Letter

Iron-Catalyzed Photoinduced LMCT: A 1° C−H Abstraction Enables Skeletal Rearrangements and C(sp^3)−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 protodemetalation allow 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.

KEYWORDS: LMCT, primary C(sp^3)−H alkylation, iron catalysis, skeletal rearrangement, Dowd−Beckwith, photocatalysis
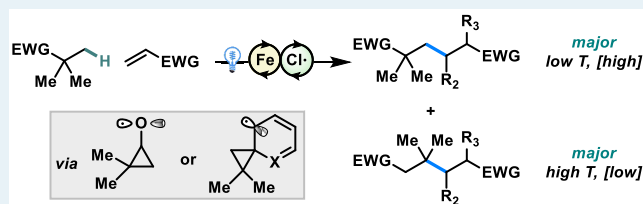
Carbon skeleton rearrangements in which C−C sigma bonds are broken provide powerful bond disconnections in organic synthesis.[1,2] Owing to the largely inert nature of C−C sigma bonds, formation of high energy intermediates such as carbocations or radicals is usually necessary to generate a sufficient thermodynamic driving force for their scission. While carbocation-mediated transformations such as 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 such as 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 toward 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 a chlorine radical which is readily generated by a photoinduced ligand-to-metal charge transfer (Scheme 1C).[43] Herein, we report a redox-neutral, photocatalytic alkylation of unactivated C(sp^3)−
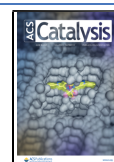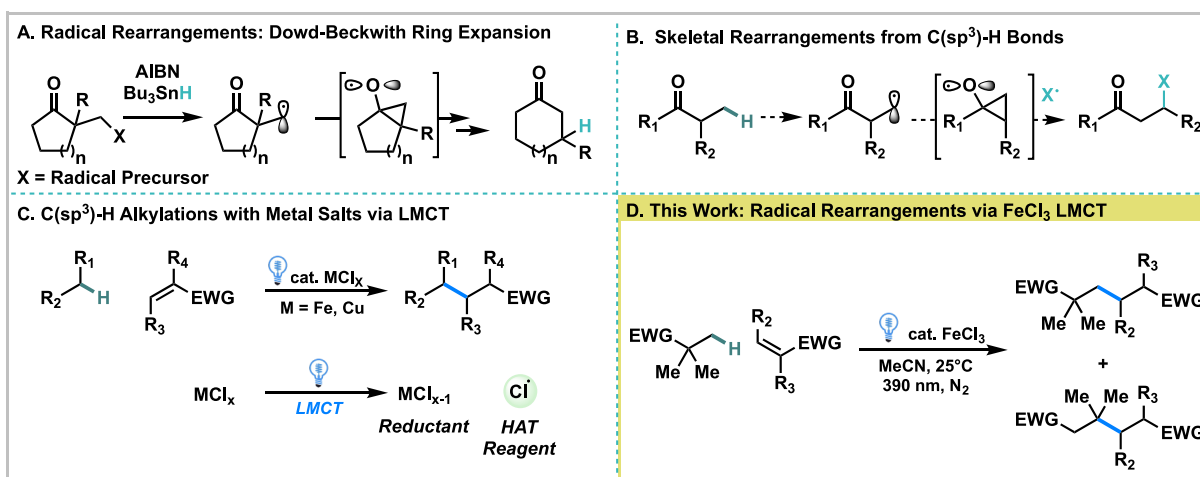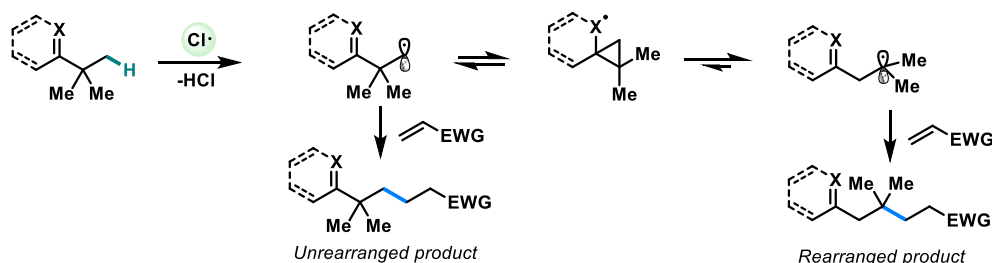
Scheme 1. Radical Rearrangement via FeCl$_3$ Ligand-to-Metal Charge-Transfer (LMCT) Provides Access to Divergent C(sp^3)–H Alkylation Products

Scheme 2. Mechanism of the 1,2-Rearrangement

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 the 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 λ_{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,
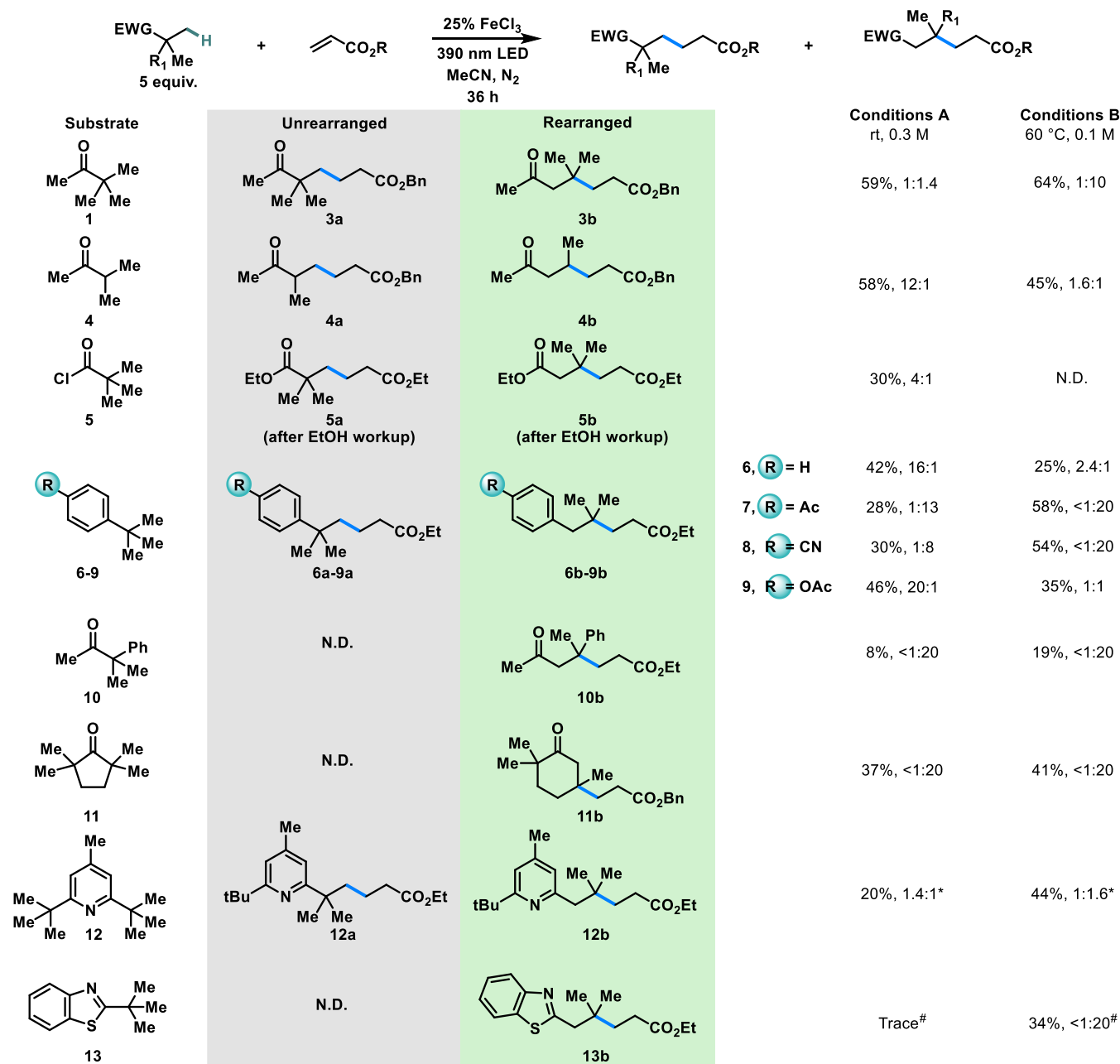
Table 1. Optimization and Control Studies[a]

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% 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

[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.

indicating that this is likely to be the photoactive species in our system.[52] The 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 h and

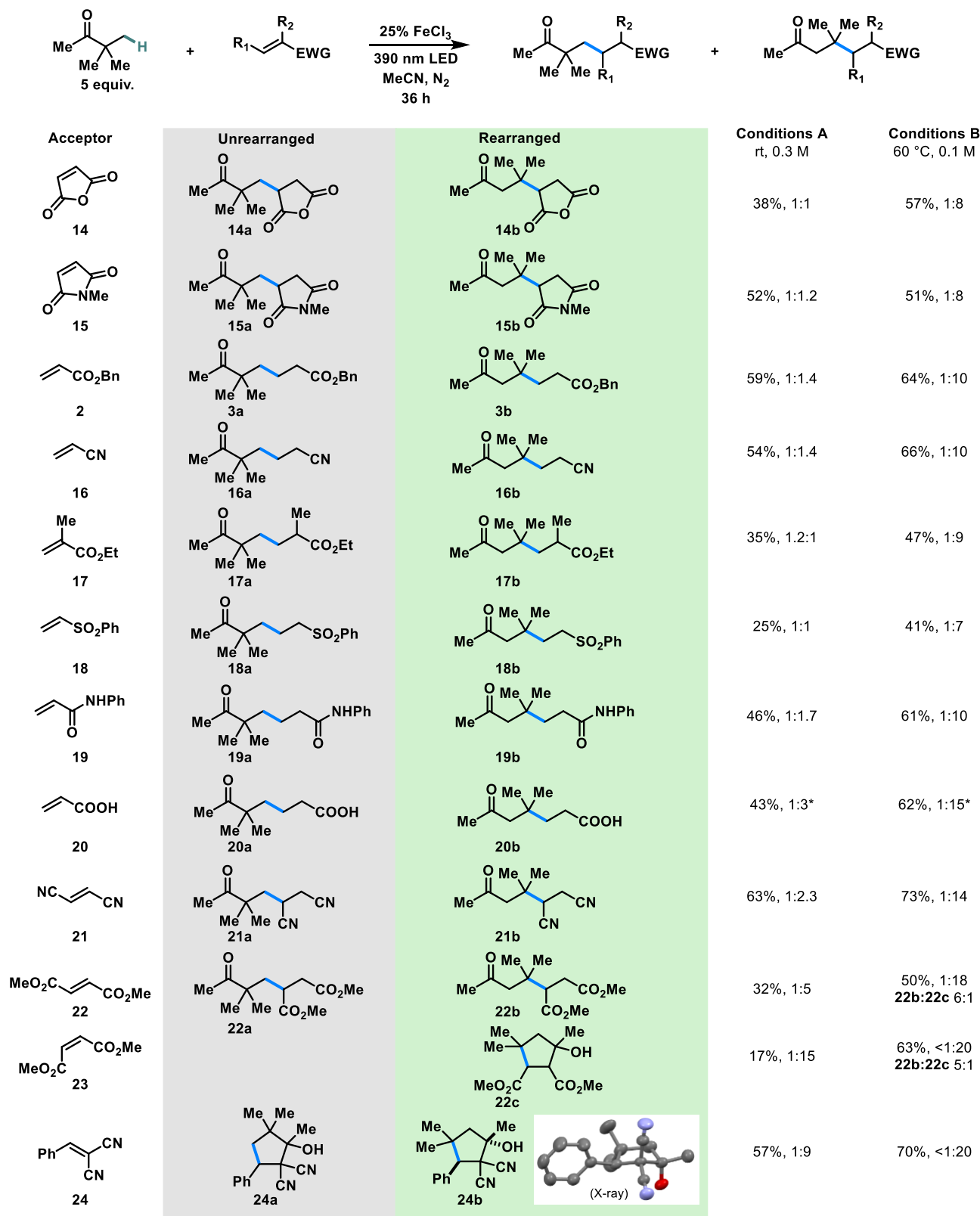**Scheme 3. Scope of C−H Pronucleophiles for the 1,2-Migration**

Substrate	Unrearranged	Rearranged	Conditions A rt, 0.3 M	Conditions B 60 °C, 0.1 M
1	3a	3b	59%, 1:1.4	64%, 1:10
4	4a	4b	58%, 12:1	45%, 1.6:1
5	5a (after EtOH workup)	5b (after EtOH workup)	30%, 4:1	N.D.
6-9	6a-9a	6b-9b	**6, R = H** 42%, 16:1	25%, 2.4:1
			7, R = Ac 28%, 1:13	58%, <1:20
			8, R = CN 30%, 1:8	54%, <1:20
			9, R = OAc 46%, 20:1	35%, 1:1
10	N.D.	10b	8%, <1:20	19%, <1:20
11	N.D.	11b	37%, <1:20	41%, <1:20
12	12a	12b	20%, 1.4:1*	44%, 1:1.6*
13	N.D.	13b	Trace#	34%, <1:20#

*With 50 mol % $FeCl_3$ and 5 equiv. CF_3COOH as an additive. #With 5 equiv. CF_3COOH as an additive. N.D.: not detected.

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 Supporting Information for additional substrates). Ketones other than pinacolone were also 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 toward 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} (298 K),[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.

Scheme 4. Scope of Acceptors for the 1,2-Migration

| Acceptor	Unrearranged	Rearranged	Conditions A rt, 0.3 M	Conditions B 60 °C, 0.1 M
14	14a	14b	38%, 1:1	57%, 1:8
15	15a	15b	52%, 1:1.2	51%, 1:8
2	3a	3b	59%, 1:1.4	64%, 1:10
16	16a	16b	54%, 1:1.4	66%, 1:10
17	17a	17b	35%, 1.2:1	47%, 1:9
18	18a	18b	25%, 1:1	41%, 1:7
19	19a	19b	46%, 1:1.7	61%, 1:10
20	20a	20b	43%, 1:3*	62%, 1:15*
21	21a	21b	63%, 1:2.3	73%, 1:14
22	22a	22b	32%, 1:5	50%, 1:18 **22b:22c** 6:1
23		22c	17%, 1:15	63%, <1:20 **22b:22c** 5:1
24	24a	24b (X-ray)	57%, 1:9	70%, <1:20

*1 equiv. trifluoroacetic acid used as an additive.

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

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)

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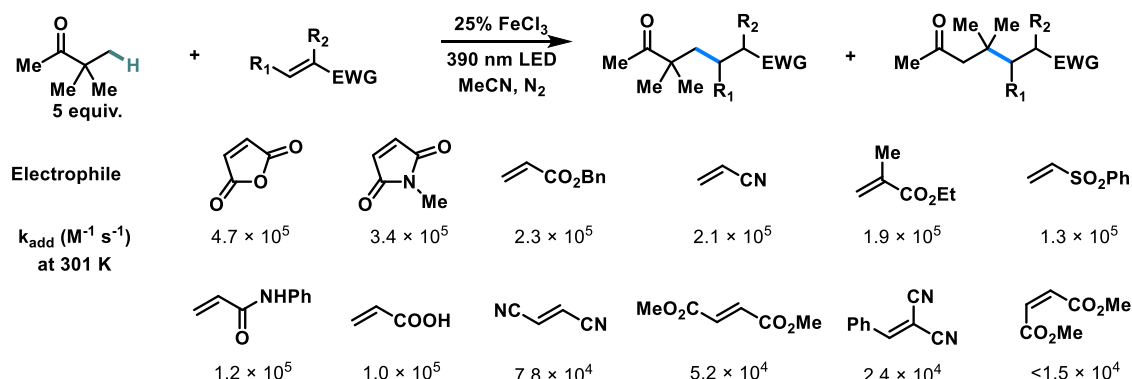
B. Controlling the isomeric ratio
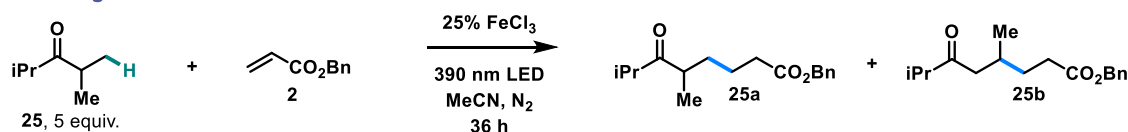
Entry	Conditions used	Yield (%)*	ir (25a:25b)
1	rt, 0.75 M	72	3.9 : 1
2	rt, 0.3 M (Conditions A)	69	2.3 : 1
3	60 °C, 0.10 M (Conditions B)	63	1 : 3.2
4	60 °C, 0.10 M, portionwise addition of **2**	76	1 : 5.9

*Yields were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard.

arene and the carbonyl moieties. We exclusively obtained the rearrangement product resulting from a 1,2-acyl shift (**10b**). This complete selectivity occurs because the rate of the 1,2-acyl shift is more than 2 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**). Exclusive 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*-methyl-maleimide in previous studies with closed-shell nucleo-philes,[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, benzyli-denemalononitrile, 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.

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 cyclo-propyloxy 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 3 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 the 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 2.9×10^4 s^{-1} (see Supporting Information). 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 the 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 prefunctionaliza-tion 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.

ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c02285.

Experimental details and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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