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Iron-Catalyzed Photoinduced LMCT: a 1° C-H Abstraction Enables Skeletal Rearrangements and C(sp³)-H Alkylation

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Abstract

Herein we disclose an iron-catalyzed method to access skeletal rearrangement reactions akin to the Dowd-Beckwith ring expansion from unactivated $C(sp^3)$-H bonds. Photoinduced ligand-to-metal charge transfer at the iron center generates a chlorine radical, which abstracts electron-rich $C(sp^3)$–H bonds. The resulting unstable alkyl radicals can undergo rearrangement in the presence of suitable functionality. Addition to an electron deficient olefin, recombination with a photoreduced iron complex, and subsequent protodemetallation allows for redox-neutral alkylation of the resulting radical. Simple adjustments to the reaction conditions enable the selective synthesis of the directly alkylated or the rearranged-alkylated products. As a radical clock, these rearrangements also enable the measurement of rate constants of addition into various electron deficient olefins in the Giese reaction.

Graphical Abstract
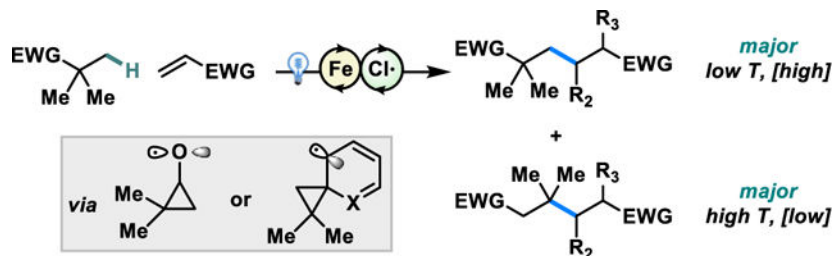
Keywords

LMCT; primary $C(sp^3)$-H alkylation; iron catalysis; skeletal rearrangement; Dowd-Beckwith; photocatalysis

Carbon skeleton rearrangements in which C-C sigma bonds are broken provide powerful bond disconnections in organic synthesis.[1,2] Due to the largely inert nature of C-C sigma bonds, formation of high energy intermediates like carbocations or radicals is

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The authors declare no competing financial interests.

Supporting Information

Experimental details and compound characterization data. The Supporting Information is available free of charge on the ACS Publications website.

usually necessary to generate sufficient thermodynamic driving force for their scission. While carbocation-mediated transformations like the Wagner-Meerwein and pinacol rearrangements have been widely studied and utilized in organic synthesis,[3–5] there has been less focus on their radical-mediated counterparts.[6–8]

The Dowd-Beckwith rearrangement is a radical-mediated skeletal rearrangement that has found synthetic applications in ketone ring expansions.[9–17] Typically, a primary alkyl radical is generated by halogen abstraction with a stannyl radical. This then adds to a carbonyl, forming a cyclopropyloxy radical which subsequently undergoes β-scission to give a more stable radical that is then quenched with tributyltin hydride (Scheme 1A). Current limitations of the rearrangement include the necessity for preinstallation of a functional handle and the use of stoichiometric tin reagents.

The key skeletal rearrangement step in the Dowd-Beckwith ring expansion is related to a family of radical 1,2-rearrangements wherein a primary radical β to a π-system adds to it, forming a transient cyclopropyl intermediate that then undergoes β-scission to form a more stable tertiary radical.[18–20] The rate constants of these rearrangements have been measured with various π-systems like alkenes, alkynes, arenes, carbonyls and nitriles, and several have been used as radical clocks.[21–25]

Hydrogen atom transfer (HAT) has emerged as a powerful mechanism for direct functionalization of $C(sp^3)$-H bonds.[26–30] Various reagents and catalysts have been developed to exhibit excellent HAT regioselectivity despite the high energy intermediates required to abstract strong unpolarized $C(sp^3)$-H bonds.[31–34] Although much attention has been paid towards the functionalization of $C(sp^3)$-H bonds adjacent to heteroatoms or other radical stabilizing functional groups, less work has focused on the functionalization of compounds bearing electron withdrawing moieties.[35] Previous investigations have shown that hydrogen atoms adjacent to electron withdrawing groups are recalcitrant to HAT due to a polarity mismatch,[36–41] despite their lower bond dissociation energies compared to unactivated $C(sp^3)$-H bonds.[42] We postulated that the directing effect of carbonyls or other electron-withdrawing groups could enable HAT selectively at the beta-position to enable a skeletal rearrangement analogous to the Dowd-Beckwith ring expansion directly from $C(sp^3)$-H bonds (Scheme 1B).

We recently reported the photocatalytic $C(sp^3)$–H alkylation of alkanes using copper (II) chloride. This system mediates intermolecular HAT via the formation of chlorine radical which is readily generated by photoinduced ligand to metal charge transfer (Scheme 1C).[43] Herein, we report a redox-neutral, photocatalytic alkylation of unactivated $C(sp^3)$–H bonds distal from electron-withdrawing moieties using an iron (III) chloride catalyst[44–49] to enable access to divergent products (Scheme 1D) via a skeletal rearrangement (Scheme 2). Of practical interest is that iron is the most abundant transition metal in the Earth's crust,[50] making it inexpensive and well-suited for use in large-scale syntheses.[51] Simple changes to the temperature and concentration of the reaction, as well as the choice of the electron-deficient olefin partner allow for control of the ratio of unrearranged and rearranged products.

Initial optimization of the reaction was conducted using pinacolone and benzyl acrylate (Table 1). Early investigations found a catalyst loading of 25 mol% $FeCl_3$ and the use of benzyl acrylate in limiting quantities to be effective. At room temperature and a concentration of 0.3 M, we obtain an isomeric ratio (*ir*) of unrearranged to rearranged product (**3a:3b**) of 1:1.4. Hypothesizing that an increase in temperature would reduce the rate of intermolecular radical trapping relative to the intramolecular skeletal rearrangement, we performed the reaction at 60 °C, and found that the *ir* indeed increases to 1:4 in favor of the rearranged product. Decreasing the reaction concentration to 0.1 M also promotes the 1,2-migration, increasing *ir* to 1:10. Given that reaction yields remain comparable under these conditions, we selected these conditions as optimal for promoting either the unrearranged product (Entry 1 – Conditions A) or the rearranged product (Entry 3 – Conditions B). UV-vis studies of $FeCl_3$ in acetonitrile reveal a peak with $\lambda_{max} = 361$ nm, with a tail into the visible region, along with two other maxima in the ultraviolet region (see SI). These peaks closely match the reported absorption spectrum of $FeCl_4^-$ in acetonitrile, indicating that this is likely to be the photoactive species in our system.[52] Addition of lithium chloride to the solution does not change any of the observed λ_{max} values, further supporting this possibility. However, unlike with $CuCl_2$,[43] we found that exogenous chloride proved slightly detrimental to the efficiency of the reaction (Entry 4). Control reactions reveal the necessity for light and $FeCl_3$ in order to furnish the desired product. Moreover, irradiating the reaction for 1 hour and continuing the reaction in the dark leads to dramatically reduced yields, disfavoring a radical chain mechanism where $FeCl_3$ acts as an initiator, although we cannot completely rule out short chain processes. 427 nm irradiation is inefficient at promoting the reaction. Finally, we found that the reaction may be performed under air without significant loss in efficiency.

The scope of substrates which undergo this 1,2-migration is summarized in Scheme 3 (see SI for additional substrates). A variety of ketones other than pinacolone were found to be amenable to the transformation. Ketone **4** demonstrates a reduced propensity to undergo the 1,2-migration (12:1 *ir*), which we propose is due to a smaller Thorpe-Ingold effect compared to pinacolone.[19,53–57] As expected, the *ir* is shifted towards the rearranged product (1.6:1) by performing the reaction under conditions B. Pivaloyl chloride was also observed to undergo 1,2-migration to a small extent, with an *ir* of 4:1 (**5**). The product was isolated as the ethyl ester after workup in alkaline ethanol. Aromatic substituents also participate in this 1,2-migration, albeit less efficiently than carbonyl substituents. *Tert*-butylbenzene gives an *ir* of 16:1 under conditions A (**6**), likely because the formation of the cyclopropyl intermediate disrupts aromaticity. The rate constant of this rearrangement is known to be 4×10^2 s^{-1} (298K),[58] which provides a lower limit for the rate of radical addition to ethyl acrylate under our reaction conditions. We found that substituent effects can exert a strong influence on the propensity of the substrate to undergo migration. Electron-withdrawing substituents (-Ac, -CN) in the para-position lead to a complete inversion in *ir*. Under conditions A, the rearranged products predominate, and under conditions B they are formed exclusively (**7–8**). As expected, weakly electron-donating substituents such as acetoxy (**9**) exert only a minor effect on the rate of the 1,2-migration, yielding comparable *ir* values to the unsubstituted substrate **6**. Ketone **10**, containing both a phenyl and an acyl substituent adjacent to the site of initial radical formation, acts as a competition experiment

between cyclization onto the arene and the carbonyl moieties. We exclusively obtained the rearrangement product resulting from a 1,2-acyl shift (**10b**). This complete selectivity can be attributed to the fact that the rate of the 1,2-acyl shift is more than two orders of magnitude greater than that of the 1,2-phenyl shift.[25] Ring-expansion products similar to the Dowd-Beckwith reaction can be obtained starting with completely unfunctionalized cyclic ketones (**11**). Complete selectivity for the ring-expanded rearrangement product **11b** is observed regardless of the conditions used. Given that electron-deficient arenes (**7–8**) strongly promote the rearrangement, we wondered whether protonated heteroarenes could function similarly. Indeed, di-*tert*-butylpyridine **12** reacts in moderate yields, favoring the rearranged product relative to *tert*butylbenzene. With benzothiazole **13**, the rearranged product is formed exclusively under Conditions B.

We next examined how the choice of electron-withdrawing olefin would affect the amount of 1,2-migration observed (Scheme 4). Maleic anhydride and N-methylmaleimide react in moderate to good yields. We isolated roughly equimolar mixtures of unrearranged and rearranged product (**14–15**) under Conditions A, but mostly rearranged product (1:8) under Conditions B. To our surprise, despite being significantly weaker electrophiles than maleic anhydride and N-methylmaleimide in previous studies with closed-shell nucleophiles[59,60], benzyl acrylate, acrylonitrile, and ethyl methacrylate react with comparable *ir* values under the two conditions (**3, 16–17**). Other electron-withdrawing groups on the olefin are also tolerated, including sulfones, amides and free acids (**18–20**). These acceptors generally give comparable to slightly higher ratios of rearranged product compared to benzyl acrylate. Reaction with fumaronitrile proceeds in good yields under both reaction conditions (**21**), with a similarly greater proportion of rearrangement product. Again, this was contrary to our expectations, since fumaronitrile is known to be a stronger electrophile than the acrylates based on previous studies of polar reactions.[60] Dimethyl fumarate (**22**) gives a slightly higher *ir* in favor of the rearrangement compared to fumaronitrile, while the *cis* isomer dimethyl maleate (**23**) heavily favors the rearrangement under both conditions. Small proportions of cyclized rearranged product **22c** are observed under conditions B but not under conditions A, suggesting a possible thermally-driven aldol-type reaction. Finally, benzylidenemalononitrile, which displays similar electrophilicity to maleic anhydride in polar reactions,[61] also unexpectedly yields high proportions of rearrangement product (**24**). The alkylated product is isolated exclusively as a cyclized adduct, presumably formed from attack of the bis(cyano)-stabilized anion onto the ketone. The diastereoselectivity of the cyclization was unambiguously confirmed by X-ray crystallography.

In order to better understand these unexpected observations, we sought to benchmark the rate constants for the addition of radical nucleophiles to these acceptors. Initial experiments demonstrated a linear dependence of the ratio of unrearranged to rearranged product on the concentration of acceptor used (see SI). This linear dependence argues against a Curtin-Hammett scenario[62,63] wherein the primary and tertiary radicals are rapidly equilibrating and the product ratio is determined by the energy barriers for the trapping of the two radicals, since the ratio of products would be largely insensitive to acceptor concentration under that regime. Along with the effect of elevated temperature on the proportion of rearranged product, this finding led us to propose a mechanism in which the addition

of the initially formed primary radical to the acceptor is in direct competition with the 1,2-migration to form the more stable tertiary radical. While the 1,2-migration is in principle reversible, two factors indicate that the reverse reaction is likely to be heavily outcompeted by trapping of the tertiary radical by the electron-deficient olefin. Tertiary radicals exhibit greater nucleophilicity compared to primary radicals,[64] so trapping of the rearranged radical is likely to be significantly more rapid. Moreover, the initial formation of the cyclopropyloxy radical is significantly accelerated by a Thorpe-Ingold effect that is absent in the reverse reaction – the cyclization of 3-butenyl radical to cyclopropylcarbinyl radical is three orders of magnitude slower than the analogous reaction with the 2,2-dimethyl-3-butenyl radical.[65] Under this regime, the rate constant for the 1,2-migration can serve as a convenient radical clock to determine the rate constants for addition of the pinacolone primary radical to various acceptors.

Working from the known rate constant for 1,2-migration for di-tert-butyl ketone,[25] we determined the corresponding rate constant for pinacolone to be $2.9 \times 10^4 \ s^{-1}$ (see SI). Initial rate experiments were then conducted using the 1,2-migration as a radical clock. The calculated rate constants for the addition of the pinacolone primary radical to the acceptors tested span slightly more than an order of magnitude (Scheme 5A). The values are also generally consistent with the *ir* values observed in our reactions, with the least reactive acceptors giving the greatest proportions of rearrangement product. Comparison of our rate constants to the known rate constants for methyl and tert-butyl radical addition to similar acceptors[64,66–69] (see SI for a detailed table) shows that the pinacolone radical generally adds more slowly than both, reflecting its high steric hindrance and low nucleophilicity (as a primary radical). The fairly low spread of the rate constants is also consistent with literature data sets. Giese-type additions are known to be highly exothermic and therefore have early transition states that are less sensitive to the structure of the electrophilic alkene relative to analogous ionic additions.[66] Rate constants for alkyl radical addition to **15**, **18**, **19**, and **24** were not previously known.

With substrates that only give moderate isomeric ratios, the selectivity can be tuned in either direction with further modifications to the reaction conditions (Scheme 5B). Under Conditions A, diisopropyl ketone **25** gives a moderate *ir* of 2.3:1. Performing the reaction at a higher concentration increases the *ir* to almost 4:1 (Entry 3). Similarly, the *ir* of 1:3.2 under conditions B can be increased to 1:5.9 by addition of benzyl acrylate in five equal portions over 60 h (Entry 4). In line with our proposed mechanism, increasing or decreasing the effective concentration of the acceptor in the reaction mixture yields a correspondingly smaller or greater proportion of rearrangement product.

In conclusion, we report an iron-catalyzed, photocatalytic method for the divergent alkylation of C(sp^3)–H bonds mediated by a 1,2-skeletal rearrangement. Unlike typical radical-mediated skeletal rearrangements, no prefunctionalization is required, and control over the ratio of unrearranged to rearranged product can be achieved by simple modifications to the reaction conditions or the choice of acceptor. The 1,2-rearrangement was also utilized as a radical clock to determine the rate constants for the addition of nucleophilic radicals to various electron-deficient olefins.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENT

REFERENCES

(1). Rojas CM Molecular Rearrangements in Organic Synthesis; John Wiley & Sons, 2015; pp 1–288.

(2). Overman LE Molecular Rearrangements in the Construction of Complex Molecules. Tetrahedron 2009, 65 (33), 6432–6446. 10.1016/j.tet.2009.05.067. [PubMed: 20640042]

(3). Hanson JR 3.1 - Wagner–Meerwein Rearrangements. In Comprehensive Organic Synthesis; Trost BM, Fleming I, Eds.; Pergamon: Oxford, 1991; pp 705–719. 10.1016/B978-0-08-052349-1.00077-9.

(4). Song Z-L; Fan C-A; Tu Y-Q Semipinacol Rearrangement in Natural Product Synthesis. Chem. Rev 2011, 111 (11), 7523–7556. 10.1021/cr200055g. [PubMed: 21851053]

(5). Gao AX; Thomas SB; Snyder SA Pinacol and Semipinacol Rearrangements in Total Synthesis. In Molecular Rearrangements in Organic Synthesis; John Wiley & Sons, Ltd, 2015; pp 1–34. 10.1002/9781118939901.ch1.

(6). Bach T; Hehn JP Photochemical Reactions as Key Steps in Natural Product Synthesis. Angew. Chem. Int. Ed 2011, 50 (5), 1000–1045. 10.1002/anie.201002845.

(7). Chen Z-M; Zhang X-M; Tu Y-Q Radical Aryl Migration Reactions and Synthetic Applications. Chem. Soc. Rev 2015, 44 (15), 5220–5245. 10.1039/C4CS00467A. [PubMed: 25954772]

(8). Kärkäs MD; Porco JA; Stephenson CRJ Photochemical Approaches to Complex Chemotypes: Applications in Natural Product Synthesis. Chem. Rev 2016, 116 (17), 9683–9747. 10.1021/acs.chemrev.5b00760. [PubMed: 27120289]

(9). Dowd P; Choi SC A New Tributyltin Hydride-Based Rearrangement of Bromomethyl .Beta.-Keto Esters. A Synthetically Useful Ring Expansion to .Gamma.-Keto Esters. J. Am. Chem. Soc 1987, 109 (11), 3493–3494. 10.1021/ja00245a069.

(10). Dowd P; Choi SC Free Radical Ring Expansion by Three and Four Carbons. J. Am. Chem. Soc 1987, 109 (21), 6548–6549. 10.1021/ja00255a071.

(11). Beckwith ALJ; O'Shea DM; Westwood SW Rearrangement of Suitably Constituted Aryl, Alkyl, or Vinyl Radicals by Acyl or Cyano Group Migration. J. Am. Chem. Soc 1988, 110 (8), 2565–2575. 10.1021/ja00216a033.

(12). Hart DJ; Havas F Complex Examples of the Dowd–Beckwith Rearrangement: A Free Radical Route to 2-Oxabicyclo〚3.3.0〛octan-3,6-Diones. Comptes Rendus Académie Sci. - Ser. IIC - Chem 2001, 4 (7), 591–598. 10.1016/S1387-1609(01)01274-9.

(13). Ardura D; Sordo TL Three-Carbon Dowd–Beckwith Ring Expansion Reaction versus Intramolecular 1,5-Hydrogen Transfer Reaction: A Theoretical Study. J. Org. Chem 2005, 70 (23), 9417–9423. 10.1021/jo051551g. [PubMed: 16268616]

(14). Zerong W Dowd-Beckwith Ring Expansion. In Comprehensive Organic Name Reactions and Reagents; John Wiley & Sons, Inc, 2010; pp 939–941. 10.1002/9780470638859.conrr201.

(15). Liu Y; Yeung Y-Y Synthesis of Macrocyclic Ketones through Catalyst-Free Electrophilic Halogen-Mediated Semipinacol Rearrangement: Application to the Total Synthesis of (±)-Muscone. Org. Lett 2017, 19 (6), 1422–1425. 10.1021/acs.orglett.7b00350. [PubMed: 28244759]

(16). Kim YJ; Kim DY Electrochemical Radical Selenylation/1,2-Carbon Migration and Dowd–Beckwith-Type Ring-Expansion Sequences of Alkenylcyclobutanols. Org. Lett 2019, 21 (4), 1021–1025. 10.1021/acs.orglett.8b04041. [PubMed: 30707588]

(17). Duecker FL; Heinze RC; Heretsch P Synthesis of Swinhoeisterol A, Dankasterone A and B, and Periconiastone A by Radical Framework Reconstruction. J. Am. Chem. Soc 2020, 142 (1), 104–108. 10.1021/jacs.9b12899. [PubMed: 31870147]

(18). Urry WH; Kharasch MS Factors Influencing the Course and Mechanism of Grignard Reactions. XV. The Reaction of β,β-Dime-thylphenethyl Chloride with Phenylmagnesium Bromide in the Presence of Cobaltous Chloride. J. Am. Chem. Soc 1944, 66 (9), 1438–1440. 10.1021/ja01237a004.

(19). Newcomb M Kinetics of Radical Reactions: Radical Clocks. In Radicals in Organic Synthesis; John Wiley & Sons, Ltd, 2001; pp 316–336. 10.1002/9783527618293.ch16.

(20). Newcomb M Radical Kinetics and Clocks. In Encyclopedia of Radicals in Chemistry, Biology and Materials; John Wiley & Sons, Ltd, 2012; pp 1–18. 10.1002/9781119953678.rad007.

(21). Maillard B; Ingold KU Kinetic Applications of Electron Paramagnetic Resonance Spectroscopy. XXIV. Neophyl Rearrangements. J. Am. Chem. Soc 1976, 98 (5), 1224–1226. 10.1021/ja00421a028.

(22). Effio A; Griller D; Ingold KU; Scaiano JC; Sheng SJ Studies on the Spiro[2.5]Octadienyl Radical and the 2-Phenylethyl Rearrangement. J. Am. Chem. Soc 1980, 102 (19), 6063–6068. 10.1021/ja00539a015.

(23). Ingold KU; Warkentin J A Homopropargyl Radical Rearrangement. Kinetics of the Rearrangement of the 2,2,5,5,-Tetramethyl-3-Hexyn-1-Yl Radical. Can. J. Chem 1980, 58 (4), 348–352. 10.1139/v80-056.

(24). Chatgilialoglu C; Ingold KU; Tse-Sheepy I; Warkentin J A Homoallyl Radical Rearrangement. Kinetics of the Isomerization of the 2,2-Dimethyl-3-Buten-1-Yl Radical to the 1,1-Dimethyl-3-Buten-1-Yl Radical. Can. J. Chem 1983, 61 (6), 1077–1081. 10.1139/v83-190.

(25). Lindsay DA; Lusztyk J; Ingold KU Kinetics of the 1,2-Migration of Carbon-Centered Groups in 2-Substituted 2,2-Dimethylethyl Radicals. J. Am. Chem. Soc 1984, 106 (23), 7087–7093. 10.1021/ja00335a037.

(26). Ludwig R Hydrogen-Transfer Reactions.Edited by Hynes JT, Klinman JP, Limbach H-H and Schowen RL. ChemPhysChem 2007, 8 (17), 2539–2539. 10.1002/cphc.200700637.

(27). Yi H; Zhang G; Wang H; Huang Z; Wang J; Singh AK; Lei A Recent Advances in Radical C–H Activation/Radical Cross-Coupling. Chem. Rev 2017, 117 (13), 9016–9085. 10.1021/acs.chemrev.6b00620. [PubMed: 28639787]

(28). Hu A; Guo J-J; Pan H; Zuo Z Selective Functionalization of Methane, Ethane, and Higher Alkanes by Cerium Photocatalysis. Science 2018, 361 (6403), 668–672. 10.1126/science.aat9750. [PubMed: 30049785]

(29). Perry IB; Brewer TF; Sarver PJ; Schultz DM; DiRocco DA; MacMillan DWC Direct Arylation of Strong Aliphatic C–H Bonds. Nature 2018, 560 (7716), 70–75. 10.1038/s41586-018-0366-x. [PubMed: 30068953]

(30). Chu JCK; Rovis T Complementary Strategies for Directed C(Sp^3)–H Functionalization: A Comparison of Transition-Metal-Catalyzed Activation, Hydrogen Atom Transfer, and Carbene/Nitrene Transfer. Angew. Chem. Int. Ed 2018, 57 (1), 62–101. 10.1002/anie.201703743.

(31). 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 (30), 8515–8517. 10.1039/C1CC12534F.

(32). 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 (1), 205–220. 10.1007/s11164-012-0643-5.

(33). Rohe S; Morris AO; McCallum T; Barriault L Hydrogen Atom Transfer Reactions via Photoredox Catalyzed Chlorine Atom Generation. Angew. Chem. Int. Ed 2018, 57 (48), 15664–15669. 10.1002/anie.201810187.

(34). 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 (39), 12661–12665. 10.1002/anie.201804844.

(35). Newhouse T; Baran PS If C H Bonds Could Talk: Selective C H Bond Oxidation. Angew. Chem. Int. Ed 2011, 50 (15), 3362–3374. 10.1002/anie.201006368.

(36). Walling C Free Radicals in Solution; John Wiley & Sons, Inc: New York, NY, USA, 1957.

(37). Zavitsas AA; Pinto JA Meaning of the Polar Effect in Hydrogen Abstractions by Free Radicals. Reactions of the Tert-Butoxy Radical. J. Am. Chem. Soc 1972, 94 (21), 7390–7396. 10.1021/ja00776a021.

(38). Roberts BP; Steel AJ An Extended Form of the Evans–Polanyi Equation: A Simple Empirical Relationship for the Prediction of Activation Energies for Hydrogen-Atom Transfer Reactions. J. Chem. Soc. Perkin Trans. 2 1994, No. 10, 2155–2162. 10.1039/P29940002155.

(39). Zavitsas A, Factors A Controlling Reactivity in Hydrogen Abstractions by Free Radicals. J. Chem. Soc. Perkin Trans. 2 1996, 0 (3), 391–393. 10.1039/P29960000391.

(40). Roberts BP Understanding the Rates of Hydrogen-Atom Abstraction Reactions: Empirical, Semi-Empirical and Ab Initio Approaches. J. Chem. Soc. Perkin Trans. 2 1996, No. 12, 2719–2725. 10.1039/P29960002719.

(41). Roberts BP Polarity-Reversal Catalysis of Hydrogen-Atom Abstraction Reactions: Concepts and Applications in Organic Chemistry. Chem. Soc. Rev 1999, 28 (1), 25–35. 10.1039/A804291H.

(42). Hudzik JM; Bozzelli JW Thermochemistry and Bond Dissociation Energies of Ketones. J. Phys. Chem. A 2012, 116 (23), 5707–5722. 10.1021/jp302830c. [PubMed: 22668341]

(43). Treacy SM; Rovis T Copper Catalyzed C(Sp3)–H Bond Alkylation via Photoinduced Ligand to Metal Charge Transfer. J. Am. Chem. Soc 2021, 143.

(44). Kochi JK Photolyses of Metal Compounds: Cupric Chloride in Organic Media. J. Am. Chem. Soc 1962, 84 (11), 2121–2127. 10.1021/ja00870a025.

(45). Shulpin GB; Kats MM Ferric Chloride Catalyzed Photooxidation of Alkanes by Air in Organic Solvents. React. Kinet. Catal. Lett 1990, 41 (2), 239–243. 10.1007/BF02097875.

(46). Shul'pin GB; Kats MM Photochemical Oxidation of Saturated and Alkylaromatic Hydrocarbons by Atmospheric Oxygen in CH3CN or CH2Cl2 Solution, Catalyzed by Iron(III) Halides. Pet. Chem 1991, 31 (5), 647–656.

(47). Shul'pin GB; Nizova GV; Kozlov YN Photochemical Aerobic Oxidation of Alkanes Promoted by Iron Complexes. New J Chem 1996, 20, 1243–1256.

(48). Takaki K; Yamamoto J; Matsushita Y; Morii H; Shishido T; Takehira K Oxidation of Alkanes with Dioxygen Induced by Visible Light and Cu(II) and Fe(III) Chlorides. Bull. Chem. Soc. Jpn 2003, 76 (2), 393–398. 10.1246/bcsj.76.393.

(49). Takaki K; Yamamoto J; Komeyama K; Kawabata T; Takehira K Photocatalytic Oxidation of Alkanes with Dioxygen by Visible Light and Copper(II) and Iron(III) Chlorides: Preference Oxidation of Alkanes over Alcohols and Ketones. Bull. Chem. Soc. Jpn 2004, 77 (12), 2251–2255. 10.1246/bcsj.77.2251.

(50). Yaroshevsky AA Abundances of Chemical Elements in the Earth's Crust. Geochem. Int 2006, 44 (1), 48–55. 10.1134/S001670290601006X.

(51). Chirik P; Morris R Getting Down to Earth: The Renaissance of Catalysis with Abundant Metals. Acc. Chem. Res 2015, 48 (9), 2495–2495. 10.1021/acs.accounts.5b00385. [PubMed: 26370392]

(52). Swanson TB; Laurie VW Electron Magnetic Resonance and Electronic Spectra of Tetrachloroferrate(III) Ion in Nonaqueous Solution1. J. Phys. Chem 1965, 69 (1), 244–250. 10.1021/j100885a036.

(53). Jung ME; Piizzi G Gem-Disubstituent Effect: Theoretical Basis and Synthetic Applications. Chem. Rev 2005, 105 (5), 1735–1766. 10.1021/cr940337h. [PubMed: 15884788]

(54). Beesley RM; Ingold CK; Thorpe JF CXIX.—The Formation and Stability of Spiro-Compounds. Part I. Spiro-Compounds from Cyclohexane. J. Chem. Soc. Trans 1915, 107 (0), 1080–1106. 10.1039/CT9150701080.

(55). Bruice TC; Pandit UK The Effect of Geminal Substitution Ring Size and Rotamer Distribution on the Intramolecular Nucleophilic Catalysis of the Hydrolysis of Monophenyl Esters of Dibasic Acids and the Solvolysis of the Intermediate Anhydrides. J. Am. Chem. Soc 1960, 82 (22), 5858–5865. 10.1021/ja01507a023.

(56). Ringer AL; Magers DH Conventional Strain Energy in Dimethyl-Substituted Cyclobutane and the Gem-Dimethyl Effect. J. Org. Chem 2007, 72 (7), 2533–2537. 10.1021/jo0624647. [PubMed: 17341119]

(57). Bachrach SM The Gem-Dimethyl Effect Revisited. J. Org. Chem 2008, 73 (6), 2466–2468. 10.1021/jo702665r. [PubMed: 18278945]

(58). Weber M; Fischer H Absolute Rate Constants for the β-Scission and Hydrogen Abstraction Reactions of the Tert-Butoxyl Radical and for Several Radical Rearrangements: Evaluating Delayed Radical Formations by Time-Resolved Electron Spin Resonance. J. Am. Chem. Soc 1999, 121 (32), 7381–7388. 10.1021/ja990837y.

(59). Mayr's Database Of Reactivity Parameters - Start page https://www.cup.lmu.de/oc/mayr/reaktionsdatenbank/(accessed Jan 27, 2021).

(60). Allgäuer DS; Mayr H Electrophilicities of 1,2-Disubstituted Ethylenes. Eur. J. Org. Chem 2014, 2014 (14), 2956–2963. 10.1002/ejoc.201301779.

(61). Lemek T; Mayr H Electrophilicity Parameters for Benzylidenemalononitriles. J. Org. Chem 2003, 68 (18), 6880–6886. 10.1021/jo0344182. [PubMed: 12946126]

(62). Seeman JI Effect of Conformational Change on Reactivity in Organic Chemistry. Evaluations, Applications, and Extensions of Curtin-Hammett Winstein-Holness Kinetics. Chem. Rev 1983, 83 (2), 83–134. 10.1021/cr00054a001.

(63). Seeman JI The Curtin-Hammett Principle and the Winstein-Holness Equation: New Definition and Recent Extensions to Classical Concepts. J. Chem. Educ 1986, 63 (1), 42–48. 10.1021/ed063p42.

(64). Beckwith ALJ; Poole JS Factors Affecting the Rates of Addition of Free Radicals to AlkenesDetermination of Absolute Rate Coefficients Using the Persistent Aminoxyl Method. J. Am. Chem. Soc 2002, 124 (32), 9489–9497. 10.1021/ja025730g. [PubMed: 12167045]

(65). Newcomb M; Glenn AG; Williams WG Rate Constants and Arrhenius Functions for Rearrangements of the 2,2-Dimethyl-3-Butenyl and (2,2-Dimethylcyclopropyl)Methyl Radicals. J. Org. Chem 1989, 54 (11), 2675–2681. 10.1021/jo00272a042.

(66). Fischer H; Radom L Factors Controlling the Addition of Carbon-Centered Radicals to Alkenes—An Experimental and Theoretical Perspective. Angew. Chem. Int. Ed 2001, 40 (8), 1340–1371. 10.1002/1521-3773(20010417)40:8<1340::AIDANIE1340>3.0.CO;2-#.

(67). Zytowski T; Fischer H Absolute Rate Constants for the Addition of Methyl Radicals to Alkenes in Solution: New Evidence for Polar Interactions. J. Am. Chem. Soc 1996, 118 (2), 437–439. 10.1021/ja953085q.

(68). Zytowski T; Fischer H Absolute Rate Constants and Arrhenius Parameters for the Addition of the Methyl Radical to Unsaturated Compounds: The Methyl Affinities Revisited. J. Am. Chem. Soc 1997, 119 (52), 12869–12878. 10.1021/ja973128y.

(69). Gilbert BC; Smith JRL; Milne EC; Whitwood AC; Taylor P Kinetic–EPR Studies of the Addition of Aliphatic Radicals to Acrylic Acid and Related Alkenes: The Interplay of Steric and Electronic Factors. J. Chem. Soc. Perkin Trans. 2 1993, No. 11, 2025–2031. 10.1039/P29930002025.
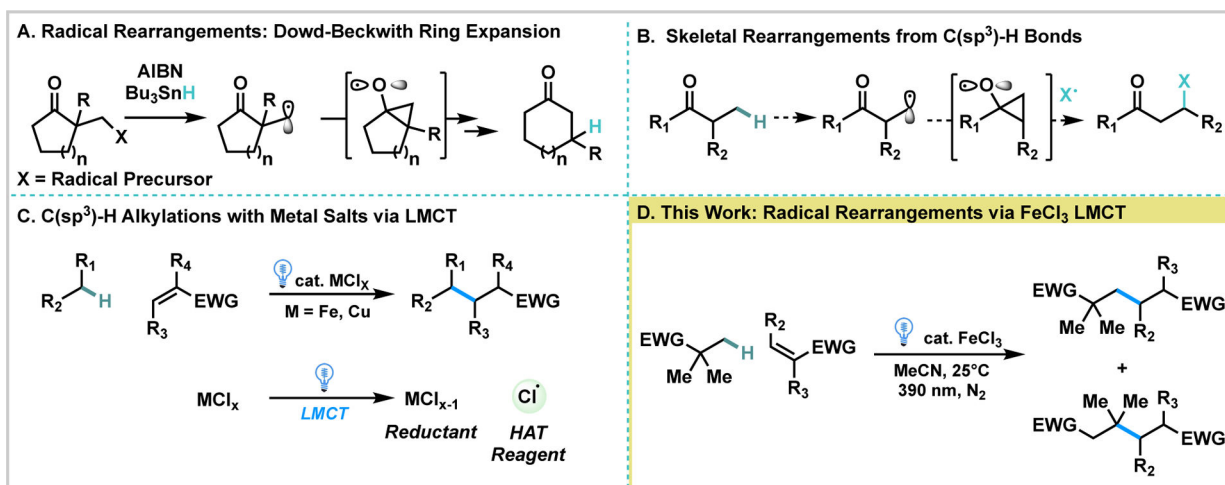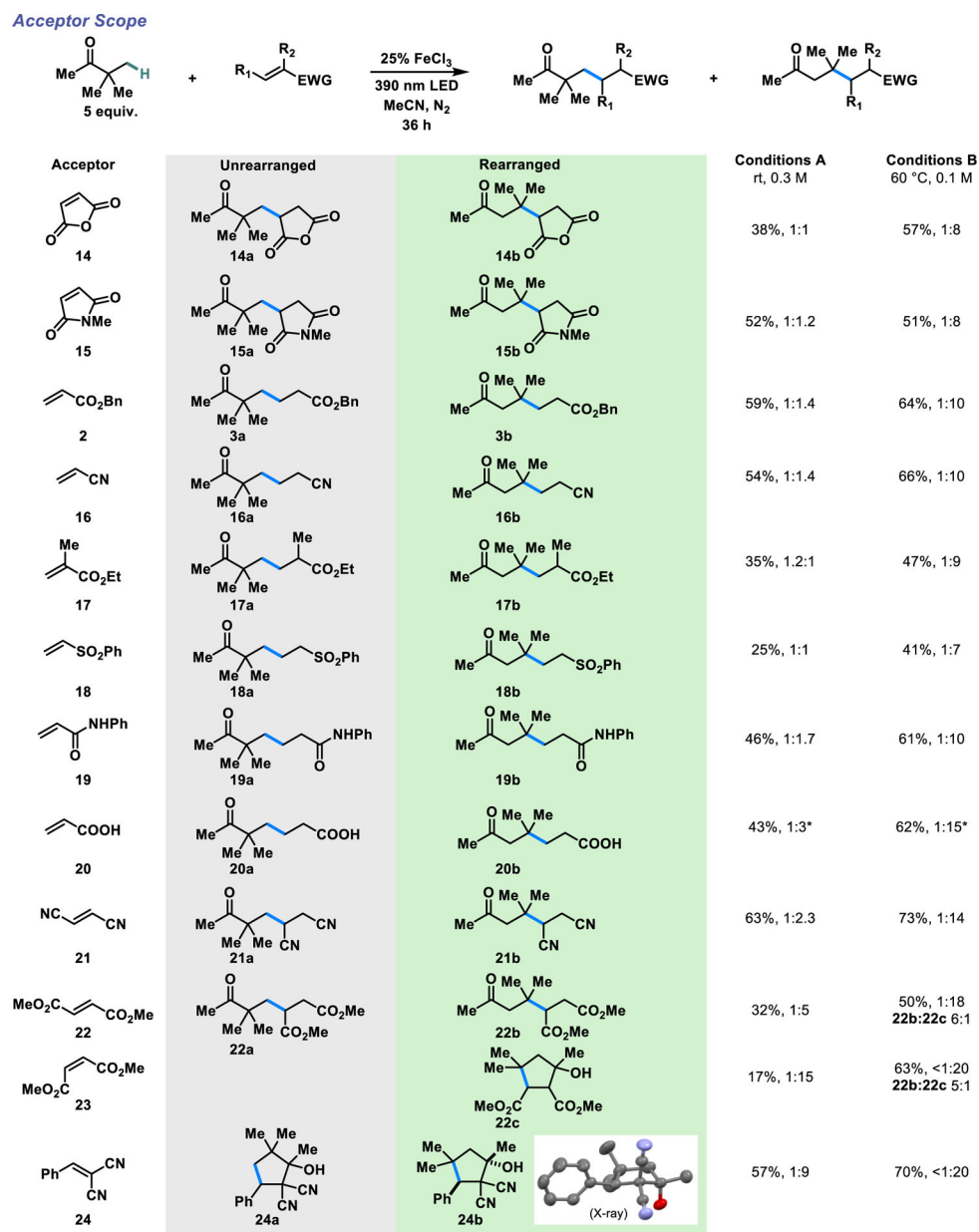
Scheme 1.
Radical rearrangement via FeCl$_3$ ligand-to-metal charge-transfer (LMCT) provides access to divergent C(sp^3)–H alkylation products.

Mechanism of 1,2-rearrangement
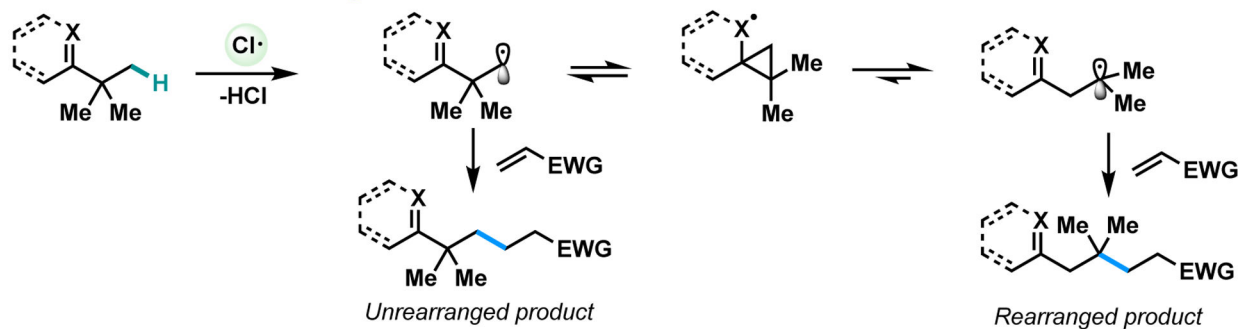
Scheme 2.
Mechanism of the 1,2-rearrangement.

Substrate Scope
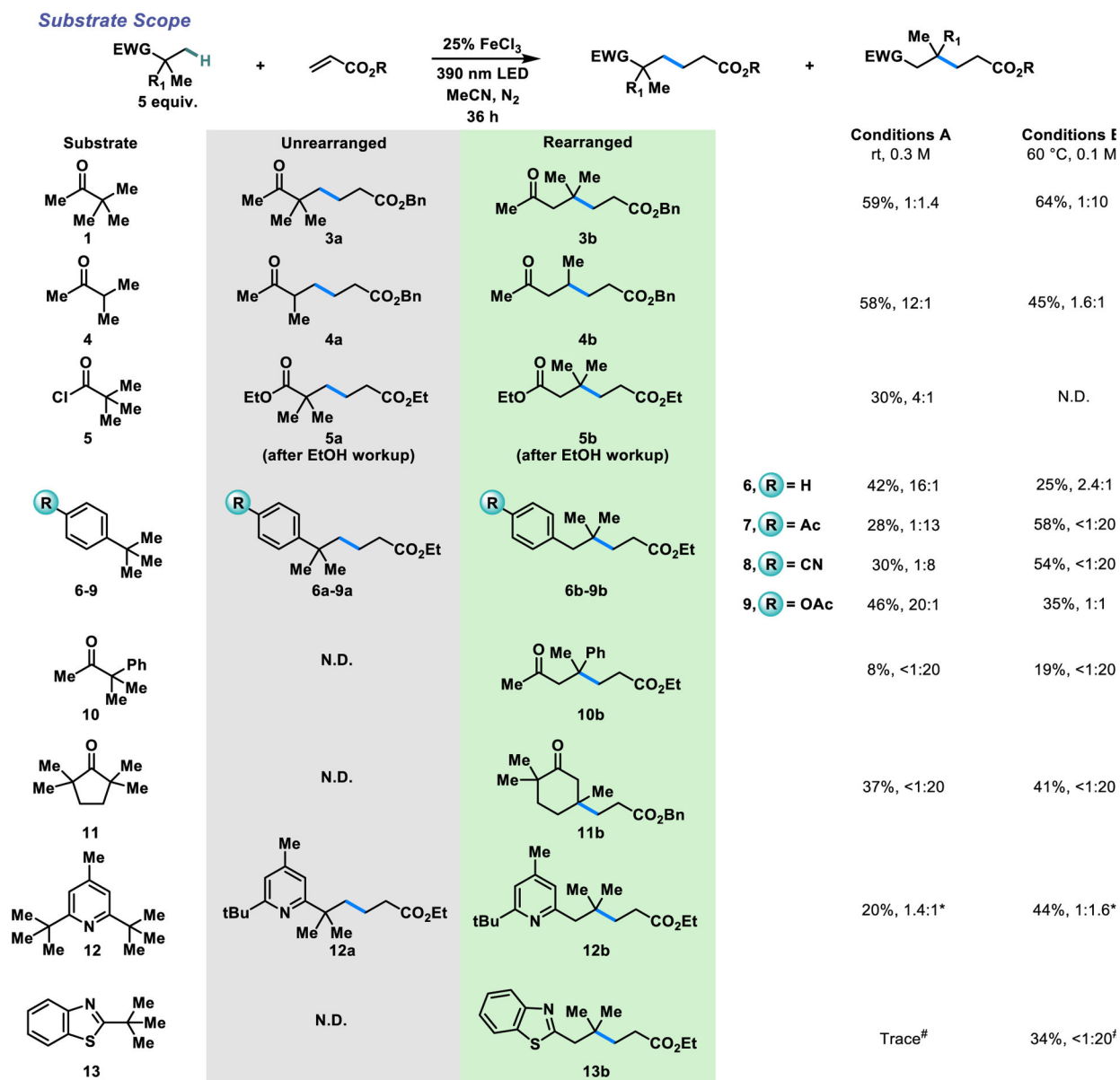
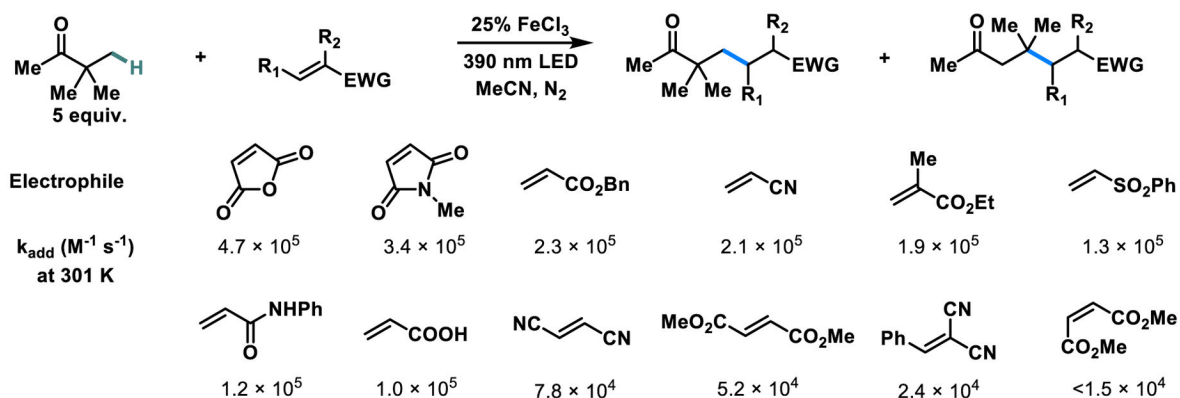

Scheme 3.

Scope of C-H pronucleophiles for the 1,2-migration. N.D.: not detected. *With 50 mol% FeCl₃ and 5 equiv. CF₃COOH as an additive. #With 5 equiv. CF₃COOH as an additive.
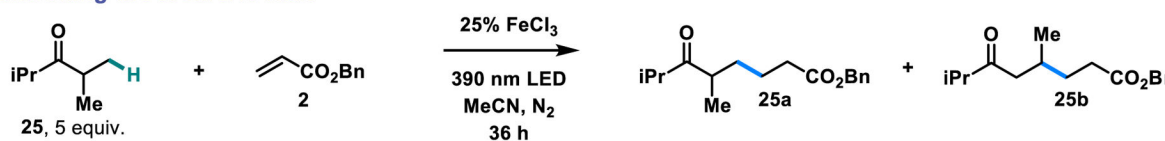
Scheme 4.
Scope of acceptors for the 1,2-migration. *1 equiv. trifluoroacetic acid used as an additive.

A. Rate constants of addition to alkenes

25% FeCl$_3$
390 nm LED
MeCN, N$_2$

5 equiv.

Electrophile					
k_{add} (M^{-1} s^{-1}) at 301 K	4.7 × 10^5	3.4 × 10^5	2.3 × 10^5	2.1 × 10^5	1.9 × 10^5	1.3 × 10^5

| 1.2 × 10^5 | 1.0 × 10^5 | 7.8 × 10^4 | 5.2 × 10^4 | 2.4 × 10^4 | <1.5 × 10^4 |

B. Controlling the isomeric ratio

25% FeCl$_3$
390 nm LED
MeCN, N$_2$
36 h

25, 5 equiv. + **2**

25a + 25b

Entry	Conditions used	Yield (%)*	*ir* (25a:25b)
1	rt, 0.75 M	72	3.9 : 1
2	rt, 0.3 M (Conditions A)	69	2.3 : 1
3	60 °C, 0.10 M (Conditions B)	63	1 : 3.2
4	60 °C, 0.10 M, portionwise addition of **2**	76	1 : 5.9

Scheme 5.
(A) Rate constants of addition to various alkenes. (B) Modifications to the reaction conditions allow for further control of the isomeric ratio (*ir*). * Yields were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard.

Table 1.

Optimization and Control Studies
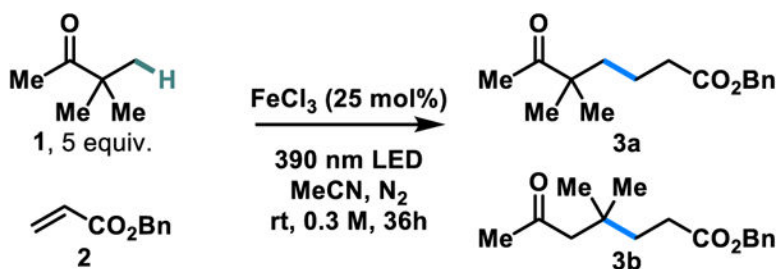
Entry	Deviation from Standard Conditions	Yield (%)	ir (3a:3b)
1	**none**	**64**	**1:1.4**
2	60 °C	65	1:4
3	60 °C, 0.1 M	67	1:10
4	added LiCl (62.5 mol%)	52	1:1
5	0% FeCl₃	0	-
6	in the dark	0	-
7	irradiate at 390 nm 1 h, then dark	2	n.d.
8	427 nm LED	3	n.d.
9	under air	47	1:1

[a]Reactions were performed on a 0.3 mmol scale. Yields were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard. n.d.: not determined.