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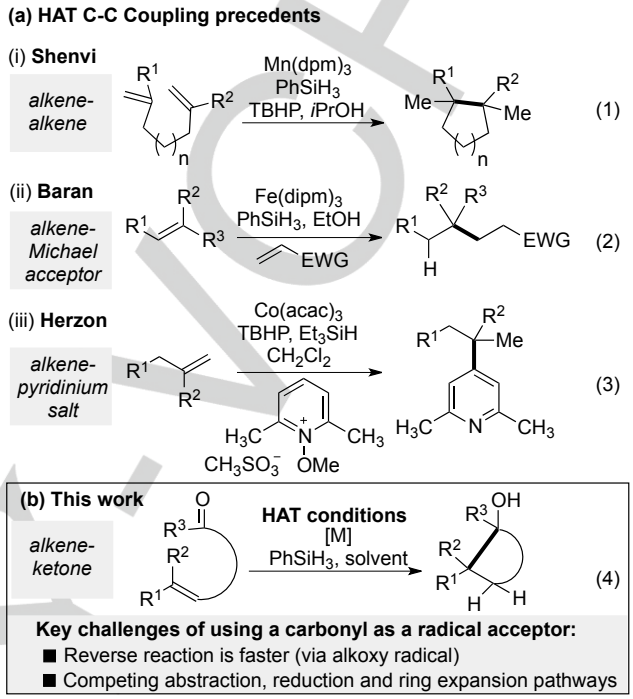
Hydrogen Atom Transfer-Initiated Radical Cyclization of Alkene-Tethered Ketones

Mar Saladrigas, Caroline Bosch, Gisela V. Saborit, Josep Bonjoch*, and Ben Bradshaw*

Abstract: An unprecedented hydrogen atom transfer-based C-C coupling reaction between alkenes and ketones using $Fe(acac)_3$ and $PhSiH_3$ in EtOH is described. This mild protocol features high site-selectivity and allows for the construction of sterically congested structures containing tertiary alcohols and quaternary centers. The overall process introduces a novel strategic bond disconnection for ring-closing reactions.

Radical reactions are important tools for the construction of carbon-carbon bonds, mainly via the addition of carbon-centered radicals to unsaturated bonds.[1] Such reactions often exhibit high chemoselectivity, lead to a particular stereochemical outcome, and are able to generate complex structures via tandem reactions.[2] Among the plethora of carboradical precursors, alkenes offer many advantages: they are generally stable under a wide range of conditions and are ubiquitous functional groups found in a variety of feedstock chemicals.

Due to these inherent advantages, the application of hydrogen atom transfer (HAT) to generate carbon-centered radicals from alkenes has become an active area of research.[3] Drago[4a] and Mukaiyama[4b] were pioneers in the use of alkenes as radical precursors via HAT, combining cobalt complexes with oxygen to access Markovnikov hydration products,[4c] although Norton[5] was the first to identify Halpern's HAT mechanism[6] in these reactions. In this century, many researchers have expanded the scope of the process to include other electrophiles or metals.[7] However, it was not until relatively recently that this methodology was shown to have potential as a general approach to C-C bond formation. In his hydrogenation studies,[8] Shenvi proved it was possible to intramolecularly couple two alkene units under HAT conditions (Scheme 1a, Eq. 1).[9] Baran´s group was the first to develop a general coupling reaction using electron-deficient alkenes as the electrophilic component in both intra- and intermolecular variants using iron catalysis (Scheme 1a, Eq. 2).[10] A number of other methodological procedures (e.g. Scheme 1a, Eq 3)[11] as well as applications in natural product synthesis[12] of HAT-promoted C-C bond formation have been subsequently reported. Nevertheless, to date the HAT-initiated process has not been applied to reductively couple alkenes to ketones, despite the carbonyl group being one of the most common unsaturated groups. While radical cyclization onto a C=O π-bond is facile, rate studies have shown that ring closure of radicals on carbonyl groups is slower than the ring opening of the alkoxy radical counterparts,[13] rendering carbonyl groups generally unfavorable as radical acceptors. This is reflected by the scarce usage of radical cyclizations to access cycloalkanols with ketones as radical



Scheme 1. General context of C-C bond formation from alkenes via HAT and the new challenge of using ketones as radical acceptors

acceptors, although in isolated examples haloalkanes,[14] a vinylbromide,[15] alkynes,[16] and epoxides[17] have been used as proradicals.

In this work, we expand the scope of the HAT process to include ketones as radical acceptors (Scheme 1b, Eq 4). Notably, this procedure overturns the character of the radical donor in classical keto alkene cyclizations, in which an initial ketyl radical is formed using either tributyltin hydride[18] or samarium iodide.[19] In the new approach the carbonyl group would play the role of the radical acceptor, allowing a new procedure for the radical cyclization of keto alkenes.[20]

As part of our search for a stereodivergent process for the hydrogenation of complex alkenes toward a unified synthesis of phlegmarine alkaloids,[21] we investigated a number of HAT reductive conditions and developed an alternative protocol[22] using stoichiometric $Mn(dpm)_3$, $PhSiH_3$ in DCE as the solvent, which allowed clean quantitative conversion to the desired products. While studying the scope of these hydrogenation reaction conditions, we observed that if the substrate bore a proximal carbonyl group, the radical intermediate was trapped, affecting a coupling rather than a reduction reaction. Unusually, in a process expected to be reversible, the starting keto alkene could be channeled to the reduced tertiary alcohol product. Thus, when keto alkene **1**[23] was treated with $Mn(dpm)_3$, and $PhSiH_3$ in DCE, the radical intermediate **II** did not evolve to the reduced compound *all*-cis-trimethyldecalin **I**,[24] but instead led to the unexpected formation of tricyclic alcohol **2** (Scheme 2 and Table 1, entry 1).

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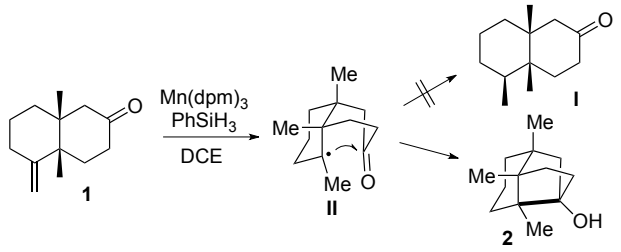
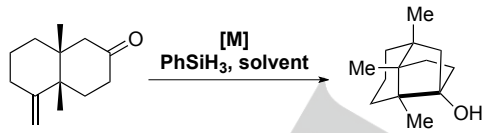


Scheme 2. Intramolecular coupling *vs* reduction under HAT reaction conditions.

This serendipitous observation opened the gates to the underexplored field of carbon-carbon bond formation by HAT, using the reaction of radical-centered carbons on ketone carbonyl groups. To further explore the parameters of the alkene-ketone coupling protocol (metal, solvent, temperature, time), compound **1** was used as a test substrate, the key results being summarized in Table 1 (see also SI). When using EtOH as a solvent, the reaction was relatively high yielding (86%), but less so than with DCE, and it also gave a small amount of by-products (entry 2). After evaluating a series of modifications, we found that an inert atmosphere was essential for a good yield, which dropped to 73% in open air (entry 3). The reaction could also be performed with catalytic quantities of $Mn(dpm)_3$, albeit with a slightly reduced yield compared to the stoichiometric version (entry 4). Switching to $Fe(acac)_3$ initially gave poor results, with the yield dropping to just 30% (entry 5). However, when EtOH was used as the solvent, the yield was not only better than with DCE, but it also matched that observed with $Mn(dpm)_3$ when used in stoichiometric quantities (entry 6). It was possible to shorten the reaction time to just 3 h or operate at room temperature (entries 7 and 8), but both modifications could not be combined without worsening the yield (entry 9).

Table 1. Screening of conditions for the radical cyclization of alkene-ketone **1**

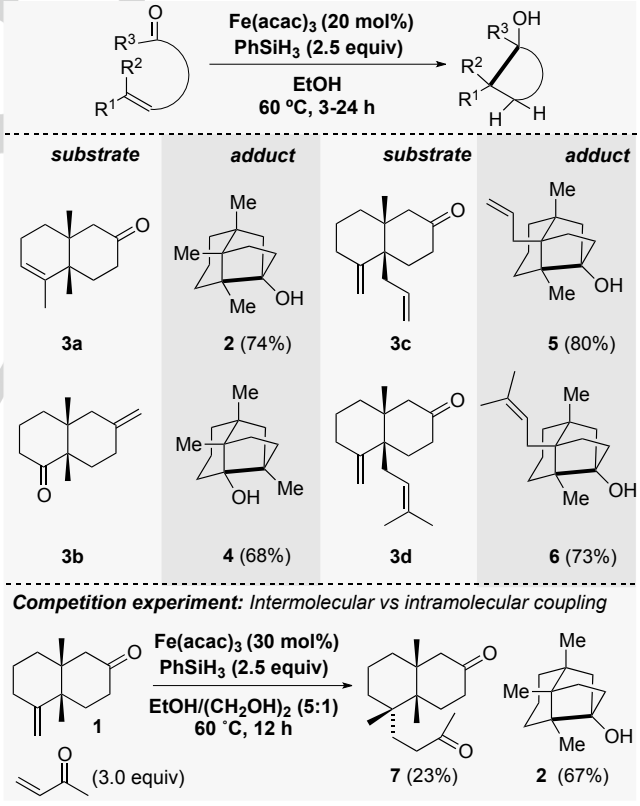


Entry[a]	Metal (equiv)	Solvent	T (ºC)	Time (h)	Yield
1	$Mn(dpm)_3$ (1)	DCE	60	24	92%
2	$Mn(dpm)_3$ (1)	EtOH	60	24	86%
3[b]	$Mn(dpm)_3$ (1)	DCE	60	24	73%
4	$Mn(dpm)_3$ (0.2)	DCE	60	24	79%
5	$Fe(acac)_3$ (0.2)	DCE	60	24	30%
6	$Fe(acac)_3$ (0.2)	EtOH	60	24	95%
7	$Fe(acac)_3$ (0.2)	EtOH	60	3	92%
8	$Fe(acac)_3$ (0.2)	EtOH	25	24	95%
9	$Fe(acac)_3$ (0.2)	EtOH	25	3	59%

[a] $PhSiH_3$ (2.5 equiv) was used. [b] Reaction carried out open to air.

With optimum conditions in hand, we evaluated this iron-triggered radical cyclization[25] in related substrates of synthetic or mechanistic interest (Table 2). The related compound **3a** with an endocyclic double bond also gave **2**. Compound **3b** with the alkene and ketone groups reversed in relation to compound **1** gave clean cyclization to tricyclic compound **4**. The decalone **3c**[26] bearing an allyl side chain was coupled in good yield to give **5** (entry 2). Notably, the allyl group remained unreacted while the formation of the radical took place exclusively at the exocyclic methylene. Thus, this constitutes a clear example of in situ selectivity dictated by the radical stability in HAT reactions upon isolated alkenes.[27] Similarly, the analogous dialkene **3d** gave clean cyclization from the methylene group onto the carbonyl, leading to alcohol **6**. To evaluate if our cyclization reaction could compete with radical cross coupling reactions, we performed the reaction of **1** in the presence of methyl vinyl ketone.[10a] Although intramolecular reactions are normally much faster, we wondered whether the formation of **7** might be favored by the potential reversibility of the reaction or by a competitive process. Indeed, a mixture of **2** and **7** (3:1) was isolated from the reaction mixture.

Table 2. Substrate scope for HAT-triggered cyclization of alkenes onto ketones.



After studying the tricyclic series, we decided to extend the iron-promoted intramolecular coupling of alkenes and ketones to another set of molecules. Starting from γ,δ-unsaturated ketones **8a**-**8c**, *cis*-ring fused hydrindane compounds[28] **9**-**11** were obtained in 76-87% yield. In the presence of the radical scavenger TEMPO (3 equiv) the reaction from **8c** was not promoted. Interestingly, although the cyclization of **8a**-**8c** took place onto a *β*-keto ester, the competitive Dowd-Beckwith ring expansion[13] was not observed. However, when keto alkene **8d**

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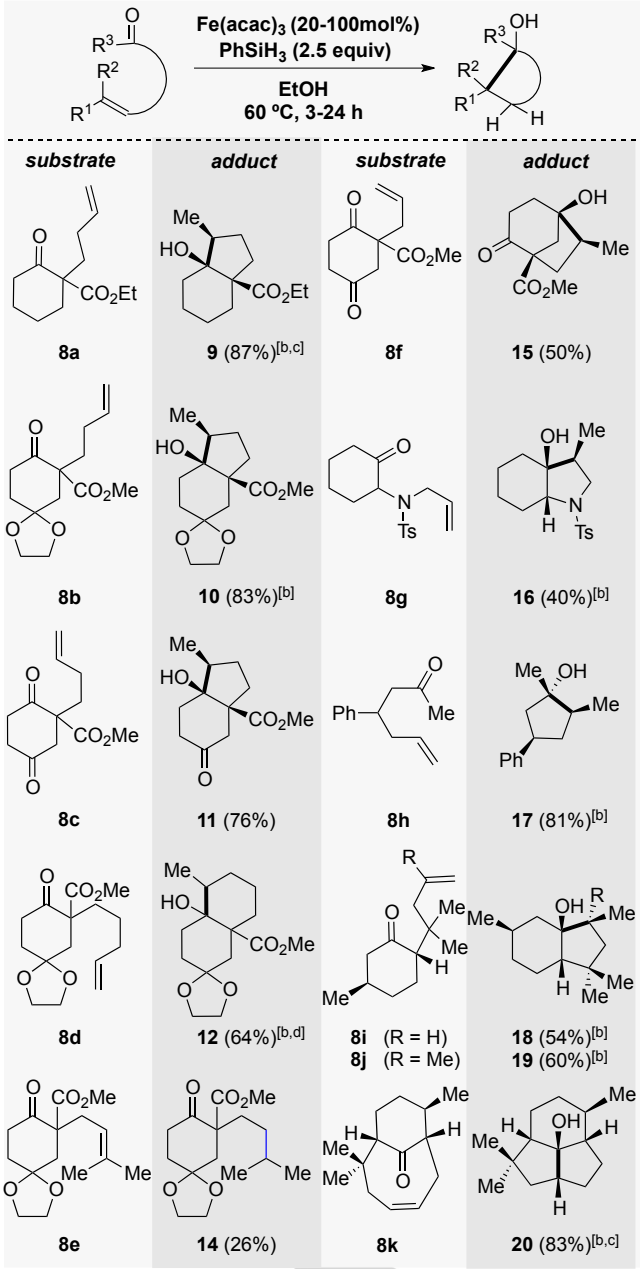
Table 3. Extended substrate scope for the HAT-triggered cyclization of alkenes onto ketones.[a]



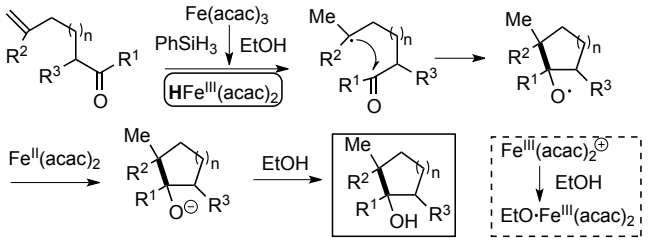
[a] Yield for combined diastereomers (see SI for details) showing the major isomer. 20 mol% $Fe(acac)_3$ used. [b] 100 mol% $Fe(acac)_3$ used. [c] Ethylene glycol was added as a cosolvent to facilitate the removal of silyl by-products. [d] 26% of ring-expanded product was also isolated.

was used as the starting material, in addition to the expected decalin **12**, the 10-membered ring expansion product **13**[29] was isolated as a minor compound (26%). For compound **8e,** bearing an isopentenyl side chain, no cyclization was observed and only a small amount of the reduced compound **14** was isolated, presumably due to steric crowding, which would involve the formation of a tertiary alcohol with two adjacent quaternary centers. Compound **8f**, bearing two carbonyls, selectively gave the bridged compound **15** and perhydroindole **16** was obtained starting from **8g**, although in only moderate yield. The cyclization of the open-chain ketone **8h** was not diastereoselective, cyclopentane **17**[14a] being isolated as a mixture of three diastereoisomers (dr 3:2.5:1).

Cyclization of compounds **8i** and **8j** gave the corresponding hydrindanols **18** and **19** in comparable yields (54% vs. 60%). This indicated that although a $R^1R^2C{=}CH_2$ *gem*-disubstituted alkene is likely a better carboradical source in the HAT process than a monosubstituted alkene, this is counterbalanced by the resulting increased steric crowding in the cyclization.

Finally, the HAT alkene coupling reaction was applied to the synthesis of a 12-demethyl analog of presilphiperfolan-8-ol.[30,31] With cyclohexane **8i** in hand, and following the reported procedure of Ito,[32] bridged compound **8k** was easily synthesized. The radical cyclization to form the 5,5-membered ring embedded in tricyclic compound **20** was achieved in very good yield, its structure being unequivocally confirmed by X-ray analysis.[33] The formation of the thermodynamically preferred stereoisomer is due to the intermediacy of a pyramidalized C-radical.[8a] This approach constitutes a straightforward synthetic entry to the characteristic tricyclo[5.3.1.$0^{4,1}$]undecane skeleton of presilphiperfolanol sequiterpenes.[34]

The reaction mechanism for the related radical C-C formation between non-activated alkenes and Michael acceptors in similar reaction conditions has been studied by Baran and Holland, who provided considerable evidence for the different intermediates.[10c] Based on this precedent, a simplified mechanism for reductive coupling of alkenes to ketones is outlined in Scheme 3. HAT from the $HFe(acac)_2$, generated *in situ*, to the olefin acts as the rate-determining step. Addition of the carbon-centered radical to the ketone provides an alkoxy radical, which, while being less favorable than the ring-opened product, is converted to an alkoxide via a SET process from the Fe(II) species with concomitant reoxidation to Fe(III). The latter allows the catalytic cycle to continue via $Fe(acac)_2(OEt)$ (Scheme 3, bottom right).



Scheme 3. **Overview of the proposed reaction mechanism.**

Summary: In summary, we have shown that an iron-mediated HAT reaction can be successfully employed to reductively couple different types of unactivated alkenes with ketones. As well as presenting a novel strategic bond disconnection for the construction of sterically congested cyclic compounds, the reaction exhibits site-selectivity between different alkenes present in the same molecule. Both factors should find application in the context of complex molecule synthesis. Studies to apply this method to natural product synthesis and expand this work to other related acceptor groups are currently ongoing.[35]

Acknowledgements

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Keywords: radical • cyclization • ketones • HAT • Iron (III)

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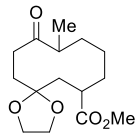

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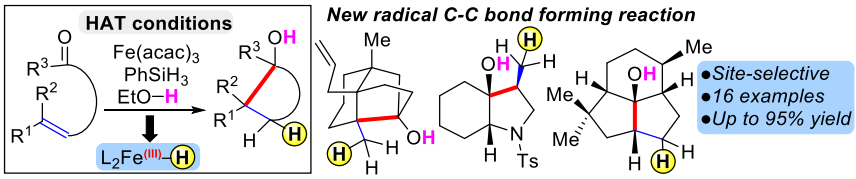

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