Copper(ii) ketimides in $sp^3$ C–H amination†

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Commercially available benzophenone imine (HN–CPh2) reacts with β-diketiminato copper(ii) tert-butoxide complexes [CuII]−O–Bu to form isolable copper(ii) ketimides [CuII]−N=–CPh2. Structural characterization of the three coordinate copper(ii) ketimide [Me2NN]Cu−N=–CPh2 reveals a short Cu–Nketimide distance (1.700(2) Å) with a nearly linear Cu–N–C linkage (178.9(2)°). Copper(ii) ketimides [CuII]−N=–CPh2 readily capture alkyl radicals R’ (PhCHMe and Cy) to form the corresponding R=N=–CPh2 products in a process that competes with N–N coupling of copper(ii) ketimides [CuII]−N=–CPh2 to form the azine Ph2C=–N=–CPh2. Copper(ii) ketimides [CuII]−N=–CAr2 serve as intermediates in catalytic $sp^3$ C–H amination of substrates R–H with ketimines HN=–CAr2 and BuOO–Bu as oxidant to form N-alkyl ketimines R−N=–CAr2. This protocol enables the use of unactivated $sp^3$ C–H bonds to give R−N=–CAr2 products easily converted to primary amines R−NH2 via simple acidic deprotection.

Introduction

Transition metal-catalysed $sp^3$ C–H amination protocols have gained immense attention in the synthetic community over the past couple of decades.¹ ¹ A majority of these protocols proceed via metal–nitrile² ² [M]=NR¹ or metal–amide [M]–NR¹” intermediates.¹ ¹ 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=CR¹” intermediates, however, have received less attention in C–H amination chemistry. The strong metal–Nketimide interaction makes ketimides effective spectator ligands. For instance, ketimides stabilize high valent homoleptic Mn(n)⁷, Fe(n)⁸ and Co(n)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 terminal 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 functional group 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

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reactions of redox-active alkyl esters (Fig. 1e)\textsuperscript{36} and Cu-catalysed benzylic sp\textsuperscript{3} C–H amination with benzophenone imine (Fig. 1f)\textsuperscript{27} 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\textsubscript{2}C=NH to azines Ar\textsubscript{2}C=NN=CAR\textsubscript{2} under aerobic or electrocatalytic conditions (Fig. 1g).\textsuperscript{18,19}

Herein we describe discrete first-row transition metal–ketimide complexes intimately involved in C–H amination chemistry. Building upon the Kharasch–Sosnovsky reaction\textsuperscript{10–22} we previously demonstrated that copper(II) alkyl amides [CuII][NHR]\textsubscript{2} and aryl oxides [CuII]OAr\textsubscript{2} serve as key intermediates in a radical relay protocol for sp\textsuperscript{3} C–H functionalisation (Fig. 2). Formed via acid–base\textsuperscript{6,23,24} or transesterification\textsuperscript{25} reactions between [CuII][Bu][H][FG] with H-FG or Ac-FG reagents, these copper(II) complexes [CuII][FG] capture sp\textsuperscript{3} C radicals R\textsuperscript{*} 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\textsuperscript{36} coupled with a preference for binding at copper with softer N-donors should enable the formation of [CuII][N]=CAR\textsubscript{2} species from [CuII][O]Bu complexes and HN=CPH\textsubscript{2} allow for an examination of 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\textsubscript{3}NN]Cu-OBu (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 (Fig. S2†). Performed on a preparative scale, this new species [Me\textsubscript{3}NN]Cu–N=CPH\textsubscript{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\textsubscript{3}NN]Cu–N=CPH\textsubscript{2} (3a) (Fig. 3a) reveals the Cu–N\textsubscript{Ketimide} distance of 1.700(2) Å, significantly shorter than the Cu–N bond found in the copper(II) amide [Cl\textsubscript{2}NN]Cu–NHAd (1.839(9) Å)\textsuperscript{23} and copper(II) anilide [Cl\textsubscript{2}NN]Cu–NHAr\textsubscript{Cl} (1.847(3) Å).\textsuperscript{6} Copper(II) ketimide 3a possesses a nearly linear Cu–N3–C24 angle of 178.9(2). The short Cu–N\textsubscript{Ketimide} distance and linear Cu–N3–C24 angle support effective sp hybridization at the ketimide N atom. These values remarkably differ from those in the homoleptic copper(I) ketimide [Cu–N=CPH\textsubscript{2}]\textsuperscript{4+}, with bridging ketimide ligands that lead to a square-like tetrameric structure with Cu–N distances 1.847(2)–1.861(2) Å and Cu–N–Cu angles of 94.17(9)–98.25(9).\textsuperscript{27} To outline differences between coordination of anionic ketimide ligands and their neutral ketimine counterparts, we prepared the corresponding benzophenone imine adducts [Me\textsubscript{3}NN]Cu(NH=CPH\textsubscript{2}) (4a) and [Cl\textsubscript{2}NN]Cu(NH=CPH\textsubscript{2}) (4b) (Fig. 3b). These copper(II) complexes feature substantially longer Cu–N\textsubscript{Ketimide} distances of 1.8940(14) and 1.8937(14) Å. These ketimine adducts 4a and 4b each exhibit a pronounced bend in the Cu–ketimide linkage with Cu–N–C angles of 132.68(12) and 130.25(12)° consistent with sp\textsuperscript{3} hybridization at N.

![Fig. 2](imageurl) Mechanism of C–H functionalisation via β-diketiminato copper(II) intermediates [CuII][FG].

![Fig. 3](imageurl) (a) Synthesis and structure of copper(II) ketimides. (b) Synthesis and structure of copper(I) imine adducts.
UV-vis analysis of copper(i) ketimide [Me3NN]Cu-N=CPh2 (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 $g_{\text{iso}} = 2.081$ with very well resolved coupling to $^{63/65}$Cu ($A_{\text{Cu}} = 298.0$ MHz) and additional hyperfine modelled with three equivalent $^{14}$N nuclei ($A_{\text{N}} = 35.0$ MHz) (Fig. S13†). The related copper(ii) ketimide [Cl2NN]Cu-N=CPh2 (3b) prepared from [Cl2NN]Cu-3b-OBu (2b) and HN=CPh2 exhibits a similar spectroscopic profile. The UV-vis spectrum of [Cl2NN]Cu-N=Ph3 (3b) exhibits a single absorption at 520 nm ($\epsilon = 3120$ M⁻¹ cm⁻¹) in toluene at room temperature and possesses a similar isotropic EPR spectrum to that of 3a (Fig. S14†). Unfortunately, the greater thermal sensitivity of [Cl2NN]Cu-N=CPh2 (3b) has precluded its crystallographic characterization.

DFT calculations reveal remarkably high unpaired electron density on the ketimide N atom of both 3a (0.58) and 3b (0.61) (Fig. 4 and S23†). These values are significantly higher than values reported for related three coordinate β-diketiminato Cu(i) anilides [Cu$i$]-NHAr (0.23–0.25)⁶ and a copper(i) amide [Cu$i$]-NHAd (0.49).₂¹ We rationalize this as a result of a 2-center 3-electron π interaction between the highest energy d orbital at the copper(i) center destabilized by the β-diketiminato N-donors and a p orbital of the sp-hybridized ketimide N atom (Fig. 4a). In addition, the orthogonal orientation of the Cu-Nketimide π-interaction relative to the conjugated ketimide N=CPh2 π system further limits the delocalization of unpaired electron density away from the ketimide N atom (Fig. 4b and c).

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

The ability of many β-diketiminato copper(i) complexes to participate in catalytic sp³ C-H functionalisation via radical relay (Fig. 2) encouraged us to assess the reactivity of copper(i) ketimides 3 towards alkyl radicals. We find that [Cu$i$]-N=CPh2 species 3a and 3b capture alkyl radicals $R^\prime$ to provide the corresponding R-N=CPh2 products (Fig. 5a). [Cu$i$] is anticipated to form in these radical capture reactions that correspond to step d in the radical relay catalytic cycle (Fig. 2). For instance, reaction of 3a and 3b with (E/Z)-azobis(2-phenylethane) at 90°C that generates the benzyl radical PhCH(="')Me upon heating provides the alkylated imine PhCH(N=CPh2)Me in 40% and 74% yields, respectively. Generation of Cy radicals in the presence of 3a and 3b by heating 'BuOO'Bu in cyclohexane (via H-atom abstraction by 'BuO' radicals) provides Cy-N=CPh2 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 Ph2C=N=CPh2 isolated in 66% and 90% yields, respectively (Fig. 5b). This represents a competing reaction for radical capture at copper(ii) ketimides 3a and 3b.

Copper(ii) ketimides in sp³ 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 [Cl2NN]Cu (1b) provides the highest yield compared to more electron-rich (1a and 1c) and electron-poor (1d) catalysts. Increasing the tBuOOBu 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≡CAr2 to the copper(i) catalyst (Fig. 3b) that inhibits tBuOOBu activation.28

While (1-(tert-butoxy)ethyl)benzene forms in trace amounts via C–H etherification,28 the azine Ph2C≡N–N≡CPh2 is the main byproduct in these catalytic C–H amination reactions, representing non-productive consumption of H–N≡CPh2. In a previous study of C–H amination with anilines H2NAr employing the [Cl2NN]Cu/tBuOOBu catalyst system, electron-poor anilines provided the highest yields in the face of competing diazene ArN≡NAr formation.23 Copper(ii) anilido intermediates [CuII]–NHAr serve as intermediates in C–H amination with anilines H2NAr, those derived from electron-poor anilines H2NAr (e.g. Ar = 2,4,6-C6H3–CF3) proved more resistant to reductive bimolecular N–N bond formation.6,24

To examine whether similar electronic changes in the ketimine H–N≡CAr2 could similarly promote more efficient catalysis, we explored two electron-poor ketimine derivatives H–N≡CPh2–diketiminato catalysts 1a and 1b (Ar = 4-ClC6H4 and 4-FC6H4) in C–H amination (Table 2). Although the p-ClF3 substituted imine provides a higher C–H amination yield with cyclohexane (C–H BDE = 97 kcal mol−1),29 the increase in yield is modest with the benzylic substrate ethylbenzene (C–H BDE = 87 kcal mol−1).28 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≡CPh2 to survey the scope of R–H substrates in sp3 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). Coordination of these substrates and/or products to the copper(i) centre that can decrease the rate of reoxidation with tBuOOBu.28 Aromatic substrates with benzylic C–H bonds undergo C–H amination in moderate to high yields (6e–6k). Cycloalkanes with stronger, unactivated sp3 C–H bonds give

![Chemical Structure](image)

**Table 1** Copper catalysed C–H amination of ethylbenzene with benzophenone imine

| Entry | Catalyst | (X, R1, R2) | Yield (%) |
|-------|----------|------------|-----------|
| 1     | [Me3NN]Cu 1a | (Me, Me, Me) | 34         |
| 2     | [Cl2NN]Cu 1b | (Me, Cl, H) | 65         |
| 3     | [Pr2NN]Cu 1c | (Me, Pr, H) | 30         |
| 4     | [Cl2NNF6]Cu 1d | (CF3, Cl, H) | 42         |

*a Conditions: 50 equiv. R–H. All yields determined by 1H NMR.

![Chemical Structure](image)

**Table 2** Copper catalysed C–H amination with benzophenone imine derivatives

| Entry | Ar | Yield (%) |
|-------|-----|-----------|
| 1     | Ph | 44 (5a)   |
| 2     | F2 | 51 (5a-CF3) |
| 3     | F  | 36 (5a-F)  |

*a Conditions: 10 equiv. R–H, 1.2 equiv. tBuOOBu, 1 mol% [Cl2NN]Cu, 90 °C, 24 h. Yields are determined by 1H NMR.

![Chemical Structure](image)

**Table 3** Copper catalyzed sp3 C–H amination with ketimines HN=CAr2

| Entry | Ar | Products isolated as ketimines |
|-------|----|--------------------------------|
| 6a    | Ph | 6a, 6g                         |
| 6b    | 50% | 6b, 6d                         |
| 6c    | 46% | 6c, 6e                         |
| 6d    | 38% | 6d, 6f                         |

*a Conditions: 10 equiv. R–H, 1.2 equiv. tBuOOBu, 1 mol% [Cl2NN]Cu, 90 °C, 24 h. Yields with HN=CPh2. Yields with HN=CAr2 (Ar = 4-CF3C6H4). H NMR yields (isolated yields) for 6f and 6g.
Ph2C
ketimine products and azine byproducts to regenerate the
potential to use recovered benzophenone from deprotection of
facile N
bonds in cycloalkanes (Table 3; entries
6l
amination. These reactive intermediates readily form
base exchange between [CuII]
CPh2 reveals the role that they play as intermediates in sp3 C
CF3C6H4) extends the scope of catalysis to unactivated sp3 C
Use of the more electron-poor ketimine HN
[CuII]
efficiently intercept alkyl radicals R
generated via H-atom abstraction by ‘BuO’ from substrates R-H
that ultimately enable the C-H amination of unactivated sp3 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 [Me2NN]Cu-N=CPh2 (3a) and [Cl2NN]Cu-N=CPh2
(3b) (Fig. 4 and S23†), respectively, opening a facile pathway for
C-N bond formation with radicals R• to form R-N=CPh2 products (Fig. 5a). Moreover, this spin density at the ketimide N
atom likely facilitates N-N bond formation via copper(III) ketimides [CuI\-N=CPh2 to give the azine Ph3C-N=N=CPh2
(Fig. 5b), a competing pathway in sp3 C-H functionalisation.
Use of the more electron-poor ketimine HN=CAR’ (Ar’ = 4- CF3C6H4) extends the scope of catalysis to unactivated sp3 C-H
bonds in cycloalkanes (Table 3; entries 6l-6o). Nonetheless, facile N-N bond formation also by copper(III) ketimides [CuI]-
N=CAR underscores the role that they may play in the (electro)
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data analysis, I. U. J. and T. H. W. wrote the manuscript with input from all authors.

Conclusions

The isolation of mononuclear copper(I) ketimides [CuI\-N=CPh2 reveals the role that they play as intermediates in sp3 C-H
amination. These reactive intermediates readily form via acid–base exchange between [CuI\-O’Bu and HN=CPh2, amenable
to spectroscopic and structural investigation. Importantly, [CuI\-N=CPh2 complexes efficiently intercept alkyl radicals R
via H-atom abstraction by ‘BuO’ from substrates R-H
that ultimately enable the C-H amination of unactivated sp3 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 [Me2NN]Cu-N=CPh2 (3a) and [Cl2NN]Cu-N=CPh2
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catalytic copper(II) promoted oxidative N-amination experiments, isolating and
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data analysis, I. U. J. and T. H. W. wrote the manuscript with input from all authors.

Conflicts of interest

There are no conflicts to declare.

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