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

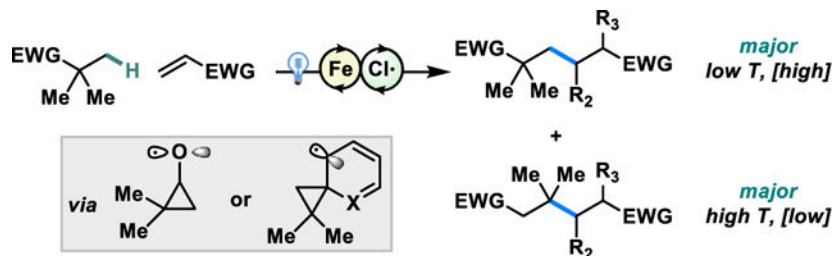
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Abstract

Herein we disclose an iron-catalyzed method to access skeletal rearrangement reactions akin to the Dowd-Beckwith ring expansion from unactivated C(sp³)-H bonds. Photoinduced ligand-to-metal charge transfer at the iron center generates a chlorine radical, which abstracts electron-rich C(sp³)-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 protodemetalation 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(sp³)-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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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(sp³)-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(sp³)-H bonds.³¹⁻³⁴ Although much attention has been paid towards the functionalization of C(sp³)-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(sp³)-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(sp³)-H bonds (Scheme 1B).

We recently reported the photocatalytic C(sp³)-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(sp³)-H bonds distal from electron-withdrawing moieties using an iron (III) chloride catalyst⁴⁴⁻⁴⁹ 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% FeCl₃ 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 FeCl₃ in acetonitrile reveal a peak with $\lambda_{\text{max}} = 361$ 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 FeCl₄⁻ 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 CuCl₂,⁴³ we found that exogenous chloride proved slightly detrimental to the efficiency of the reaction (Entry 4). Control reactions reveal the necessity for light and FeCl₃ 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 FeCl₃ 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 $4 \times 10^2 \text{ s}^{-1}$ (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 $2.9 \times 10^4 \text{ s}^{-1}$ (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.

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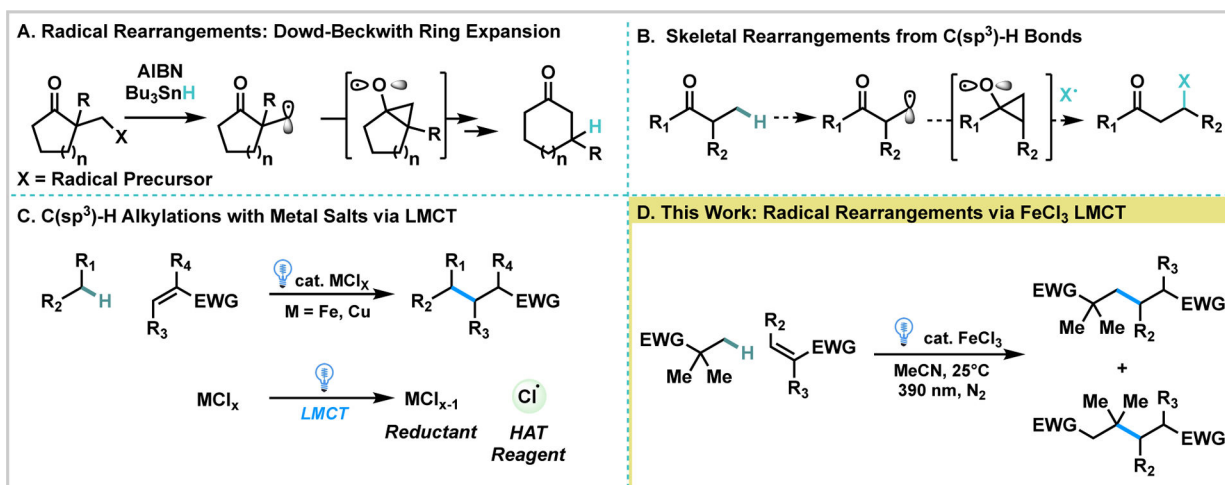
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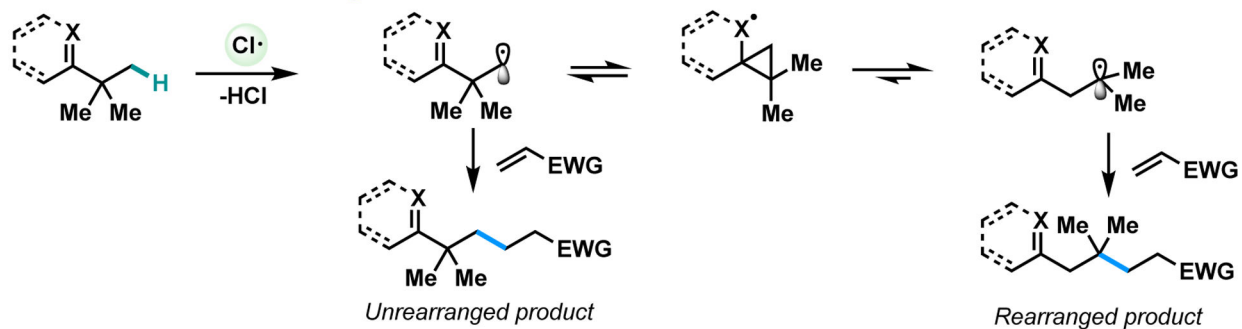
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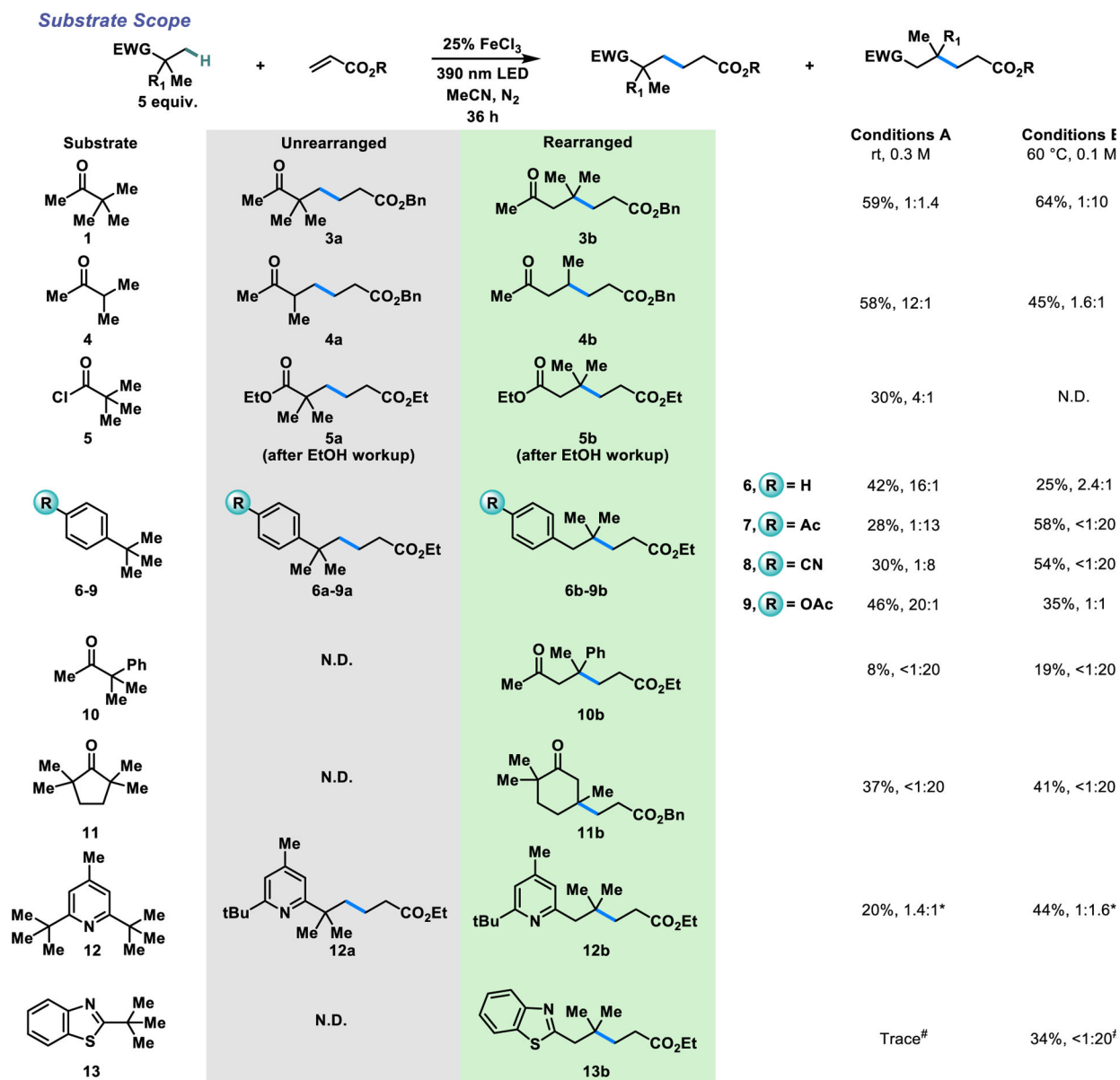
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**Scheme 1.**

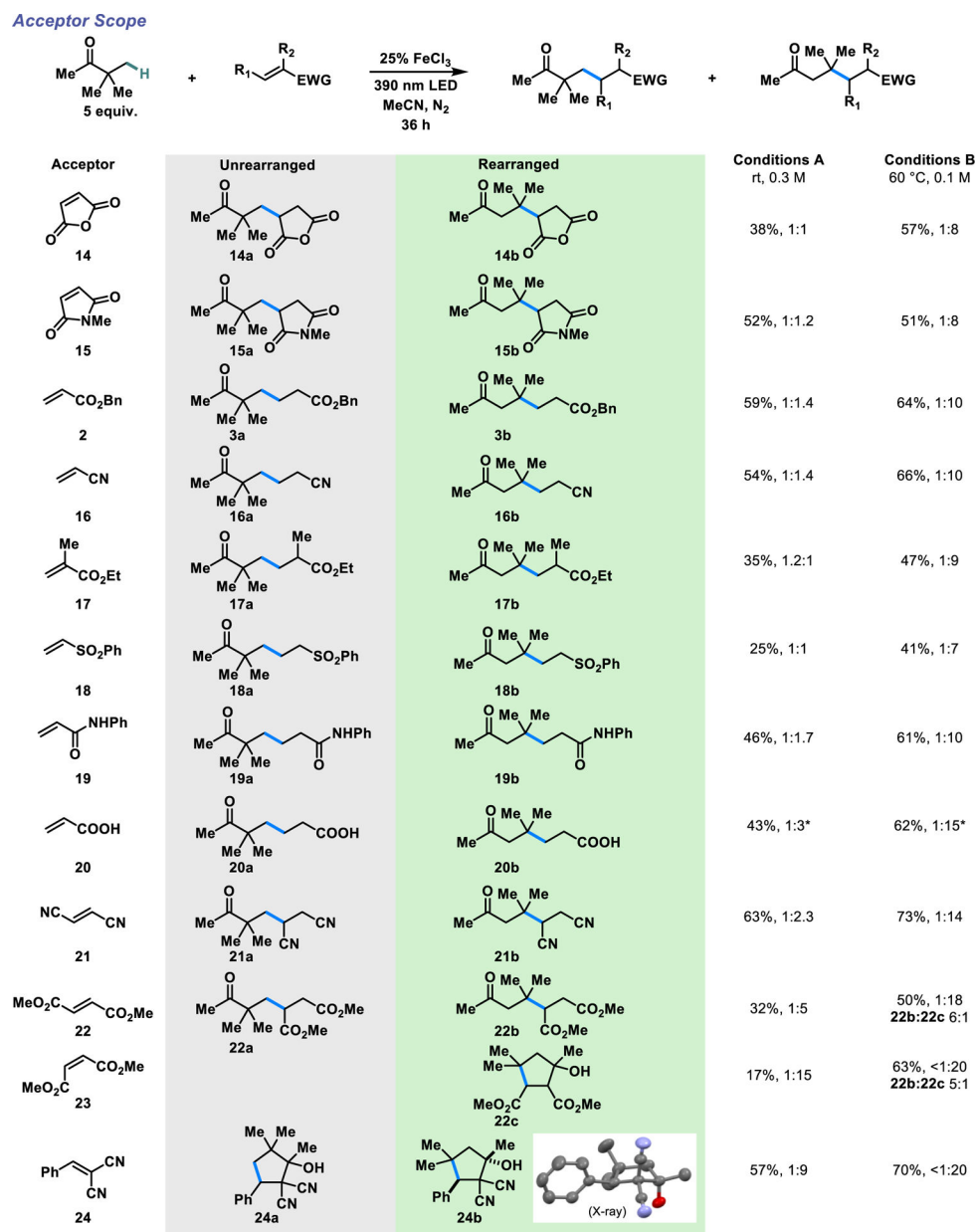
Radical rearrangement via FeCl₃ ligand-to-metal charge-transfer (LMCT) provides access to divergent C(sp³)-H alkylation products.

Mechanism of 1,2-rearrangement

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

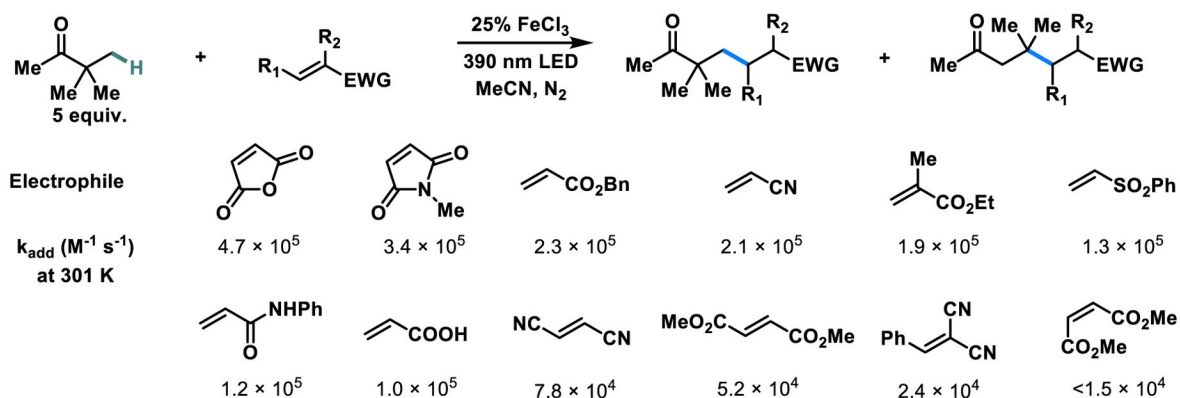
**Scheme 3.**

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.

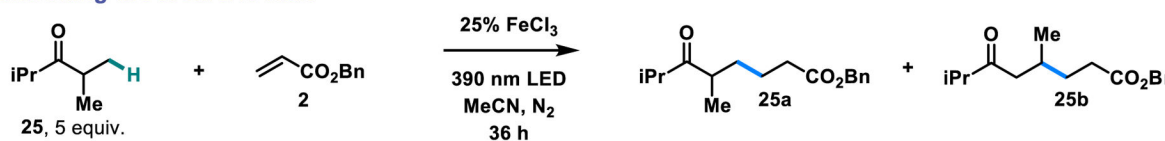
**Scheme 4.**

Scope of acceptors for the 1,2-migration. *1 equiv. trifluoroacetic acid used as an additive.

A. Rate constants of addition to alkenes



B. Controlling the isomeric ratio



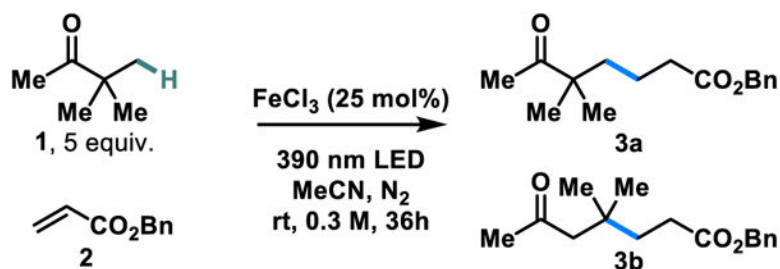
Entry	Conditions used	Yield (%)*	<i>ir</i> (25a:25b)
1	rt, 0.75 M	72	3.9 : 1
2	rt, 0.3 M (Conditions A)	69	2.3 : 1
3	60 °C, 0.10 M (Conditions B)	63	1 : 3.2
4	60 °C, 0.10 M, portionwise addition of 2	76	1 : 5.9

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 ^1H NMR using 1,3,5-trimethoxybenzene as the internal standard.

Table 1.

Optimization and Control Studies



Entry	Deviation from Standard Conditions	Yield (%)	<i>ir</i> (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% FeCl ₃	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

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