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Copper Catalyzed sp3 C-H α-Acetylation

Otome Okoromoba, Eun Sil Jang, Claire McMullin, Thomas Cundari, Timothy H. Warren

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α-substituted ketones are important chemical targets as synthetic intermediates as well as functionalities in in natural products and pharmaceuticals. We report the sp^3 C-H α-acetylation of sp^3 C-H substrates R-H with arylmethyl ketones ArC(O)Me to provide α-alkylated ketones $ArC(O)CH_2R$ at RT with $^tBuOO^tBu$ as oxidant via copper(I) β-diketiminato catalysts. Proceeding via alkyl radicals R•, this method enables α-substitution with bulky substituents without competing elimination that occurs in more traditional alkylation reactions between enolates and alkyl electrophiles. DFT studies suggest the intermediacy of copper(II) enolates $[Cu^{II}](CH_2C(O)Ar)$ that capture alkyl radicals R• to give $R\text{-}CH_2C(O)Ar$ under competing dimerization of the copper(II) enolate to give the 1,4-diketone $ArC(O)CH_2CH_2C(O)Ar$.

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Otome E. Okoromoba,[a,b] Eun Sil Jang,[a] Claire L. McMullin,[c] Thomas R. Cundari,[c,*] and Timothy H. Warren[a,*]

[a]Department of Chemistry, Georgetown University, Box 571227-1227, Washington, D. C. 20057 USA; [b]Department of Chemistry and Biochemistry, George Mason University, Manassas VA, 22030 USA; [c]Department of Chemistry, Center for Advanced Scientific Computing and Modeling (CASCaM), University of North Texas, Denton, TX 78203 USA

Supporting Information Placeholder

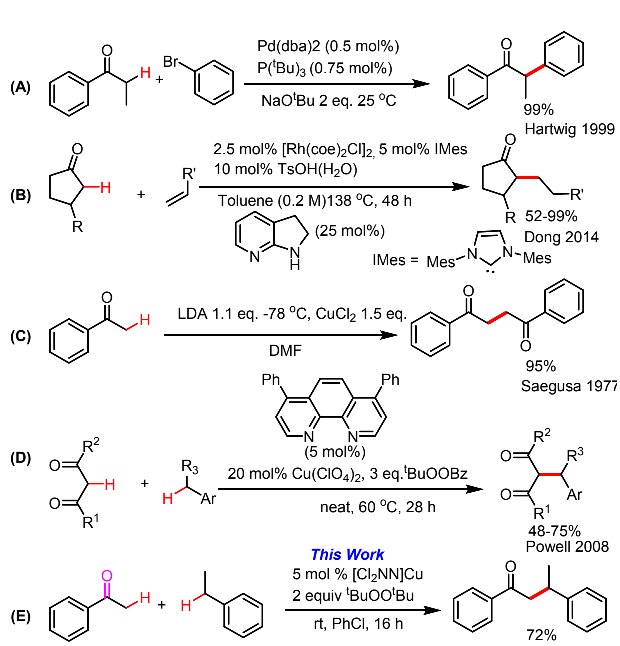
ABSTRACT: α-substituted ketones are important chemical targets as synthetic intermediates as well as functionalities in in natural products and pharmaceuticals. We report the sp^3 C-H α-acetylation of sp^3 C-H substrates R-H with arylmethyl ketones ArC(O)Me to provide α-alkylated ketones $ArC(O)CH_2R$ at RT with $^tBuOO^tBu$ as oxidant via copper(I) β-diketiminato catalysts. Proceeding via alkyl radicals R•, this method enables α-substitution with bulky substituents without competing elimination that occurs in more traditional alkylation reactions between enolates and alkyl electrophiles. DFT studies suggest the intermediacy of copper(II) enolates $[Cu^{II}](CH_2C(O)Ar)$ that capture alkyl radicals R• to give $R\text{-}CH_2C(O)Ar$ under competing dimerization of the copper(II) enolate to give the 1,4-diketone $ArC(O)CH_2CH_2C(O)Ar$.

Ketones with multiple substituents on the α-carbon represent important targets for chemical synthesis. The value of this structural motif stems from their prevalence in both natural products and pharmaceuticals[1] as well as the ability of α-substituted ketones to participate in olefenations, stereoselective 1,2-additions and enolate reactions.[2-4] While stoichiometric α-alkylation of enolates with electrophiles such as alkyl halides represents a common approach,[5] competing side reactions such as elimination with hindered electrophiles, aldol condensations or even *O*-alkylations can lead to a range of byproducts.[6] α-alkylation of ketones with alcohols have been widely investigated with a number of heterogenous and homogenous catalysts.[7-10] This approach employs a hydrogen borrowing process where the alcohol is converted to the aldehyde and is coupled with the corresponding ketone to give the alkylated product.

Transition metal-catalyzed processes may proceed through metal-enolates thought to be intermediates in coupling of aryl halides to ketones by Pd with bulky, unidentate ligands (Scheme 1a).[11] Alternatively, ketones have been oxidatively coupled with an olefin using a bifunctional catalyst that simultaneously activates the α-C-H bonds of the ketone and olefin as described by the Dong group (Scheme 1b).[12] Not all transition metal enolate intermediates, however, are stable. Addition of preformed enolates to copper(II) salts is a well-established method for the C-C coupling of enolates to 1,4-diones (Scheme 1c).[12b]

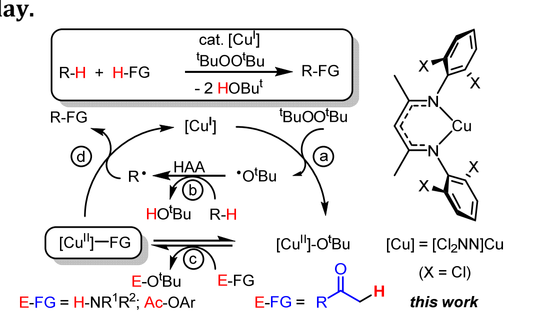
The direct use of substrates that possess sp^3 C-H bonds for C-C bond formation represents an attractive route for the α-functionalization of ketones. Powell reported in 2008 that 1,3-diketones may undergo C-H functionalization when catalyzed by copper with a phenanthroline ligand. As these conditions appear familiar to a family of copper-catalyzed radical relay

Scheme 1. Approaches to C-C Bond Formation via Enolates



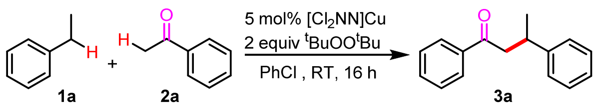
reactions that we[13-15] and others[16-19] have recently outlined, we were eager to examine the possibility of copper(II) enolate intermediates, even if transient, in radical capture (Scheme 2). In related radical relay reactions, $^tBuOO^tBu$ reacts swiftly with the copper(I) β-diketiminate $[Cl_2NN]Cu$ to give $[Cu^{II}]\text{-}O^tBu$ and the *t*-butoxy radical (Scheme 2a)[13] that readily reacts via H-atom abstraction with sp^3 C-H bonds in substrates R-H to generate the C-based radical R• (Scheme 2b).[20] As with facile acid-base exchange that occurs with anilines we hypothesized

Scheme 2. Catalytic C-H Functionalization via Radical Relay.



that acid-base exchange between $[Cu^{II}]$-O^{t}Bu and the ketone could form $[Cu^{II}]$-enolate species capable of efficient capture of organic radicals R• to form a new C-C bond (Scheme 2).

Table 1. Optimization of Reaction Conditions



Entry	Variation of standard conditions	Conversion[a] %	Yield[b] %
1	None	87	73
2	Neat	85	66
3	90 °C	70	54
4	PhH as solvent	75	60
5	PhF as solvent	80	66
6	1 eq. ^{t}BuOO^{t}Bu	70	33
7	50 eq. ethylbenzene	90	75
8	10 mol% $[Cl_2NN]Cu$	85	69
9	2.5 mol% $[Cl_2NN]Cu$	65	< 23

(a) conversion of acetophenone (b) yields determined by isolation.

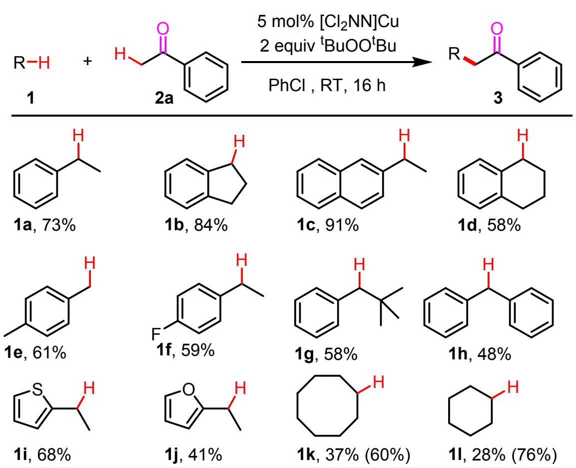
We were delighted to observe that mixing acetophenone and ethylbenzene in the presence of $[Cl_2NN]Cu$ as catalyst with ^{t}BuOO^{t}Bu as oxidant at 90 °C afforded the α-alkylated ketone **3a** in 54% isolated yield with ca. 30% recovered ketone (Table 1). Subsequent screening identified that the reaction is most effficient at room temperature along with 5 mol% $[Cl_2NN]Cu$, 2 equiv. ^{t}BuOO^{t}Bu and chlorobenzene as solvent (Table 1). Conditions involving lower or higher concentrations of ^{t}BuOO^{t}Bu, C-H substrates, or catalyst loading did not simprove the yield of the α-alkylated product **3a**. A modest screening of other β-diketiminato catalyst structures did not lead to improved yields or conditions (Table 1).

Following initial optimization, we investigated the scope and effectiveness of our methodology on several sp^3 C-H substrates (Table 2). Substrates with benzylic sp^3 C-H bonds (**1a** - **1h**) gave good to excellent yields under our protocol (Table 2). Additionally, unactivated C-H substrates such as cyclooctane and cyclohexane (**1k** and **1l**) gave good NMR yields of the coupling product, but isolated yields suffered due to competing C-H etherification to give R-O^{t}Bu by capture of the alkyl radical R• with the $[Cu^{II}]$-O^{t}Bu intermediate.[13] Heteroaromatic C-H substrates like ethylfuran (**1i**) and ethylthiophene (**1j**) gave moderate to good yields of alkylated products.

We then examined the ketone substrate scope with (hetero)aryl methyl ketones which provide C-C coupling products as single diastereomers with prochiral 2° and 3° alkyl radicals (Table 3). Using ethylbenzene as the sp^3 C-H substrate, substituted aryl ketones (**2a** - **2g**) gave moderate to good yields of the α-alkylated products. Some substrates required heating to encourage higher yields (**2g** - **2k**). For instance, 3-acyl pyridine (**2c**) gave a trace amount of product at RT, but afforded an isolable amount (22%) when the reaction was run at 90 °C. We suspect that binding of the pyridyl substrate to the $[Cu^I]$ catalyst may hinder peroxide activation by the $[Cu^I]$ center.[13] *Ortho*-disubstituted aryl methyl ketones react sluggishly at RT but gave the C-H functionalized products when the reaction was heated to 90 ˚C. Electron withdrawing ketones such as dichloroacetophenone (**2i**) and pentafluoroacetophenone (**2j**) gave moderate yields while the electron releasing trimethylacetophenone (**2k**) gave only a trace amount of product. The simple ketone acetone (**2l**) may be used in C-H functionalization with ethylbenzene, providing the C-H α-acetylation product in 41% yield.

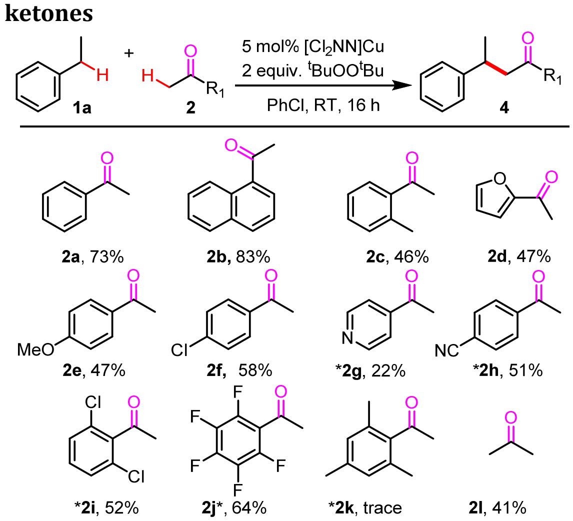
Since quaternary carbon centers are common features in nature and biologically active small molecules,[21] we anticipated that our radical route could potentially overcome challenges inherent in constructing a crowded carbon center.[22] Radical carbon centers are generally stable to elimination or isomerization,[23] although few, there are reports that demonstrate the construction of quaternary C-C bonds from carbon radicals.[24-26] For instance, Murphy and co-workers recently demonstrated how the generation of carbon radical center from α,β-unsaturated ketones are trapped to form asymmetric quater-

Table 2. C-H Acetylation of Ethylbenzene with Various ketones



Reaction conditions: 0.5 mmol acetophenone, 10 equiv. C-H substrate, 5 mol% $[Cl_2NN]Cu$, 2 equiv. ^{t}BuOO^{t}Bu at RT for 16 h in 0.5 mL chlorobenzene; (NMR yield).

Table 3. C-H Acetylation of Ethylbenzene with Various ketones



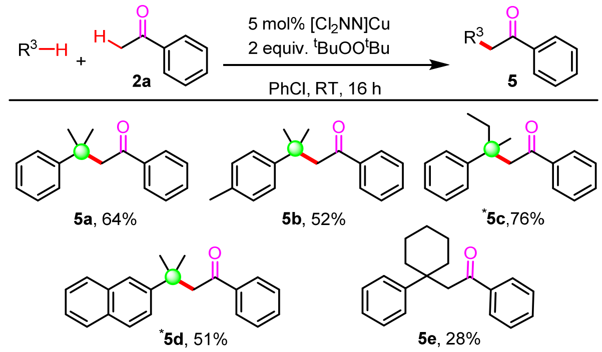
Reaction conditions: 10 equiv. **1a**, 0.5mmol **2,** 5 mol% $[Cl_2NN]Cu$, 2 equiv. ^{t}BuOO^{t}Bu at RT for 16 h in 0.5 mL solvent. **(*)** Reactions were run at 90 °C.

nary centers from the combination of photoredox and asymmetric organic catalysis.[25]

Quaternary carbons may be formed in the reaction of acetophenone with C-H substrates that possess 3° C-H bonds (Table 4). Cumene, *sec*-butylbenzene, cymene and 2-isopropylnaphthalene coupled effectively with acetophenone giving quaternary carbon-containing products **5a** - **5d** in 51 - 76% yield. We observed a low yield (28%), however, in the coupling of cyclohexylbenzene (**5c**) with acetophenone, perhaps due to competing side reactions that involve the cyclohexyl C-H bonds.

Based on previous radical relay catalysis by copper β-diketiminates, we believe that the copper(II) enolate $[Cl_2NN]Cu(CH_2C(O)Ph)$ (**6**) serves as a key intermediate (Scheme 2). Despite a number of synthetic approaches, we have not been able to isolate such a copper(II) enolate intermediate. Indeed, we are only aware of a recently reported copper(II) enolate $\{[NNN]Cu(OC{=}C(Me)Ph)\}^-$ derived from 2-phenylpropionaldehyde and supported by a tridentate, dianionic pyridine dicarboxamide ligand.[27] Nonetheless, addition of excess acetophenone to $[Cl_2NN]Cu\text{-}O^tBu$ results in second order decay of the otherwise stable copper(II) *t*-butoxide (Fgures S1-S2). GC/MS analysis of the resulting solution reveals the homocoupled diketone product $PhC(O)CH_2CH_2C(O)Ph$ in 82% yield. Based on these observations, it is likely K_{eq} for acid base exchange is small while the rate of bimolecular $[Cu^{II}]$-enolate decay is fast.

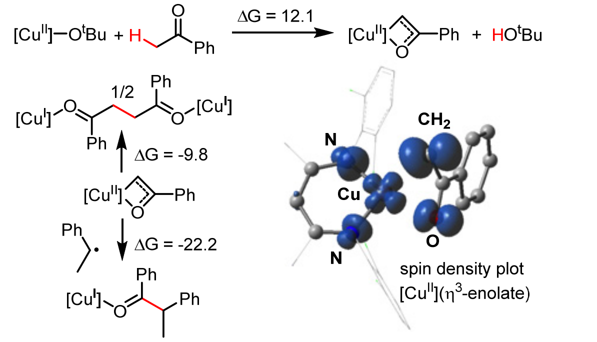
Table 4. Quaternary C-C bond formation.



Reaction conditions: 0.5 mmol acetophenone, 10 equiv. C-H substrate, 5 mol% $[Cu^I]$, 2 equiv. $^tBuOO^tBu$ at RT for 16 h in 0.5 mL chlorobenzene.
* Performed at 90 ^oC.

We examined putative copper(II) enolates by DFT at the ONIOM(bp86/6-311+g(d):UFF) level of theory. We considered three binding modes that reveal the η^3-CCO bonded $[Cl_2NN]Cu^{II}(\eta^3\text{-}CH_2C(O)Ph)$ (**6**) to be lowest in energy, with κ^1-O and η^2-CC binding modes 7.6 and 8.5 kcal/mol higher in free energy (Figure S3, SI). Nonetheless, reaction of $[Cu^{II}]$-O^tBu with PhC(O)Me to give $[Cu^{II}](\eta^3\text{-}CH_2C(O)Ph)$ and HO^tBu is endergonic by 12.1 kcal/mol. Complexation to this copper(II) center results in delocalization of a significant amount of unpaired electron density onto the enolate ligand (Scheme 4). This enables facile bimolecular C-C coupling to the coordinated 1,4-diketone **5** which is exergonic by 19.6 kcal/mol. Importantly, capture of the ethylbenzene radical to the κ^1-O bound substituted ketone is exergonic by 22.2 kcal/mol.

Scheme 4. Structure and Reactivity of Copper(II) Enolate Intermediate Assessed by DFT



In summary, we have developed a novel intermolecular copper catalyzed sp^3 C-H α-acetylation for the construction of C-C bonds via copper catalyzed C-H functionalization of unactivated C-H compounds and ketones. This approach that features readily available simple sp^3 C-H substrates and a variety of ketones offers a complementary catalytic Csp^3–Csp^3 disconnection strategy to prepare small molecules that may be building blocks for the assembly of biologically active and/or other synthetically useful products.

ASSOCIATED CONTENT

Supporting Information. Experimental and characterization details (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

* thw@georgetown.edu

Notes

The authors declare no competing financial interest.

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