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Iron-Catalyzed Hydroamination and Hydroetherification of Unactivated Alkenes

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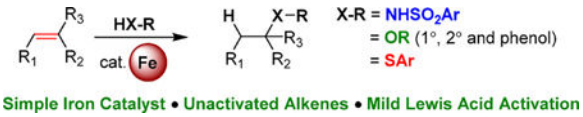
Abstract

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 that require different ligands for each class of hydrofunctionalization, thereby limiting generality. This Letter describes a general iron-based system that catalyzes the hydroamination and hydroetherification of simple unactivated olefins.

Graphical Abstract



The hydrofunctionalization of alkenes offers a direct method to forge beneficial carbon—heteroatom bonds. Starting from abundant alkene or alkyne building block thermodynamically favorable addition[1] o f 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 hydroetherification[3] 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]

Of the first-row transition metal-catalyzed methods, copper and iron catalysts offer the most generality. While copper catalysts can require specific ligands[9] or substrates[10] for difficult hydrothiolation reactions, simple iron salts can be used under “ligandless” conditions to

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Supporting Information

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

The authors declare no competing financial interest.

provide Markovnikov selectivity.[8] Furthermore, iron(III) salts enable the hydrofunctionalization of styrene derivatives or strained alkenes to form carbon–nitrogen,[11,12] carbon–xygen,[13] and carbon–sulfur[14] bonds under different sets of conditions. Similar approaches rely on Bronsted acids,[15–17] such as trifluoromethanesulfonic acid[18] 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 noncoordinating silver salts[33] greatly enhanced the Lewis acidity of the iron catalyst, providing the hydroamination product in modest-to-good yields (Table 1, entries 4–10). While the combination of FeC l_3 with $AgAsF_6$ gave marginally higher yield (Table 1, entry 5), $AgSbF_6$ (Table 1, entry 4) was chosen due to the significantly lower cost compared to $AgAsF_6$. Catalytic amounts of strong Bronsted acids, such as an aqueous solution of H SbF_6 (Table 1, entry 10) or concentrated H Cl (Table 1, entry 11), were unable to promote hydroamination. Furthermore, the reaction does not seem to be driven by "hidden Bronsted acid catalysis"[34] as evidenced by product formation in the presence of Cs_2CO_3 (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 electrondeficient anilines, amides, and carbaates 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–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 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 reactions[32]—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 hydroethericaton and inhibit Friedel- Crafts side products —even *p*-fluorophenol led primarily to Friedel-C rafts 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. Trisubsituted olefins produced moderate yields of the hydroetherification products **7f–1**. 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).

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 Bronsted acid catalysts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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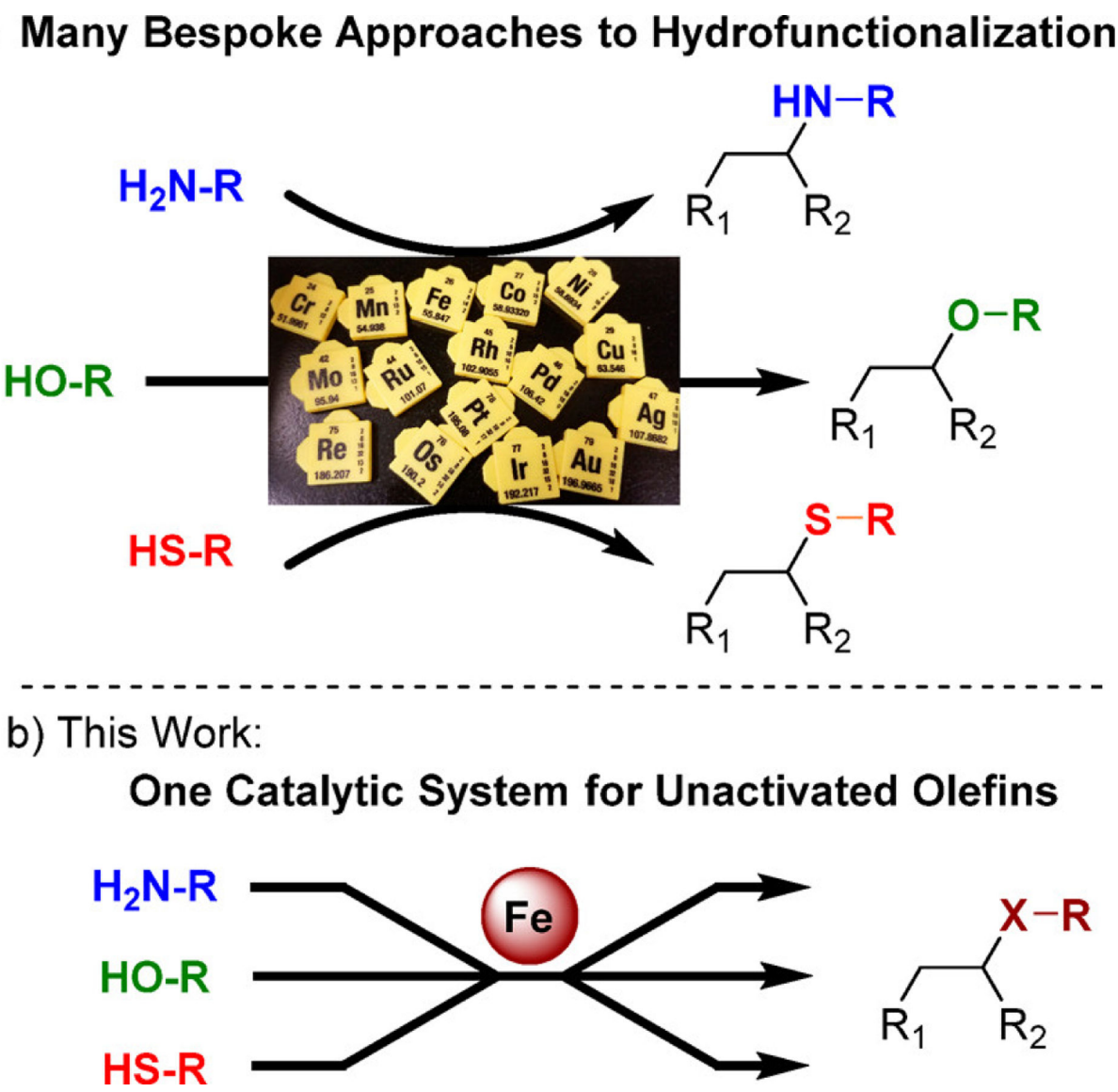
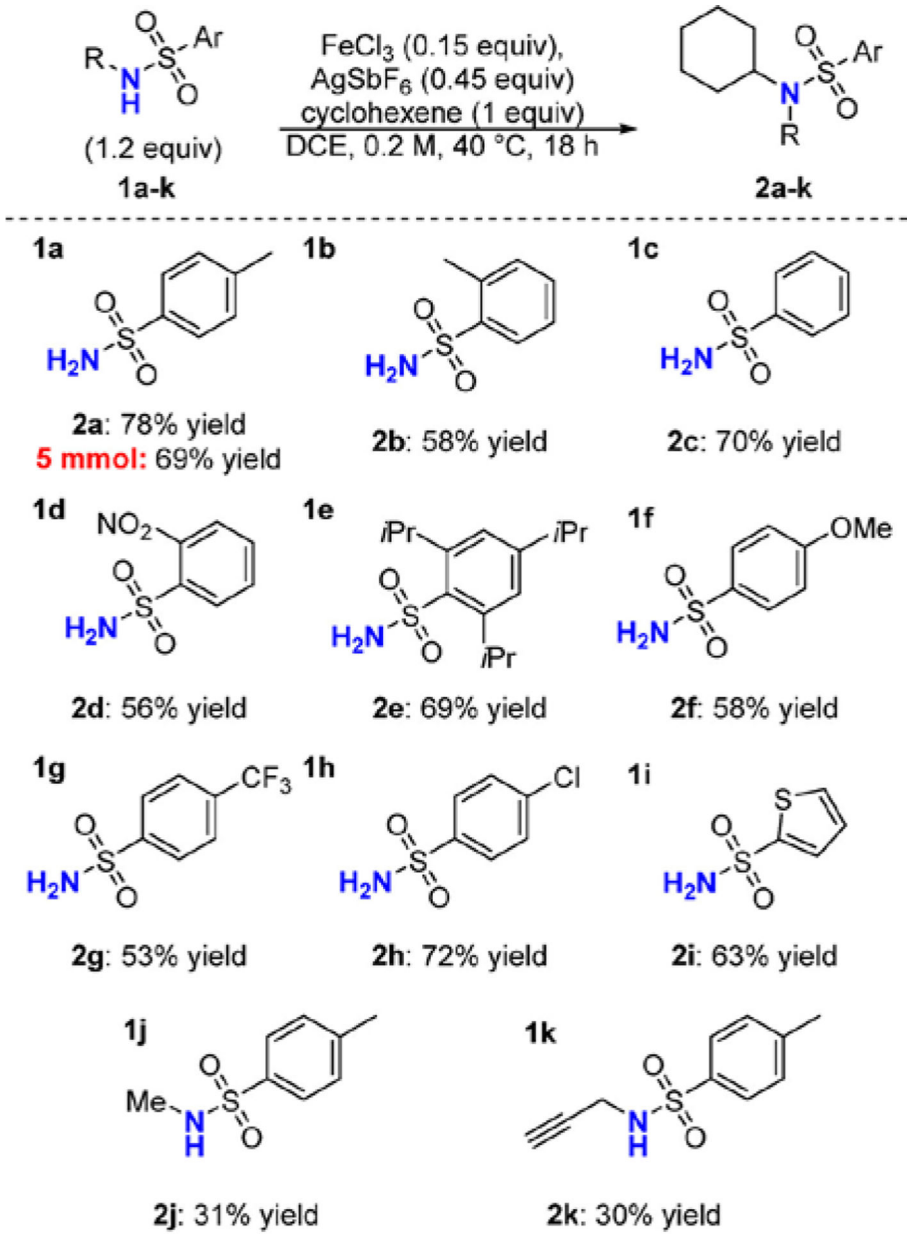


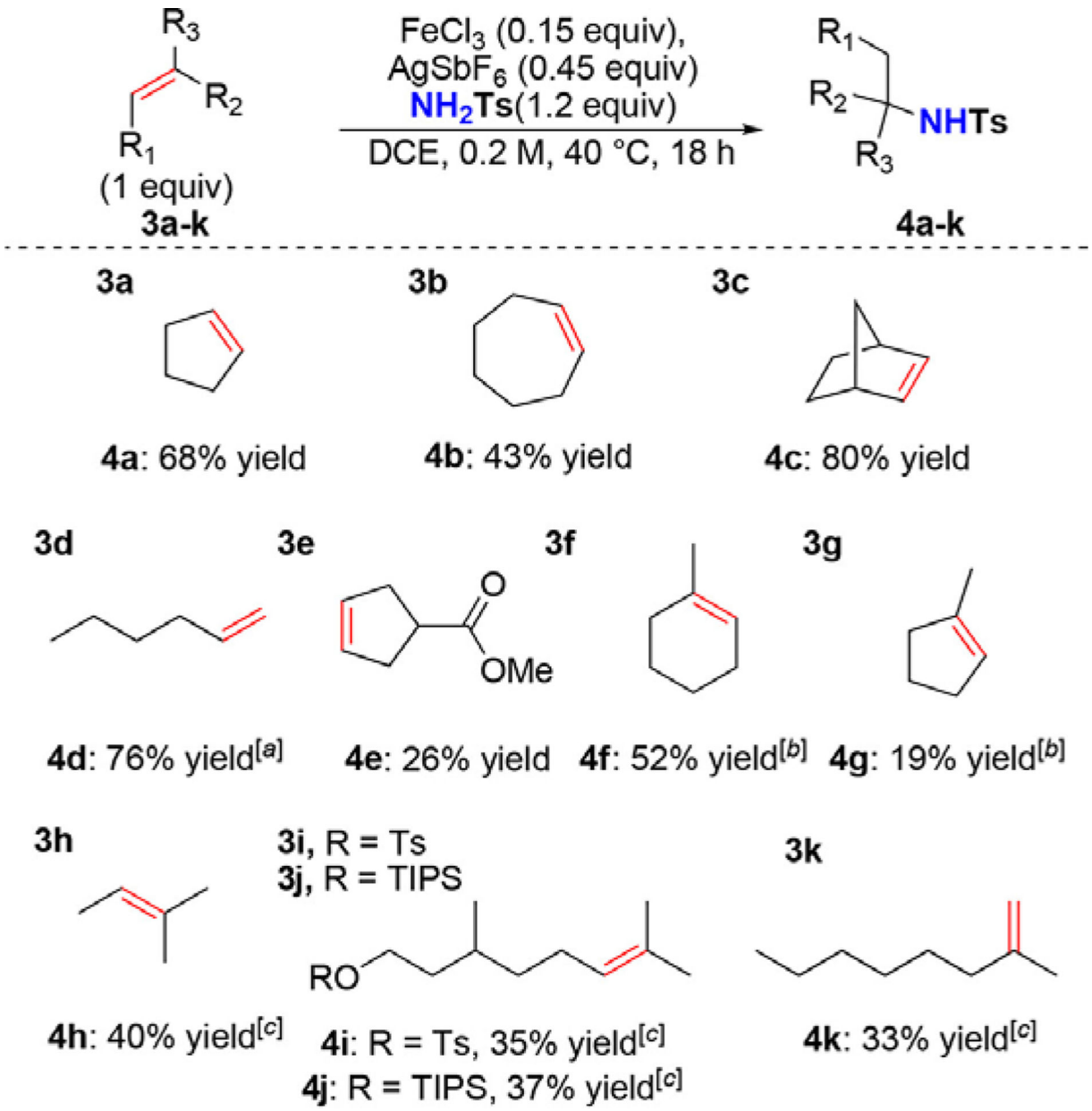
Figure 1.

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



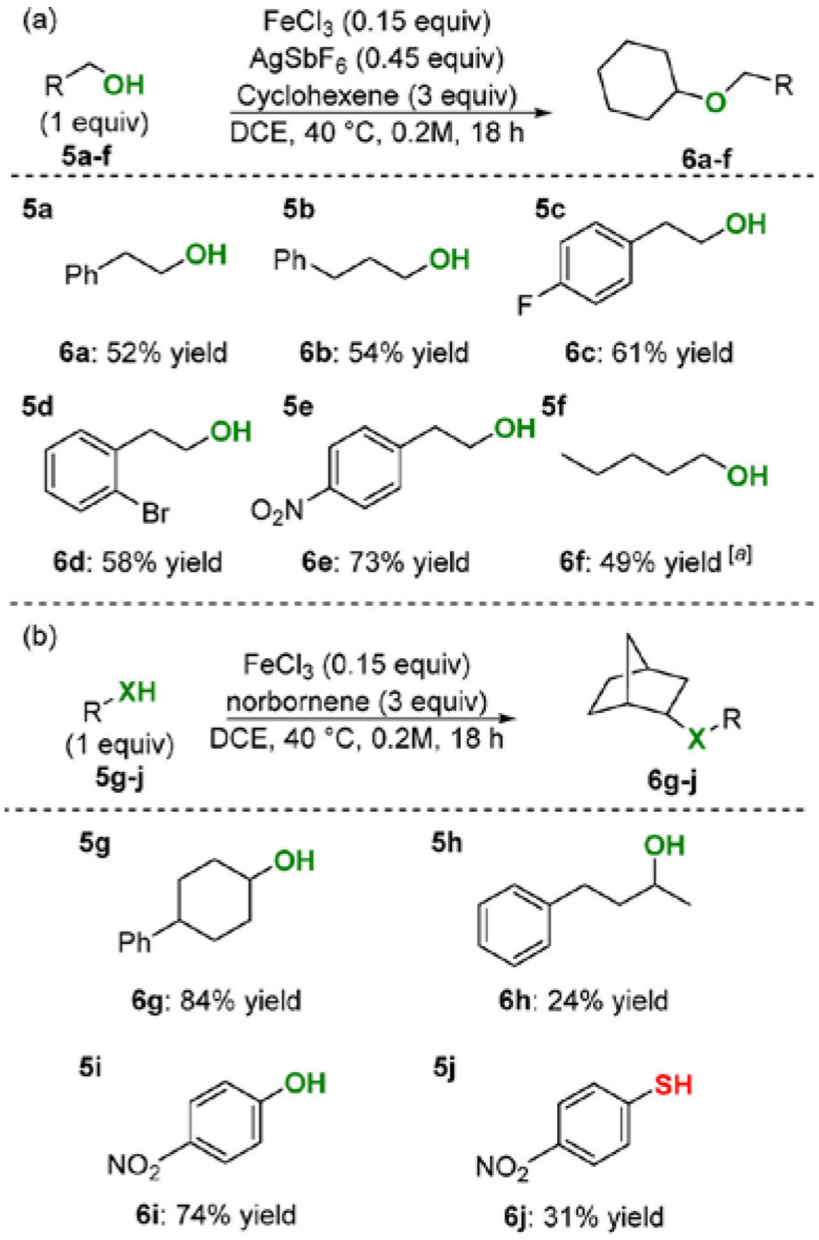
Scheme 1. Hydroam ination with Sulfonamide Nucleophiles

Reactions run at 0.5mmol scale.



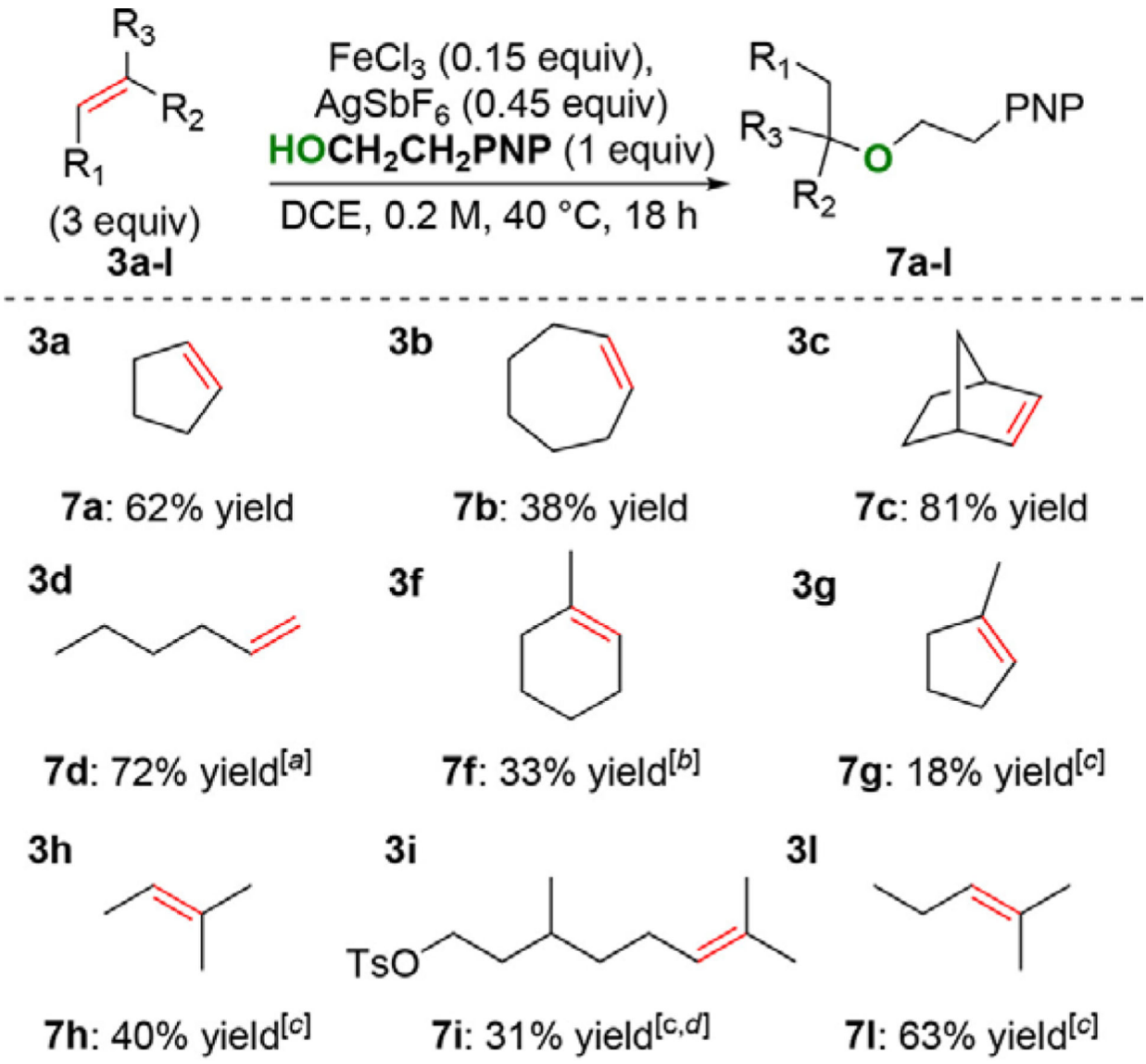
Scheme 2. Alkene Scope for Hydroam ination

Reactions run at 0.5 mmol scale, [a] Mixture of 2- and 3-substituted products, [b] FeCI3 only, [c] FeCI3 only, reaction run at r.t.



Scheme 3. Hydroetherification and Hydrothiolation

Reactions run at 0.5 mmol scale, [a] Yield obtained by GC using dodecane internal standard.

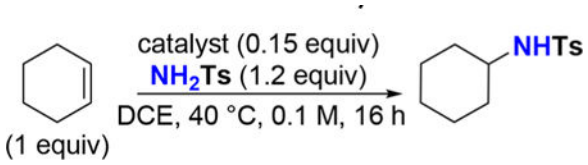


Scheme 4. Alkene Scope for Hydroetherification

PNP = 4-Nitrophenyl. Reactions run at 0.5 mmol scale, [a] Mixture of 2- and 3-substituted products. [b] FeCI3 only, [c] FeCk only, run at r.t. [d] 1 equiv alkene used.

Table 1.

Evaluation of Acid Catalysts



entry	catalyst	yield (%)[a]
1	$A1C1_3$	0
2	$FeCl_3$	<5
3	$AgSbF_6$	0
4	$FeCI_3$w/3 $AgSbF_6$	78
5	$FeCI_3$ w/3 $AgAsF_6$	82
6	$FeCl_3$ w/3 $AgBF_4$	43
7	$FeCl_3$ w/3 AgOTf	17
8	$FeCI_3$-$6H_2O$ w/3 $AgSbF_6$	58
9	$FeBr_3$ w/3 $AgSbF_6$	79
10	$FeCl_2$ w/2 $AgSbF_6$	33
11[b]	$HSbF_6$	0
12[c]	HCI	0
13[d]	$FeCl_3$ w/3 $AgSbF_6$	68
14[e]	$FeCl_3$ w/3 $AgSbF_6$	42

[a] NMR yields using 1,3,5-trimethoxybenzene standard.

[b] 65–75% aqueous solution.

[c] 12 M concentrated.

[d] Cs_2CO_3(0.15equiv) added.

[e] 2,6-Di-*terf*-butyl-4-methylpyridine (0.15 equiv) added.