How to cite: *Angew. Chem. Int. Ed.* **2025**, *64*, e202418692
doi.org/10.1002/anie.202418692

Transition-Metal Catalysis

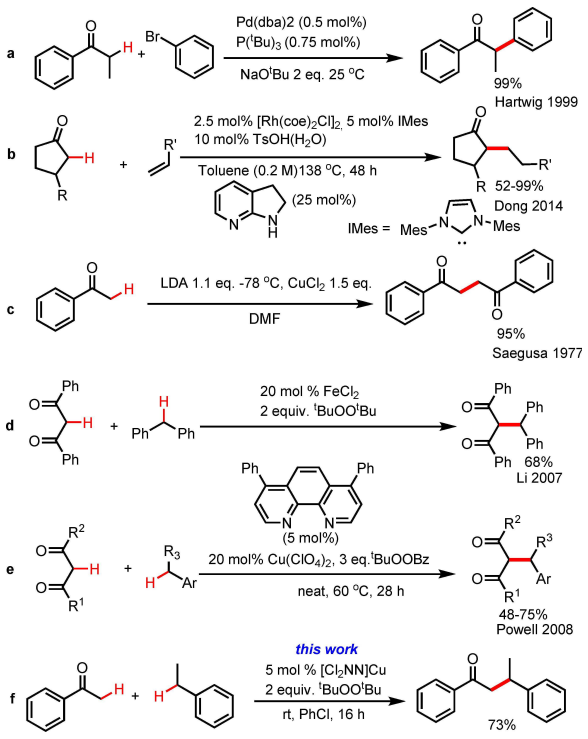
Copper-Catalyzed C(sp^3)–H α-Acetylation: Generation of Quaternary Centers

Otome E. Okoromoba, Ting-An Chen, Eun Sil Jang, Claire L. McMullin, Thomas R. Cundari, and Timothy H. Warren**

Abstract: α-substituted ketones are important chemical targets as synthetic intermediates as well as functionalities in natural products and pharmaceuticals. We report the α-acetylation of C(sp^3)–H substrates R–H with arylmethyl ketones ArC(O)Me to provide α-alkylated ketones ArC(O)CH_2R at RT with ^{t}BuOO^{t}Bu 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–CH_2C(O)Ar outcompeting 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 bioactive compounds[1] as well as the ability of α-substituted ketones to participate in olefinations, 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 heterogeneous and homogeneous catalysts.[7] 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-enolate intermediates in the coupling of aryl halides to ketones by Pd with bulky, unidentate ligands (Scheme 1a).[8] 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).[9] Transition metal free routes can convert cinnamic acids to alkyl-substituted acetophenones ArC(O)CH_2–R under oxidative conditions with substrates R–H.[10] Not all transition metal enolates intermediates, however, are stable. Addition



Scheme 1. Approaches to C–C bond formation via enolates.

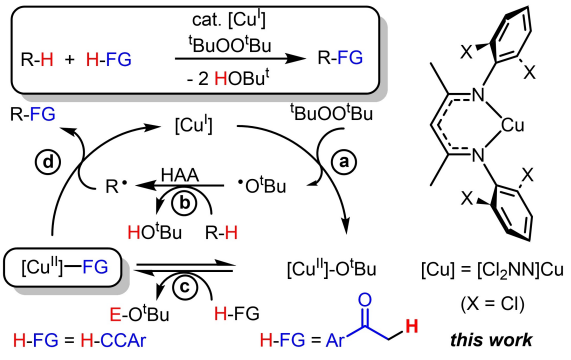
[*] Dr. O. E. Okoromoba, Dr. T.-A. Chen, Dr. E. S. Jang, Prof. Dr. T. H. Warren
Department of Chemistry, Georgetown University
Box 571227, 20057-1227 Washington, DC (USA)
Dr. T.-A. Chen, Prof. Dr. T. H. Warren
Department of Chemistry, Michigan State University
578 S. Shaw Lane, 48824 East Lansing, MI (USA
E-mail: warre155@msu.edu
Prof. Dr. C. L. McMullin
Department of Chemistry, University of Bath
BA2 7AY Bath (UK)
Prof. Dr. T. R. Cundari
Department of Chemistry, Center for Advanced Scientific Computing and Modeling (CASCaM), University of North Texas
76203 Denton, TX (USA)
E-mail: t@unt.edu

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).[11]

The direct use of substrates that possess sp^3 C–H bonds for C–C bond formation[12–13] represents an attractive route for the α-functionalization of ketones. Studies with $FeCl_2$ and $^tBuOO^tBu$ revealed that $PhCH_2Ph$ undergoes C–H functionalization to deliver the corresponding C–C cross-coupling product (Scheme 1d).[14] Powell reported in 2008 that 1,3-diketones undergo C–H functionalization when catalyzed by copper with a phenanthroline ligand and ^tBuOOBz as oxidant.[15] As these conditions appear familiar to those employed in the Kharasch–Sosnovsky reaction,[16] we considered the possibility that copper(II) enolates could serve as intermediates in a copper catalyzed radical relay protocol[13] for C–H α-acetylation to functionalize substrate R–H to $R–CH_2C(O)Ar$.

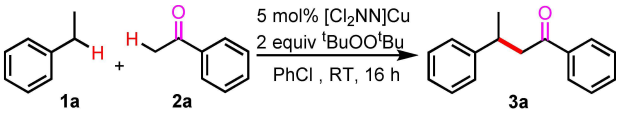
Inspired by the ability of copper β-diketiminate catalysts to generate reactive copper(II) species $[Cu^{II}]–R'$ (R'= alkynyl,[17] methyl,[18] and alkenyl[19]) that function in radical relay catalysis, we sought to explore the possibility that copper(II) enolate intermediates $[Cu^{II}]–CH_2C(O)Ph$, even if transient, could similarly lead to C–C bond formation (Scheme 2).[13] In related radical relay reactions, $^tBuOO^tBu$ reacts swiftly with the copper(I) β-diketiminate $[Cl_2NN]Cu$ to give $[Cu^{II}]–O^tBu$ and the *t*-butoxy radical (Scheme 2a)[20] 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).[21] Since facile acid-base exchange occurs with terminal acetylenes,[17] we hypothesized that reaction between $[Cu^{II}]–O^tBu$ 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).

We were delighted to observe that mixing acetophenone and ethylbenzene in the presence of $[Cl_2NN]Cu$ as catalyst with $^tBuOO^tBu$ 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 efficient at room temperature along with 5 mol % $[Cl_2NN]Cu$, 2 equiv. $^tBuOO^tBu$ and chlorobenzene as solvent (Table 1). Conditions involving lower or higher concentrations of $^tBuOO^tBu$, C–H substrates, or catalyst loading did not improve the yield of the α-alkylated product



Scheme 2. Catalytic C–H functionalization via radical relay.

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. $^tBuOO^tBu$	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

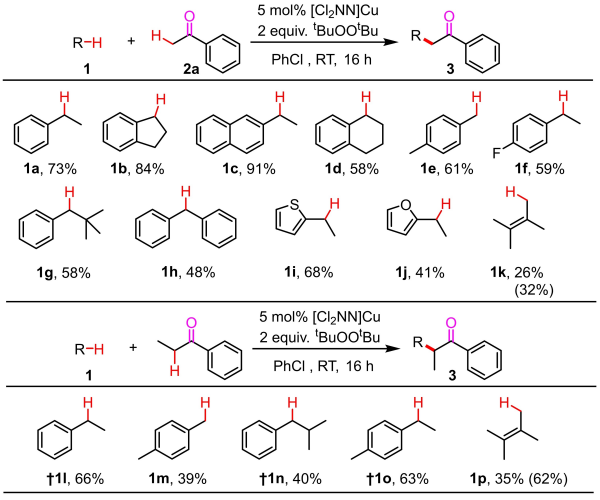
(a) conversion of acetophenone, (b) yields determined by isolation.

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).

Heteroaromatic C–H substrates such as ethylfuran (**1i**) and ethylthiophene (**1j**) gave moderate to good yields of alkylated products. Tetramethylethylene (**1j**) also undergoes α-acetylation at an allylic C–H bond. We find that

Table 2: Catalytic sp^3 C–H acetylation with acetophenone.



Reaction conditions: 0.5 mmol acetophenone, 10 equiv. C-H substrate, 5 mol% $[Cl_2NN]Cu$, 2 equiv. $^tBuOO^tBu$ at RT for 16 h in 0.5 mL chlorobenzene; †dr = 1:1; (NMR yield).

cyclohexane, however, provides poor conversion to the desired functionalization product. Instead, Cy–O^{t}Bu is the primary product, likely a result of C–H etherification of cyclohexane via [Cu^{II}]–O^{t}Bu (Figure S1).[20]

Propiophenone also undergoes functionalization with benzylic and allylic R–H substrates (**1l**–**1p**), generating a mixture of diastereomer products upon C–H functionalization by 2° benzylic substrates (**1l**, **1n**, **1o**; dr = 1:1). Notably, 4-ethyltoluene (**1o**) undergoes selective functionalization at the 2° benzylic position. The use of N-heteoaromatic substrates such as 8-methylquinoline or ethylpyrazine led to the unexpected α-etherification product PhC(O)CH(O^{t}Bu)Me (Figure S2).

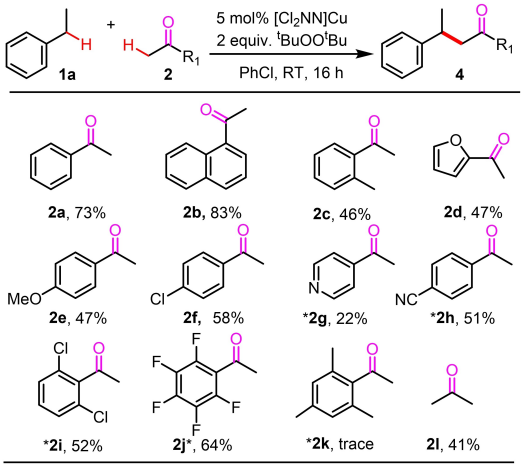
We then examined the ketone substrate scope with (hetero)aryl methyl ketones which provide C–C coupling products as single diastereomers with prochiral 2° and 3° alkyl radicals (Table 3). Using ethylbenzene as the sp^3 C–H substrate, substituted aryl ketones (**2a**–**2g**) gave moderate to good yields 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.[20] *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. In fact, competition experiments between acetophenone and 4-Cl or 4-Me substituted acetophenones show a mild preference for C–H functionalization with the more electron-poor ketone (Scheme S2). Importantly, the simple ketone acetone (**2l**) may be used in C–H functionalization with ethylbenzene, providing the C–H α-acetylation product in 41 % yield.

We anticipated that this radical route to C–C bonds could potentially overcome challenges inherent in constructing quaternary carbon centers[22] that are common features in natural products and biologically active small molecules.[23] As sp^3 carbon-based radicals are reasonably stable towards elimination or isomerization,[24] several recent reports demonstrate the construction of quaternary C–C bonds from carbon radicals.[25] For instance, Liu and coworkers recently disclosed a C-arylation protocol that forms quaternary carbons via tertiary radicals derived from α-substituted acrylamides that are proposed to undergo capture by Cu^{II}-aryl intermediates.[26]

Quaternary carbons form 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 with acetophenone (**5e**), perhaps due to competing side reactions that involve the cyclohexyl C–H bonds.

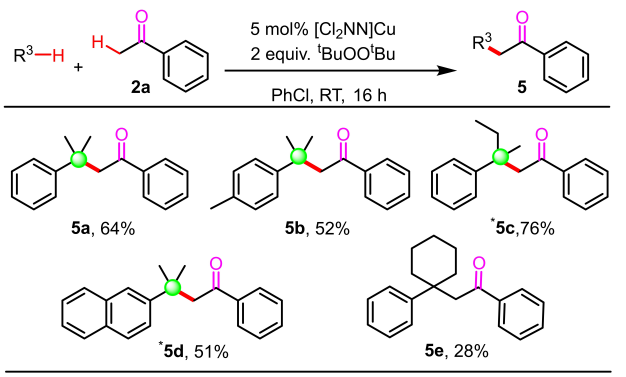
Based on previous radical relay catalysis by copper β-diketiminates, we believe that the copper(II) enolate [Cl$_2$NN]Cu(CH$_2$C(O)Ph) (**6**) serves as a key intermediate (Scheme 3).[17–20,27] Despite a number of synthetic approaches, we have not been able to isolate such a copper(II) enolate intermediate. 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.[28] Nonetheless, addition of excess acetophenone to [Cl$_2$NN]Cu–O^{t}Bu results in second order decay of the otherwise stable copper(II) *t*-butoxide (Figures S3–S4). GC/MS analysis of the resulting solution reveals the homocoupled diketone product PhC(O)CH$_2$CH$_2$C(O)Ph in 82 % yield (Scheme 3). Based on these observations, it is likely that K_{eq} is small for acid-base exchange between [Cu^{II}]–O^{t}Bu and H–CH$_2$C(O)Ph to form the copper(II) enolate [Cu^{II}](CH$_2$C(O)Ph) while the rate of bimolecular coupling of the copper(II) enolate is fast.

Table 3: C–H acetylation of ketones with ethylbenzene.

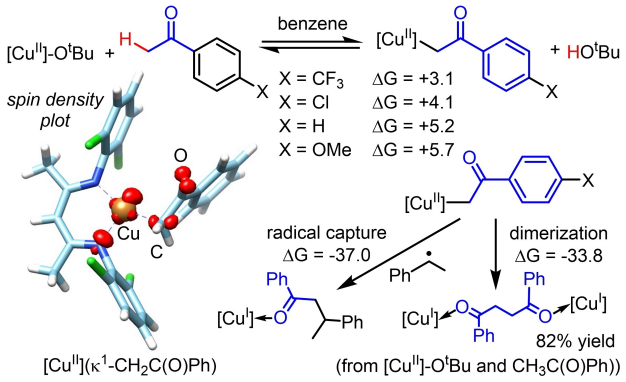


Reaction conditions: 10 equiv. **1a**, 0.5mmol **2**, 5 mol% [Cl$_2$NN]Cu, 2 equiv. ^{t}BuOO^{t}Bu at RT for 16 h in 0.5 mL solvent. * Performed at 90 °C. †dr = 1:1.

Table 4: Quaternary carbon formation via sp^3 C–H acetylation.



Reaction conditions: 0.5 mmol acetophenone, 10 equiv. C-H substrate, 5 mol% [Cu^I], 2 equiv. ^{t}BuOO^{t}Bu at RT for 16 h in 0.5 mL chlorobenzene.
* Performed at 90 °C.



Scheme 3. Computational analysis of copper(II) enolate formation and reactivity. Free energies in kcal/mol at 298.15 K.

We employed DFT calculations at the BP86-D3BJ/6-311 + G(d,p)/SMD-benzene//BP86/6-311 + G(d,p) level of theory to illuminate the nature of the reactive intermediates in this C–C coupling reaction. Indeed, the reaction between $[Cu^{II}]$–O^{t}Bu and PhC(O)CH$_3$ to give the most stable copper-(II) enolate $[Cu^{II}](\kappa^1$–CH$_2$C(O)Ph) is endergonic by 5.2 kcal/mol at 298 K corresponding to an equilibrium constant $K_{eq} = 1.5 \times 10^{-4}$ for acid-base exchange.

Three different enolate binding modes were considered that reveal the κ^1–C isomer to be 2.0 and 2.6 kcal/mol lower in free energy than η^3–CCO and κ^1–O conformations, respectively (Figure S5 and Table S3). DFT analysis suggests that reaction of $[Cu^{II}]$–O^{t}Bu initally proceeds with a barrier of 20.0 kcal/mol through a κ^1–O isomer that converts with low barriers to the lowest energy κ^1–C species via the η^3–CCO isomer (Figure S7). Consistent with copper(II) enolate formation occuring via acid-base reaction between the acetophenone and $[Cu^{II}]$–O^{t}Bu, acetophenones with electron-withdrawing substituents favor formation of the copper(II) enolate. This mirrors competiton studies that show electron-withdrawing acetophenones preferentially participate in C–H functionalization in the presence of more electron-rich ketones (Scheme S2).

While the Cu center in these T-shaped copper(II) enolates $[Cu^{II}](\kappa^1$–CH$_2$C(O)Ar^X) (X = CF$_3$, Cl, H, OMe) represents the site of largest unpaired electron density (0.43–0.46 e$^-$), significant unpaired electron density also exists at the α-C atom (0.17–0.19 e$^-$) that identifies the enolate α-carbon as a site for C–C coupling (Scheme 3, Table S5). Accordingly, bimolecular dimerization of $[Cu^{II}](\kappa^1$–CH$_2$C(O)Ph) ($\Delta G = -37.0$ kcal/mol) competes with capture of the ethylbenzene radical PhCH(•)Me ($\Delta G = -33.8$ kcal/mol) (Scheme 3). Nonetheless, these endergonic formation of the copper(II) enolates from acetophenone with $[Cu^{II}]$–O^{t}Bu combined with low barriers for radical capture or enolate coupling (Figure S7) suggests that copper(II) intermediates would not be directly observable by UV/Vis spectroscopy.

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 benzylic and allylic substrates with acetophenones. This approach that features readily available sp^3 C–H substrates and alkyl aryl ketones, as well as acetone, 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.

Supporting Information

Detailed experimental methods and characterization of all products is given in the Supporting Information. The authors have cited additional references within the Supporting Information

Acknowledgements

T. H. W. is grateful to NSF for support of this work (CHE-1665348 and 1955942/2303206). T. R. C. thanks the U.S. Department of Energy, Office of Basic Energy Sciences (Division of Chemical Sciences, Geosciences, and Biosciences) for partial support of this research via grant DE-FG02-03ER15387. Some calculations employed the UNT Chemistry high-performance computing facility, purchase of which was supported by NSF grant CHE-1531468.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Acetylation · Copper · Ketones · C–H Functionalization · Catalysis

[1] D. J. Foley, H. Waldmann, *Chem. Soc. Rev.* **2022**, *51*, 4094–4120.
[2] N. Yoshikawa, Y. M. A. Yamada, J. Das, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1999**, *121*, 4168–4178.
[3] D. H. Camacho, I. Nakamura, B. H. Oh, S. Saito, Y. Yamamoto, *Tet. Lett.* **2002**, *43*, 2903–2907.
[4] C. S. Cho, B. T. Kim, T.-J. Kim, S. C. Shim, *Tet. Lett.* **2002**, *43*, 7987–7989.
[5] I. Ibrahem, A. Córdova, *Angew. Chem. Int. Ed.* **2006**, *45*, 1952–1956.
[6] R. B. Bates, S. R. Taylor, *J. Org. Chem.* **1993**, *58*, 4469–4470.
[7] a) F. Huang, Z. Liu, Z. Yu, *Angew. Chem. Int. Ed.* **2016**, *55*, 862–875; b) Y. Obora, *ACS Catal.* **2014**, *4*, 3972–3981.
[8] a) M. Kawatsura, J. F. Hartwig, *J. Am. Chem. Soc.* **1999**, *121*, 1473–1478; b) J. M. Fox, X. Huang, A. Chieffi, S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 1360–1370.
[9] a) F. Mo, G. Dong, *Science* **2014**, *345*, 68–72; b) Z. Huang, H. N. Lim, F. Mo, M. C. Young, G. Dong, *Chem. Soc. Rev.* **2015**, *44*, 7764–7786.

[10] J. Ji, P. Liu, P. Sun, *Chem. Commun.* **2015**, *51*, 7546–7549.
[11] Y. Ito, T. Konoike, T. Saegusa, *J. Am. Chem. Soc.* **1975**, *97*, 2912–2914.
[12] H. Yi, G. Zhang, H. Wang, Z. Huang, J. Wang, A. K. Singh, A. Lei, *Chem. Rev.* **2017**, *117*, 9016–9085.
[13] a) D. L. Golden, S.-E. Suh, S. S. Stahl, *Nat. Chem. Rev.* **2022**, *6*, 405–427; b) Z. Zhang, P. Chen, G. Liu, *Chem. Soc. Rev.* **2022**, *51*, 1640–1658.
[14] Z. Li, L. Cao, C.-J. Li, *Angew. Chem. Int. Ed.* **2007**, *46*, 6505–6507.
[15] N. Borduas, D. A. Powell, *J. Org. Chem.* **2008**, *73*, 7822–7825.
[16] a) M. S. Kharasch, G. Sosnovsky, *J. Am. Chem. Soc.* **1958**, *80*, 756; b) M. S. Kharasch, G. Sosnovsky, N. C. Yang, *J. Am. Chem. Soc.* **1959**, *81*, 5819–5824; c) D. J. Rawlingson, G. Sosnovsky, *Synthesis* **1972**, 1–28; d) M. B. Andrus, J. C. Lashley, *Tetrahedron* **2002**, *58*, 845–866.
[17] A. Bakhoda, O. E. Okoromoba, C. Greene, M. R. Borougeni, J. A. Bertke, T. H. Warren, *J. Am. Chem. Soc.* **2020**, *142*, 28483–18490.
[18] B. C. Figula, T.-A. Chen, J. A. Bertke, T. H. Warren, *ACS Catal.* **2022**, *12*, 11854–11859.
[19] T.-A. Chen, R. J. Staples, T. H. Warren, *Chem. Sci.* **2024**, *15*, 17685–17690.
[20] R. T. Gephart, C. L. McMullin, N. G. Sapiezynski, E. S. Jang, M. J. B. Aguila, T. R. Cundari, T. H. Warren, *J. Am. Chem. Soc.* **2012**, *134*, 17350–17353.
[21] M. Finn, R. Friedline, N. K. Suleman, C. J. Wohl, J. M. Tanko, *J. Am. Chem. Soc.* **2004**, *126*, 7578–7584.
[22] C. J. Douglas, L. E. Overman, *PNAS* **2004**, *101*, 5363–5367.
[23] C. Li, S. S. Ragab, G. Liu, W. Tang, *Nat. Prod. Rep.* **2020**, *37*, 276–292.
[24] M. B. Smith, *C[a] Disconnect Products: Electrophilic Carbon-Carbon Bond-Forming Reactions. In Organic Synthesis (3rd Ed), Chapter 12, M. B. Smith, Ed. Academic Press:* Oxford, **2010**; pp 1161–1255.
[25] a) J. J. Murphy, D. Bastida, S. Paria, M. Fagnoni, P. Melchiorre, *Nature* **2016**, *532*, 218–222; b) Z. Wang, H. Yin, G. C. Fu *Nature* **2018**, *563*, 379–383; c) C. A. Gould, A. L. Pace, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2023**, *145*, 16330–16336.
[26] L. Wu, F. Wang, P. Chen, G. Liu *J. Am. Chem. Soc.* **2019**, *141*, 1887–1892.
[27] a) E. S. Jang, C. L. McMullin, M. Käß, K. Meyer, T. R. Cundari, T. H. Warren, *J. Am. Chem. Soc.* **2014**, *136*, 10930–10940; b) T. K. Salvador, C. H. Arnett, S. Kundu, N. G. Sapiezynski, J. A. Bertke, M. Raghibi Boroujeni, T. H. Warren, *J. Am. Chem. Soc.* **2016**, *138*, 16580–16583.
[28] W. D. Bailey, N. L. Gagnon, C. E. Elwell, A. C. Cramblitt, C. J. Bouchey, W. B. Tolman, *Inorg. Chem.* **2019**, *58*, 4706.

Manuscript received: September 27, 2024
Accepted manuscript online: October 30, 2024
Version of record online: November 22, 2024