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Synthesis of Tetrahydroisoquinolines Through an Iron-Catalyzed Cascade: Tandem Alcohol Substitution and Hydroamination

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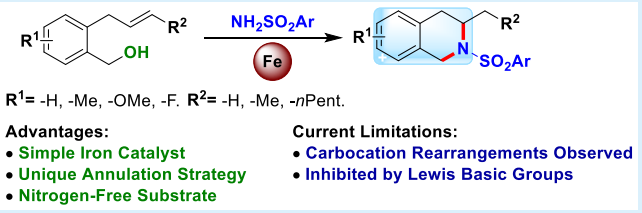
Supporting Information

ABSTRACT: Rapid assembly of saturated nitrogen heterocycles—the synthetically more challenging variants of their aromatic relatives—can expedite the synthesis of biologically relevant molecules. Starting from a benzylic alcohol tethered to an unactivated alkene, an iron-catalyzed tandem alcohol substitution and hydroamination provides access to tetrahydroisoquinolines in a single synthetic step. Using a mild iron-based catalyst, the combination of these operations forms two carbon−nitrogen bonds and provides a unique annulation strategy to access this valuable core.



Tetrahydroisoquinoline represents a common heterocyclic motif occurring in natural products, drug candidates, and bioactive compounds.[1−3] This scaffold has been the focus of numerous synthetic methods, including classic annulation chemistry.[4,5] Of the methods developed, the venerable Pictet−Spengler reaction remains a frequent method to prepare diverse structures with the tetrahydroisoquinoline core.[6,7] More recent strategies have included intramolecular hydroamination,[8−11] amino-functionalization of alkenes,[12−14] electrophilic aromatic substitution reactions,[15−17] or the nucleophilic displacement of allyl alcohols.[18−20] Modern annulation approaches rely on transition-metal-mediated directed C−H activation and cyclization onto π-systems.[21,22] In all of these examples, the existing chemistry requires the preinstallation of the nitrogen prior to the key ring-forming step—which only forms a single C−N bond.

Recently, we described an iron-based catalyst that performs as an unusually powerful and mild Lewis acid that can activate both alcohols and alkenes for functionalization with sulfonamide nucleophiles.[23,24] Given that both alcohol and alkene activation proceed with the same catalyst system, and under similar reaction conditions, we postulated that these two methods could be merged into a valuable reaction cascade. By tethering an alcohol to an alkene, the tandem functionalization of this scaffold with a sulfonamide nucleophile would afford a unique annulation reaction (Figure 1). This strategy would leverage readily accessible functional groups and allow rapid entry to nitrogen-containing saturated heterocycles. This operation would form two carbon−nitrogen bonds—avoiding the preinstallation of nitrogen. For example, by utilizing substituted allyl benzenes with an *o*-benzyl alcohol, the target cascade could, in one step, produce tetrahydroisoquinolines (Figure 1).

The initial studies of an iron-catalyzed tandem alcohol substitution and hydroamination (TASH) focused on an unactivated alcohol/alkene (**1a**) combination to target the synthesis of pyrrolidine rings, such as **2a**, (eq 1). Catalytic

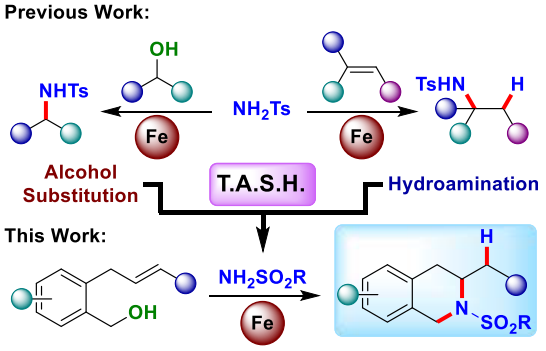


Figure 1. Iron-catalyzed tandem alcohol substitution and hydroamination (TASH) provides a unique disconnection for the synthesis of tetrahydroisoquinolines.

activation of this substrate with the powerful combination of $FeCl_3$ with $AgSbF_6$ failed to produce substantial annulation product (18% yield). Unfortunately, intramolecular hydroetherification eclipsed the target reaction and formed substituted tetrahydrofuran product **3a**.[25,26] In order to outcompete the intramolecular process, the rate of intermolecular substitution of the alcohol with the sulfonamide nucleophile required acceleration. Substitution of benzylic alcohols with sulfonamides proceeds rapidly with a range of mild catalysts.[27,28] Consequently, we hypothesized that a benzylic alcohol substrate would expedite intermolecular alcohol substitution and enable the overall annulation. Designing these two operations into a substrate tethers a benzylic alcohol to allyl benzene—a system primed for the synthesis of tetrahydroisoquinolines (Figure 1).

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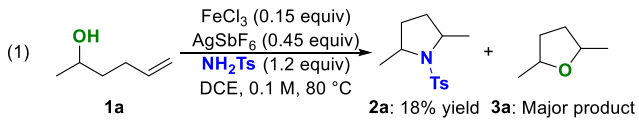
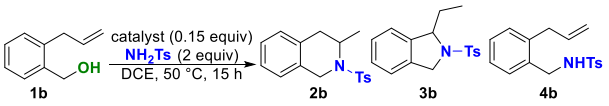


With substrate **1b** designed to test TASH with a sulfonamide nucleophile, various catalysts could be evaluated (Table 1).

Table 1. Evaluation of Acid Catalysts



		yield[a] (%)		
entry	catalyst	2b	3b	4b
1	$FeCl_3$	0	0	50
2	$FeBr_3$	0	0	32
3	$FeCl_3$ w/3 $AgSbF_6$	55	9	0
4	**$FeBr_3$ w/3 $AgSbF_6$**	**68**	**10**	0
5	$FeBr_3$ w/3 $AgAsF_6$	28	4	52
6	$FeBr_3$ w/3 $AgPF_6$	0	0	37
7	$FeBr_3$ w/3 $AgBF_4$	0	0	66
8	$FeBr_3$ w/3 AgOTf	24	ND	46
9	$FeBr_2$ w/2 $AgSbF_6$	0	0	55
10	$AgSbF_6$	0	0	0
11	$HSbF_6$ (aq)	0	0	54
12	HCl (conc)	0	0	15
13[b]	$FeBr_3$ w/3 $AgSbF_6$	0	0	66
14[c]	$FeBr_3$ w/3 $AgSbF_6$	0	0	58

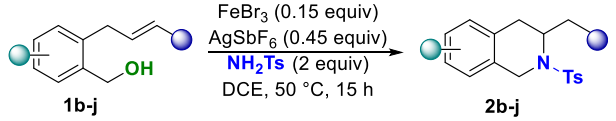
[a]NMR yields with 1,3,5-trimethoxybenzene standard. [b]Cs_2CO_3 (0.15 equiv) added. [c]2,6-Di-*tert*-butyl-4-methylpyridine (0.15 equiv) added.

Since iron(III) halide salts have been reported to catalyze both the substitution of benzylic alcohols[27] and the intramolecular hydroamination of alkenes,[25] mild Lewis acids $FeCl_3$ (Table 1, entry 1) and $FeBr_3$ (Table 1, entry 2) provided obvious starting points. These salts catalyzed the benzyl alcohol substitution reaction but not the hydroamination, forming benzyl sulfonamide side product **4b**. To enhance the Lewis acidity of the iron species, we surveyed silver salts containing "non-coordinating" counterions (Table 1, entries 3–9).[29] The combination of $FeCl_3$ with $AgSbF_6$ (Table 1, entry 3) catalyzed both the alcohol substitution and subsequent hydroamination reaction with annulation compound **2b** as the major product. Switching to $FeBr_3$ and $AgSbF_6$ (Table 1, entry 4) improved the yield to 68% of the tetrahydroisoquinoline product **2b** while also providing 10% yield of the regioisomeric isoindoline product **3b**. The five-membered side product **3b** could arise from a carbocation rearrangement to the more stabilized benzylic carbocation.[30] The combination of $FeBr_3$ with other "non-coordinating" silvers salts were inferior to $AgSbF_6$, affording primarily the benzyl sulfonamide side product **4b** (Table 1, entries 5–8).

While there exists precedent for iron promoting both independent reactions,[25,27] the influence of Brønsted acids created in situ required evaluation. To investigate the possibility of Brønsted acid catalysis, we attempted to catalyze the reaction with $HSbF_6$ and HCl (Table 1, entries 11 and 12). While both $HSbF_6$ and HCl catalyze the alcohol substitution with *p*-toluenesulfonamide, the subsequent hydroamination failed (Table 1, entries 11 and 12). Additionally, to test for "hidden Brønsted acid catalysis,"[31,32] bases Cs_2CO_3 (Table 1, entry 13) or sterically hindered 2,6-di-*tert*-butyl-4-methylpyridine (Table 1, entry 14) were added to the reaction. The addition of either base inhibited the hydroamination reaction, while activity for alcohol substitution remained. These results are inconsistent with "hidden Brønsted acid catalysis" as the sole promotor of the reaction. Moreover, the TASH proceeds most effectively with the privileged combination of FeX_3 with $AgSbF_6$, regardless of the potential contribution of "hidden Brønsted acid catalysis" toward hydroamination.

With suitable conditions for TASH, we next evaluated the substrate scope and found a range of simple substrates compatible with the reaction (Table 2). 3-Methyl-2-tosyltetrahydroisoquinoline (**2b**) could be synthesized in 62% isolated yield as a 6:1 regioisomeric ratio (rr). Similar yield of **2b** was obtained when **1b** was reacted on 1 mmol scale. Trisubstituted olefin **1c** was tolerated, but the yield of tetrahydroisoquinoline product **2c** was reduced due to competitive formation of an isochroman through an intramolecular hydroetherification reaction. Placing an electron-withdrawing fluorine at the 6-position (**1d**) had little effect on the yield of the reaction but inhibited rearrangement, as **2d** was isolated in 18:1 rr. Placing an electron-withdrawing fluorine at the 7-position (**1e**) inhibited alcohol substitution and favored hydroetherification, with only a modest 21% of desired product **2d** isolated. Electron-donating groups such as methyl (**1f**) or methoxy (**1e**) placed at the 7-position were tolerated. Placing an electron-donating at the 6-position, however, proved problematic since this activates the benzylic alcohol and

Table 2. Iron-Catalyzed TASH for the Synthesis of Tetrahydroisoquinolines



alcohol	product	alcohol	product
1b	**2b**: 62% yield (6:1 r.r.) **1 mmol:** 60% yield (4:1 r.r.)	**1c**	**2c**: 38% yield
1d	**2d**: 61% yield (18:1 r.r.)	**1e**	**2e:** 21% yield (3.5:1 r.r)
1f	**2f**: 48% yield (5:1 r.r.)	**1g**	**2g**: 30% yield (6:1 r.r.)
1h	**2h**: 11% yield (4:1 r.r.)	**1i**	**2i**: 71% yield (3:1 r.r.)
1j	**2j:** 53% yield (3.1 r.r.)		

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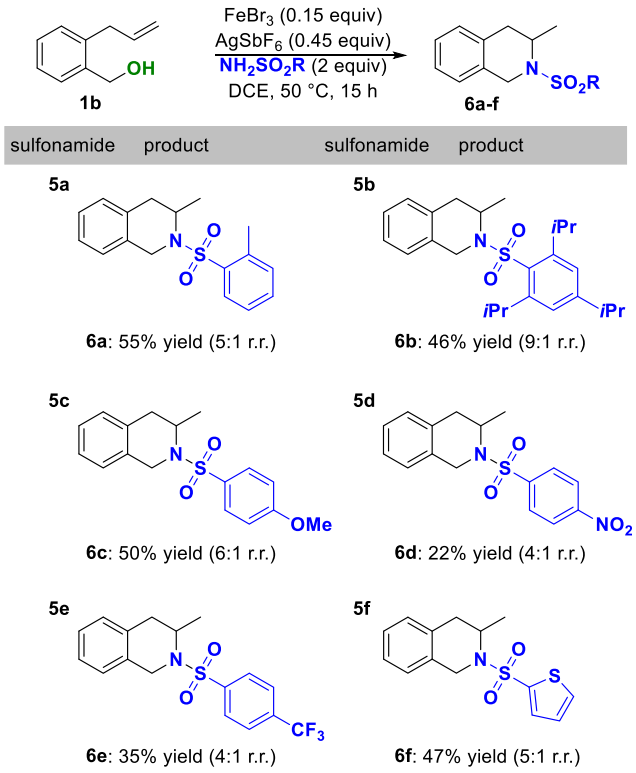
leads to significant decomposition—likely through quinone methide formation.[16] For example, while trace amounts of **2h** could be isolated, replacing the methyl group of **1h** with a methoxy group led to complete decomposition of the product (data not shown). While methyl proved general at the 3-position (**1b**−**1h**), longer alkyl chains could be installed. For example, internal alkenes were tolerated (**1i**, **1j**) with the tetrahydroisoquinoline isolated as the major products (**2i**, **2j**). However, the 7-membered ring products were also detected, complicating analysis. Overall, the activating effect of the aromatic ring needs to be carefully weighed against rearrangements and side product formation.

We next investigated the composition of the sulfonamide nucleophile (Table 3). *o*-Toluenesulfonamide (**5a**) gave yields

Table 3. Evaluation of Sulfonamide Nucleophiles



similar to that of *p*-toluenesulfonamide, affording **6a** in 55% yield. More sterically bulky 2,4,6-triisopropylbenzenesulfonamide (**5b**) gave a higher regiomeric ratio with a stronger preference to form the tetrahydroisoquinoline product (**6b**). Placing a methoxy on the sulfonamide (**5c**) had little effect on the yield of the reaction. Decreasing the nucleophilicity of nitrogen by placing an electron-withdrawing nitro (**5d**) or trifluoromethyl (**5e**) group on the sulfonamide, however, significantly decreased the yield of the reaction. In addition, heteroaryl 2-thiophenesulfonamide (**5f**) also performed well in the reaction. Overall, the sulfonamide scope proved relatively general and synthetically useful.

The novel annulation method described here offers access to tetrahydroisoquinolines from starting material devoid of nitrogen. The iron-catalyzed tandem alcohol substitution and hydroamination using a sulfonamide nucleophile provides an unusual disconnection for an annulation approach to this heterocyclic core. Starting from a benzylic alcohol and an alkene, this approach forms two bonds in a single synthetic step and does not require the preinstallation of nitrogen. The aromatic backbone can be altered with varying substitution patterns from the choice of building blocks used. This method provides a simple approach to access 3-substituted tetrahydrosoquinolines and is complementary to classic approaches to synthesize this valuable heterocycle.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02353.

Experimental details, compound characterization and NMR data (PDF)

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Notes

The authors declare no competing financial interest.

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