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Iron-Catalyzed α-Alkylation of Ketones with Secondary Alcohols: Access to β-Disubstituted Carbonyl Compounds

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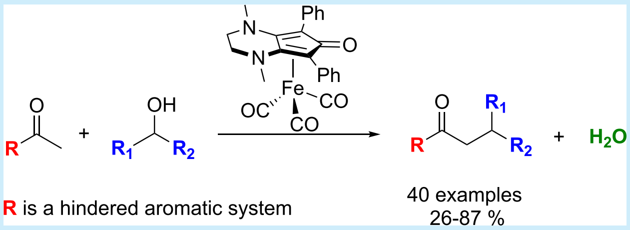
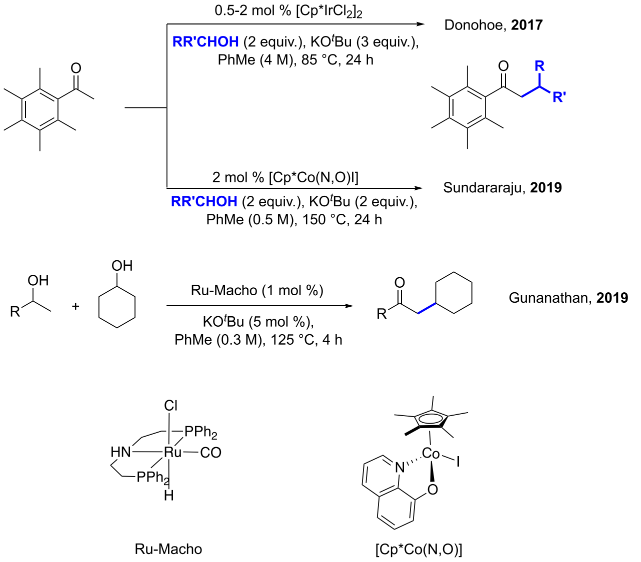
ABSTRACT: An iron-catalyzed borrowing hydrogen strategy has been applied in the synthesis of β-branched carbonyl compounds. Various secondary benzylic and aliphatic alcohols have been used as alkylating reagents under mild reaction conditions. The ketones have been isolated in good to excellent yield. Deuterium labeling experiments provide evidence that the alcohol is the hydride source in this reaction and that no reversible step or hydrogen/deuterium scrambling takes place during the process.



The α-alkylation of ketones is one of the well-studied carbon−carbon bond-forming reactions. Traditionally, this reaction implies the formation of an enolate and the addition of halide or pseudohalide derivatives under cryogenic conditions.[1] Although this method is still often used, it presents severe drawbacks such as the generation of waste and the use of hazardous and toxic chemicals.[2] Finally, whereas the alkylation of enolate with primary electrophiles is usually a powerful process, the alkylation with secondary alkyl halides is much more challenging because competitive side reactions such as elimination can occur. In this context, new strategies have recently been developed. The borrowing hydrogen is now an alternative to the traditional enolate chemistry. This hydrogen autotransfer process consists of a cascade of dehydrogenation, condensation, and reduction steps and allows the direct coupling of a ketone and alcohol under basic conditions.[3] The advantages of this methodology, besides the use of alcohols as electrophiles, rely on the formation of water as the only sole side product and the employment of noncryogenic conditions. A plethora of metal-based complexes, including Earth-abundant ones, have already been reported in the literature.[4,5] However, whereas the alkylation of ketones with primary alcohols is well explored, alkylation with secondary alcohols is still underexplored.[6−8] Donohoe and coworkers reported that an iridium catalyst could catalyze the α-alkylation of pentamethylphenyl (Ph*) acetophenone with primary and secondary alcohols in the presence of an excess of base (3−5 equiv) at 85−115 °C (Scheme 1).[6] The corresponding alkylated ketones were isolated in good to excellent yield. The introduction of the Ph* substituent was the key for the success of the procedure for the following reasons: (a) The ortho-disubstitution of the phenyl ring generates a steric hindrance and consequently a twist out of the conjugation with the carbonyl function; (b) the Ph* group prevents the self-dimerization of the starting ketone; and (c) the Ph* alkylated ketones can be further functionalized via a treatment with bromine and the formation of an acyl bromide.[6] Sundararaju described the first example of an Earth-abundant metal-based complex for the alkylation of the Ph* ketone with secondary alcohols.[7] The cobalt(III)-catalyzed hydrogen autotransfer strategy with an excess of secondary alcohols (2 equiv) and of base (2 equiv) at high temperature (150 °C) led to the alkylated ketones in moderate to good yield (33−86%,

Scheme 1. Previous Work in the Alkylation of Ketones with Secondary Alcohols



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Scheme 1). Again, the Ph* group appeared to be crucial for the favorable outcome of the strategy. Other ortho disubstituted phenyl rings proved to be less successful, and almost no alkylated product was isolated from the nonsubstituted aryl ketones.[7] Gunanathan explored a ruthenium-catalyzed cross-coupling reaction of secondary alcohols, leading to β-substituted aromatic ketones (Scheme 1).[8] This methodology allowed the synthesis of a variety of β-branched aromatic ketones in moderate to excellent yield (30–90%) and was not limited to the use of Ph* benzylic alcohol. Remarkably, the Ru-Macho complex oxidized the alkyl alcohols faster than the benzylic ones, and the aromatic enones were selectively formed and reduced.

Even if these pioneer works open new opportunities in sustainable chemistry, some limitations are still present. These procedures are based on the use of platinum-based metal complexes or of expensive phosphine ligands or required high reaction temperatures.

We and Morrill have recently demonstrated that the diaminocyclopentadienone iron tricarbonyl complex **Fe1** was an efficient catalyst for the alkylation of ketones, amines, oxindoles, indoles, and alcohols with a large variety of primary alcohols, including methanol.[9,10] We have also showed that **Fe1** could catalyzed the chemoselective reduction of various α,β-unsaturated ketones into saturated ketones under basic conditions.[11] Interestingly, trisubstituted alkenes were hydrogenated under these hydride transfer conditions.[11] These precedents open the way to the alkylation of ketones with secondary alcohols catalyzed by a phosphine-free cyclopentadienone iron carbonyl complex (Scheme 2).

Scheme 2. Layout of the Iron-Catalyzed Hydrogen Autotransfer with Secondary Alcohols

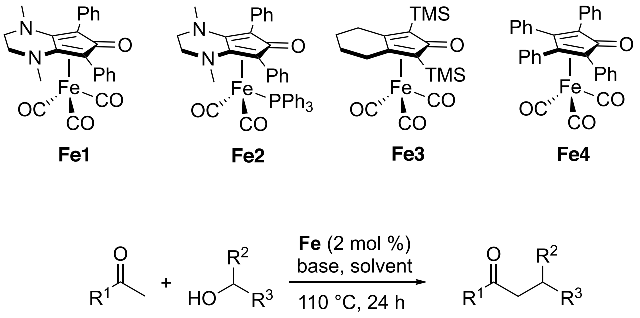
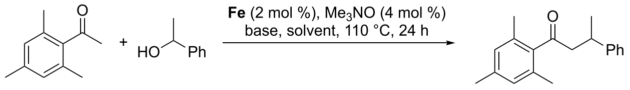


Table 1. Optimization of the Reaction Conditions[a]



entry	Fe	base	alcohol (equiv)	solvent	conv. (%)[b]
1	**Fe1**	Cs_2CO_3[c]	2	toluene	-
2	**Fe1**	Cs_2CO_3	2	toluene	61
3	**Fe1**	K_3PO_4	2	toluene	10
4	**Fe1**	NaOMe	2	toluene	32
5	**Fe1**	NaOH	2	toluene	48
6	**Fe1**	NaO^{t}Bu	2	toluene	98
7	**Fe1**	NaO^{t}Bu	1.5	toluene	98 (87)[d]
8	**Fe1**	NaO^{t}Bu	1.5	CPME	76
9	**Fe1**	NaO^{t}Bu	1.5	^{t}BuOH	79
10	**Fe2**	NaO^{t}Bu	1.5	toluene	78
11	**Fe3**	NaO^{t}Bu	1.5	toluene	80
12	**Fe4**	NaO^{t}Bu	1.5	toluene	84

[a] General conditions: ketone (0.5 mmol), **Fe** (2 mol %), Me_3NO (4 mol %), base (1 equiv), and toluene (1 mL). [b] Conversions were determined by ^1H NMR analysis of the crude mixture. [c] Base (0.1 equiv). [d] Yield in bracket was based on isolated product.

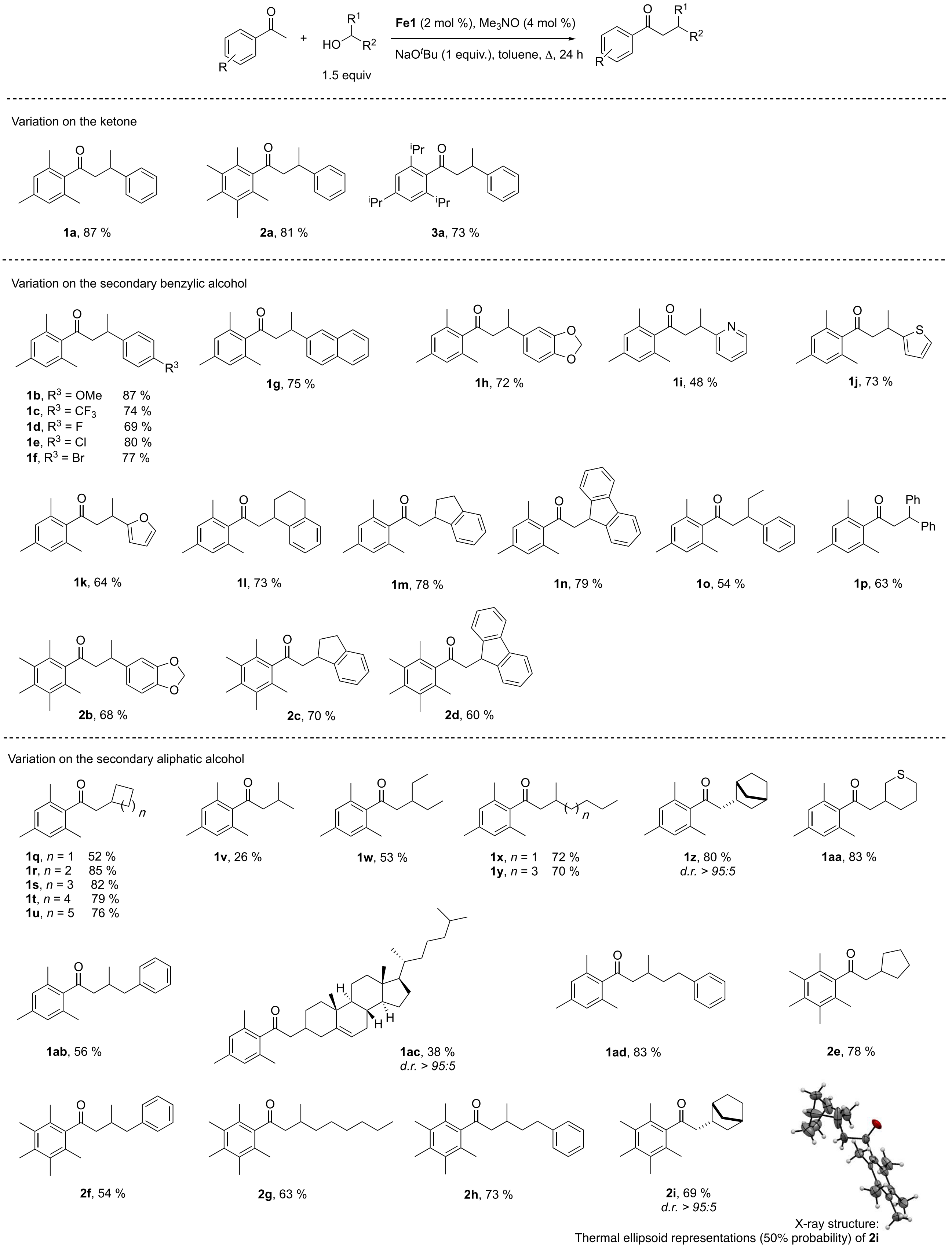
The borrowing hydrogen reaction between 1-mesitylethan-1-one and 1-phenylethan-1-ol was initially chosen as a model reaction to define the optimized reaction conditions (Table 1 and Table S1). Me_3NO was used to activate **Fe1**, **Fe3**, and **Fe4** and liberate a vacant site,[12,13] and **Fe2** was thermally activated at 70 °C.[10d,11] A rapid examination of the temperature, in the presence of **Fe1** as a catalyst, 1 equiv of ketone, and 2 equiv of alcohol in toluene, showed that almost no reaction occurred below 110 °C (entries 1–3, Table S1). Apart from the temperature, the key parameter was the base. NaO^{t}Bu gave a full conversion when other bases such as Cs_2CO_3, NaOMe, NaOH, or K_3PO_4 led to the alkylated ketone in a much lower conversion (entries 2–6, Table 1). Moreover, a stoichiometric amount of base has to be used to maintain a high activity (entries 1 and 2, Table 1). Reducing the amount of alcohol to 1.5 equiv did not modify the activity (entries 6 and 7, Table 1). Various solvents, such as cyclopentyl methyl ether (CPME) and *tert*-butanol, could be introduced in this alkylation, but the conversions were somewhat lower (76 and 79% conversion, respectively, Table 1 entries 8 and 9). Whereas complex **Fe1** was the sole efficient complex in the α-alkylation of ketones with primary alcohols, β-branched ketones have been obtained under these reaction conditions from secondary alcohols with other cyclopentadienone iron tricarbonyl complexes (**Fe2**, **Fe3**, and **Fe4**), albeit in lower conversions (Table 1 entries 10–12). Finally the best conditions were as follows: 0.5 mmol of 2,4,6-trimethylphenyl ketone underwent alkylation in the presence of 2 mol % of **Fe1** and 4 mol % of *N*-trimethylamine oxide, 1.5 equiv of 2-phenylethanol, and 1 equiv of NaO^{t}Bu in refluxing toluene to give the β-branched ketone in 87% isolated yield (entry 7, Table 1).

Having established an optimized protocol, we set out the scope of the iron-catalyzed borrowing hydrogen alkylation with secondary alcohols. First, the aryl group of the starting ketone was modified. As previously stated by Donohoe and Sundararaju,[6,7] a substituted aromatic ring at the ortho, ortho′ positions was a prerequisite for good overall reactivity (Scheme 3), as it orientates the aromatic ring and the carbonyl function orthogonally and consequently avoids competitive reactions, such as dimerization and reduction. The alkylation of various aromatic ketones with 2-phenyl ethanol illustrates this precondition (Scheme 3). A complex mixture was obtained when acetophenone or 1-(naphthalen-2-yl)ethan-1-one was used as the enolate precursor, whereas the β,β'-disubstituted ketones **1a**–**3a** were isolated in good yield from 2,4,6-trimethylphenyl, pentamethyl, and 2,4,6-tris(*iso*-propyl) acetophenone (73–87%, Scheme 3).

To promote the synthetic utility of our protocol, a gram-scale alkylation of 1-mesitylethan-1-one was carried out. The corresponding 1-mesityl-3-phenylbutan-1-one **1a** was isolated in 83% yield.

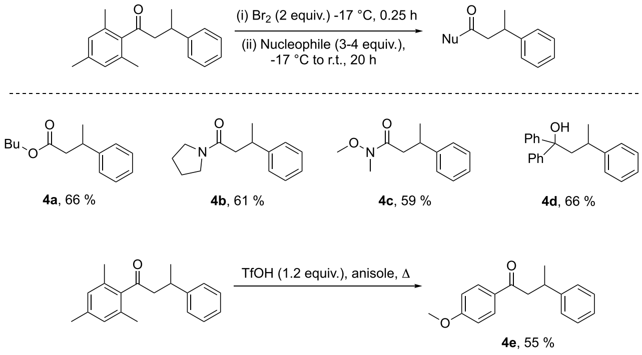
We then examined the **Fe1**-catalyzed alkylation of both 2,4,6-trimethylphenyl and pentamethyl ketone with a variety of secondary benzylic type alcohols (Scheme 3). Various electron-donating, electron-withdrawing substituents (such as halides and ether) within the aromatic ring and naphthyl group were tolerated, and the corresponding β,β'-disubstituted

Scheme 3. Scope of the Iron-Catalyzed Alkylation of Ketones with Secondary Alcohols

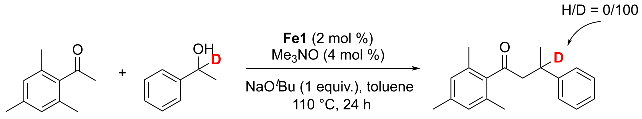


ketones **1a**–**h** and **2a**,**b** were isolated in good yield (69–87%, Scheme 3). Heterocyclic structures, including pyridine, thiophene, and furan, were accepted under these conditions, and the *β*-branched ketones were prepared in 48–72% yield

Scheme 4. Functionalization of β-Branched Ketones



Scheme 5. Deuterium Labeling Experiment



(Scheme 3). Cyclic secondary alcohols afforded the ketones **1l**, **1m**, and **2c** in 70−78% yield (Scheme 3). This work was also extended to bis-benzylic derivatives, and compounds **1n**, **1p**, and **2d** were synthesized in 60−79% yield (Scheme 3). Remarkably, whatever the ortho-substituted ketone (trimethylphenyl or pentamethyl acetophenone) engaged as a nucleophile, the corresponding alkylated ketones were obtained in similar yields (**1h** vs **2b**, **1m** vs **2c**, **1n** vs **2d**, Scheme 3).

Gratifyingly, our methodology was successfully diversified to various more challenging secondary aliphatic alcohols (Scheme 3). Cyclic or acyclic secondary aliphatic alcohols were engaged in the hydrogen autotransfer process. The ketones **1q−ac** and **2e−g** were isolated in moderate to excellent yield (28−85%, Scheme 3). In more detail, except for the alkylation with isopropanol, alkylation with long-chain acyclic aliphatic alcohols provided the ketones **1w−y** and **1ab** in 50−72% yield. With isopropanol, the best result was obtained when the reaction was performed in pure isopropanol and the yield in ketone **1v** reached only 26%. The cyclic secondary alcohols furnished the ketones **1q−u** and **1z−aa** in 52−85% yield. The ring size did not modify the reactivity, and even a heterocyclic derivative could be used. As an example, the tetrahydrothiopyran-substituted ketone **1aa** was obtained in 83% yield (Scheme 3). The late-stage functionalization of cholesterol with trimethylphenyl ketone yielded the ketone **1ac** in 38% yield. As previously noticed, alkylation using pentamethyl acetophenone could also be performed, albeit in lower yield. **2e−g** were obtained in 54−78% yield. Remarkably, ketones **1z**, **1ac**, and **2i** were obtained as a single diastereomer, whereas the cobalt-catalyzed borrowing hydrogen methodology with secondary alcohols delivered the ketone **1ab** without any stereocontrol.[7] This observation is in agreement with our previous work on the **Fe1**-catalyzed reduction of various α,β-unsaturated ketones.[11] Chiral trisubstituted enones, such as verbenone, carvone, testosterone, (+)-4-cholesten-3-one, and progesterone, were diastereoselectively and chemoselectively reduced under hydride transfer conditions. Overall, the new iron-catalyzed synthesis of β,β-disubstituted ketones also appears quite competitive compared with the iridium approach, as the chemical yields are comparable.

Next, the derivatization of products was evaluated. Following the procedure developed by Donohoe, namely, a retro-Friedel−Crafts acylation reaction followed by the addition of a nucleophile on the acyl bromide intermediate, ester **4a**, amides **4b**,**c**, and alcohol **4d** were produced from the trimethylphenyl ketone **1a** in reasonable yield (59−66%, Scheme 4). Finally, a retro-Friedel−Crafts/Friedel−Crafts sequence with anisole under acidic conditions[6a] furnished the substituted ketone **4e** in 55% yield.

To obtain mechanistic insights into this alkylation reaction, a deuterium labeling experiment was performed (Scheme 5). The alkylation of 1-mesitylethan-1-one with 1-phenylethan-1-ol-d_1 under the optimized conditions led to the formation of **1a**-$\boldsymbol{d_1}$ in 82% yield. This chemical yield is as good as the nondeuterated alkylation (Scheme 3). Deuterium was fully incorporated on the benzylic position (Scheme 5). This experiment confirmed that the alcohol is the source of hydride and also showed that there is no deuterium/hydrogen exchange in the borrowing hydrogen methodology. This observation is in sharp contrast with the cobalt-catalyzed alkylation with a secondary alcohol.[7] In this previous work, the deuterium was incorporated in both the α- and β-positions, highlighting either reversible steps or a deuterium/hydrogen scrambling on the cobalt complex. Moreover, in contrast with the work by Rueping et al. on the manganese-catalyzed α-methylation of ketones,[14] no deuteration of the benzylic positions in trimethylphenyl ketone was noticed, demonstrating a higher chemoselectivity with **Fe1**.

In conclusion we have reported the first phosphine-free iron-complex-catalyzed alkylation of hindered aromatic ketones with various secondary alcohols via a hydrogen autotransfer methodology, providing β-branched carbonyl compounds in moderate to excellent yield. Both aliphatic and aromatic alcohols could be engaged. Labeling studies demonstrate that the secondary alcohol is the source of hydride, and in contrast with the cobalt-catalyzed alkylation, no reversible step or deuterium/hydrogen scrambling occurs during the process. Consequently, the alkylation can also be diastereoselective. These results pave the way to new developments in iron-catalyzed alkylation.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00549.

Preparation details, optimization conditions, and NMR spectra (PDF)

Accession Codes

CCDC 1982548 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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