Simple, Chemoselective Hydrogenation with Thermodynamic Stereocontrol

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S *Supporting Information*

ABSTRACT: Few methods permit the hydrogenation of alkenes to a thermodynamically favored configuration when steric effects dictate the alternative trajectory of hydrogen delivery. Dissolving metal reduction achieves this control, but with extremely low functional group tolerance. Here we demonstrate a catalytic hydrogenation of alkenes that affords the thermodynamic alkane products with remarkably broad functional group compatibility and rapid reaction rates at standard temperature and pressure.

Hydrogenation of alkenes is among the cardinal reactions available to synthetic chemists. Applied retrosynthetically, this transform adds points of unsaturation to carbon skeletons, which can be used to dissect complex bond networks into simple fragments.[1] However, a long-standing challenge in complex molecule synthesis is hydrogenation of alkenes to a thermodynamically favored configuration[2] when steric constraints of the substrate favor hydrogenation to a non-thermodynamic (kinetic) alkane product (see **1**→*cis*-**2**, Figure 1a). Dissolving metal reduction provides a means to achieve thermodynamic control and can reduce conjugated[3] or electron-poor alkenes[4] at low temperature (see **1**→*trans*-**2**), but requires ambient or elevated temperature to reduce electron-neutral alkenes.[5] These latter substrates are therefore seldom employed because chemoselectivity is unsatisfactory: most other functional groups are reduced preferentially to electron-neutral alkenes. This problem is especially evident in chemical syntheses of terpenoid secondary metabolites, which include the FDA approved steroid, taxoid, artemisinin, and ingenoid classes. Thus, many terpenes that contain equatorial methyl groups, for instance **3**–**5**, have proven difficult to access, since hydrogenation of the corresponding exomethylene using standard methods yields either the wrong epimer or an equimolar mixture of two epimers (Figure 1b).[6–8] The origin of the poor chemoselectivity associated with dissolving metal reduction is the low reduction potential of electron neutral alkenes ($E_{red} < -3$ V, Pb cathode),[9] which form high-energy radical anions (**6**→**7**, Figure 1c) prior to protonation to lower energy tertiary radicals (**8**) and further reduction, protonation to alkanes (**9**). We thought that circumvention of radical anion **7** via direct hydrogen atom transfer (HAT)[10] might increase chemoselectivity but lead to the same stereochemical preferences as dissolving metal reduction. Here we show that manganese and cobalt catalysts can effect this stepwise radical hydrogenation of electron-neutral alkenes and exhibit the same
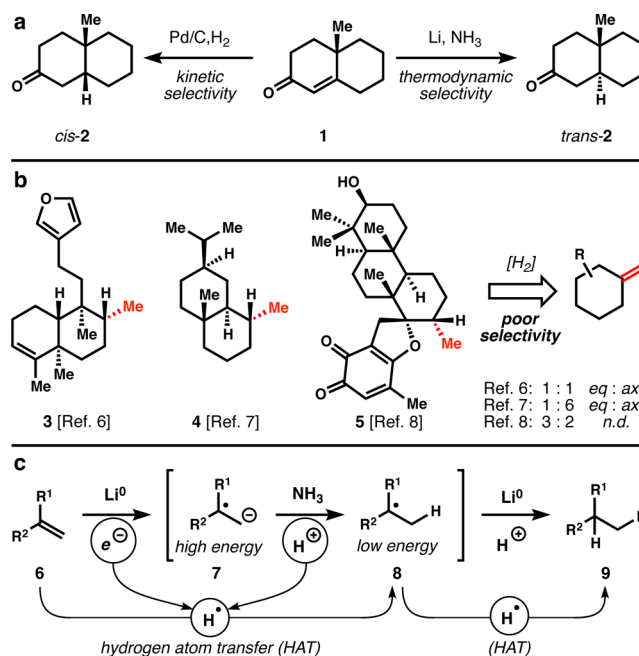

Figure 1. Kinetic versus thermodynamic hydrogenation. (a) Example of stereodivergent hydrogenation; (b) examples where kinetic hydrogenation yields the incorrect stereoisomer; (c) poor chemoselectivity of dissolving metal reduction might be circumvented by HAT hydrogenation.

stereochemical preferences as dissolving metals but spare a variety of reactive functional groups that are normally reduced.

As a representative model system for the terpenes shown in Figure 1b and as a starting point to probe the concept and consequences of HAT hydrogenation, we chose 4-*tert*-butylmethylenecyclohexane **10**, since extensive data on its hydrogenation are available (Table 1).[11,12] Whereas hydrogenation of **10** with Wilkinson's[12] or Adam's catalyst[13] delivers primarily **12** (*cis*), bearing an axial methyl, and diimide reduction gives a 1:1 mixture,[14] dissolving metal reduction instead provides high selectivity for **11** (95:5).[15] It seemed reasonable that hydrogenation via a tertiary carbon radical might lead to high selectivity for an equatorial methyl group, since methyl-substituted cyclohexyl radicals are known to trap tributyltin deuteride with high axial selectivity for C—D bond formation, owing to the nonplanar ground state[16] and transition state pyramidalization of tertiary radicals.[17] We

Table 1. Comparison to Existing Methods

conditions	yield	11:12
homogeneous: 5 mol % RhCl(PPh$_3$)$_3$, 1 atm H$_2$, PhH, 18 °C	100%	32:68
heterogeneous: 9 mol % PtO$_2$, 2 atm H$_2$, AcOH	100%	21:79
pericyclic: N$_2$H$_4$, O$_2$, EtOH, 55 °C	ND	49:51
dissolving metal: Li^0, EDA, 35 °C	ND	95:5
radical: 10 mol % Mn(dpm)$_3$, 1.0 equiv PhSiH$_3$, 1.5 equiv TBHP, i-PrOH (0.5 M), 22 °C, 1 h	86%	84:16
or: 10 mol % Co(dpm)$_2$, 1.0 equiv PhSiH$_3$, 1.5 equiv TBHP, i-PrOH (0.5 M), 22 °C, 1 h	69%	86:14

considered the redox hydration conditions of Mukaiyama[18] as a good starting point for an iterative HAT hydrogenation of alkenes since tertiary radicals are readily generated from electron-neutral alkenes, and the cobalt or manganese catalysts[19] are inexpensive and air-stable. However, the oxidizing conditions required for this transformation appeared to be an ostensible barrier to implementation of a reductive reaction.[20] Even so, Carreira demonstrated that *tert*-butyl hydroperoxide can serve as a replacement activator and/or reoxidant in the context of cobalt-catalyzed hydroazidation[19] and hydrocyanation of alkenes.[21] Similarly, we found that if TBHP is added in stoichiometric quantities to a mixture of alkene **10**, phenylsilane, and a manganese catalyst in the absence of heteroatom radical traps, the reaction rapidly produces **12** (*trans*) with high selectivity, albeit in poor yield. Higher conversion to hydrogenated products is highly ligand and solvent dependent; the dipivaloyl-methane (dpm) ligand and isopropanol solvent were found to be optimal.[22] Most appealingly, the experimental procedure is simple, conversion occurs usually within 1 h, and no hydrogen atmosphere is required. Nonanhydrous conditions are tolerated, however excess water does inhibit conversion (10 equiv = 5 M water in i-PrOH, 33% conversion at 1 h; see Supporting Information (SI) for an optimization table and corresponding observations). Co(dpm)$_2$ induces equally high levels of stereoselectivity and also allows nonpolar solvents and hydrophobic substrates to be used (*vide infra*), however Mn(dpm)$_3$-catalyzed reactions are generally higher yielding.

As illustrated by Table 2a, *trans*-selective hydrogenation of cyclohexenes is difficult to achieve by standard methods. For instance **13a** and **b** afford poor stereoselectivity using Pd/C catalysis, and only marginally better ratios using Crabtree's catalyst, due to the poor directivity afforded by sterically encumbered substituents.[23] However, using HAT hydrogenation, where directivity is irrelevant, *trans*-substitution with high stereoselectivity is favored in both cases.

As a result, diversely substituted cyclohexenes now can be hydrogenated to the thermodynamically preferred *trans*-isomers (Table 2b) in the absence of any directing groups.[23b] Remarkably, chloro- and bromoalkenes, which generally do not tolerate dissolving metal conditions and are challenging substrates even with standard hydrogenation methods, are efficiently reduced to equatorial halo-cyclohexanes **15** and **16**. Electron-releasing siloxy (enolsilane) and acetamide (enamide) groups are also efficiently reduced to the *trans*-isomers **17** and **18**, illustrating the electronic flexibility of the method.

As suggested by substrates **15–18**, the functional group compatibility of our method is significantly better than dissolving metal reduction and a fuller scope is illustrated by

Table 2. Initial Survey of Method's Utility

Conditions	yield	*trans : cis* (14a)	*trans : cis* (14b)
X = Me; Pd/C, H$_2$, EtOH	n.d.	2.1 : 1.0	1.2 : 1.0
X = Me; [Ir(cod)(PCy$_3$)(py)]PF$_6$, CH$_2$Cl$_2$, H$_2$	85, 45%	3.5 : 1.0	1.7 : 1.0
X = Me; Mn(dpm)$_3$, PhSiH$_3$, TBHP, i-PrOH	79, 77%	**10.0 : 1.0**	**7.5 : 1.0**

Table 3. For instance, not only alcohols (**19**) but also their corresponding alkyliodides (**20**) are viable substrates for this transformation. Selectivity against the reduction of aromatic rings is excellent, and therefore carboxybenzyl (Cbz) groups (**21**) are spared from reduction, as are phenyl ethers (**22**), aryl chlorides and fluorides (**23**), aryl bromides (**24**), and aryl
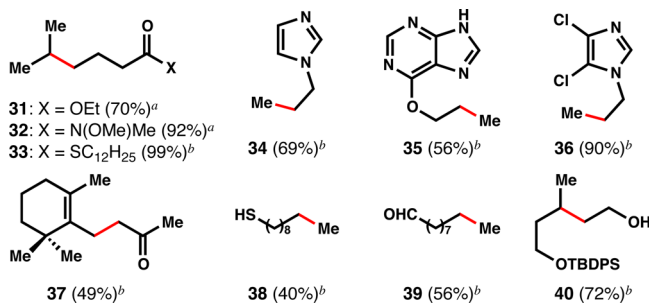
Table 3. Functional Group Tolerance

iodides (**25**), although some deiodination was observed by GCMS (~5%). Trifluoromethyl ethers (**26**), electron-rich arenes (**27**), phenyl thioethers (**28**), trifluoromethylarenes (**29**), and heterocycles like imidazole **30** are all well tolerated, although some rate decrease is observed with this last entry, likely due to equilibrium coordination/deactivation of the catalyst.

Weinreb amides, which suffer N−O bond cleavage under dissolving metal conditions,[24] do not react competitively with the reduction of trisubstituted alkenes (**32**, Table 4). Thioesters

**Table 4. Diverse Unsaturated Substrates are Reduced**

31: X = OEt (70%)[a]
32: X = N(OMe)Me (92%)[a]
33: X = SC$_{12}$H$_{25}$ (99%)[b]

34 (69%)[b]　　**35** (56%)[b]　　**36** (90%)[b]

37 (49%)[b]　　**38** (40%)[b]　　**39** (56%)[b]　　**40** (72%)[b]

[a]Using Co(dpm)$_2$ conditions, [b]Using Mn(dpm)$_3$ conditions.

undergo facile reduction to aldehydes using tributylstannyl radical reduction (Bu$_3$SnH, AIBN) or palladium catalysis (Pd/C, Et$_3$SiH),[25] but using our method, saturated thioester **33** is produced and no aldehyde or alcohol is observed. When the alkene is allylic to a potentially labile C-heteroatom bond, simple to complex heterocycles (**34**−**36**) are tolerated and no scission of the allylic bond is observed, which might argue against the intermediacy of a carbon−metal bond.[18,19] No Minisci addition products were observed using these substrates. Interestingly, β-ionone can be selectively reduced at the α,β-positions (**37**),[20b] in contrast to the selectivity observed using Mukaiyama's hydration.[20] Unsaturated thiols, aldehydes, and allylic alcohols (**38**−**40**) are also chemoselectively reduced; the thiol is oxidized *in situ* to the disulfide which can be cleaved on workup.

Polycyclic systems can also be predictably hydrogenated to the thermodynamically stable diastereomer in preference to the normally observed kinetic stereochemistry (Scheme 1). For instance, Δ^{9,10}-octalin (**41**) is preferentially hydrogenated with iridium catalysis to *cis*-decalin (**42a**) via syn-hydrogenation of the alkene.[26] However, using HAT hydrogenation, a formal anti-addition of hydrogen is observed to produce the lower-energy *trans*-decalin (**42b**) with nearly the same selectivity as dissolving metal conditions.[5] Similarly, 1,2-dimethyl cyclohexene (**43**) is hydrogenated to the *cis*-stereoisomer **44a** using iridium catalysis,[27] whereas our method produces *trans*-1,2-dimethylcyclohexane (**44b**), albeit with lower selectivity. Nevertheless, this stereochemical dichotomy between existing hydrogenation methods and the title reaction can be most vividly illustrated using problems already encountered in terpene syntheses. For example, en route to the putative structure of a sesquiterpene isolated from *Cistus creticus*, Katerinopoulos could not directly access a targeted *trans*-decalone framework since hydrogenation of their intermediate ketone **45** using heterogeneous catalysis produced *cis*-decalone **46a** with high selectivity.[28] In contrast, HAT hydrogenation can directly access this thermodynamically preferred but kinetically disfavored configuration (**46b**). Additionally, the terpene-

**Scheme 1. Examples of Divergent Stereocontrol**
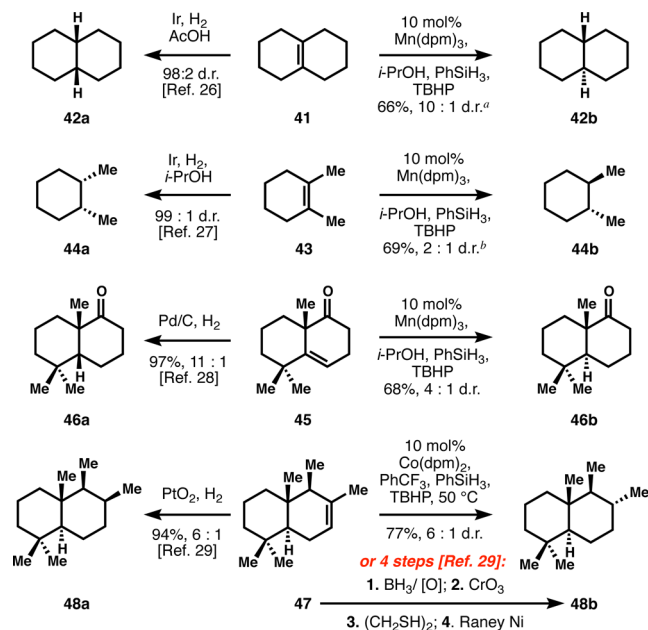
[a]**41** contained 16% of the 1,9-isomer. [b]**43** contained 26% of the 1,6-isomer.

derived petroleum biomarker drimane (**48b**) could not be directly accessed via hydrogenation of drimene **47**, since use of Adam's catalyst delivers the kinetically favored axial methyl substituent in **48a**, and a four-step work-around was devised instead.[29] In contrast, our method directly yields drimane (**48b**), which bears the thermodynamically favored equatorial methyl.

An unusual aspect of this hydrogenation is its general disregard for alkene substitution or electronic patterning (Scheme 2a). Unlike dissolving metal reduction, which exhibits

Scheme 2. Observed Reactivity Trends and Cyclizations
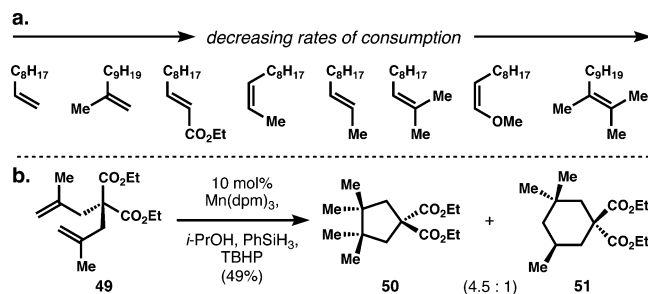
profound rate acceleration when the alkene is conjugated to an electron acceptor,[5] various substitution patterns are readily reduced by our HAT method with little influence by directly attached functionality (see SI for competition experiments). These minor effects of electron-modulating groups may indicate a direct hydrogen atom transfer to generate a carbon-centered radical,[30b] rather than the intermediacy of a carbon−metal bond en route to carbon−metal bond homolysis, as often proposed.[18,19,22] Based on competition experiments, some trends are observed: increased substitution decreases the rate of consumption; electron-withdrawing groups have a minor accelerating effect on reaction rate; and electron-donating groups are weakly deactivating. Consequently, simple reductive

cyclizations of polyenes are possible (Scheme 2b).[30] For instance, diene **49** is readily cyclized to cyclopentane **50**, which bears vicinal all-carbon quaternary centers, highlighting the ability of carbon-centered radicals to overcome severe steric clash via early transition states.[31] This preliminary example paves the way for a general approach to reductive mono- and polycyclizations of unconjugated polyenes and a "traceless" approach to fully saturated molecules like terpenes.[32]

The demonstrated utility of this new method for the thermodynamic hydrogenation of alkenes illustrates its potential to solve current and future problems in complex molecule synthesis, especially the reduction of halogenated alkenes (see Table 2b).[33] Given the frequency with which hydrogenations are employed and their breadth of applications in chemistry, a new tool is advantageous. We expect that the experimental ease, broad scope, and orthogonal stereoselectivity of HAT hydrogenation will lead to its extensive use.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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