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Fascinating Hydrogen Atom Transfer Chemistry of Alkenes Inspired by Problems in Total Synthesis**

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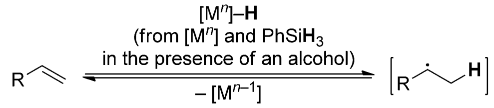
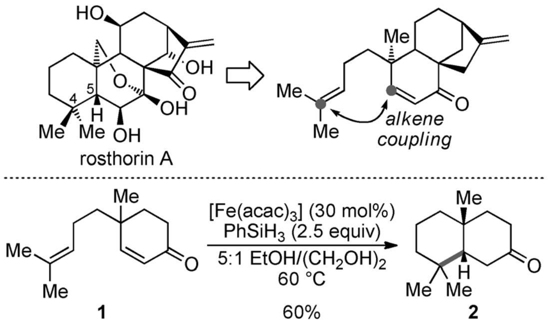
Reductive transformations of alkenes—hydrogenation, hydrohalogenation, and hydroboration perhaps being particularly representative examples— allow the synthetic chemist to build molecular complexity from basic chemicals. Whereas transition-metal-catalyzed hydrogenation and hydrofunctionalization reactions of alkenes have been a flourishing area of research for decades, radical-based versions have remained underestimated, probably owing to the erroneous idea that it is difficult to control radical intermediates. However, several breakthroughs were accomplished over the past couple of years, and a series of catalytic hydrogen-atom-transfer-triggered transformations were developed that helped to overcome great synthetic challenges.

Historically, synthetic alkene chemistry initiated by hydrogen atom transfer (HAT) began with reduction and hydration reactions that employed dihydrogen or borohydrides in combination with first-row transition-metal catalysts.[1] Shortly thereafter, in connection with the pioneering work of Mukaiyama[2] on hydrofunctionalization reactions, hydrosilanes emerged as practical and milder alternative hydride sources. Depending on the radical acceptor, several methods that employ hydrosilanes and are based on manganese, iron, and cobalt catalysts were designed to construct carbon–carbon and carbon–heteroatom bonds as well as to hydrogenate alkenes.[3] These methods share the involvement of open-shell systems as a mechanistic feature: Reversible HAT from the transition-metal hydride onto a carbon–carbon double bond generates a carbon-centered radical (Scheme 1).[4] The implementation of knowledge that was collected over three decades is now culminating in the development of new catalytic carbon–carbon bond-forming reactions as well as alkene hydrogenations and isomerizations that outcompete established methods. This remarkable progress was driven by problems arising along total syntheses of natural products.



Scheme 1. Reversible HAT from a first-row transition-metal hydride onto a carbon–carbon double bond.



Scheme 2. Retrosynthetic analysis of rosthorin A (top) as an inspiration for the development of an alkene coupling method (bottom). acac = acetylacetonate.

While retrosynthetically analyzing the diterpenoid rosthorin A, Baran and co-workers became interested in designing a reductive alkene coupling to construct the C4–C5 motif of the target molecule (Scheme 2, top). After a brief examination of HAT conditions, the authors were able to cyclize α,β-unsaturated carbonyl compound **1** to *cis*-decalin **2** in good yield using substoichiometric amounts of cheap $[Fe(acac)_3]$ and excess $PhSiH_3$ (Scheme 2, bottom).[5] Although the *cis* configuration of the ring junction in **2** was not the desired one, the efficiency and practicality of this reaction prompted the authors to investigate further intramolecular alkene couplings. Strikingly, the reaction also succeeded in more sterically demanding settings, and vicinal all-carbon quaternary centers were accessible.

The Baran group also investigated an intermolecular version with various components to explore the generality of the method. For example, protected alcohols, amines, or heterocycles are tolerated in the donor alkene and acrylamides or acrylonitriles also act as radical acceptors. A major step forward in these reductive alkene couplings was achieved just recently when the same group managed to make

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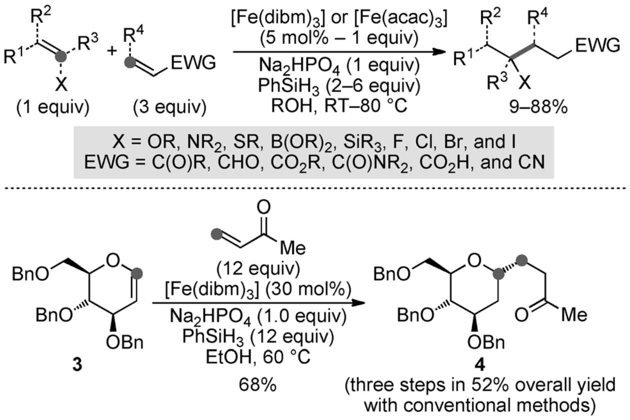
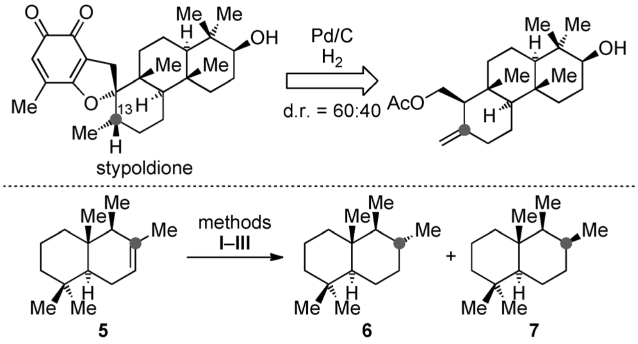
heteroatom-substituted alkenes amenable to these processes.[6] As a result, functionalized quaternary centers that were previously inaccessible or constructed through extensive functional group manipulations can be formed in a single synthetic operation. The innate reactivity of enol ethers, enol thioethers, enamides as well as vinyl boronates, silanes, or halides was overruled as the HAT produces a nucleophilic radical centered on the carbon atom bearing the heteroatom, a position generally considered to be electrophilic. Reactions were performed with a diverse set of electron-poor alkene acceptors, either using the previously employed [Fe(acac)$_3$] catalyst or the optimized [Fe(dibm)$_3$] complex in combination with PhSiH$_3$ and a weak base (Scheme 3, top). To illustrate the power of this method and to compare it to traditional routes, Baran and co-workers realized a single-step synthesis of C-glycosyl compound **4** from enol ether **3**, which would normally require three tedious steps (Scheme 3, bottom).



Scheme 3. Intermolecular reductive couplings of heteroatom-substituted alkenes (top) allowing for a one-step carbohydrate modification (bottom). dibm = diisobutyrylmethane, EWG = electron-withdrawing group.

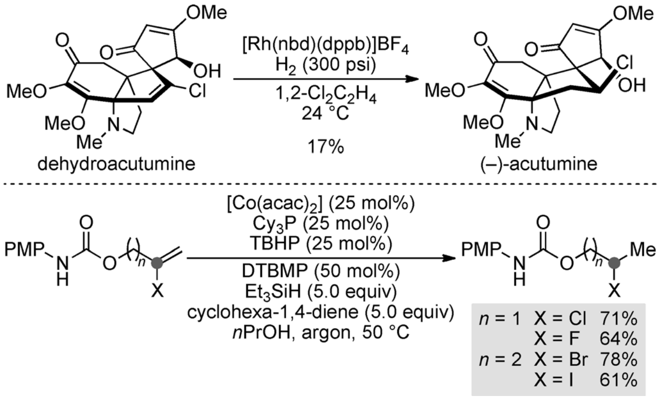
The Shenvi group also benefitted from catalytic HAT in their design of a chemoselective alkene hydrogenation under thermodynamic control.[7] Hydrogenations leading to the thermodynamic product are particularly challenging when steric constraints bias the reaction towards the kinetic product. This is generally solved by the use of dissolving metal reductions, methods suffering from rather poor functional group compatibility. The authors exemplified that issue with the unselective reduction of an *exo*-methylene group to establish the C13 stereocenter of stypoldione (Scheme 4, top).[8] HAT methods with mangenese or cobalt catalysts then allowed Shenvi and co-workers to achieve the same selectivities as with dissolving metal reductions. The power of their method is well demonstrated by the reduction of sesquiterpenoid **5** to drimane **6**. Whereas Adams' catalyst affords kinetic product **7**, the cobalt-catalyzed HAT method delivers **6** selectively. Again, a conventional multistep route is circumvented (Scheme 4, bottom). It must be emphasized once more that this hydrogenation method features a much broader substrate scope than dissolving metal reductions. The most impressive examples are the conversions of vinyl halides into alkyl halides without dehalogenation.



	Method	d.r.	Yield
I	[Co(dpm)$_2$] (10 mol%), PhSiH$_3$, TBHP, PhCF$_3$, 50 °C	86:14	77%
II	PtO$_2$, H$_2$	14:86	94%
III	four steps with conventional methods	100:0	30%

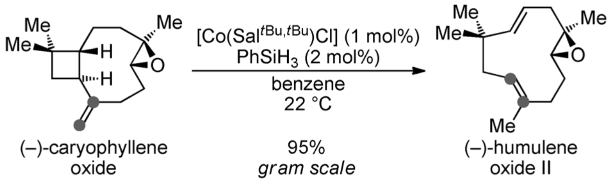
Scheme 4. Unselective conventional hydrogenation en route to stypoldione (top) and a thermodynamically controlled HAT hydrogenation in comparison with other methods (bottom). dpm = dipivaloylmethane, TBHP = *tert*-butyl hydroperoxide.

Shortly after Shenvi's publication, Herzon and co-workers reported their detailed investigation of the reduction of vinyl halides.[9] Inclined to find an alternative to the low-yielding final hydrogenation step in the total synthesis of (−)-acutumine (Scheme 5, top),[10] the authors introduced a HAT hydrogenation catalyzed by [Co(acac)$_2$]. Interestingly, careful optimization revealed the beneficial effect of various additives (Cy$_3$P, DTBMP, and TBHP) as well as the presence of the hydrogen donor cyclohexa-1,4-diene. Herzon and co-workers were able to reduce vinyl fluorides, chlorides, bromides, and iodides with great efficiency (Scheme 5, bottom). Even 1,1-dihaloalkenes underwent the hydrogenation albeit with stoichiometric amounts of [Co(acac)$_2$] (not shown).



Scheme 5. Low-yielding hydrogenation of the vinyl chloride in dehydroacutumine (top) and a reliable HAT hydrogenation method of vinyl halides (bottom). DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine, PMP = *para*-methoxyphenyl.

The knowledge acquired through the development of these hydrogenation reactions inspired the Shenvi group to apply the HAT concept to alkene transpositions.[11] Switching to cobalt salen complex $[Co(Sal^{tBu,tBu})Cl]$ as the catalyst and employing catalytic or substoichiometric amounts of $PhSiH_3$, the authors were able to perform alkene isomerizations and diene cycloisomerizations. Such reactions are in fact difficult to promote with carbophilic Lewis acids owing to the weak Lewis basicity and back-bonding ability of alkenes. As a showcase reaction, Shenvi and co-workers prepared the expensive fragrance and flavor molecule (−)-humulene oxide II from cheap, commercially available (−)-caryophyllene oxide in a single, high-yielding step through a "radical retro-ene reaction" (Scheme 6).



Scheme 6. A catalytic HAT alkene transposition allowing for the gram-scale preparation of (−)-humulene oxide II.

It is almost for certain that HAT-triggered alkene transformations will find an echo in the synthetic community. Their operational simplicity (air-stable reagents and catalysts, open flasks allowed, mild reaction temperatures, and short reaction times), low cost (inexpensive reagents and catalysts), and broad substrate scope render these reactions highly attractive, also in the light of redox economy, and the above selection of reactions shows how this process helps to surmount synthetic challenges. A better understanding of the underlying mechanism(s), particularly the transition-metal hydride generation, will lead to the rational design of more active and robust catalysts.

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