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Communication

Directed Hydrogen Atom Transfer for Selective Reactions of Polyenols

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ABSTRACT: Directed hydrogen atom transfer to alkenes is described. The process is catalyzed by iron complexes and allows for the site-selective hydrofunctionalization of polyenols. Experimental data suggest that coordination of the hydroxy group to the iron hydride intermediate plays an important role in preferential engagement of the allylic alcohol motif and provides a new basis for selectivity in radical hydrofunctionalization events. As a proof of concept, β- and γ-amino alcohols are prepared from the corresponding polyenols in a selective manner.

Metal hydride-mediated hydrogen atom transfer (HAT) to alkenes has emerged as a chemoselective and general method for the introduction of a broad range of functional groups into the structure of hydrocarbons.[1−4] The regiochemical outcome of these hydrofunctionalization reactions is governed by the intrinsic preference for the generation of the most stable alkyl radical, favoring the formation of Markovnikov products. In contrast, control over site selectivity of the HAT when multiple alkenes are present among the reactants can be difficult to achieve, although several approaches have evolved to address this challenge.[5] The apparent dependence of the rate of HAT on the substitution patterns at the alkene can be leveraged for selective isomerization and reduction.[6−8] Iron-catalyzed coupling of unsaturated fragments via Giese addition relies on the differences in electronic properties and finds growing application in the synthesis of natural products.[9−11] While these examples likely capitalize on the varying aptitudes toward the HAT among the alkenes, introducing new elements of control that override the innate selectivity patterns can significantly expand the utility of the corresponding transformations and enable new applications. Here we show a straightforward approach to directed HAT that allows for site-selective hydrofunctionalization of polyenes.[12] The process is catalyzed by iron complexes and exhibits a strong preference for the engagement of allylic alcohol motifs (Figure 1). We present evidence pointing to the successful competition between the hydroxy-controlled generation of alkyl radicals and the corresponding bimolecular HAT events. As a proof of concept, we apply this approach to the selective synthesis of β- and γ-amino alcohols from the corresponding polyenols.

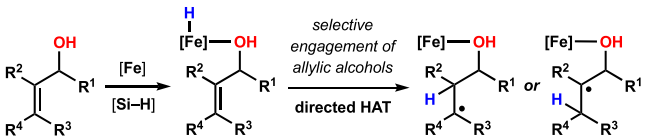

Figure 1. Directed HAT allows for the selective engagement of allylic alcohol motifs.

Recent mechanistic studies revealed that alcohols play an important role in the iron-catalyzed HAT processes by facilitating generation of metal hydride intermediates, and they may also serve as ligands at other points in the catalytic cycle.[13−16] We reasoned that a combination of these features with rapid and irreversible HAT from the iron complexes could enable control over reactions of alkenes containing pendant hydroxy groups and chose a recently reported hydrohydrazination as a vehicle for our initial studies.[17] We found that treatment of geraniol (**1**) with phenylsilane and dimethyl diazomalonate (**2**) in the presence of catalytic amounts of iron(III) acetylacetonate generates a mixture of hydrazones **3**−**5**, and the distribution of products exhibits a pronounced dependence on the composition of the solvent (Table 1). Remarkably, performing the reaction in toluene resulted in the highly selective formation of hydrazone **3** with only small quantities of isomeric product **4** and diamine derivative **5** (entry 1). This outcome is in stark contrast to the distribution of products obtained in ethanol—a typical solvent for this and related transformations—where nearly indiscriminate engagement of all alkenes and extensive double hydrofunctionalization was observed (entry 2). Analysis of the mixture at short reaction times confirmed low site selectivity associated with HAT to geraniol in ethanol (entry 3). Similar results were obtained in other alcoholic solvents, with low levels of conversion recorded in the case of *tert*-butanol.[18] Unlike the case of geraniol, hydrofunctionalization of geranyl methyl ether (**6**) proceeded with low selectivity in both toluene and ethanol, but the observed change in the ratio of isomeric products also

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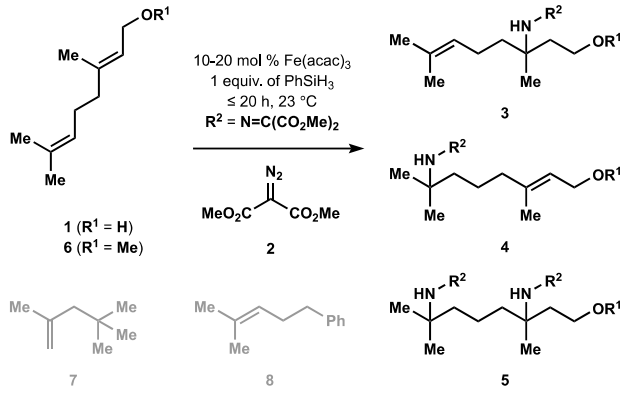
Table 1. Discovery of the Directed HAT and the Site-Selective Hydrofunctionalization



entry	conditions[a]	3 (%)[b]	4 (%)[b]	5 (%)[b]
1	**1**, PhMe[c]	39	4	4
2	**1**, EtOH	20	23	35
3	**1**, EtOH, ca. 0.5 h[c]	13	11	3
4	**6**, PhMe, $PhSiH_2(O\textit{i}\text{-}Pr)$[c,d]	21	14	7
5	**6**, EtOH, ca. 1 h[c]	10	18	3
6	**1**, PhMe, 1 equiv. of EtOH	48	5	16
7	**1**, PhMe, 3 equiv. of EtOH	35	5	36
8	**1**, PhMe, 1 equiv. of EtOH, 20 mol % of $Fe(acac)_3$[e]	60	7	23
9	**1**, PhMe, 1 equiv. of EtOH, 1 equiv. of **7**[c]	39	4	4
10	**1**, PhMe, 1 equiv. of EtOH, 1 equiv. of **8**	51	6	15
11	3 equiv. of **1**, PhMe, 20 mol % of $Fe(acac)_3$[f,g]	81	10	6

[a]10 mol % $Fe(acac)_3$, 1 equiv of $PhSiH_3$, 1.25−1.5 equiv of **2**, 0.2 M in substrate, 20 h. Additional details are indicated in the entries. [b]Determined by ^1H NMR analysis. [c]Diene accounted for the majority of the remaining material. [d](Isopropoxy)phenylsilane in place of phenylsilane. [e]Isolated 55% yield of **3**. [f]1 equiv of **2**, 3 equiv of **1**, 1 equiv of $PhSiH_3$, 20 mol % $Fe(acac)_3$. [g]Isolated 74% yield of **3**, partially recovered **1** (1.65 equiv).

suggests that the ether functionality may be able to exert a weak directing effect (entries 4 and 5). Reactions of other geraniol derivatives, including acetate and *tert*-butyldimethylsilyl ether, proceeded with preferential engagement of the distal alkene, and the selectivity was independent of the solvent. Hydrofunctionalization of these protected substrates in the absence of alcohols required application of (isopropoxy)phenylsilane, a powerful hydride source, to enable appreciable conversion.[13] Overall, the hydroxy group appears to offer an efficient handle for selective engagement of the allylic alcohol motif and is also required for the efficient generation of the iron hydride intermediates.

Evaluation of different solvents revealed that aromatic hydrocarbons are best suited for the directed reaction while polar aprotic solvents resulted in significant deterioration of site selectivity and a greater contribution from the double hydrofunctionalization events.[18] Phenylsilane proved to be the optimal reductant, and iron(III) acetylacetonate demonstrated superior performance compared to other β-diketonate complexes. Addition of stoichiometric amounts of exogenous primary alcohols allowed for increased production of the desired hydrazone with limited impact on site selectivity (Table 1, entry 6; see entry 7). This approach can be employed to secure useful quantities of the desired hydrofunctionalization product **3**, despite the amplified contribution from the double hydrofunctionalization pathways (entry 8). To attenuate the impact of undesired hydrofunctionalization events in the presence of alcohol additives, we evaluated the effects of exogenous alkenes, which were expected to compete in the conventional HAT pathways. As predicted, introduction of alkene **7** led to reduced formation of the double hydrofunctionalization product, but it also resulted in decreased conversion of the dienol (entry 9).[19] Thus, exogenous alcohols and alkenes appear to exert opposing effects and can be employed to tune the reaction conditions for specific substrates (cf. entries 1, 6, and 9). Notably, the structure of the alkene additive significantly impacts the magnitude of its effects, and application of trisubstituted alkene **8** imparted little to no change in the outcome of the hydrofunctionalization (entry 10), which can be attributed to a difference in aptitudes toward the HAT between compounds **7** and **8**.[4] Employing the radical acceptor as a limiting reagent allowed for the preparation of hydrazone **3** in good yield (entry 11). In this case, unreacted dienol could be recovered to a significant extent.

Evaluation of the substrate scope suggests that the directed hydrofunctionalization is generally applicable to a broad range of polyenols, allowing for preferential engagement of allylic alcohol motifs in all cases examined. The combination of this process with the reduction of the resulting hydrazones enables the selective synthesis of β- and γ-amino alcohols from the corresponding polyenols.[20] Thus, aminocitronellol **26** is readily prepared from diazomalonate and **1** using the newly developed protocol (Table 2). Introduction of an additional prenyl unit is tolerated, allowing for the selective hydrofunctionalization of farnesol (**9**) and its constitutional isomer **10** and providing access to aminodienes **27** and **28**. Skipped diene **11** is also amenable to the directed hydrofunctionalization, enabling the selective synthesis of amino alcohol **29**. Changes in the substitution pattern (dienols **12** and **13**) and introduction of cyclic alkenes (dienols **14** and **15**) do not significantly affect the levels of selectivity, and the corresponding unsaturated amino alcohols **30**−**33** are obtained in good yields. Introduction of additional hydroxy groups is tolerated in substrates **16** and **17**, which is consistent with the limited impact of alcohol additives on the selectivity, securing access to aminodiols **34** and **35**. The directed hydrofunctionalization also enables preferential engagement of the allylic alcohol motif among highly reactive 1,1-disubstituted alkenes, providing access to amino alcohol **36** from methallyl alcohol derivative **18**. As expected, the selectivity for the alkallyl alcohol motif under the conditions favoring the directed HAT is particularly high in substrate **19**, and the corresponding hydrazone is observed as a sole product of the hydrofunctionalization en route to amino alcohol **37**. In this case, the relatively high aptitude toward the HAT also favors engagement of the 1,1-disubstituted alkene over its trisubstituted counterpart under the conventional conditions, but a mixture of mono- and difunctionalization products is formed at appreciable conversions of the starting material. Secondary allylic alcohols also proved to be competent directing groups, enabling conversion of dienols **20** and **21** to cyclic amino alcohols **38** and **39**, respectively, with a preference for *trans* arrangement of the hydroxy group and the newly formed C−N bond. The corresponding acyclic motifs in substrates **22** and **23** were less reactive and exerted weaker directing effects, but careful choice of alcohol and alkene additives allowed for preparation of amino alcohols **40** and **41**.

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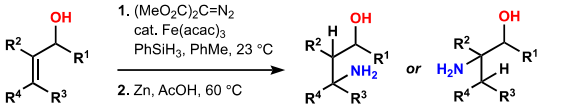
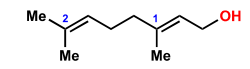
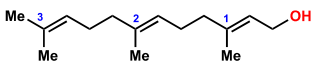
Table 2. Directed HAT Enables Synthesis of β- and γ-Amino Alcohols from Polyenols[a,b]



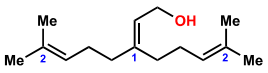
selectivity in the directed HAT



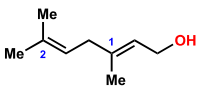
1; directed: C1:C2 = 10:1
(cf. in EtOH: C1:C2 = 1:1)



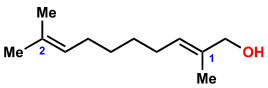
9; directed: C1:∑C2&3 = 4:1
(cf. in EtOH: C1:∑C2&3 = 1:1)



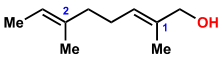
10; directed: C1:C2 = 7:1
(cf. in EtOH: C1:C2 = 1:2)



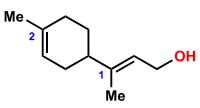
11; directed: C1:C2 > 10:1
(cf. in EtOH: C1:C2 = 2:1)



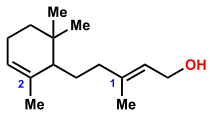
12; directed: C1:C2 = 6:1
(cf. in EtOH: C1:C2 = 1:1)



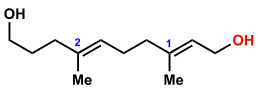
13; directed: C1:C2 = 7:1
(cf. in EtOH: C1:C2 = 1:1)



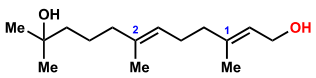
14; directed: C1:C2 = 7:1
(cf. in EtOH: C1:C2 = 1:2)



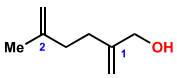
15; directed: C1:C2 = 9:1
(cf. in EtOH: C1:C2 = 2:1)



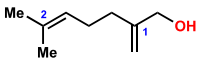
16; directed: C1:C2 = 5:1
(cf. in EtOH: C1:C2 = 2:1)



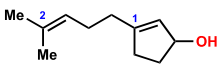
17; directed: C1:C2 = 10:1
(cf. in EtOH: C1:C2 = 2:1)



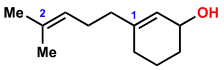
18; directed: C1:C2 = 5:1
(cf. in EtOH: C1:C2 = 1:1)



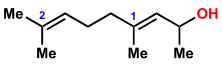
19; directed: C1:C2 > 10:1
(cf. in EtOH: C1:C2 = 3:1)



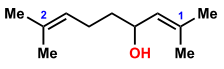
20; directed: C1:C2 = 5:1
(cf. in EtOH: C1:C2 = 1:1)



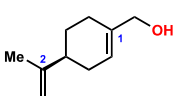
21; directed: C1:C2 = 6:1
(cf. in EtOH: C1:C2 = 1:1)



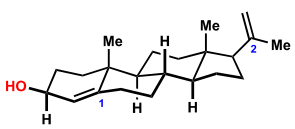
22; directed: C1:C2 = 4:1
(cf. in EtOH: C1:C2 = 1:1.5)



23; directed: C1:C2 = 3:1
(cf. in EtOH: C1:C2 = 1:1.5)

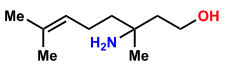


24; directed: C1:C2 = 2.5:1
(cf. in EtOH: C1:C2 = 1:5)

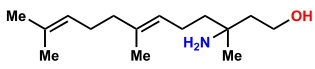


25; directed: C1:C2 = 1.5:1
(cf. in EtOH: C1:C2 = 1:6)

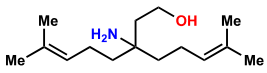
synthesis of β- and γ-aminoalcohols



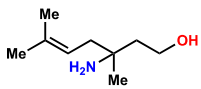
26 (73%, 2 steps)



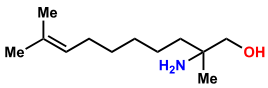
27 (63%, 2 steps)



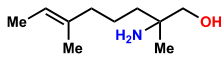
28 (52%, 2 steps)



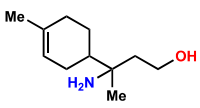
29 (68%, 2 steps)



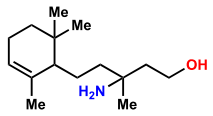
30 (50%, 2 steps)



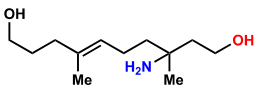
31 (48%, 2 steps)



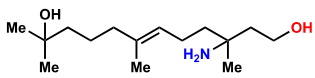
32 (d. r. 1:1, 57%, 2 steps)



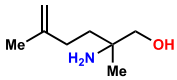
33 (d. r. 1:1, 75%, 2 steps)



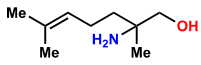
34 (47%, 2 steps)



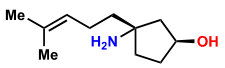
35 (52%, 2 steps)



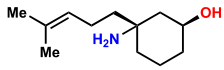
36 (60%, 2 steps)



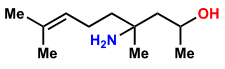
37 (61%, 2 steps)



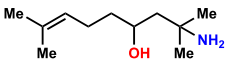
38 (d. r. 2:1, 60%, 2 steps)[c]



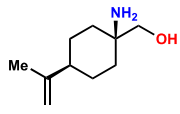
39 (d. r. 5:1, 53%, 2 steps)[c]



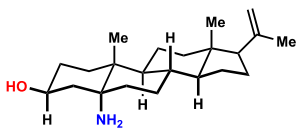
40 (d. r. 1:1, 43%, 2 steps)[d]



41 (53%, 2 steps)[e]



42 (d. r. 3:1, 49%, 2 steps)[c,e]



43 (36%, 2 steps)

[a]Determination of selectivity: 10−20 mol % $Fe(acac)_3$, 1 equiv of polyenol, 1.25−1.5 equiv of diazomalonate, and 1 equiv of $PhSiH_3$ in PhMe (10−20 h) or EtOH (0.5−3 h); ^1H NMR analysis. [b]Synthesis of amino alcohols: 10−20 mol % $Fe(acac)_3$, 1 equiv of diazomalonate, 1−2 equiv of $PhSiH_3$, and 3 equiv of polyenol in PhMe at 23 °C for 20 h; 25 equiv of Zn dust in AcOH, THF, H_2O at 60 °C for 4−14 h. [c]The major diastereomer is depicted. [d]5 equiv of EtOH, 2 equiv of 7 (step 1). [e]3 equiv of EtOH (step 1).

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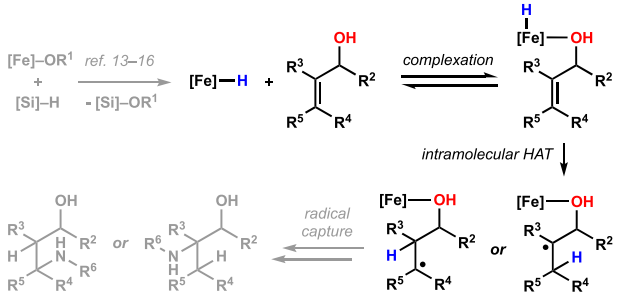
Notably, in the majority of the above-mentioned cases, experiments in ethanol confirm that inherent reactivity of polyenols in the iron-catalyzed HAT-initiated hydrofunctionalization does not allow for selective engagement of the allylic alcohol motif and often yields preference for the reaction at a distal alkene.[21] Furthermore, double hydrofunctionalization products are typically prevalent at appreciable levels of conversion. These challenges are exaggerated in the synthesis of amino alcohols **42** and **43** from perillyl alcohol (**24**) and progesterone derivative **25**, respectively, where strong innate preference for engagement of the 1,1-disubstituted alkenes is observed. In contrast, directed HAT enables access to the desired products in useful yields, even though the site selectivity for the cyclic trisubstituted alkene is lower compared to the other examples examined in our study.

We propose that the directing effect arises from coordination of a polyenol to an iron hydride intermediate, and subsequent intramolecular HAT allows for preferential engagement of the allylic alcohol motif (Scheme 1). Formation of the

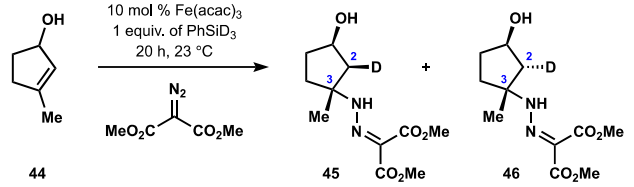
Scheme 1. Proposed Mechanism of the Directed HAT



corresponding complexes is likely reversible because the selectivity is largely retained in the presence of stoichiometric amounts of alcoholic additives and previous computational studies found binding of alcohols to iron hydride intermediates to be weak.[15,22] These considerations suggest that the rate of HAT is higher within the complex than in the corresponding bimolecular process. The inferior performance of nucleophilic solvents can be attributed to competing coordination to the iron hydride or destabilization of its complex with the allylic alcohol, thus reducing the contribution from the directed HAT pathway. This effect is maximized when alcohols are used as solvents, likely approaching the innate distribution of products associated with the bimolecular HAT pathways. According to the previous studies, generation of the iron hydride is mediated by the iron alkoxide and accompanied by conversion of an alcohol to the corresponding silyl ether.[13−16,23] Formation of the iron hydride should therefore be suppressed at high conversions when the polyenol is employed as a limiting reagent and the sole source of the alkoxide. Addition of stoichiometric amounts of exogenous alcohols or employing an excess of the polyenol with respect to the radical acceptor likely counteracts this limitation and leads to the observed improvements in the overall efficiency of the reaction. We note that remote alcohol functionalities do not exert strong directing effects, and low site selectivity is recorded in the reaction with homogeraniol.[24] This conclusion is also in agreement with the preferential engagement of the allylic alcohol motif in diol **16** under conditions favoring the directed HAT (Table 2).

Additional support for the role of coordination in selectivity is offered by the stereochemical outcome of HAT to the allylic alcohol. Analysis of the isotopically labeled hydrazones obtained from cyclopentenol **44** revealed preferential placement of the deuterium atom in the *cis* orientation relative to the hydroxy group, affording diastereomer **45** as a major product in toluene (Scheme 2).

Scheme 2. Stereochemical Outcome of the Directed HAT[a]



solvent	ratio, **45**:**46**
PhMe	77:23
EtOH	20:80

>95% D at C2
major diastereomers at C3 are shown
(d. r. at C3 3:1)

[a]Based on ^{1}H NMR analysis.

In contrast, innate selectivity appears to favor the opposite stereochemical outcome, as determined by the *trans* arrangement of the C−D and C−O bonds in major product **46** from the reaction in ethanol. These results suggest a significant contribution of the directed HAT pathway during hydrofunctionalization in toluene, and the magnitude of the effect appears to be consistent with the site selectivity observed for dienols containing cyclic allylic alcohol motifs (**20** and **21**, Table 2).

In summary, we demonstrate the first examples of directed HAT from metal hydrides to alkenes, which enables preferential engagement of allylic alcohol motifs. Our straightforward approach exploits solvent effects to reveal the directing ability of the hydroxy group, allowing for selective conversion of polyenols to the corresponding β- and γ-amino alcohols. This new synthetic relationship highlights the potential application of the directed HAT in hydrofunctionalization of polyunsaturated systems.[25] Preliminary mechanistic inquiries support coordination of the alcohol to the iron hydride and rapid intramolecular HAT as the origin of the directing effect. We expect these findings to provide a starting point for the development of a broad range of HAT-initiated reactions with new selectivity patterns.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c06601.

Experimental and computational procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(18) See the Supporting Information for an extended version of Table 1 with relevant additional entries.
(19) Introduction of alkene **7** in the absence of added ethanol led to a marked decrease in the hydrofunctionalization of geraniol, and minimal formation of the corresponding products was observed with 3 equiv of added alkene **7**. See the Supporting Information for an extended version of Table 1 with relevant additional entries. As expected, hydrohydrazination of alkene **7** was observed in these experiments.
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(21) The innate preference for the engagement of the distal alkene can be attributed to the electron-withdrawing effect of the hydroxy group.
(22) We cannot rule out an analogous mechanism that involves reversible formation of the corresponding (alkoxo)iron hydrides as reactive intermediates in the directed HAT.
(23) The important role of iron alkoxides suggests an alternative mechanistic hypothesis where the directing effect is associated with rapid and irreversible HAT from the iron hydride intermediate generated in proximity to the allylic alcohol motif. The computed rate constant for the relevant HAT from the iron hydride may be within the range of the values for diffusion-controlled processes (ca. 10^9 s^{-1} M^{-1}; see ref 14). Therefore, the HAT to the proximal alkene may outcompete rearrangement of the solvent cage to accommodate reaction with a distal alkene or diffusion into the bulk solvent. This hypothesis is inconsistent with our observation that the selectivity is largely retained in the presence of stoichiometric amounts of alcoholic additives and that introduction of alkene **7** suppresses the directed hydrofunctionalization of geraniol (see Table 1 and accompanying discussion). Should the directed HAT be associated with generation of the iron hydride in proximity to the allylic alcohol motif and occur within the resulting cage pair, little to no impact of exogenous alkenes on the corresponding product formation would be expected. Although this mechanism does not appear to be operable in our system, we do not rule out a possibility that it may be attainable in other metal hydride-mediated HAT events.
(24) An approximately 1.5:1 ratio of monohydrofunctionalization products was observed in toluene, slightly favoring engagement of the homoallylic alcohol motif. The ratio was reversed in ethanol, indicating only limited solvent effects.
(25) A search in CAS SciFinder suggests that the amino alcohols prepared during our studies are not known in the current scientific literature with the exception of product **37**, which is associated with one patent.

NOTE ADDED AFTER ASAP PUBLICATION

This paper published ASAP on June 25, 2024 with an incorrect version of Table 1. This production error was corrected and the revised version was reposted on June 27, 2024.

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