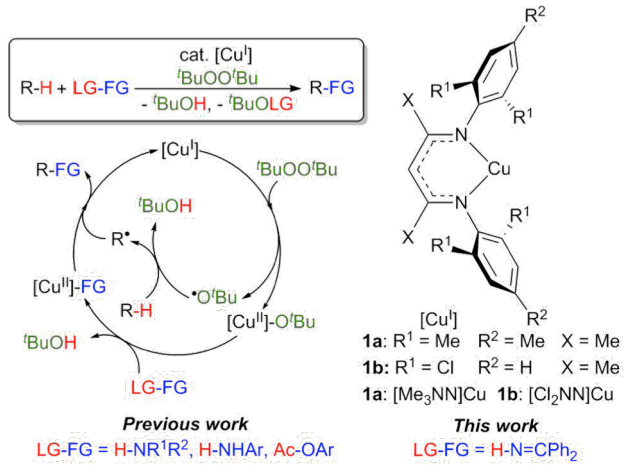


Fig. 2. Mechanism of C-H functionalisation via β-diketiminato copper(II) intermediates [Cu^{II}]-FG.

chemistry. Building upon the Kharasch-Sosnovsky reaction,[20-22] we have demonstrated that copper(II) alkyl amides [Cu^{II}]-NHR',[23] anilides [Cu^{II}]-NHAr,[6,24] and aryloxides [Cu^{II}]-OAr[25] serve as key intermediates in a radical relay protocol for sp^3 C-H functionalisation (Fig. 2). Formed via acid-base[6,23,24] or transesterification[25] reactions between [Cu^{II}]-O^{t}Bu with H-FG or Ac-FG reagents, these copper(II) complexes [Cu^{II}]-FG capture sp^3-C radicals R• generated via H-atom abstraction from R-H to furnish the functionalized product R-FG. We anticipated that the relatively high acidity of the imine N-H bond[26] coupled with a preference for binding at copper with softer N-donors should enable the formation of [Cu^{II}]-N=CAr$_2$ species from [Cu^{II}]-O^{t}Bu complexes and HN=CPh$_2$ to examine copper(II) ketimides in C-H amination catalysis.

Results and discussion

Synthesis and characterization of copper(II) ketimides

Monitored by UV-vis spectroscopy, addition of benzophenone imine (1 equiv.) to a solution of [Me$_3$NN]Cu-O^{t}Bu (**2a**) in toluene at -80 °C results in decay of the characteristic UV-vis absorption of **2a** at 470 nm with growth of a new band at 570 nm (Figure S2). Performed on a preparative scale, this new species [Me$_3$NN]Cu-N=CPh$_2$ (**3a**) may be isolated as dark purple crystals from pentane at -35 °C in 78% yield (Fig. 3a).

The X-ray crystal structure of [Me$_3$NN]Cu-N=CPh$_2$ (**3a**) (Fig 3a) reveals the Cu-N$_{ketimide}$ distance of 1.700(2) Å, significantly shorter than the Cu-N bond found in the copper(II) amide [Cl$_2$NN]Cu-NHAd (1.839(9) Å)[23] and copper(II) anilide [Cl$_2$NN]Cu-NHAr^{Cl3} (1.847(3) Å).[6] Copper(II) ketimide **3a** possesses a nearly linear Cu-N3-C24 angle of 178.9(2)°. These values remarkably differ from those in the homoleptic copper(I) ketimide [Cu-N=CPh$_2$]$_4$ with bridging ketimide ligands that lead to a square-like tetrameric structure with Cu-N distances 1.8471(19)–1.8613(19) Å and Cu-N-Cu angles of 94.17(9)–98.25(9).[27] To outline difference between coordination of anionic ketimide ligands and their neutral ketimine counterparts, we prepared the corresponding benzophenone imine adducts [Me$_3$NN]Cu(NH=CPh$_2$) (**4a**) and [Cl$_2$NN]Cu(NH=CPh$_2$) (**4b**) (Fig 3b). These copper(I) complexes feature substantially longer Cu-N$_{ketimine}$ distances of 1.8940(14) and 1.8937(14) Å with a pronounced bend in the Cu-ketimide linkage with Cu-N-C angles of 132.68(12) and 130.25(12)°.

UV-vis analysis of copper(II) ketimide [Me$_3$NN]Cu-N=CPh$_2$ (**3a**) reveals the presence of a single low energy absorption band at 570 nm (ε = 1910 M^{-1}cm^{-1}) in toluene at room temperature. The EPR spectrum of **3a** in a mixture of toluene and pentane at room temperature shows a signal centred at g_{iso} = 2.081 with very well resolved coupling to $^{63/65}$Cu (A_{Cu} = 298.0 MHz) and additional hyperfine modelled with three equivalent ^{14}N nuclei (A_N = 35.0 MHz) (Figure S13). The related copper(II) ketimide [Cl$_2$NN]Cu-N=CPh$_2$ (**3b**) prepared from [Cl$_2$NN]Cu-O^{t}Bu (**2b**) and HN=CPh$_2$ exhibits a similar spectroscopic profile. The UV-vis spectrum of [Cl$_2$NN]Cu-N=Ph$_2$ (**3b**) exhibits a single absorption at 520 nm (ε = 3120 M^{-1}cm^{-1}) in toluene at room temperature and possesses a similar isotropic EPR spectrum to that of **3a** (Figure S14). Unfortunately, the greater thermal sensitivity of [Cl$_2$NN]Cu-N=Ph$_2$ (**3b**) has precluded its crystallographic characterization.

Copper(II) ketimide reactivity: radical capture and N-N bond formation

The ability of many β-diketiminato copper(II) complexes to participate in catalytic sp^3 C-H functionalisation via radical relay (Fig. 2) encouraged us to assess the reactivity of copper(II) ketimides **3** towards alkyl radicals. We find that [Cu^{II}]-N=CPh$_2$ species **3a** and **3b** capture alkyl radicals R• to provide the corresponding R-N=CPh$_2$ products (Fig. 4a). For instance, reaction of **3a** and **3b** with (*E/Z*)-azobis(α-phenylethane) at 90 °C that generates the benzylic radical

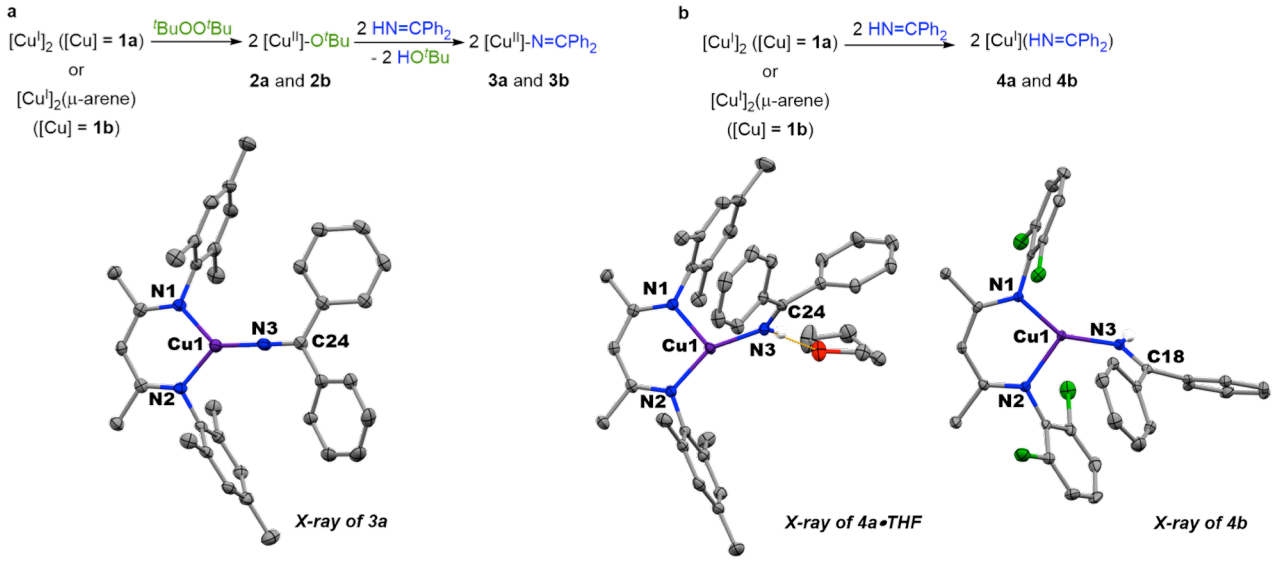


Fig. 3. (a) Synthesis and structure of copper(II) ketimides. (b) Synthesis and structure of copper(I) imine adducts.

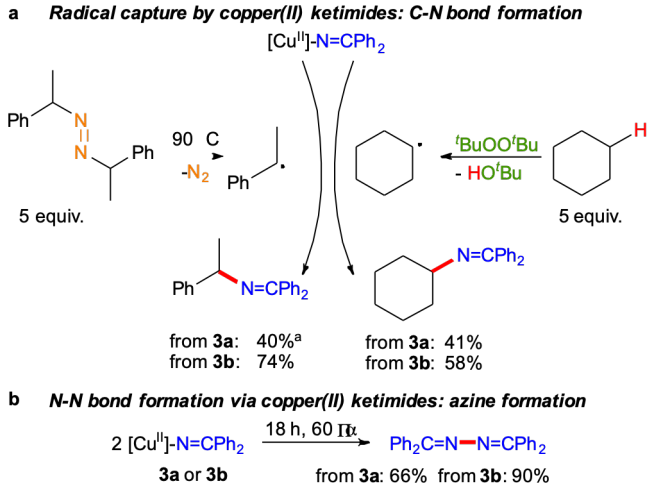


Fig. 4. Reactivity of copper(II) ketimides. [a]2 equiv. diazene radical precursor.

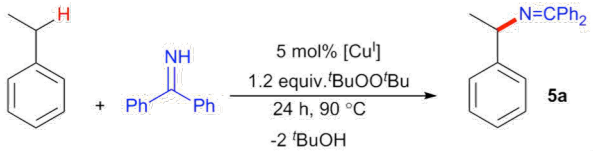
PhCH(•)Me upon heating provides the alkylated imine PhCH(N=CPh$_2$)Me in 40% and 74% yields, respectively. Generation of Cy• radicals in the presence of **3a** and **3b** by heating ^{t}BuOO^{t}Bu in cyclohexane (via H-atom abstraction by ^{t}BuO• radicals) provides Cy-N=CPh$_2$ in 58% and 41% yields, respectively.

Upon heating to 60 °C, copper(II) ketimides **3a** and **3b** undergo N-N coupling to form benzophenone azine Ph$_2$C=N-N=CPh$_2$ isolated in 66% and 90% yields, respectively (Fig. 4b). This is identified as a competing reaction for radical capture at copper(II) ketimides **3a** and **3b**.

Copper(II) ketimides in sp^3 C-H amination

With a fundamental understanding of copper(II) ketimide formation and reactivity, we explored these complexes in catalytic C-H amination via radical relay. Using ethylbenzene as a model R-H substrate, we screened a modest range of copper(I) β-diketiminato catalysts **1** that possess different electronic and steric properties (Table 1). The catalyst [Cl$_2$NN]Cu (**1b**) provides the highest yield compared to more electron-rich (**1a** and **1c**) and electron-poor (**1d**) catalysts. Increasing the ^{t}BuOO^{t}Bu oxidant amount does not significantly improve the yield. Lowering the temperature from 90 °C reduces the yield drastically (Table S1), possibly due to binding of the ketimine HN=CAr$_2$ to the copper(I) catalyst (Fig. 3b) that inhibits ^{t}BuOO^{t}Bu activation.[28]

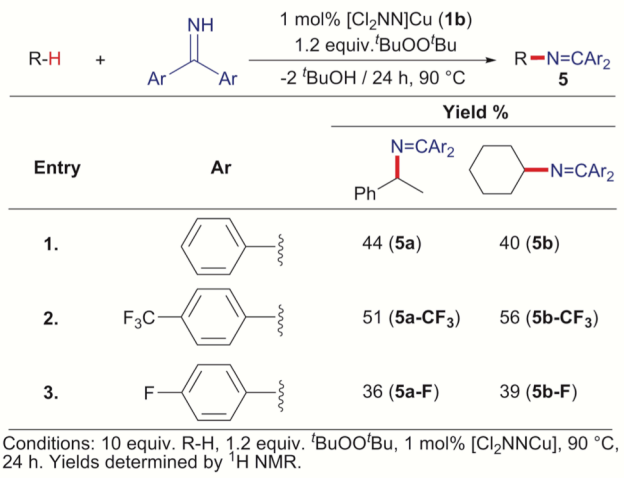
Table 1. Copper catalyzed C-H amination of ethylbenzene with benzophenone imine.



Entry	Catalyst	(X, R^1, R^2)	Yield (%)
1.	[Me$_3$NN]Cu **1a**	(Me, Me, Me)	34
2.	**[Cl$_2$NN]Cu 1b**	**(Me, Cl, H)**	65
3.	[^{i}Pr$_2$NN]Cu **1c**	(Me, ^{i}Pr, H)	30
4.	[Cl$_2$NN$_{F6}$]Cu **1d**	(CF$_3$, Cl, H)	42

Conditions: 50 equiv. R-H. All yields determined by ^{1}H NMR.

Table 2. Copper catalyzed C-H amination with benzophenone imine derivatives.



Conditions: 10 equiv. R-H, 1.2 equiv. ^{t}BuOO^{t}Bu, 1 mol% [Cl$_2$NNCu], 90 °C, 24 h. Yields determined by ^{1}H NMR.

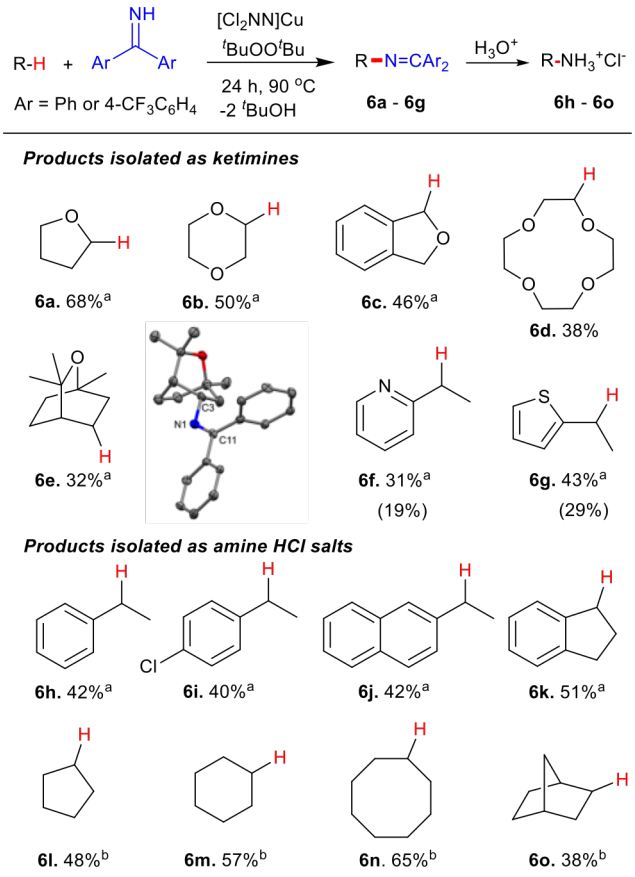
The azine Ph$_2$C=N-N=CPh$_2$ is the main byproduct in these catalytic C-H amination reactions, representing non-productive consumption of H-N=CPh$_2$. In a previous study of C-H amination with anilines H$_2$NAr employing the [Cl$_2$NN]Cu/^{t}BuOO^{t}Bu catalyst system, electron-poor anilines provided the highest yields in the face of competing diazene ArN=NAr formation.[24] Copper(II) anilido intermediates [Cu^{II}]-NHAr serve as intermediates in C-H amination with anilines H$_2$NAr; those derived from electron-poor anilines H$_2$NAr (e.g. Ar = 2,4,6-Cl$_3$C$_6$H$_2$) proved more resistant to reductive bimolecular N-N bond formation.[6,24]

To examine whether similar electronic changes in the ketimine H-N=CAr$_2$ could similarly promote more efficient catalysis, we explored two electron-poor ketimine derivatives H-N=CAr$_2$ (Ar = 4-CF$_3$C$_6$H$_4$ and 4-FC$_6$H$_4$) in C-H amination (Table 2). Although the *p*-CF$_3$ substituted imine provides a higher C-H amination yield with cyclohexane (C-H BDE = 97 kcal/mol),[29] the increase in yield is modest with the benzylic substrate ethylbenzene (C-H BDE = 87 kcal/mol).[29] No significant differences were observed between benzophenone imine and the *p*-F substituted analogue.

While electron-poor imines can give somewhat higher C-H amination yields, we most broadly examined the commercially available H-N=CPh$_2$ to survey the scope of R-H substrates in sp^3 C-H amination (Table 3). Ethers such as THF, 1,4-dioxane, or even 12-crown-4 undergo C-H amination at the α-carbon in relatively high yields (**6a** - **6d**). Amination of the benzylic secondary C-H bonds in heteroaromatic substrates occurs (**6f** - **6g**), though yields may be lower due to the possibility of coordination of these substrates and/or products to the copper(I) centre that can decrease the rate of reoxidation with ^{t}BuOO^{t}Bu.[28] Aromatic substrates with benzylic C-H bonds undergo C-H amination in moderate to high yields (**6h** - **6k**). Cycloalkanes with stronger, unactivated sp^3 C-H bonds give moderate yields with electron-poor ketimine HN=CAr'$_2$ (Ar' = 4-CF$_3$C$_6$H$_4$) (**6l** - **6o**). The bicyclic eucalyptol undergoes C-H amination in 32% yield (**6e**). These aminated products may be isolated either as benzophenone derivatives R-N=CPh$_2$ (**6a** - **6g**)

or as the primary ammonium salts [R-NH_3]Cl via deprotection upon acidic work up (**6h** - **6o**).

Table 3. Copper catalyzed sp^3 C-H amination with ketimines HN=CAr_2.



Conditions: 10 equiv. R-H, 1.2 equiv. ^{t}BuOO^{t}Bu, 1 mol% [Cl_2NN]Cu, 90 °C, 24 h. [a]Yields with HN=CPh_2. [b]Yields with HN=CAr'$_2$ (Ar' = 4-$CF_3C_6H_4$). ^{1}H NMR yields (isolated yields) for **6f** and **6g**.

Conclusions

The isolation of mononuclear copper(II) ketimides [Cu^{II}]-N=CPh_2 reveals the role that they play as intermediates in sp^3 C-H amination. These reactive intermediates readily form via acid-base exchange between [Cu^{II}]-O^{t}Bu and HN=CPh_2, amenable to spectroscopic and structural investigation. Importantly, [Cu^{II}]-N=CPh_2 complexes efficiently intercept alkyl radicals R• generated via H-atom abstraction by ^{t}BuO• from substrates R-H that ultimately enable the C-H amination of unactivated sp^3 C-H substrates. DFT analysis reveals a significant amount of unpaired electron density at the ketimide N atom of 0.58 and 0.61 e^- for [Me_3NN]Cu-N=CPh_2 (**3a**) and [Cl_2NN]Cu-N=CPh_2 (**3b**) (Fig. S23), respectively, opening a facile pathway for C-N bond formation with radicals R• to form R-N=CPh_2 products (Fig 4a). Moreover, this spin density at the ketimide N-atom likely facilitates N-N bond formation via copper(II) ketimides [Cu^{II}]-N=CPh_2 to give the azine Ph_2C=N-N=CPh_2 (Fig. 4b), a competing pathway in sp^3 C-H functionalisation. Use of the more electron-poor ketimine HN=CAr' (Ar' = 4-$CF_3C_6H_4$) extends the scope of catalysis to unactivated sp^3 C-H bonds in cycloalkanes (Table 3; entries 6l - 6o). Nonetheless, facile N-N bond formation also by copper(II) ketimides [Cu^{II}]-N=CAr_2 underscores the role that they may play in the (electro)catalytic copper(II) promoted oxidative N-N coupling of benzophenone imine to form benzophenone azine (Fig 1g).[18]

Experimental section

Detailed experimental procedures are provided in the Supporting Information.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful to NSF (CHE-1665348 and CHE-1955942) for support of this work.

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