

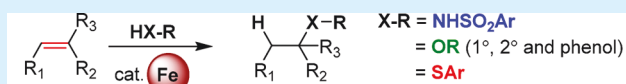
Iron-Catalyzed Hydroamination and Hydroetherification of Unactivated Alkenes

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S Supporting Information

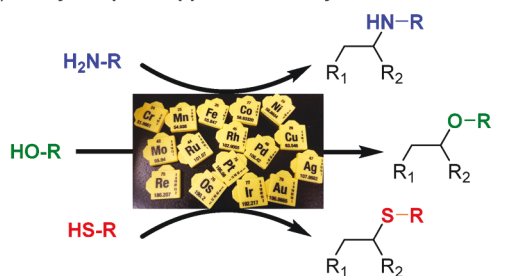
ABSTRACT: The hydrofunctionalization of alkenes, explored for over 100 years, offers the potential for a direct, atom-economical approach to value-added products. While thermodynamically favored, the kinetic barrier to such processes necessitates the use of catalysts to control selectivity and reactivity. Modern variants typically rely on noble metals for hydrofunctionalization, thereby limiting generality. This Letter describes a general iron-based system that catalyzes the hydroamination and hydroetherification of simple unactivated olefins.



Simple Iron Catalyst • Unactivated Alkenes • Mild Lewis Acid Activation

The hydrofunctionalization of alkenes offers a direct method to forge beneficial carbon–heteroatom bonds. Starting from abundant alkene or alkyne building blocks, the thermodynamically favorable addition¹ of a hydrogen–heteroatom bond (H–N, H–O, or H–S) across a unit of unsaturation builds molecular complexity succinctly. Within the context of hydrofunctionalization, hydroamination is the most studied,² with less attention given to hydroetherification³ and hydrothiolation.⁴ Traditionally, precious metals such as palladium, rhodium, ruthenium, and gold have been used to activate the π -system (Figure 1a).⁵ Recently, earth-abundant, first-row transition metals have enabled unique variants of these reactions,^{6,7} with iron offering new vistas in hydrofunctionalization over a diverse range of X–H bonds.⁸

a) Many Bespoke Approaches to Hydrofunctionalization



b) This Work:

One Catalytic System for Unactivated Olefins

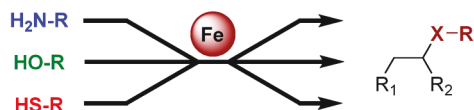


Figure 1. (a) Hydroamination, hydroetherification, and hydrothiolation require different conditions for each reaction. (b) This work offers a single catalyst for sulfonamides, alcohols, and a thiophenol.

Of the first-row transition metal-catalyzed methods, copper and iron catalysts offer the most generality. While copper catalysts can require specific ligands⁹ or substrates¹⁰ for difficult hydrothiolation reactions, simple iron salts can be used under “ligandless” conditions to provide Markovnikov selectivity.⁸ Furthermore, iron(III) salts enable the hydrofunctionalization of styrene derivatives or strained alkenes to form carbon–nitrogen,^{11,12} carbon–oxygen,¹³ and carbon–sulfur¹⁴ bonds under different sets of conditions. Similar approaches rely on Brønsted acids,^{15–17} such as trifluoromethanesulfonic acid¹⁸ or those generated in situ from metal triflate salts.^{19–24} In spite of these advances, functionalizing unactivated alkenes with iron(III) catalysts is limited to intramolecular reactions.^{25–28} Previously, we have disclosed a powerful, yet mild, iron system capable of catalytically activating aliphatic alcohols toward substitution reactions.^{29–31} In our studies of alcohol substitution with sulfonamide nucleophiles, reaction monitoring revealed that cyclohexanol can undergo an iron-promoted E1 elimination, forming cyclohexene.³² The in situ-generated alkene also proved competent in the reaction. Enticed by this promising lead, we postulated that alkene could be used directly in hydrofunctionalization reactions. Here, we report a general iron catalyst capable of the intermolecular hydrofunctionalization of unactivated alkenes with sulfonamides, alcohols, and select thiols (Figure 1b).

To begin, we evaluated the hydroamination of cyclohexene with *p*-toluenesulfonamide in the presence of select acid catalysts (Table 1). Strong Lewis acids, such as AlCl_3 , were unable to promote the desired reaction (Table 1, entry 1). Likewise, mild Lewis acid FeCl_3 provided only trace yield (Table 1, entry 2). The combination of FeCl_3 with non-coordinating silver salts³³ greatly enhanced the Lewis acidity of the iron catalyst, providing the hydroamination product in

Received: January 31, 2019

Published: February 21, 2019

Table 1. Evaluation of Acid Catalysts

entry	catalyst	yield (%) ^a
1	AlCl ₃	0
2	FeCl ₃	<5
3	AgSbF ₆	0
4	FeCl ₃ w/3 AgSbF ₆	78
5	FeCl ₃ w/3 AgAsF ₆	82
6	FeCl ₃ w/3 AgBF ₄	43
7	FeCl ₃ w/3 AgOTf	17
8	FeCl ₃ ·6H ₂ O w/3 AgSbF ₆	58
9	FeBr ₃ w/3 AgSbF ₆	79
10	FeCl ₃ w/2 AgSbF ₆	33
11 ^b	HSbF ₆	0
12 ^c	HCl	0
13 ^d	FeCl ₃ w/3 AgSbF ₆	68
14 ^e	FeCl ₃ w/3 AgSbF ₆	42

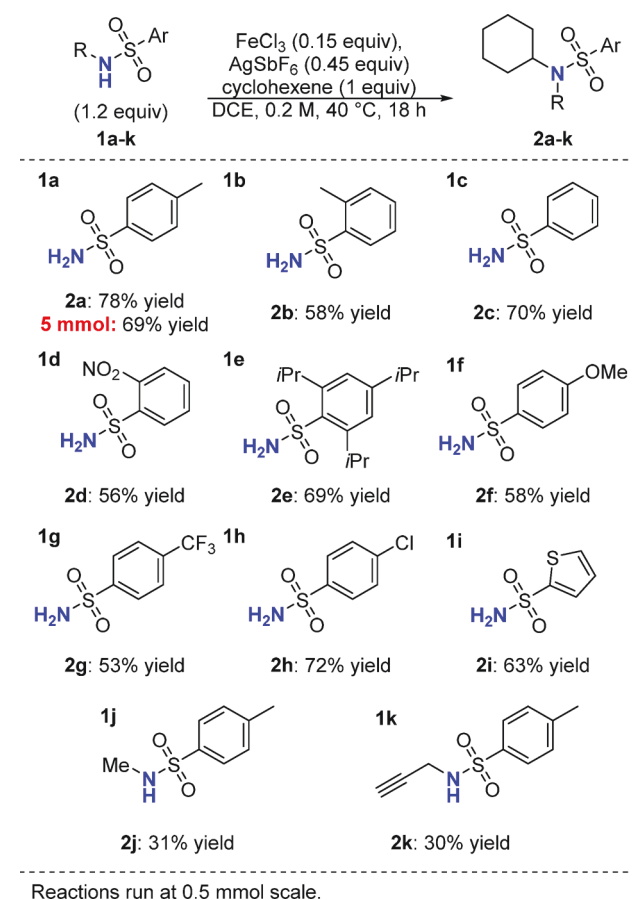
^aNMR yields using 1,3,5-trimethoxybenzene standard. ^b65–75% aqueous solution. ^c12 M concentrated. ^dCs₂CO₃ (0.15 equiv) added. ^e2,6-Di-*tert*-butyl-4-methylpyridine (0.15 equiv) added.

modest-to-good yields (Table 1, entries 4–10). While the combination of FeCl₃ with AgAsF₆ gave marginally higher yield (Table 1, entry 5), AgSbF₆ (Table 1, entry 4) was chosen due to the significantly lower cost compared to AgAsF₆. Catalytic amounts of strong Brønsted acids, such as an aqueous solution of HSbF₆ (Table 1, entry 10) or concentrated HCl (Table 1, entry 11), were unable to promote hydroamination. Furthermore, the reaction does not seem to be driven by “hidden Brønsted acid catalysis”³⁴ as evidenced by product formation in the presence of Cs₂CO₃ (Table 1, entry 13) and 2,6-di-*tert*-butyl-4-methylpyridine (Table 1, entry 14).^{23,35} While these bases imposed a slight decrease in yield, the retention of catalytic activity suggests that iron is the primary catalyst.

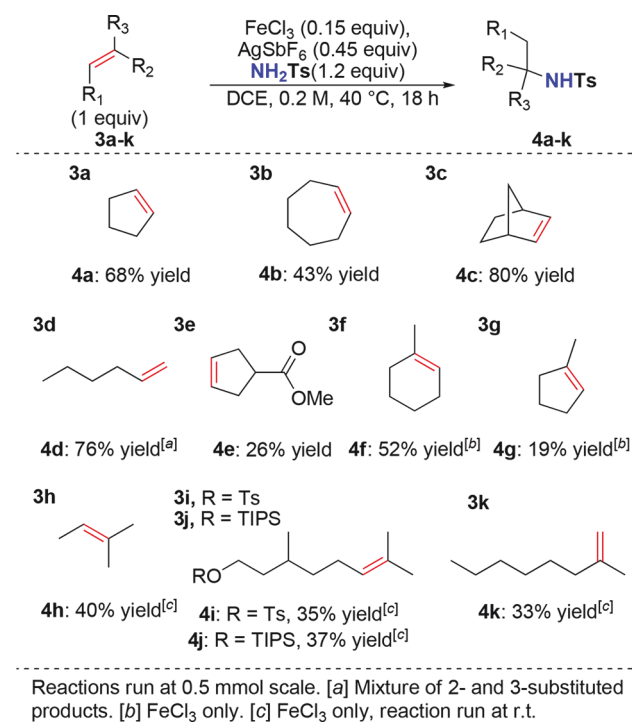
With suitable conditions for the hydroamination of cyclohexene, a variety of sulfonamide nucleophiles were evaluated (Scheme 1). Sulfonamides were a privileged amine source for our catalytic system. Other amine classes such as electron-deficient anilines, amides, and carbamates provided no hydroamination products, likely due to strong binding to the iron catalyst (see Supporting Information). The highest yields were achieved with *p*-toluenesulfonamide (1a) affording hydroamination product (2a) in good yield, even on 5 mmol scale. Similar sulfonamides, such as *o*-toluenesulfonamide (1b) and benzenesulfonamide (1c), gave reasonable yields. More easily removable 2-nitrobenzenesulfonamide (1d) was tolerated.³⁶ Sterically bulky (1e), electron-rich (1f), as well as electron-poor (1g–h) sulfonamides gave moderate-to-good yields. Heterocycles, such as the thiophene in 1i, could be incorporated as in 1i. Additionally, secondary sulfonamides 1j and 1k produced tertiary amine products (2j–k) in modest yields.

With a wide range of viable sulfonamides, we next evaluated the scope of alkenes (Scheme 2). Smaller cyclic alkenes cyclopentene (3a) and cycloheptene (3b) worked well, while larger cyclooctene and cyclododecane surprisingly failed to produce product (data not shown). Strained norbornene (3c) reacted smoothly to afford 4c in 80% yield. Unsymmetric alkenes, such as 1-hexene (3d), gave a mixture of the 2- and 3-

Scheme 1. Hydroamination with Sulfonamide Nucleophiles



Scheme 2. Alkene Scope for Hydroamination

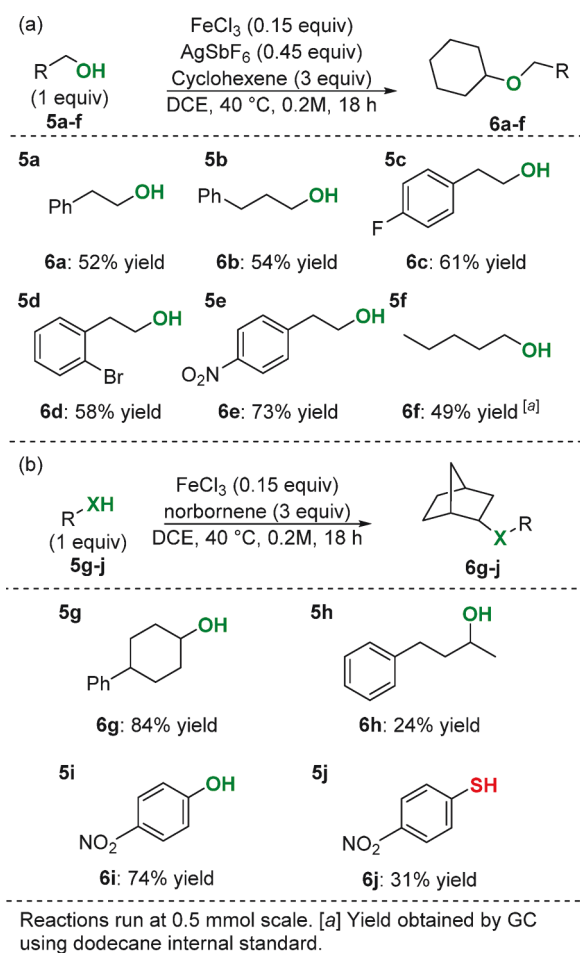


substituted products (4d), likely through a carbocation rearrangement.³⁷ Ester-containing substrates (3e) appear to inhibit the reaction, producing relatively low yields. More

reactive trisubstituted alkenes (**3f–j**) proceeded in moderate-to-good yields. Cyclic, trisubstituted alkenes (**3f–g**) gave superior yields with FeCl_3 alone. The modest yields of this substrate class are due to competitive dimerization of the alkene. Furthermore, the addition of AgSbF_6 led to increased dimerization and gave little to no hydroamination products. Derivatives of citronellol, elaborated either with a tosylate leaving group (**3i**) or protected with TIPS (**3j**), were tolerated without nucleophilic displacement of the tosylate (**4i**) or deprotection (**4j**). Additionally, 2,2-disubstituted alkenes, such as **3k**, could be used to produce **4k** in serviceable yield.

We next sought to translate this methodology to form C–O through hydroetherification reactions (Scheme 3). Under our

Scheme 3. Hydroetherification and Hydrothiolation



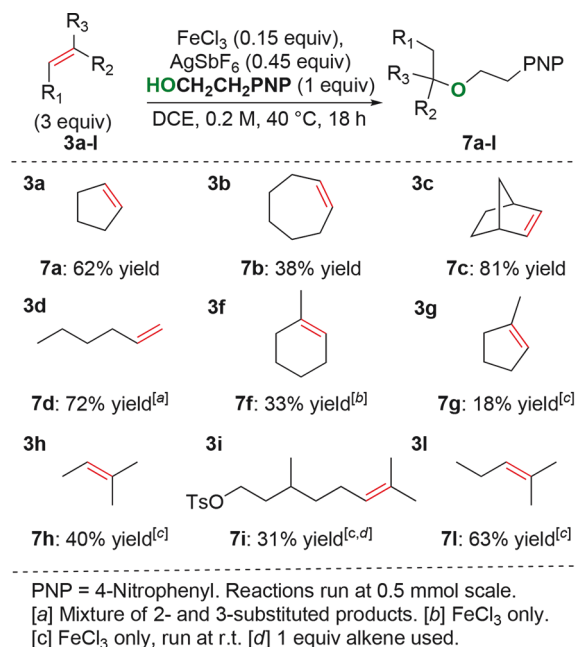
reaction conditions, the combination of FeCl_3 and AgSbF_6 can activate alcohols, leading to deleterious substitution reactions instead of the desired hydroetherification products. To eliminate this side reaction, primary alcohols—a challenging substrate for substitution reactions³²—were chosen as the class of nucleophile for hydroetherification (Scheme 3a). Primary alcohols were less reactive than sulfonamides under our catalytic conditions. In order to achieve suitable yields, excess alkene was necessary. Primary alcohols with pendant benzene rings (**5a–b**) gave the desired hydroetherification products (**6a–b**) with the majority of the remaining mass balance being recovered starting alcohol. Placing an electron-withdrawing group on the pendant benzene ring, such as fluoride (**5c**), bromide (**5d**), or nitro (**5e**), gave the highest yields. Simple

primary alcohols, such as *n*-pentanol (**5f**), were also competent nucleophiles.

In a quest to expand the nucleophile scope to secondary alcohols, phenols, and thiophenols, milder conditions were employed. Since FeCl_3 alone does not activate secondary alcohols, these reactions could employ this cheap catalyst system. Using strained alkene norbornene, the hydroetherification of secondary alcohols proceeded with good yields (Scheme 3b). Secondary alcohol 4-phenylcyclohexanol (**5g**) afforded the desired product **6g** in excellent yield, while 4-phenyl-2-butanol (**5h**) gave only modest yield. Additionally, *p*-nitrophenol (**5i**) formed the hydroetherification product in 74% yield. The strongly withdrawing nitro group proved critical to promote hydroetherification and inhibit Friedel–Crafts side products—even *p*-fluorophenol led primarily to Friedel–Crafts products (data not shown). Excitingly, *p*-nitrothiophenol (**5j**) gave the desired hydrothiolation product **6i**. Thiols represent a difficult substrate class since disulfide formation competes under the reaction conditions.¹⁴

To evaluate the alkene scope for hydroetherification, primary alcohol **5e** was evaluated over a range of alkenes. Similar to the hydroamination, small cyclic alkenes cyclopentene (**3a**) and cycloheptene (**3b**), as well as strained norbornene (**3c**) performed well. 1-Hexene (**3d**) produced a mixture of carbocation-rearranged products. Trisubstituted olefins produced moderate yields of the hydroetherification products **7f–i**. While 2-methyl-2-butene (**3h**) reacted efficiently at 40 °C with only FeCl_3 , 2-methyl-2-pentene (**3l**) proceeded in high yield at room temperature. Finally, tosylated citronellol **3i** afforded **7i** without excess olefin (Scheme 4).

Scheme 4. Alkene Scope for Hydroetherification



In summary, we have developed an efficient iron-based catalytic system for the hydrofunctionalization of unactivated alkenes. Using a simple, air- and moisture-tolerant catalyst, the efficient construction of C–N, C–O, and C–S bonds can be accomplished under the same conditions. This modular approach functionalizes mono-, di-, and trisubstituted olefins with a wide range of sulfonamides along with primary and

secondary alcohol nucleophiles. Proceeding with Markovnikov selectivity, this method offers a mild alternative to strong Brønsted acid catalysts.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/acs.orglett.9b00427](https://doi.org/10.1021/acs.orglett.9b00427).

Experimental details, compound characterization, and NMR data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge funds from Indiana University in partial support of this work. We also gratefully acknowledge the NSF CAREER Award (CHE-1254783). Eli Lilly & Co. and Amgen supported this work through the Lilly Grantee Award and the Amgen Young Investigator Award. P.T.M. was supported by the Graduate Training Program in Quantitative and Chemical Biology (T32 GM109825) and Indiana University. IU mass spectrometry for HRMS (NSF Grant CHE1726633).

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