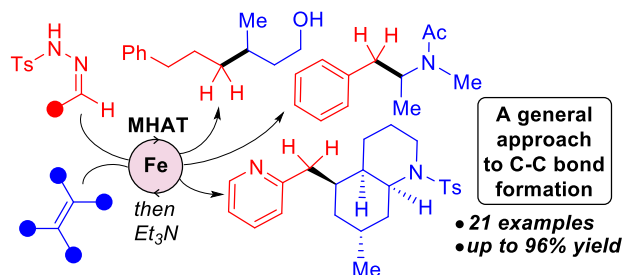# Iron-Hydride Radical Reductive Alkylation of Unactivated Alkenes

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*Supporting Information Placeholder*

ABSTRACT: Iron-catalyzed hydrogen atom transfer-mediated intermolecular C–C coupling reactions between alkenes and tosylhydrazones, followed by in situ cleavage of the tosylhydrazine intermediates using Et_3N, are described. The process involves a new strategic bond disconnection resulting in the reductive alkylation of non-activated alkenes. The reaction is operationally simple, proceeds under mild conditions, and has a wide substrate scope.

The formation of carbon-carbon bonds via radicals has gained widespread application in organic synthesis.[1] The catalytic metal-hydride hydrogen atom transfer (MHAT) reaction[2] has recently become established as a robust strategy to develop new bond-forming reactions via radical pathways. Building upon the pioneering work of Mukaiyama[3] and others,[4] it has been shown that direct alkene functionalizations can be achieved by employing earth-abundant non-toxic metals (e.g. Fe(III), Mn(III), or Co(II)) in combination with a hydrogen source to generate a putative metal hydride species able to carry out a HAT to non-activated alkenes.[5] The reactions often proceed under mild conditions with good regioselectivity, site-selectivity and broad functional group tolerance. The nucleophilic carbon-centered radical that is generated via this MHAT process can be then reacted with a wide range of electrophiles to give a diversity of structures. However, the potential of these reactions to form C–C bonds was not demonstrated until relatively recently, when the Baran group employed electron-deficient alkenes as the electrophilic component.[6] Since then, new acceptors enabling C–C bond formation have been discovered at an ever accelerating rate[7] and the application of MHAT reactions in total synthesis is also a rapidly growing area.[8] Moreover, new insights into the mechanism for alkene cross-coupling by Fe-acac catalysts have been proposed.[9]

As part of our contribution to this emerging field, it was demonstrated for the first time that ketones[10] could serve as suitable acceptors when tethered to the alkene radical precursor (Figure 1A).

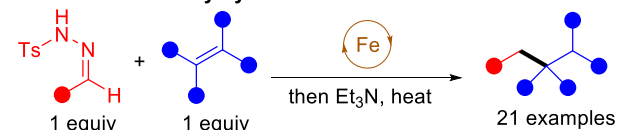**A. Our previous work:** *Coupling of alkenes to carbon-heteroatom sp² centers via MHAT*
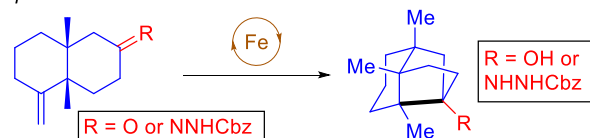
B. Radical couplings of alkenes with *N*-sulfonylhydrazones
(i) Kim´s radical cyclization (ii) Baran's hydromethylation reaction
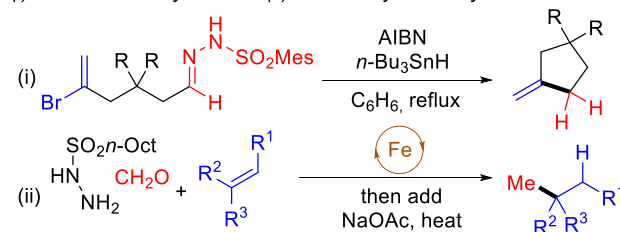
C. *This work:* MHAT reductive alkylation of unactivated alkenes with tosylhydrazones

- A general disconnection approach to C-C bond formation
- Wide substrate scope
- Cheap, readily available starting materials and reagents

Figure 1. Background for the development of the radical N-tosylhydrazone-alkene coupling

We also showed that Cbz-hydrazones[11] could be used as radical acceptors (intra- and intermolecular variants) resulting in a new method to achieve valuable α-tertiary amines (after cleavage of the initially formed hydrazine). It was during these studies in search of suitable C=N acceptors for MHAT reactions that it was observed that in the presence of stoichiometric iron and heating, a tosylhydrazone would undergo intramolecular coupling and in situ fragmentation (of the intermediate tosylhydrazine species) to give the corresponding tricyclic hydrocarbon. It should be noted that Kim demonstrated that in the presence of Bu_3SnH, vinyl radicals will add to mesityl substituted hydrazones in an intramolecular manner with concomitant fragmentation (Figure 1B(i)).[12] Baran subsequently showed that under MHAT conditions, alkenes could be methylated using a formylhydrazone, constituting a method for the late-stage diversification of natural products and pharmaceuticals (Figure 1B(ii)).[13]

Based on these precedents from the aforementioned literature and our own research, we believed it would be possible to develop a general and effective C–C coupling methodology with wide applicability in organic synthesis using only inexpensive and readily available starting materials. Moreover, we hoped this process would provide new retrosynthetic design options for the construction of C–C bonds.[14] Herein we describe the development of this intermolecular MHAT-triggered cross-coupling alkylation reaction, its wide scope and C–C bond-forming potential even in demanding contexts (Figure 1C).

To develop the radical tosylhydrazone–alkene cross-coupling, we began our studies by utilizing tosylhydrazone **1** as the acceptor and 4-phenylbutene **2** as the radical precursor in the presence of one equivalent of $Fe(acac)_3$ in EtOH. We were pleased to observe clean coupling to the hydrazine **3** in 81% yield along with traces of the desired elimination product **4** (Table 1, entry 1). Several factors were modified without achieving any improvement: the solvent (entry 2),[13] type of sulfonamide group (entries 3 and 4),[12,13] catalyst loading (entry 5), temperature (entry 6), reaction time (entry 7) and the ratio of the coupling partners (entries 8 and 9). Notably, in the great majority of evaluated conditions the amount of fragmentation product **4** was low.

The initial conditions used for the intramolecular version suggested that heating the reaction and stoichiometric Fe were both essential for fragmentation to occur. However, as high temperatures had proved to be detrimental (see Table 1, entry 6), an alternative strategy was sought. When the coupled product mixture was heated after the addition of a base (NaOAc),[15] the elimination (loss of sulfinic acid and nitrogen) proceeded in good yield (Table 1, entry 10). Moreover, the base could be added at the beginning of the reaction without any significant drop in yield (entry 11). Decreasing the quantity of iron catalyst to 0.4 equiv was viable with only a slight loss of yield (entry 12). Finally, evaluation of other bases, such as Et_3N, enabled us to streamline the process by removing the aqueous

work-up step, and to obtain the product in excellent yield (entry 13). Overall, the procedure was more efficient than our previously developed intermolecular reaction using N-Cbz-protected hydrazones,[11] as the tosyl group was a better radical acceptor. Thus, the reaction only required 8 h (vs 48 h) and an equimolecular ratio of the two components.

Table 1. Optimization of the Reaction Conditions

(a) Coupling

entry	modification	yield **3**	yield **4**
1	---	81%	traces
2	THF/MeOH (2 equiv)	60%	6%
3	R = Mesityl	9%	33%
4	R = $SO_2 n$-Octyl	70%	---
5	0.2 equiv of $Fe(acac)_3$	69%	traces
6	60 °C	10%	traces
7	48 h	33%	16%
8	2 equiv of acceptor **1**	68%	7%
9	2 equiv of donor **2**	56%	9%

(b) Coupling and fragmentation
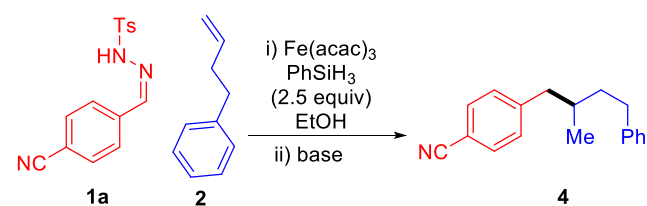
| entry	Fe(III)	base[a]	T(°C)[b]	time(h)[b]	yield
10	1	NaOAc	rt → 80	24 → 3	82%
11	1	NaOAc[c]	rt → 80	24 → 3	78%
12	0.4	NaOAc	rt → 80	8 → 1	76%
13	0.4	Et_3N	rt → 80	8 → 1	96%

[a]4 equiv of base was used. [b]Coupling → elimination process conditions. [c]Added at the start of the reaction.

Having established the optimum conditions for the coupling reaction, we investigated the scope of the alkene coupling partner. As can be seen in Table 2, a wide range of functional groups were tolerated. Monosubstituted alkenes bearing free alcohols, silyl ethers, esters, amides and

Boc-protected amines (**2a-e**) were all viable coupling part-ners giving the corresponding coupled products in good to excellent yields (**4a-e**). It should be mentioned that in Baran's study on hydromethylation, the reaction of alkene **2d** using the formaldehyde-derived tosylhydrazone gave a 19% yield,[13] with 36% of the reduced alkane proceeding from **2d**.

The results reported here, a 78% yield for the cross-cou-pling of tosylhydrazone **1a** with the same alkene **2d** (Table 2), indicate that our hydroalkylation process behaves dif-ferently from Baran's methylation reaction.[13]

Table 2. Scope of the Alkene Component
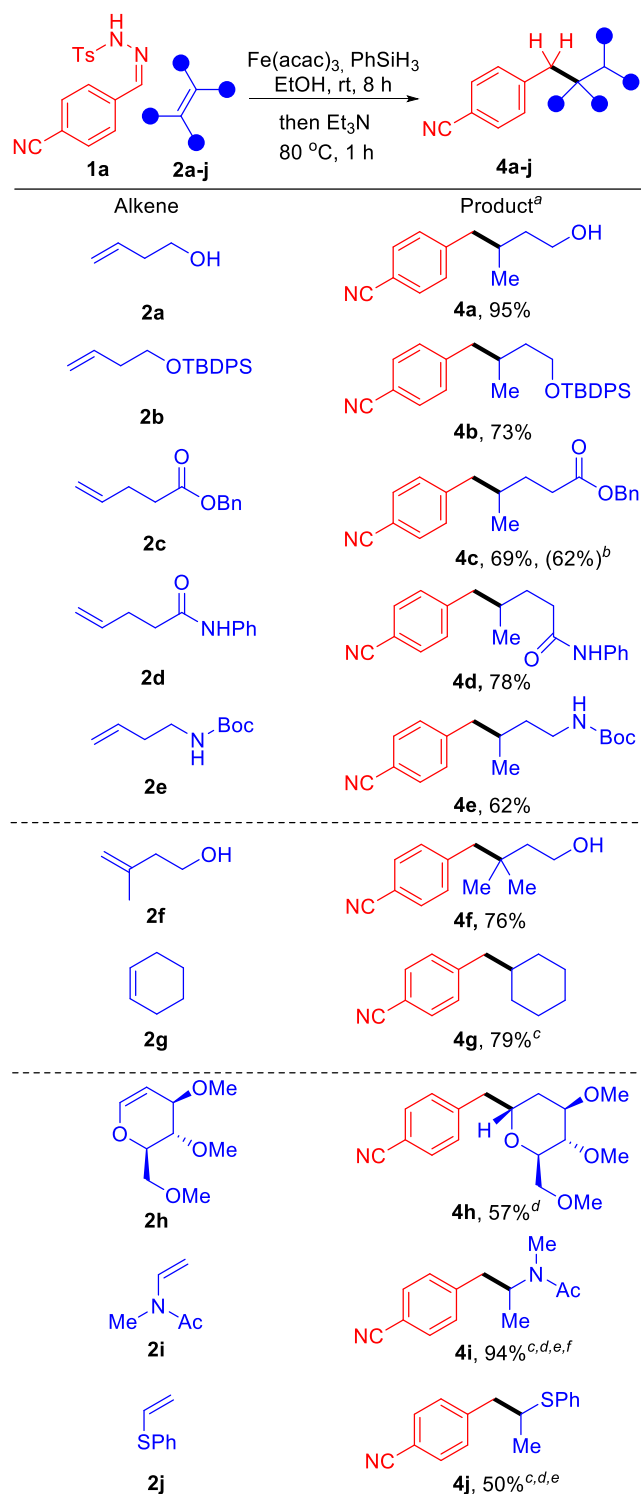
[a]All reactions were carried out with **1a** and **2** in stoichiometric quantities, Fe(acac)$_3$ (0.4 equiv), PhSiH$_3$ (2.5 equiv) and Et$_3$N (4 equiv) in EtOH [0.04 M] unless otherwise noted. [b]2 mmol scale. [c]NaOAc was used instead of Et$_3$N. [d]1 equiv of Fe(acac)$_3$ was used. [e]3 equiv of alkene was used. [f]Fe(dpm)$_3$ was used.

1,1-Disubstituted alkenes and cyclic alkenes (**2f-g**) were also good partners, as were compounds bearing heteroa-toms, such as oxygen (**2h**), nitrogen (**2i**) and sulfur (**2j**),

which were used to generate the corresponding C–C coupling compounds **4h-j**. It should be noted that although heteroatom-substituted alkenes gave good results under the standard reaction conditions, improvements were obtained by changing the Fe catalyst,[6a] the number of reagent equivalents or the base, depending on the heteroatom in question (see Table 2 footnotes for details).

Next to be evaluated was the scope of the tosylhydrazone acceptors. For this study, alkene **2a** was chosen as the coupling partner to prevent volatility issues with some of the products. As can be seen in Table 3 the reaction tolerates a wide range of groups: aromatic rings bearing electron-neutral (**5a-b**) electron-withdrawing (**5c-e**), heterocycles (**5f-g**) and aliphatic (**5h**) groups were all practicable partners. Although electron donating groups proved problematic, this problem can be circumvented using our previously reported hydrazone coupling methodology followed by hydrogenation.[11]

Table 3. Scope of Acceptor Hydrazones[a]

5a, 51%   **5b**, 51%

5c, 52%   **5d**, 63%

**5e**, 44%   **5f**, 67%

5g, 49%   **5h**, 66%
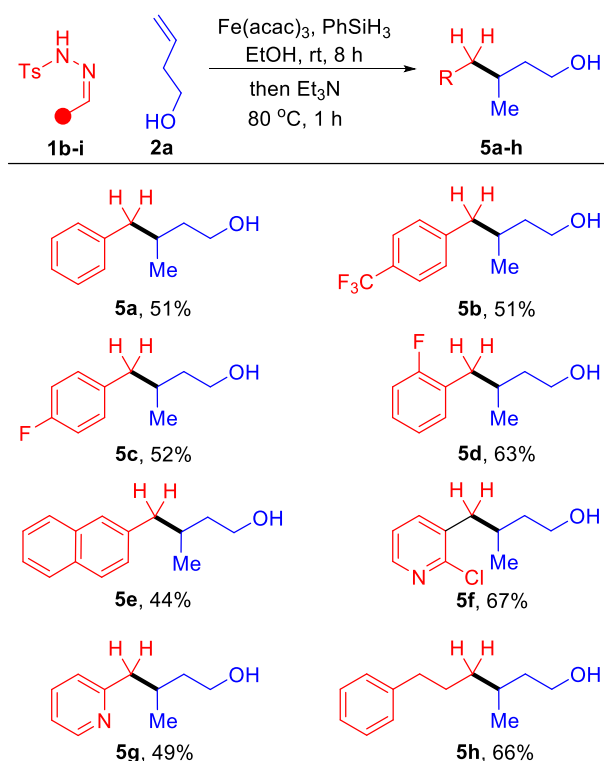
[a]All reactions were carried out according to the general method depicted in Table 2.

Finally, to show that this reaction can be carried out with a wide range of substrates, new synthetic pathways to access two biologically interesting compounds are described (Scheme 1). The coupling between hydrazone **1b** and alkene **2j** gave compound **5i** which is a precursor of the pharmaceutical compound methamphetamine.[16] On the other hand, the building block **6** for the synthesis of *Lycopodium* alkaloids[17] was converted into alkene **8** via enol triflate for-

mation followed by reduction.[18] Due to the steric hindrance of **8**, the reaction required more time but fortunately competitive reduction of the alkene was minimal. Regioselective coupling with pyridine **1h** gave **9** along with its epimer (dr 2:1) The achievement of compound **9** constitutes a formal synthesis of Serratezomine E, as we have previously demonstrated that intermediate **9** can be converted to this *Lycopodium* alkaloid in a few steps.[19]

Scheme 1. Synthetic Applications of Alkene–Tosylhydrazone Cross-Coupling
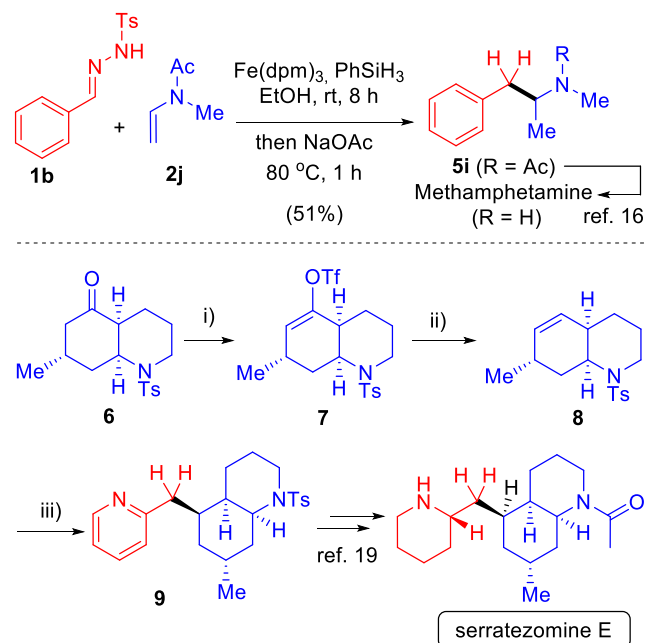
Reagents and conditions: *i)* Comins' reagent (2,5-chloropyridyltriflimide) (3.2 equiv), KHMDS (3.0 equiv), THF [0.03 M], −78 °C, 30 min; a combined yield of 94% for a 1:1 separable regioisomeric mixture. See Supporting Information for experimental details; *ii)* Bu₃N (3 equiv), Ph₃P (0.2 equiv), Pd(OAc)₂ (0.1 equiv), HCO₂H (2 equiv), DMF [0.2 M], 60 °C, 3 h, 83%; *iii)* Hydrazone **1h** (1 equiv), Fe(acac)₃ (1 equiv), PhSiH₃ (2.5 equiv), EtOH [0.04 M], 60 °C, 24 h; then Et₃N (4 equiv), 80 °C, 1h, 36% yield (78% brsm) as a 2:1 mixture of epimers at C-5.

In summary, we have developed an efficient iron-catalyzed hydrogen atom transfer (MHAT) reductive cross coupling reaction between alkenes and tosylhydrazones. Overall, this work provides an effective new strategy for the formation of sp³–sp³ carbon bonds and offers new retrosynthetic design options for the synthesis of complex molecules. Considering its use of ubiquitous functional groups, readily available reagents, high functional group tolerance, non toxicity and operational simplicity, we believe this methodology should find wide application as a general C–C bond-forming reaction in target-oriented synthesis.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures characterization, and spectral data (PDF)

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Notes
The authors declare no competing financial interest.

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