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Copper(II) Ketimides in sp³ C-H Amination

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Commercially available benzophenone imine (HN=CPh₂) reacts with β-diketiminato copper(II) tert-butoxide complexes [Cu²⁺]:O'Bu to form isolable copper(II) ketimides [Cu²⁺]:N=CPh₂. Structural characterization of the three coordinate copper(II) ketimide [Me₃NN]Cu-N=CPh₂ reveals a short Cu-N_{substrate} distance (1.700(2) Å) with a nearly linear Cu-N-C linkage (178.9(2)°). Copper(II) ketimides [Cu²⁺]:N=CPh₂ readily capture alkyl radicals R• (PhCH•)Me and Cy• to form the corresponding R-N=CPh₂ products in a process that competes with N-N coupling of copper(II) ketimides [Cu²⁺]:N=CPh₂ to form the azine Ph₂C=N-N=CPh₂. Copper(II) ketimides [Cu²⁺]:N=CAr₂ serve as intermediates in catalytic sp³ C-H amination of substrates R-H with ketimines HN=CAr₂ and Bu₃O'Bu as oxidant to form N-alkyl ketimines R-N=CAr₂. This protocol enables the use of unactivated sp³ C-H bonds to give R-N=CAr₂ products easily converted to primary amines R-NH₂ via simple acidic deprotection.

Introduction

Transition metal-catalysed sp³ C-H amination protocols have gained an immense attention in the synthetic community over the past couple of decades. A majority of these protocols proceed via metal-nitrene or metal-amide intermediates. Extensive studies on such intermediates and underlying mechanisms have paved the way towards more efficient sp³ C-H amination protocols.

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 homogeneous 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, reversible C-C bond formation/cleavage in related copper complexes provides access to free copper nitrenes [Cu]=NAr that participate in sp³ C-H amination. Fewer examples of ketimides exist, however, in which the ketimide ligand serves as a reactive functional group in discrete transition metal complexes. Metal ketimide intermediates have been proposed in several Pd-catalysed cross-coupling reactions of aryl (Fig. 1c) and alkyl halides (Fig. 1d) with benzophenone imine. Cu-catalysed photoredox cross-coupling reactions of redox-active alkyl esters (Fig. 1e)⁶

**Fig. 1.** Transition metal ketimide complexes.

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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=NN=NAr\(_2\) under aerobic or electrocatalytic conditions (Fig. 1g).\(^{18, 19}\)

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\(^{-}\)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\(_{\text{ketimide}}\) distance of 1.700(2) Å, significantly shorter than the Cu-N bond found in the copper(II) amide [Cl\(_3\)NN]Cu-NHAd (1.839(9) Å)\(^{23}\) and copper(II) anilide [Cl\(_3\)NN]Cu-NHAr\(_{\text{C13}}\) (1.847(3) Å).\(^{6}\) Copper(II) ketimide 3a possesses a nearly linear Cu-N3-C24 angle of 178.9(2)°. The short Cu-N\(_{\text{ketimide}}\) distance and linear Cu-N3-C24 angle support effective sp\(^3\)-hybridization at the ketimide N atom. These values remarkably differ from those in the homoleptic copper(I) ketimide [Cu-N=CPh\(_2\)] 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)°.\(^{27}\) 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\(_3\)NN]Cu(NH=CPh\(_2\)) \((4b)\) (Fig 3b). These copper(I) complexes
feature substantially longer Cu-N\text{ketimine} 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 sp² hybridization at N.

UV-vis analysis of copper(II) ketimide \([\text{Me_2NN}]\text{Cu-N=CPH}_2\) (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 \(g_{\text{iso}} = 2.081\) with very well resolved coupling to \(^{63/65}\text{Cu} (A_{\text{Cu}} = 298.0\) MHz) and additional hyperfine modelled with three equivalent \(^{14}\)N nuclei (\(A_{\text{N}} = 35.0\) MHz) (Figure S13). The related copper(II) ketimide \([\text{Cl_2NN}]\text{Cu-N=CPH}_2\) (3b) prepared from \([\text{Cl_2NN}]\text{Cu-OBu\•} \) (2b) and \(\text{H=NCPH}_2\) exhibits a similar spectroscopic profile. The UV-vis spectrum of \([\text{Cl_2NN}]\text{Cu-N=Ph}_2\) (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 (Fig. S14). Unfortunately, the greater thermal sensitivity of \([\text{Cl_2NN}]\text{Cu-N=Ph}_2\) (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) (Figs. 4 and S23). These values are significantly higher than values reported for related three coordinate β-diketiminato Cu(II) anilides \([\text{Cu}^\beta]\text{-NHAr} \) (0.23-0.25)\(^\text{a}\) and a copper(II) amide \([\text{Cu}^\beta]\text{-NHAd} \) (0.49).\(^\text{a}\) We rationalize this as a result of a 2-center 3-electron π interaction between the highest energy d orbital at the copper(II) 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-N\text{ketimide} 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 (Figs. 4b and 4c).

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

The ability of many β-diketiminato copper(II) complexes to participate in catalytic sp² 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 \([\text{Cu}^\beta\text{N}]\text{-CPH}_2\) species 3a and 3b capture alkyl radicals \(\text{R•}\) to provide the corresponding R-N=CPH₂ products (Fig. 5a). \([\text{Cu}]\) 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(α-phenylethane) at 90 °C that generates the benzylic radical \(\text{PhCH(\•)}\text{Me}\) upon heating provides the alkylated imine \(\text{PhCH(N=CPH}_2\)Me in 40% and 74% yields, respectively. Generation of \(\text{Cy•}\) radicals in the presence of 3a and 3b by heating \(\text{BuOO\•}\) in cyclohexane (via H-atom abstraction by \(\text{BuOO\•}\) radicals) provides \(\text{Cy-N=CPH}_2\) in 58% and 41% yields, respectively.

**Radical capture by copper(II) ketimides: C-N bond formation**

\[
\text{PhN} \quad \text{90 °C} \quad \text{PhN} \quad \text{[Cu\text{Cu}^\beta\text{N=CPH}_2\]}
\]

5 equiv.

from 3a: 40% \(\text{from 3b: 74%}\)

**N-N bond formation via copper(II) ketimides: azine formation**

\[
2 \text{[Cu\text{Cu}^\beta\text{N=CPH}_2\] + Ph}_2\text{C=N-N=CPH}_2 \quad \text{18 h, 60 °C, phenylethane} \quad \text{[Cu\text{Cu}^\beta\text{N=CPH}_2\]}
\]

from 3a: 66% \(\text{from 3b: 90%}\)

**Fig. 5. Reactivity of copper(II) ketimides.** 2 equiv. diazene radical precursor.

Upon heating to 60 °C, copper(II) ketimides 3a and 3b undergo N-N coupling to form benzophenone azine \(\text{Ph}_2\text{C=N-N=CPH}_2\) 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 sp² 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(II) β-diketiminato catalysts 1 that possess different electronic and steric properties (Table 1). The catalyst \{[Cl₃NN]Cu \} 1b provides the highest yield compared to more electron-rich \{1a and 1c\} and electron-poor \{1d\} catalysts. Increasing the BuOOBu 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(II) catalyst (Fig. 3b) that inhibits \(^3\)BuOOBu activation. 2⁸

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Entry</th>
<th>Catalyst</th>
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<tbody>
<tr>
<td>1</td>
<td>[Me₂NN]Cu</td>
<td>1a</td>
<td>(Me, Me, Me)</td>
</tr>
<tr>
<td>2</td>
<td>[Cl₃NN]Cu</td>
<td>1b</td>
<td>(Me, Cl, H)</td>
</tr>
<tr>
<td>3</td>
<td>[Ph₂NN]Cu</td>
<td>1c</td>
<td>(Me, Pr, H)</td>
</tr>
<tr>
<td>4</td>
<td>[Cl₂N₂]Cu</td>
<td>1d</td>
<td>(CF₃, Cl, H)</td>
</tr>
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Conditions: 50 equiv. R-H. All yields determined by \(^1\)H NMR.

While (1-(tert-butoxy)ethyl)benzene form in trace amounts via C-H etherification⁹ 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 \{[Cl₃NN]Cu/\(^3\)BuOOBu\} catalyst system, electron-poor anilines provided the highest yields in the face of competing diazene \(HN=NR₂\) formation. 2⁴ Copper(II) anilido intermediates \[\text{Cu}^{	ext{II}}\]-\(H₂NAr\) serve as intermediates in C-H amination with anilines \(H₂NAr\); those derived from electron-poor anilines \(H₂NAr\) (e.g. \(Ar = 2,4,6\)-Cl₃C₆H₃) proved more resistant to reductive bimolecular N-N bond formation. 6, 2⁴

To examine whether similar electronic changes in the ketimine \(H=NCPh₂\) could similarly promote more efficient catalysis, we explored two electron-poor ketimine derivatives \(H=NCPh₂\) in C-H amination (Table 2). Although the \(p-F\), 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 benzylc 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 \(H=NCPh₂\) to survey the scope of R-H substrates in sp² 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

**Table 3. Copper catalyzed sp² C-H amination with ketimines H=NCPh₂.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
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<tr>
<td>1</td>
<td>Ph</td>
<td>6a</td>
<td>6b</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>6c</td>
<td>6d</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>6e</td>
<td>6f</td>
</tr>
</tbody>
</table>

Conditions: 10 equiv. R-H, 1.2 equiv. \(^3\)BuOOBu, 1 mol% \{[Cl₃NN]Cu\}, 90 °C, 24 h. *Yields with \(H=NCPh₂\). ²Yields with \(H=NCPh₂\) \((Ar = 4-CF₃C₆H₄)\). ³H NMR yields (isolate yields) for 6f and 6g.
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(II) centre that can decrease the rate of reoxidation with \( ^1 \)BuOO\(^{3}\)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 \(HN=\text{C}Ar'\) (\(Ar' = 4\text{-CF}_3\text{C}_6\text{H}_4\)) (6l - 6o). The bicyclic eucalyptol undergoes C-H amination in 32% yield (6e). These aminated products may be isolated either as synthetically versatile protected primary amines R-N=CPh\(_2\) via column chromatography (6a - 6g) or as the primary ammonium salts [R-NH\(_2\)]Cl via deprotection upon simple acidic work up (6h - 6o) under mild conditions. The potential to use recovered benzophenone from deprotection of ketimine products and azide byproducts to regenerate the \(\text{Ph}_2\text{C}=\text{NH}\) starting material\(^{10}\) enhances the overall atom economy of this amination protocol.

**Conclusions**

The isolation of mononuclear copper(II) ketimides \([\text{Cu}^{II}]\)-N=\text{C}Ph\(_2\) reveals the role that they play as intermediates in sp\(^3\) C-H amination. These reactive intermediates readily form via acid-base exchange between \([\text{Cu}^{III}]\)-O\(^{3}\)Bu and HN=\text{C}Ph\(_2\), amenable to spectroscopic and structural investigation. Importantly, \([\text{Cu}^{II}]\)-N=\text{C}Ph\(_2\) complexes efficiently intercept alkyl radicals R\(^*\) generated via H-atom abstraction by \(^1\)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 \([\text{Me}_2\text{NN}][\text{Cu}-\text{N}=\text{C}Ph\(_2\)]\) (3a) and \([\text{Cl}_2\text{NN}][\text{Cu}-\text{N}=\text{C}Ph\(_2\)]\) (3b) (Figs. 4 and S23), respectively, opening a facile pathway for C-N bond formation with radicals R\(^*\) to form R-N=\text{C}Ph\(_2\) products (Fig 5a). Moreover, this spin density at the ketimide N-atom likely facilitates N-N bond formation via copper(II) ketimides \([\text{Cu}^{II}]\)-N=\text{C}Ph\(_2\) to give the azine \(\text{Ph}_2\text{C}=\text{N}=\text{N}=\text{C}Ph\(_2\)\) (Fig 5b), a competing pathway in sp\(^3\) C-H functionalisation. Use of the more electron-poor copper(II) ketimide \(HN=\text{C}Ar'\) (\(Ar' = 4\text{-CF}_3\text{C}_6\text{H}_4\)) 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 \([\text{Cu}^{II}]\)-N=\text{C}Ar' underscores the role that they may play in the electrocatalytic 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 ESI.\(^+\)

**Conflicts of interest**

There are no conflicts to declare.

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**Notes and references**