

Copper Catalyzed C(sp³)–H Bond Alkylation via Photoinduced Ligand-to-Metal Charge Transfer

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ABSTRACT: Utilizing catalytic CuCl₂, we report the functionalization of numerous feedstock chemicals via the coupling of unactivated C(sp³)–H bonds with electron-deficient olefins. The active cuprate catalyst undergoes Ligand-to-Metal Charge Transfer (LMCT) to enable the generation of a chlorine radical which acts as a powerful hydrogen atom transfer reagent capable of abstracting strong electron-rich C(sp³)–H bonds. Of note is that the chlorocuprate catalyst is an exceedingly mild oxidant (0.5 V vs SCE) and that a proposed protodemetalation mechanism offers a broad scope of electron-deficient olefins, offering high diastereoselectivity in the case of endocyclic alkenes. The coupling of chlorine radical generation with Cu reduction through LMCT enables the generation of a highly active HAT reagent in an operationally simple and atom economical protocol.

The catalytic functionalization of unactivated C(sp³)–H bonds has been a long-standing goal in synthetic methods development.^{1,2} Due to the inert and nonpolarized nature of C(sp³)–H bonds, manipulation of these positions requires the formation of high energy intermediates that must differentiate comparable sites of reactivity to enable selectivity,^{3,4} a challenge made more profound when one also targets the desirable outcome of sustainability.⁵

In recent years, intermolecular hydrogen atom transfer (HAT) has evolved into a synthetically viable mechanism for the selective C–H functionalization of alkanes^{6–10} (Scheme 1 A). The generated alkyl radical provides a reactive intermediate poised for bond formation with myriad coupling partners including those activated via transition-metal catalysis.^{11–15} Selectivity of HAT is governed by the electronic and steric characteristics of both the C(sp³)–H bonds of the substrate as well as the HAT reagent.^{16–21} The recent expansion of photoredox catalysis in organic synthesis has enabled the formation of reactive radicals capable of HAT for myriad functional groups in a catalytic fashion.^{22–31}

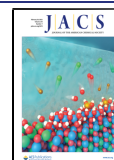
Due to the abundance and inexpensive nature of chloride salts, the formation of a chlorine radical from a chloride anion for use as a HAT reagent has long been an attractive strategy toward the functionalization of C(sp³)–H bonds. HAT with chlorine radical forms a strong polarized bond in HCl (BDE = 103 kcal/mol), enabling the abstraction of strong electron-rich C(sp³)–H bonds to form the corresponding alkyl radical (Scheme 1B-1). While there exists a surfeit of HAT reagents capable of abstracting relatively weak C(sp³)–H bonds, there are relatively few methods capable of HAT of strong C(sp³)–H bonds.^{32–36} Classical methods of chlorine radical generation require the employment of reactive reagents such as chlorine gas or *N*-chlorosuccinimide,^{37,38} but recent methods have enabled the generation of chlorine radicals via direct oxidation of dissolved chloride through photoredox catalysis.^{39–42} This direct oxidation requires potentials exceeding +1.21 V vs SCE,⁴² limiting synthetic utility due to oxidation sensitivity of

the substrate as well as diminishing the coupling partners available for the generated alkyl radical due to the limited reduction potentials available to highly oxidizing photocatalysts (Scheme 1B-2).

Photoinduced ligand-to-metal charge transfer (LMCT) has proven to be an effective means toward the formation of HAT reagents in organic synthesis.⁴³ Coordination of the reactive functional group with the metal complex enables chemo-selective oxidation via direct excitation of the metal–ligand complex. Through the coupling of the ligand oxidation with metal reduction, the reactive radical may be generated under low electrochemical potentials, complementing strategies enabled by SET. Pioneering work by the Doyle, Wu, and Zuo laboratories has shown LMCT as an effective strategy to catalyze the formation of chlorine and alkoxy radicals to functionalize strong C(sp³)–H bonds^{43–47} (Scheme 1B-3). Previous work in our group demonstrated the ability of Co^{II}–acetylides to undergo LMCT toward Co^I catalyzed [2 + 2 + 2] cycloaddition of alkynes.⁴⁸ Hypothesizing that other air stable metal salts could complement these HAT centered protocols in terms of substrate scope, selectivity, and reactivity, we explored the competency of various metal halides to undergo LMCT to enable novel reactivity in HAT catalysis. Stimulated by early work from Kochi who proved the competence of cupric chloride in the stoichiometric chlorination of alkanes in acetonitrile,^{49–54} we noted Tarnovsky's follow-up work characterizing the various photoactive species capable of LMCT for Cu^{II} chlorocomplexes in acetonitrile.⁵⁵ Recent reports have utilized this mechanism toward the chlorination

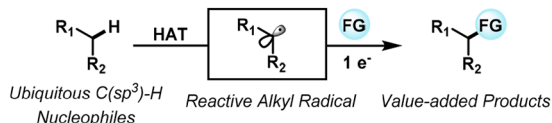
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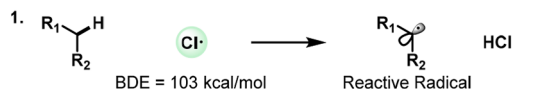


Scheme 1. Cu Catalyzed Formation of Chlorine Radical via Ligand-to-Metal Charge Transfer (LMCT) Enables Unactivated C(sp³)-H Alkylation

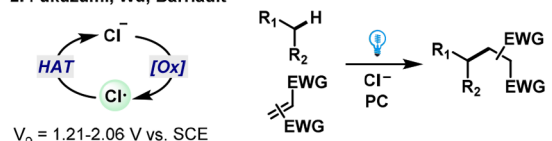
A. C(sp³)-H Functionalization via HAT



B. Unactivated C(sp³)-H Functionalization via Chlorine HAT



2. Fukuzumi, Wu, Barriault



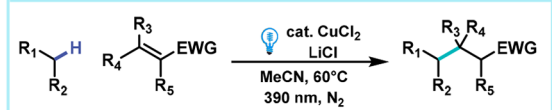
3. Doyle, Wu



C. Catalyzing Chloride Oxidation via LMCT



D. This Work: Photocatalytic C(sp³)-H Alkylation with Cu Salts

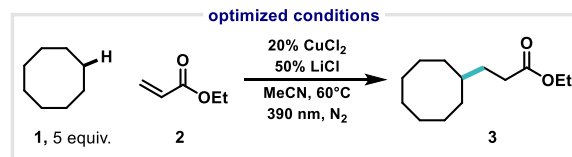


of unactivated olefins and oxidation of diarylalkynes with air as the terminal oxidant to enable catalytic loadings of Cu^{56,57} (Scheme 1C).

Herein we report a catalytic method of alkane functionalization using a common base-metal salt —CuCl₂— in which photoirradiation enables LMCT of a Cu^{II} species to generate a highly reactive chlorine radical. This permits the selective C(sp³)-H alkylation and amination of feedstock alkanes with abundant commodity chemicals such as acrylates and vinyl sulfones to synthesize value-added materials (Scheme 1D). The protocol operates effectively on a number of alkane nucleophiles, including the remote functionalization of aliphatic carboxylic acids which has been enabled by the low oxidation potential of the Cu catalyst (+0.5 V vs SCE).^{58,59} For endocyclic electron-deficient alkenes we also observe high diastereoselectivity which we propose stems from facially selective protonation of an intermediate Cu-enolate.

Initial reaction optimization focused on the coupling of cyclooctane with ethyl acrylate, an abundant and inexpensive electrophile (Table 1).⁶⁰ Initial investigations revealed a moderate yield with 20% loading of the CuCl₂ catalyst and ethyl acrylate as the limiting component. The addition of exogenous chloride was found to increase turnover numbers. UV-vis spectra of CuCl₂ in MeCN with and without exogenous chloride reveal the active CuCl₃[−] catalyst to be present as a greater mole fraction of photoactive species in

Table 1. Optimization and Control Studies

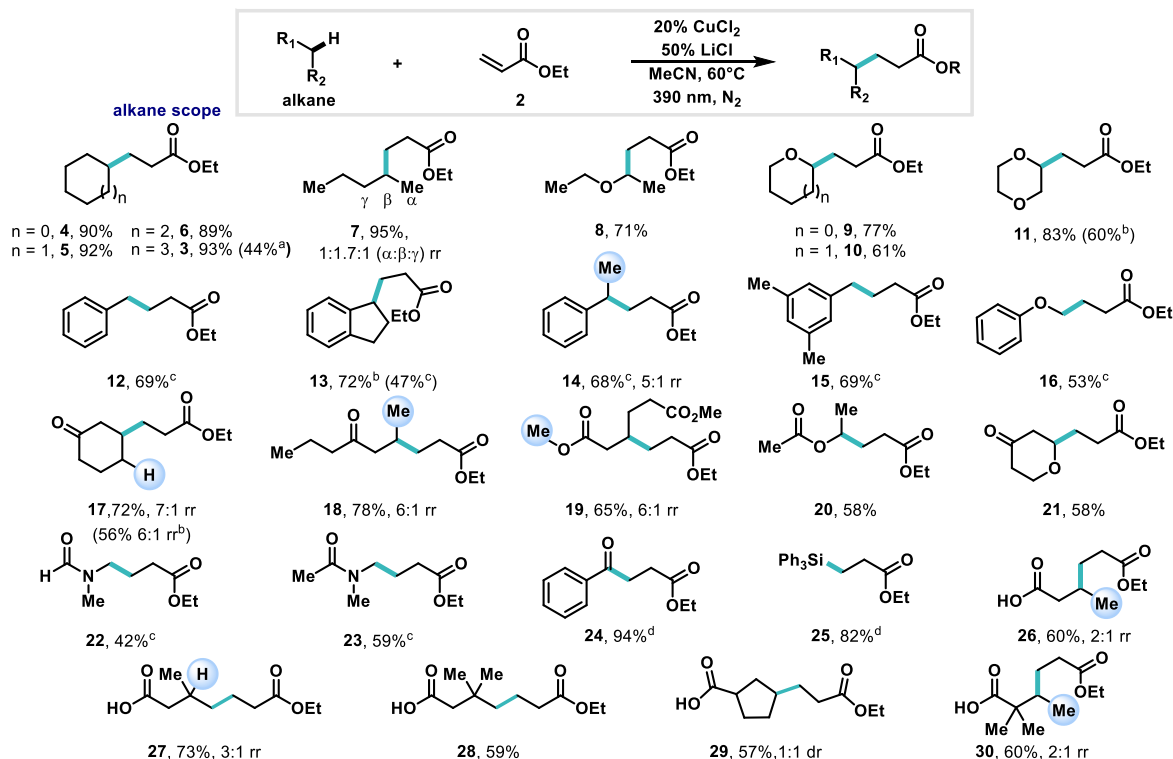


Entry	Deviation from Standard Conditions	Yield 3 (%)
1	none	93
2	3 equiv of cyclooctane	73
3	0% CuCl ₂	0
4	0% LiCl	79
5	in the dark	0
6	440 nm LED	66
7	30 °C	45
8	under air	55
9	with 10% Cs ₂ CO ₃	22
10	Irradiated 1 h, then in the dark	14

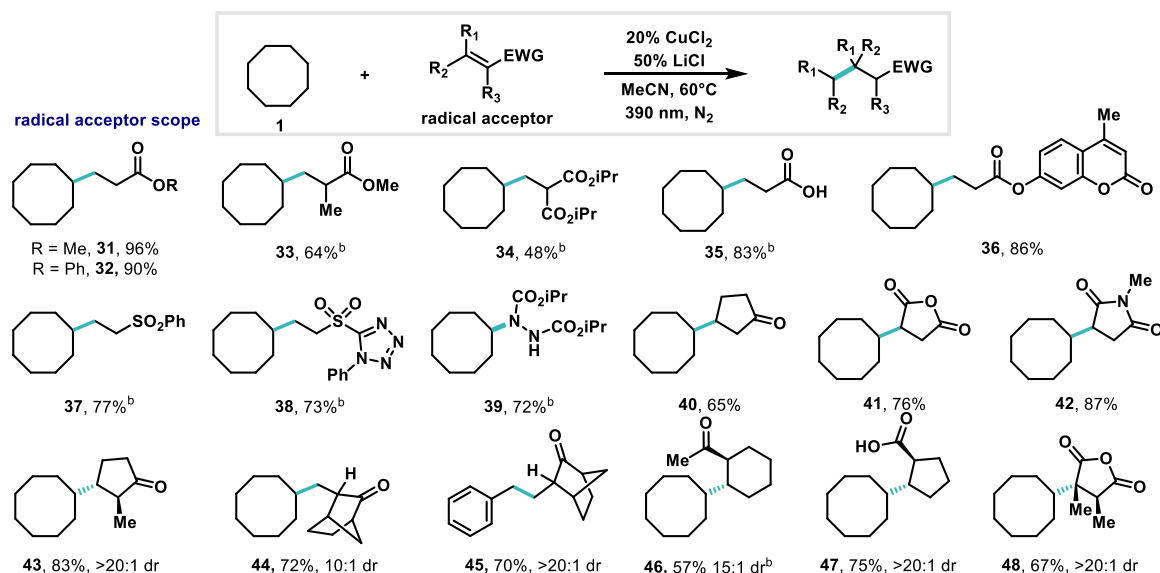
^aOptimizations were performed on a 0.3 mmol scale using 5 equiv of 1 and 1 equiv of 2.

solutions with added LiCl as well as demonstrating higher solubility (see Supplemental Figure S6). Due to the propensity of the product to undergo alkylation when in competitive concentration with the starting material, improved yields are observed when an excess of up to 5 equiv of C-H nucleophile is used. Yields increase at elevated temperatures, with the conditions shown corresponding to the radiant heat generated by the 390 nm lamps. 440 nm irradiation also furnished product albeit in lower yield. Control studies revealed the necessity of light and CuCl₂ for the reaction to occur. While anhydrous CuCl₂ produces higher yields of 3, the air and moisture stable CuCl₂ dihydrate also performs the coupling effectively, giving 3 in 83% yield.

With optimized conditions, we sought to explore the scope of nucleophiles capable of selective C-H functionalization (Scheme 2). Unfunctionalized cyclic alkanes proved to be effective coupling partners (3–6). In the case of cyclooctane (3) the protocol scales well up to at least 3 mmol, delivering a yield of 86%. *n*-Pentane (7) shows a regioselectivity profile of 1:1.7:1 with preferential alkylation at the 2-C position and high overall reactivity. This selectivity matches previous reports of Giese alkylation via chlorine radical formation in MeCN.⁴⁰ Ethers (8–11, 16) show selectivity for the α -position to oxygen which is expected due to the stabilization granted to the resulting radical by the proximal O atom. Benzylic positions (12–15) prove reactive toward alkylation selectively in the presence of other aliphatic positions, giving 5:1 rr in the case of 14. Ketones and esters drive selectivity toward more electron-rich positions enabling the selective β -alkylation of cyclohexanone and 4-heptanone with good regioselectivity (17–18). Amides also proved to be effective nucleophiles with high selectivity for the hydrogen atoms at the α -position to the N atom (22–23). The product of the alkylation of dimethyladipate (19) demonstrates the unfavorability of functionalization proximal to carbonyls, showing reactivity both at the β -position of the carbonyl and at the α -position of oxygen of the ester (6:1 rr). Both triphenyl silane (25) and benzaldehyde (24) show high reactivity demonstrating the propensity of electron-rich C-H and Si-H bonds to undergo the transformation effectively even at lower equivalents of alkane nucleophile (3 equiv). Butanoic acid's (26) ability to

Scheme 2. Representative Examples of Alkane Nucleophiles^a

^aReactions were run on 0.3 mmol scale with 5 equiv of alkane nucleophile, 20 mol % CuCl₂, 50 mol % LiCl, in 1.0 mL of MeCN for 36 h. For inseparable regioisomeric mixtures, the C(sp³)-H bond corresponding to the minor product site of functionalization is highlighted. ^b1 equiv of alkane nucleophile, 1.1 equiv of ethyl acrylate. ^c50 mol % CuCl₂, 1.25 equiv of LiCl. ^d3 equiv of alkane nucleophile.

Scheme 3. Representative Examples of Electrophiles^a

^aReactions were run on 0.3 mmol scale with 5 equiv of alkane nucleophile, 20 mol % CuCl₂, 50 mol % LiCl, in 1.0 mL of MeCN for 36 h. ^b50 mol % CuCl₂, 1.25 equiv of LiCl.

undergo alkylation with moderate regioselectivity motivated the employment of other alkyl acids (27–30) for which coupling proceeded at the β- and γ-positions with moderate to high regioselectivity. Alkyl carboxylic acids are commonly employed as alkyl radical precursors via oxidation–decarboxylation,^{61–64} and we observe no products corresponding to this mechanism. Finally, we have synthesized 5, 11, 13, and 15

utilizing the alkane as the limiting reagent with 1.1 equiv of ethyl acrylate to furnish products in synthetically useful isolated yields (44–60%).

We next sought to evaluate the scope of electrophiles capable of coupling with cyclooctane. A number of electron-deficient unsaturated systems are competent for the reaction including various acrylates (3, 31–34, 36), vinyl sulfones (37–

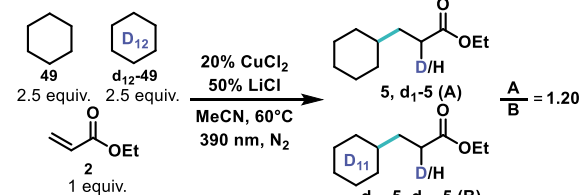
38), and diisopropyl azodicarboxylate (39). The ability to append the functional group 1-phenyl-5-(sulfonyl)-1H-tetrazole (PT-sulfone) found in 38 onto alkanes provides a useful functional handle for further derivatization.^{65–70} Vinyl ketones, carboxylic acids, and acid anhydrides (40–41, 43–48) all proved to be effective coupling partners. Maleic anhydride and its derivatives are prone to reduction (−0.98 V vs SCE⁵⁹) illustrating the mild reduction potentials generated by the CuCl_2^- reductant. Substrates bearing endocyclic alkenes (43, 46–48) provide high diastereoselectivity which we propose is enabled by the intermediacy of a Cu^{II} -enolate which undergoes stereoselective protonation to regenerate the oxidized copper catalyst. This compares favorably to decatungstate based systems in which 45 is reported to be formed in 29% yield with 2:1 dr.^{61,71}

Giese reactions of alkanes have been conducted previously, but typically require multiple electron-withdrawing substituents on the olefin acceptor to promote electrophilicity, stabilize the resulting radical, and facilitate reduction in the case of a SET mechanism.^{41,47} A notable exception lies in decatungstate anion catalysis, which permits the alkylation of cyclohexane with methyl acrylate to proceed in moderate yield (65%) under 310 nm irradiation.⁷² Previous work in radical Giese reactions displays low diastereoselectivity except for in the case of highly strained enolate intermediates (see Scheme 3, 44, 45).^{9,47,73–75} In the presented system, all endocyclic alkene coupling partners demonstrate high (>10:1) dr, augmenting previously reported radical Giese reactions.

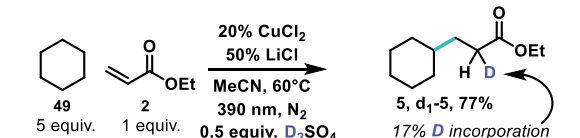
We next sought to interrogate the mechanism of this reaction through a series of probes. Based on previous reports,⁵⁵ the concentration of chloride in cupric-acetonitrile solutions produces various $\text{CuCl}_x^{(x-2)-}$ complexes, of which only conditions known to produce CuCl_3^- proved effective for this reaction. This was further confirmed via UV–vis spectroscopy of the catalyst mixture (see Supplemental Figure S1). A competition experiment between cyclohexane and cyclohexane- d_{12} at low conversion (6 h) revealed a secondary kinetic isotope effect, alluding that the (H/D)AT event is not a turnover limiting step of the catalytic cycle (Scheme 4A). The addition of catalytic base, sufficient to neutralize the acid produced via HAT, results in depressed yield with complete consumption of acrylate through polymerization (Table 1, entry 9). Adding exogenous D_2SO_4 to the normal reaction conditions, as shown in Scheme 4B, permits the incorporation of deuterium into the product. The limited incorporation (17%), despite much higher initial concentrations of deuterio acid as compared to proteo acid, reveals that protonation must occur faster than deuteration, which is in accordance with an expected kinetic isotope effect in a protodemetalation mechanism. In the isotopically inverted experiment in which cyclohexane- d_{12} is used as the nucleophile with added H_2SO_4 , deuterium incorporation is even lower (7%) in agreement with the proposed mechanism (see Supporting Information). To ensure that D incorporation does not occur after product formation, 3 was subjected to alkylation conditions and reisolated to show that D incorporation must occur in an intermediate en route to product (Scheme 4C). Previous investigations into the Cu catalyzed amidation of alkyl halides through a photoexcited intermediate presented the possibility that an in situ generation of an alkyl chloride could precede and enable alkylation through $\text{Cu}(\text{I})$ halide abstraction.^{76,77} To ensure that the reaction did not proceed via an alkyl chloride intermediate, chlorocyclohexane was subjected to the reaction

Scheme 4. Mechanistic Investigations

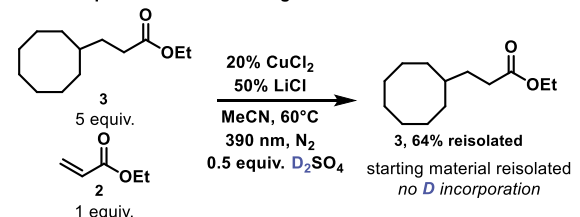
A. Competition Study Reveals Secondary KIE for (H/D)AT



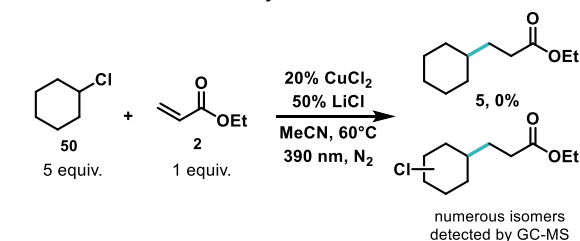
B. Intermolecular D Incorporation Attenuated: Inverse KIE



C. D Incorporation Occurs During Product Formation



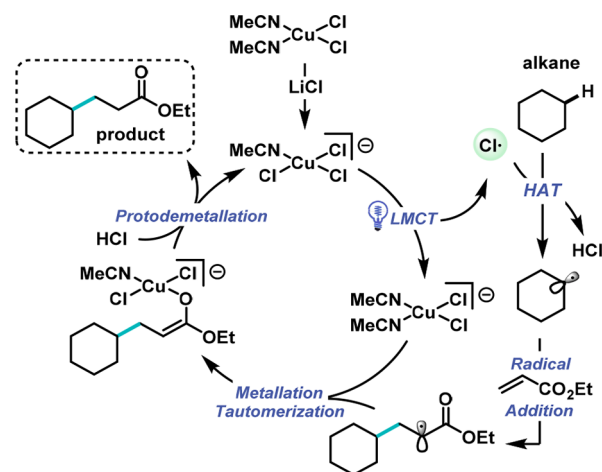
D. Product Not Formed via Alkyl-Chloride Intermediate



conditions to reveal no production of the alkylated cyclohexane. Instead various regio- and stereoisomers of alkylated chlorocyclohexane were detected by GC-MS (Scheme 4D).

Based on our mechanistic experiments and previous photochemical studies of copper-chloro complexes in acetonitrile,⁵⁵ we propose the mechanism shown in Scheme 5. First, coordination of chloride to dissolved CuCl_2 produces the photoactive CuCl_3^- . Then, irradiation enables LMCT to generate a reactive chlorine radical. This radical undergoes HAT with the alkane nucleophile to form HCl and a reactive

Scheme 5. Proposed Mechanism



alkyl radical. The alkyl radical attacks ethyl acrylate to form a more stable radical α to an ester. This electron-deficient radical recombines with CuCl_2^- to form a stable Cu^{II} -enolate. Protodemetalation with HCl forms the product and regenerates the photoactive CuCl_3^- .

In conclusion, we report an effective protocol for the alkylation of alkanes with electron-deficient olefins via the photosensitization of Cu^{II} salts. This work offers a synthetically useful and operationally simple method to couple feedstock chemicals to create value-added products. Further efforts are underway to apply LMCT for the functionalization of more selective and powerful HAT reagents under mild conditions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.1c00687>.

Experimental procedures and characterization data, including supplemental Figures S1–S7 (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) Hartwig, J. F.; Larsen, M. A. Undirected, Homogeneous C-H Bond Functionalization: Challenges and Opportunities. *ACS Cent. Sci.* **2016**, *2* (5), 281–292.
- (2) Bergman, R. G. Organometallic Chemistry: C-H Activation. *Nature* **2007**, *446*, 391.
- (3) Newhouse, T.; Baran, P. S. If C-H Bonds Could Talk: Selective C-H Bond Oxidation. *Angew. Chem., Int. Ed.* **2011**, *50*, 3362.
- (4) Chu, J. C. K.; Rovis, T. Complementary Strategies for Directed $\text{C}(\text{sp}^3)$ -H Functionalization: A Comparison of Transition-Metal-Catalyzed Activation, Hydrogen Atom Transfer, and Carbene/Nitrene Transfer. *Angew. Chem., Int. Ed.* **2018**, *57*, 62.
- (5) Chirik, P.; Morris, R. Getting Down to Earth: The Renaissance of Catalysis with Abundant Metals. *Acc. Chem. Res.* **2015**, *48*, 2495–2495.
- (6) Ludwig, R. Hydrogen-Transfer Reactions. *ChemPhysChem* **2007**, *8*, 2539–2539.
- (7) Hu, A.; Guo, J. J.; Pan, H.; Zuo, Z. Selective Functionalization of Methane, Ethane, and Higher Alkanes by Cerium Photocatalysis. *Science* **2018**, *361*, 668–672.
- (8) Perry, I. B.; Brewer, T. F.; Sarver, P. J.; Schultz, D. M.; DiRocco, D. A.; MacMillan, D. W. C. Direct Arylation of Strong Aliphatic C–H Bonds. *Nature* **2018**, *560*, 70–75.

- (9) Laudadio, G.; Deng, Y.; van der Wal, K.; Ravelli, D.; Nuño, M.; Fagnoni, M.; Guthrie, D.; Sun, Y.; Noël, T. $\text{C}(\text{sp}^3)$ -H Functionalizations of Light Hydrocarbons Using Decatungstate Photocatalysis in Flow. *Science* **2020**, *369*, 92–96.
- (10) Yi, H.; Zhang, G.; Wang, H.; Huang, Z.; Wang, J.; Singh, A. K.; Lei, A. Recent Advances in Radical C–H Activation/Radical Cross-Coupling. *Chem. Rev.* **2017**, *117* (13), 9016–9085.
- (11) Tilton, J.; Le, C.; Zhang, P.; Shaw, M. H.; Evans, R. W.; MacMillan, D. W. C. The Merger of Transition Metal and Photocatalysis. *Nature Reviews Chemistry* **2017**, *1*, 52.
- (12) De Abreu, M.; Belmont, P.; Brachet, E. Synergistic Photoredox/Transition-Metal Catalysis for Carbon-Carbon Bond Formation Reactions. *Eur. J. Org. Chem.* **2020**, *2020*, 1327–1378.
- (13) Biswas, S.; Weix, D. J. Mechanism and Selectivity in Nickel-Catalyzed Cross-Electrophile Coupling of Aryl Halides with Alkyl Halides. *J. Am. Chem. Soc.* **2013**, *135*, 16192–16197.
- (14) Tellis, J. C.; Primer, D. N.; Molander, G. A. Single-Electron Transmetalation in Organoboron Cross-Coupling by Photoredox/Nickel Dual Catalysis. *Science* **2014**, *345*, 433–436.
- (15) Zuo, Z.; Ahneman, D. T.; Chu, L.; Terrett, J. A.; Doyle, A. G.; MacMillan, D. W. C. Merging Photoredox with Nickel Catalysis: Coupling of α -Carboxyl sp^3 -Carbons with Aryl Halides. *Science* **2014**, *345*, 437–440.
- (16) Capaldo, L.; Ravelli, D. Hydrogen Atom Transfer (HAT): A Versatile Strategy for Substrate Activation in Photocatalyzed Organic Synthesis. *Eur. J. Org. Chem.* **2017**, *2017*, 2056–2071.
- (17) Jeffrey, J. L.; Terrett, J. A.; MacMillan, D. W. C. O-H Hydrogen Bonding Promotes H-Atom Transfer from α C-H Bonds for C-Alkylation of Alcohols. *Science* **2015**, *349*, 1532–1536.
- (18) Le, C.; Liang, Y.; Evans, R. W.; Li, X.; MacMillan, D. W. C. Selective sp^3 C-H Alkylation via Polarity-Match-Based Cross-Coupling. *Nature* **2017**, *547*, 79–83.
- (19) Roberts, B. P. Polarity-Reversal Catalysis of Hydrogen-Atom Abstraction Reactions: Concepts and Applications in Organic Chemistry. *Chem. Soc. Rev.* **1999**, *28*, 25–35.
- (20) Mayer, J. M. Understanding Hydrogen Atom Transfer: From Bond Strengths to Marcus Theory. *Acc. Chem. Res.* **2011**, *44*, 36–46.
- (21) Bietti, M. Activation and Deactivation Strategies Promoted by Medium Effects for Selective Aliphatic C-H Bond Functionalization. *Angew. Chem., Int. Ed.* **2018**, *57*, 16618–16637.
- (22) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. Visible Light Photoredox Catalysis with Transition Metal Complexes: Applications in Organic Synthesis. *Chem. Rev.* **2013**, *113*, 5322–5363.
- (23) Romero, N. A.; Nicewicz, D. A. Organic Photoredox Catalysis. *Chem. Rev.* **2016**, *116*, 10075–10166.
- (24) Narayanan, J. M. R.; Stephenson, C. R. J. Visible Light Photoredox Catalysis: Applications in Organic Synthesis. *Chem. Soc. Rev.* **2011**, *40*, 102–113.
- (25) Hu, X. Q.; Chen, J. R.; Xiao, W. J. Controllable Remote C-H Bond Functionalization by Visible-Light Photocatalysis. *Angew. Chem., Int. Ed.* **2017**, *56*, 1960–1962.
- (26) Choi, G. J.; Zhu, Q.; Miller, D. C.; Gu, C. J.; Knowles, R. R. Catalytic Alkylation of Remote C-H Bonds Enabled by Proton-Coupled Electron Transfer. *Nature* **2016**, *539*, 268–271.
- (27) Chu, J. C. K.; Rovis, T. Amide-Directed Photoredox-Catalyzed C-C Bond Formation at Unactivated sp^3 C-H Bonds. *Nature* **2016**, *539*, 272–275.
- (28) Chen, D. F.; Chu, J. C. K.; Rovis, T. Directed γ - $\text{C}(\text{sp}^3)$ -H Alkylation of Carboxylic Acid Derivatives through Visible Light Photoredox Catalysis. *J. Am. Chem. Soc.* **2017**, *139*, 14897–14900.
- (29) Mukherjee, S.; Maji, B.; Tlahuext-Aca, A.; Glorius, F. Visible-Light-Promoted Activation of Unactivated $\text{C}(\text{sp}^3)$ -H Bonds and Their Selective Trifluoromethylthiolation. *J. Am. Chem. Soc.* **2016**, *138*, 16200–16203.
- (30) Cuthbertson, J. D.; MacMillan, D. W. C. The Direct Arylation of Allylic sp^3 C-H Bonds via Organic and Photoredox Catalysis. *Nature* **2015**, *519*, 74–77.
- (31) Tanaka, H.; Sakai, K.; Kawamura, A.; Oisaki, K.; Kanai, M. Sulfonamides as New Hydrogen Atom Transfer (HAT) Catalysts for

Photoredox Allylic and Benzylic C-H Arylations. *Chem. Commun.* **2018**, 54, 3215–3218.

(32) Shen, Y.; Gu, Y.; Martin, R. sp^3 C-H Arylation and Alkylation Enabled by the Synergy of Triplet Excited Ketones and Nickel Catalysts. *J. Am. Chem. Soc.* **2018**, 140, 12200–12209.

(33) Protti, S.; Fagnoni, M.; Ravelli, D. Photocatalytic C-H Activation by Hydrogen-Atom Transfer in Synthesis. *ChemCatChem* **2015**, 7, 1516–1523.

(34) Okada, M.; Fukuyama, T.; Yamada, K.; Ryu, I.; Ravelli, D.; Fagnoni, M. Sunlight Photocatalyzed Regioselective β -Alkylation and Acylation of Cyclopentanones. *Chem. Sci.* **2014**, 5, 2893–2898.

(35) Schmidt, V. A.; Quinn, R. K.; Brusoe, A. T.; Alexanian, E. J. Site-Selective Aliphatic C-H Bromination Using N-Bromoamides and Visible Light. *J. Am. Chem. Soc.* **2014**, 136, 14389–14392.

(36) Margrey, K. A.; Czaplyski, W. L.; Nicewicz, D. A.; Alexanian, E. J. A General Strategy for Aliphatic C-H Functionalization Enabled by Organic Photoredox Catalysis. *J. Am. Chem. Soc.* **2018**, 140, 4213–4217.

(37) Fokin, A. A.; Schreiner, P. R. Selective Alkane Transformations via Radicals and Radical Cations: Insights into the Activation Step from Experiment and Theory. *Chem. Rev.* **2002**, 102, 1551–1594.

(38) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry Part A: Structure and Mechanisms*; Springer: New York, 2007; pp 965–1063.

(39) Ohkubo, K.; Fujimoto, A.; Fukuzumi, S. Metal-Free Oxygenation of Cyclohexane with Oxygen Catalyzed by 9-Mesityl-10-Methylacridinium and Hydrogen Chloride under Visible Light Irradiation. *Chem. Commun.* **2011**, 47, 8515–8517.

(40) Ohkubo, K.; Mizushima, K.; Fukuzumi, S. Oxygenation and Chlorination of Aromatic Hydrocarbons with Hydrochloric Acid Photosensitized by 9-Mesityl-10-Methylacridinium under Visible Light Irradiation. *Res. Chem. Intermed.* **2013**, 39, 205–220.

(41) Deng, H.-P.; Zhou, Q.; Wu, J. Microtubing-Reactor-Assisted Aliphatic C-H Functionalization with HCl as a Hydrogen-Atom-Transfer Catalyst Precursor in Conjunction with an Organic Photoredox Catalyst. *Angew. Chem., Int. Ed.* **2018**, 57, 12661–12665.

(42) Rohe, S.; Morris, A. O.; McCallum, T.; Barriault, L. Hydrogen Atom Transfer Reactions via Photoredox Catalyzed Chlorine Atom Generation. *Angew. Chem., Int. Ed.* **2018**, 57, 15664–15669.

(43) Hu, A.; Guo, J. J.; Pan, H.; Tang, H.; Gao, Z.; Zuo, Z. δ -Selective Functionalization of Alkanols Enabled by Visible-Light-Induced Ligand-to-Metal Charge Transfer. *J. Am. Chem. Soc.* **2018**, 140, 1612–1616.

(44) Shields, B. J.; Doyle, A. G. Direct C(sp^3)-H Cross Coupling Enabled by Catalytic Generation of Chlorine Radicals. *J. Am. Chem. Soc.* **2016**, 138, 12719–12722.

(45) Deng, H. P.; Fan, X. Z.; Chen, Z. H.; Xu, Q. H.; Wu, J. Photoinduced Nickel-Catalyzed Chemo- and Regioselective Hydroalkylation of Internal Alkynes with Ether and Amide α -Hetero C(sp^3)-H Bonds. *J. Am. Chem. Soc.* **2017**, 139, 13579–13584.

(46) Ackerman, L. K. G.; Martinez Alvarado, J. I.; Doyle, A. G. Direct C-C Bond Formation from Alkanes Using Ni-Photoredox Catalysis. *J. Am. Chem. Soc.* **2018**, 140, 14059–14063.

(47) An, Q.; Wang, Z.; Chen, Y.; Wang, X.; Zhang, K.; Pan, H.; Liu, W.; Zuo, Z. Cerium-Catalyzed C-H Functionalizations of Alkanes Utilizing Alcohols as Hydrogen Atom Transfer Agents. *J. Am. Chem. Soc.* **2020**, 142, 6216–6226.

(48) Ravetz, B. D.; Wang, J. Y.; Ruhl, K. E.; Rovis, T. Photoinduced Ligand-to-Metal Charge Transfer Enables Photocatalyst-Independent Light-Gated Activation of Co(II). *ACS Catal.* **2019**, 9, 200–204.

(49) Kochi, J. K. Photolyses of Metal Compounds: Cupric Chloride in Organic Media. *J. Am. Chem. Soc.* **1962**, 84, 2121–2127.

(50) Shul'pin, G. B.; Kats, M. M. Ferric Chloride Catalyzed Photooxidation of Alkanes by Air in Organic Solvents. *React. Kinet. Catal. Lett.* **1990**, 41, 239.

(51) Shul'pin, G. B.; Nizova, G. V. Photo-oxidation of Cyclohexane by Atmospheric Oxygen in Acetonitrile Catalysed by Chloride Complexes of Iron, Copper, and Gold. *Petrol. Chem.* **1993**, 33, 107.

(52) Shul'pin, G. B.; Nizova, G. V.; Kozlov, Y. N. Photochemical Aerobic Oxidation of Alkanes Promoted by Iron Complexes. *New J. Chem.* **1996**, 20, 1243.

(53) Takaki, K.; Yamamoto, J.; Matsushita, Y.; Morii, H.; Shishido, T.; Takehira, K. Oxidation of Alkanes with Dioxxygen Induced by Visible Light and Cu(II) and Fe(III) Chlorides Oxidation of Alkanes by Visible Light. *Bull. Chem. Soc. Jpn.* **2003**, 76, 393–398.

(54) Takaki, K.; Yamamoto, J.; Komeyama, K.; Kawabata, T.; Takehira, K. Photocatalytic Oxidation of Alkanes with Dioxxygen by Visible Light and Copper(II) and Iron(III) Chlorides: Preference Oxidation of Alkanes over Alcohols and Ketones. *Bull. Chem. Soc. Jpn.* **2004**, 77, 2251–2255.

(55) Mereshchenko, A. S.; Olshin, P. K.; Karimov, A. M.; Skripkin, M. Y.; Burkov, K. A.; Tveryanovich, Y. S.; Tarnovsky, A. N. Photochemistry of Copper(II) Chlorocomplexes in Acetonitrile: Trapping the Ligand-to-Metal Charge Transfer Excited State Relaxations Pathways. *Chem. Phys. Lett.* **2014**, 615, 105–110.

(56) Charpe, V. P.; Sagadevan, A.; Hwang, K. C. Visible light-induced aerobic oxidation of diarylalkynes to α -diketones catalyzed by copper-superoxo at room temperature. *Green Chem.* **2020**, 22, 4426–4432.

(57) Lian, P.; Long, W.; Li, J.; Zheng, Y.; Wan, X. Visible-Light-Induced Vicinal Dichlorination of Alkenes through LMCT Excitation of CuCl_2 . *Angew. Chem., Int. Ed.* **2020**, 59, 23603–23608.

(58) Manahan, S. E.; Iwamoto, R. T. Chloro Complexes of Copper(II) and Copper(I) in Acetonitrile. *Inorg. Chem.* **1965**, 4, 1409–1413.

(59) Roth, H. G.; Romero, N. A.; Nicewicz, D. A. Experimental and Calculated Electrochemical Potentials of Common Organic Molecules for Applications to Single-Electron Redox Chemistry. *Synlett* **2016**, 27, 714–723.

(60) As of the date of this submission (08/2020), the price per gram of ethyl acrylate from Fisher Scientific is \$0.02–0.03/gram.

(61) Chu, L.; Ohta, C.; Zuo, Z.; MacMillan, D. W. C. Carboxylic Acids as A Traceless Activation Group for Conjugate Additions: A Three-Step Synthesis of ($\pm$)-Pregabalin. *J. Am. Chem. Soc.* **2014**, 136, 10886–10889.

(62) Griffin, J. D.; Zeller, M. A.; Nicewicz, D. A. Hydrodecarboxylation of Carboxylic and Malonic Acid Derivatives via Organic Photoredox Catalysis: Substrate Scope and Mechanistic Insight. *J. Am. Chem. Soc.* **2015**, 137, 11340–11348.

(63) Johnston, C. P.; Smith, R. T.; Allmendinger, S.; MacMillan, D. W. C. Metallaphotoredox-catalysed sp^3 – sp^3 cross-coupling of carboxylic acids with alkyl halides. *Nature* **2016**, 536, 322–325.

(64) Sun, X.; Chen, J.; Ritter, T. Catalytic dehydrogenative decarboxylefination of carboxylic acids. *Nat. Chem.* **2018**, 10, 1229–1233.

(65) Blakemore, P. R.; Cole, W. J.; Kociński, P. J.; Morley, A. A Stereoselective Synthesis of *Trans* -1,2-Disubstituted Alkenes Based on the Condensation of Aldehydes with Metallated 1-Phenyl-1 *H*-Tetrazol-5-Yl Sulfones. *Synlett* **1998**, 1998, 26–28.

(66) Blakemore, P. R. The Modified Julia Olefination: Alkene Synthesis via the Condensation of Metallated Heteroarylalkylsulfones with Carbonyl Compounds. *J. Chem. Soc. Perkin 1* **2002**, 2, 2563–2585.

(67) Aissa, C. Mechanistic Manifold and New Developments of the Julia-Kociński Reaction. *Eur. J. Org. Chem.* **2009**, 2009, 1831–1844.

(68) Rodrigo, E.; Morales, S.; Duce, S.; Ruano, J. L. G.; Cid, M. B. Enantioselective Organocatalytic Formal Allylation of α -Branched Aldehydes. *Chem. Commun.* **2011**, 47, 11267–11269.

(69) Rodrigo, E.; Alonso, I.; García Ruano, J. L.; Cid, M. B. Expanding the Potential of Heteroaryl Vinyl Sulfones. *J. Org. Chem.* **2016**, 81, 10887–10899.

(70) For a recent innovative development involving the use of PT-sulfones as effective substrates for Ni catalyzed cross-coupling, see: Merchant, R. R.; Edwards, J. T.; Qin, T.; Kruszyk, M. M.; Bi, C.; Che, G.; Bao, D. H.; Qiao, W.; Sun, L.; Collins, M. R.; Fadeyi, O. O.; Gallego, G. M.; Mousseau, J. J.; Nuhant, P.; Baran, P. S. Modular

Radical Cross-Coupling with Sulfones Enables Access to sp^3 -Rich (Fluoro)Alkylated Scaffolds. *Science* **2018**, 360, 75–80.

(71) We also synthesized **43** using 2% tetrabutylammonium decatungstate in 78% yield and 1:1 dr under otherwise identical reaction conditions to our copper catalyzed method.

(72) Dondi, D.; Fagnoni, M.; Albini, A. Tetrabutylammonium Decatungstate-Photosensitized Alkylation of Electrophilic Alkenes: Convenient Functionalization of Aliphatic C–H Bonds. *Chem. - Eur. J.* **2006**, 12, 4153–4163.

(73) Qrareya, H.; Ravelli, D.; Fagnoni, M.; Albini, A. Decatungstate Photocatalyzed Benzoylation of Alkenes with Alkylaromatics. *Adv. Synth. Catal.* **2013**, 355, 2891–2899.

(74) Dondi, D.; Cardarelli, A. M.; Fagnoni, M.; Albini, A. Photomediated synthesis of β -alkylketones from cycloalkanes. *Tetrahedron* **2006**, 62 (23), 5527–5535.

(75) Capaldo, L.; Merli, D.; Fagnoni, M.; Ravelli, D. Visible Light Uranyl Photocatalysis: Direct C–H to C–C Bond Conversion. *ACS Catal.* **2019**, 9 (4), 3054–3058.

(76) Do, H. Q.; Bachman, S.; Bissember, A. C.; Peters, J. C.; Fu, G. C. Photoinduced, Copper-Catalyzed Alkylation of Amides with Unactivated Secondary Alkyl Halides at Room Temperature. *J. Am. Chem. Soc.* **2014**, 136, 2162–2167.

(77) Kainz, Q. M.; Matier, C. D.; Bartoszewicz, A.; Zultanski, S. L.; Peters, J. C.; Fu, G. C. Asymmetric Copper-Catalyzed C–N Cross-Couplings Induced by Visible Light. *Science* **2016**, 351, 681–684.