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Stereoinversion of Unactivated Alcohols by Tethered Sulfonamides

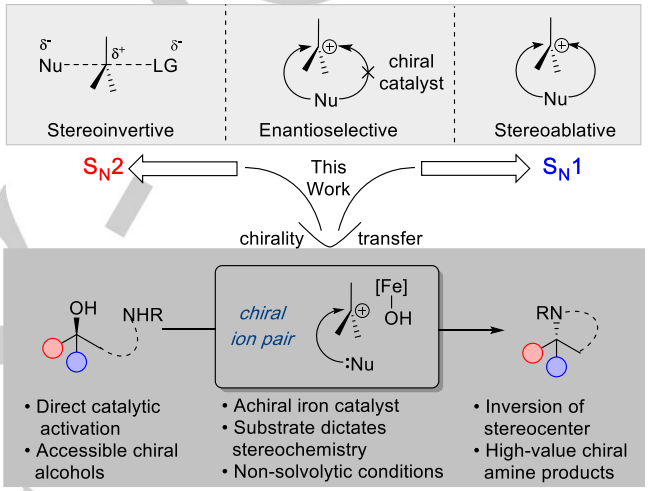
Paul T. Marcyk, Latisha R. Jefferies, Deyaa I. AbuSalim, Maren Pink, Mu-Hyun Baik* and Silas P. Cook*

Abstract: The direct, catalytic substitution of unactivated alcohols remains an undeveloped area of organic synthesis. Moreover, catalytic activation of this difficult electrophile with predictable stereooutcomes presents an even more formidable challenge. Described here is a simple iron-based catalyst system which provides a mild, direct conversion of secondary and tertiary alcohols to sulfonamides. Starting from enantioenriched alcohols, the intramolecular variant proceeds with stereoinversion to produce enantioenriched 2- and 2,2-subsituted pyrrolidines and indolines—without prior derivatization of the alcohol or solvolytic conditions.

The interconversion of functional groups represents an archetypal operation in organic synthesis. These transformations can leverage the reactivity of a common functional group to install a new, more valuable motif. Classic examples include the S_N2 and S_N1 reactions (Scheme 1). While the S_N2 proceeds stereospecifically with inversion of configuration,[1] the S_N1 reaction, due to the carbocation intermediate, generally proceeds with loss of stereochemistry.[2] Chemists have gone to great lengths to control the facial selectivity of nucleophile attack on the carbocation through the use of enantioenriched catalysts.[3] Transferring the stereochemical information of the starting electrophile that undergoes an ionization event remains a challenge.[4] Here we demonstrate that secondary and tertiary alcohols can be used *directly* as electrophiles with *inversion of stereochemistry* when displaced with tethered sulfonamides.

Due to their ubiquity and stability, aliphatic alcohols are attractive electrophiles for functional group interconversion. The 2018 ACS Green Chemical Institute Pharmaceutical Roundtable highlighted the activation of alcohols for nucleophilic substitution as a key reaction in need of development.[5] Conventional methods for alcohol substitution often involve converting the alcohol to a halide or pseudohalide before nucleophilic substitution or employ the Mitsunobu reaction.[6][7] Direct, *catalytic activation* of alcohols for substitution is an attractive approach to form carbon-heteroatom bonds because water is the only stoichiometric byproduct. One approach is the Lewis or Brønsted acid-promoted S_N1 substitution[8] of benzylic,[9] allylic,[10] and propargylic[11] alcohols. While π-activated or tertiary alcohols can be substituted with a wide range of nucleophiles,[12] unactivated alcohols remain a significant challenge.[13] Recently, we reported an iron-catalyzed intramolecular Friedel-Crafts arylation of unactivated secondary alcohols that proceeds with chirality transfer.[14] We sought to translate this system into a general conceptual framework for the direct amination of alcohols.

Scheme 1. An Ion-Pair Approach to Enantioselective Substitution.



In certain limited cases, enantioenriched secondary alcohols can be utilized directly to transfer chiral information to new carbon-heteroatom bonds. For example, Samec and co-workers used a Brønsted acid catalyst to control the facial approach of the nucleophile for a stereoinvertive dehydrative cyclization.[15] Inverting free tertiary alcohols for this type of substitution, however, remains problematic. Solvolysis represents the only successful approach to transfer the chirality of tertiary electrophiles to the substituted product.[16] Moreover, the starting alcohols must be activated as a nitrobenzoyl ester,[17] alkoxydiphenyl phosphine,[18] or trifluoroacetate[4] to permit ionization. While a substitution of an unactivated tertiary alcohol exists, in studies of α-tocopherol, this too proceeds under solvolytic conditions.[19] The direct substitution of unactivated tertiary alcohols with nitrogen nucleophiles would represent a major advance in this field; providing access to α-tertiary chiral amine products—an amine class that currently necessitates lengthy synthetic sequences.[20] Here, we report an iron-catalyzed system capable of directly substituting aliphatic alcohols as well as the stereoinvertive, intramolecular substitution of chiral secondary and *tertiary alcohols* by sulfonamide nucleophiles.

To gain insight into the reactivity of unactivated alcohols in an amination reaction, we began our investigation by treating cyclohexanol with *p*-toluenesulfonamide in the presence of select acid catalysts (see Supporting Information). Iron(II) or iron(III) salts alone proved ineffective in this difficult transformation. Consistent with the enhanced Lewis acidity of Fe(III) salts containing "non-coordinating" counterions,[14, 21] the combination

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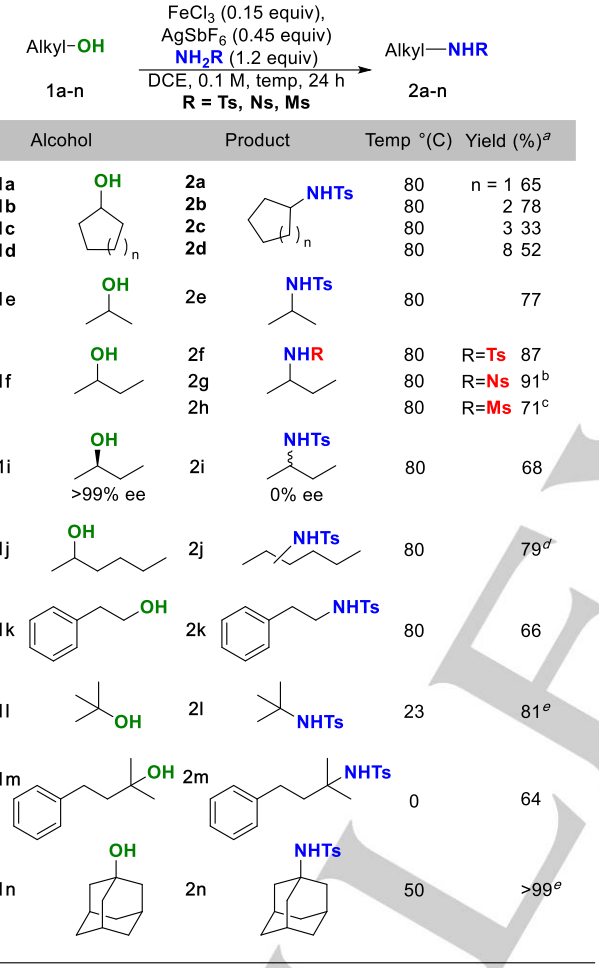
of iron(III) chloride with $AgSbF_6$ in 1,2-dichloroethane at 80 °C for 24 hours afforded the desired amination product in 78% yield (see SI). Three equivalents of $AgSbF_6$ relative to iron proved superior to fewer equivalents, consistent with the exchange of all three chlorides for hexafluoroantimonate ions. Brønsted acids, including $HSbF_6$, produced low yield, thereby providing support for an iron-based Lewis acid as the primary activator of the alcohol. However, select bases (e.g., Cs_2CO_3, K_2CO_3, and 2,6-di-*tert*-butyl-4-methylpyridine) did measurably lower the yield, suggesting some background Brønsted acid catalysis (see SI).

Table 1. Substrate Scope for the Intermolecular Alcohol Substitution with Sulfonamides.



Alcohol		Product		Temp °(C)	Yield (%)[a]
1a		2a		80	n = 1 65
1b		2b		80	2 78
1c		2c		80	3 33
1d		2d		80	8 52
1e		2e		80	77
1f		2f		80	R=Ts 87
		2g		80	R=Ns 91[b]
		2h		80	R=Ms 71[c]
1i	>99% ee	2i	0% ee	80	68
1j		2j		80	79[d]
1k		2k		80	66
1l		2l		23	81[e]
1m		2m		0	64
1n		2n		50	>99[e]

[a] Isolated yields. [b] 4-Nitrobenzenesulfonamide nucleophile used. [c] Methanesulfonamide nucleophile used. [d] 1:1 Mixture of 2 and 3 substituted product. [e] $FeCl_3$ only.

With suitable conditions for the amination of cyclohexanol **1b**, we next evaluated the performance of the intermolecular reaction across a variety of aliphatic alcohols. We were pleased to find that cyclic and symmetric acyclic secondary alcohols resulted in the desired amination products in moderate-to-good yields (**2a-f**, Table 1). Unfortunately, 2-hexanol (**1j**) resulted in a 1:1 mixture of 2 and 3 substituted products **2j,** suggesting a facile carbocation rearrangement.[22] To test whether the intermolecular reaction proceeds with stereoinversion, enantioenriched (*R*)-2-butanol (**1i**) was subjected to the reaction conditions and provided racemic product **2i**, possibly due to background Brønsted acid catalysis. Reaction monitoring by GC/MS indicated the formation and consumption of alkene, suggesting an E1 elimination followed by hydroamination of the alkene as an alternative and competing pathway to the substitution.[23] In addition to *p*-toluenesulfonamide, *p*-nitrobenzenesulfonamide also functioned well as the nucleophile, providing an easily removable nosyl protecting group in product **2g**, while methanesulfonamide provided **2h** in 71% yield. Efforts to extend this methodology to other nitrogen nucleophiles such as carbamates, amides, anilines, and aliphatic amines were unsuccessful potentially due to competitive iron coordination to nitrogen. Primary alcohols proved difficult. While phenethylalcohol (**1k**) functions well in the reaction, likely through anchimeric assistance,[24] other primary alcohols resulted in low yields (data not shown). Conversely, tertiary alcohols were excellent substrates, affording the amination products in good (**2l-m**)-to-near quantitative yields (**2n**). Contrary to primary and secondary alcohols, tertiary alcohols worked better at lower temperature or without the use of $AgSbF_6$.

While the intermolecular amination of secondary alcohols resulted in racemic products, we hypothesized that an intramolecular amination of enantioenriched alcohols would proceed rapidly to provide access to stereodefined pyrrolidines and indolines, a motif present in many natural products and bio-active molecules.[25] Current methods to set this difficult stereocenter[26] involve enantioselective hydroaminations,[27] asymmetric hydrogenation,[28] and kinetic resolutions,[29] all of which rely on chiral catalysts. Other approaches required the prefunctionalization of chiral alcohols[30] We found that the intramolecular substitution of enantioenriched secondary alcohols proceeded with high yield and enantiospecificity, transferring chirality to the formed pyrrolidine ring (Table 2). The reactions did not proceed with Brønsted acids instead of iron and were not inhibited by exogenous bases, in contrast to the intermolecular variants.

The scope of the intramolecular substitution of chiral secondary alcohol was explored by varying the alcohol sidechain. Simple chains such as methyl in **3a** and *n*-propyl in **3b** formed the 2-substituted pyrrolidine with excellent yield and 96% es. Alcohols with larger sidechains, such as 2-methylpropyl in **3c**, performed better with complete chirality transfer to form **4c**. The benzylic alcohol in **3d** formed the desired pyrrolidine product **4d** as a racemic mixture due to formation of the stabilized benzylic carbocation. Enantioenriched 2-substituted indolines were also accessible with this method, Once again, simple alkyl groups such as methyl in **3e** and ethyl in **3f** proved high yielding with high levels of enantiospecificity *even on gram scale*. The electronic properties of the nitrogen nucleophile could be modified with electron-donating or -withdrawing groups on the aniline without reducing the enantiospecificity of the reaction. The reaction tolerated remote functional groups. For example, the inclusion of a primary bromide in **3i** or tosylate in **3j** proceeded well to provide a synthetic handle for further functionalization. Furthermore, the tosyl group can be efficiently removed affording the deprotected indoline product without racemization (see SI).[31] Extending this methodology to six-membered piperadine rings produced an inseparable mixture of six- and five-membered products—arising from a rapid carbocation rearrangement (see SI).

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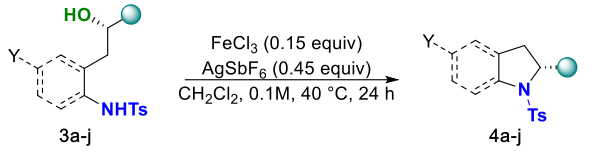
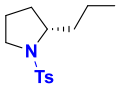
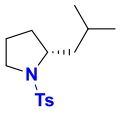
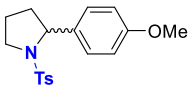
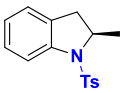
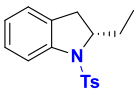
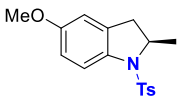
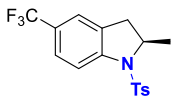
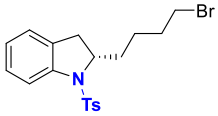
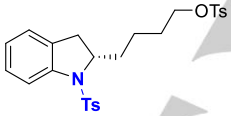
Table 2. Intramolecular Stereoinvertive Substitution of Secondary Alcohols.

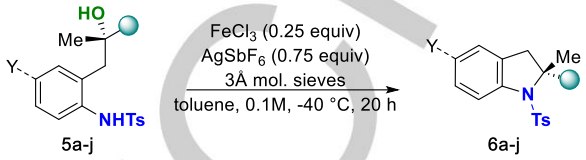


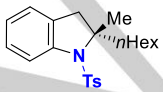
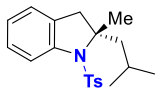
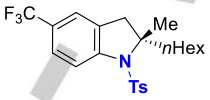
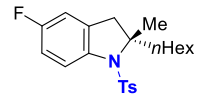
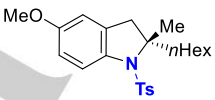
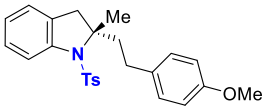
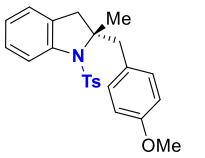
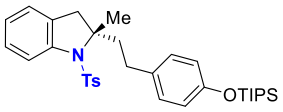
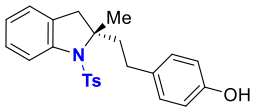
Alcohol	Product[a]	Alcohol	Product[a]
3a		3b	
	4a: 96% (89% ee, 98% es)		**4b:** 98% (75.5% ee, 96% es)
3c		3d	
	4c: 98% (72% ee, >99% es)		**4d:** 98% (0% ee, 0% es)
3e		3f	
	4e: 94% (97.7% ee, 98.5% es) **Gram Scale**: 75% (97.5% ee, 98.5% es)		**4f:** 99% (90% ee, 95% es)
3g		3h	
	4g: 42% (98% ee, 99% es)		**4h:** 98% (97.5% ee, 98.5% es)
3i		3j	
	4i: 70% (99% ee, 99% es)		**4j:** 61% (96% ee, 96% es)

[a] Isolated yields. Enantiomeric excess determined by chiral HPLC analysis.

Since the intramolecular substitution of secondary alcohols proceeded in high yield and enantiospecificity, we suspected that enantioenriched tertiary alcohols could be substituted via a non-racemic mechanism. We reasoned that the developing tertiary carbocation could be attacked from the face opposite of the departing alcohol, resulting in chirality transfer. To intercept a tertiary carbocation with minimal racemization under non-solvolytic conditions, the iron-ate/carbocation ion pair needs to be tightly associated to block one face of the carbocation (Scheme 2b).[32] We reasoned that a solvent with lower dielectric constant combined with decreased reaction temperature would fortify the ion pair and favor stereoinversion. To our delight, decreasing the reaction temperature to –40 ºC and switching the solvent to toluene produced the enantioenriched 2,2-disubstituted indoline products (Table 3). Indoline **6a** with alkyl side chains was formed in 79% ee—transferring 89% of the chiral information from starting alcohol **5a**. The electronic properties of the sulfonamide nucleophile could be altered by placing an electron-withdrawing or -donating group at the para position of the aniline ring. Attenuating the nucleophilicity with electron-withdrawing groups, such as CF_3 in **5c** or F in **5d**, decreased both the yield and the enantiospecificity of the reaction. The more electron-rich nucleophile in **5e** had little effect on the reaction. In addition to alkyl side chains, electron-rich aromatic rings (**5f** and **5g**) also proceeded with good es. Silyl protected phenols were compatible with the reactions conditions. While the triisopropylsilyl (TIPS) group in **5h** group proved stable to the reaction conditions, the *tert*-butyldimethyl silyl (TBS) group for **5i** was partially deprotected over the course of the reaction. In all, Table 3 presents an expeditious route to 2,2-disubstituted indolines with serviceable ee and good yields—a previously challenging and labor-intensive synthetic endeavor.

Table 3. Intramolecular Stereoinvertive Substitution of Tertiary Alcohols.



Alcohol	Product[a]	Alcohol	Product[a]
5a		5b	
	6a: 62% (79% ee, 89% es)		**6b:** 51% (47% ee, 75% es)
5c		5d	
	6c: 37% (50% ee, 54% es)		**6d:** 49% (55% ee, 58% es)
5e		5f	
	6e: 63% (80 ee, 82% es)		**6f:** 72%[b] (90% ee, 91% es)
5g		5h	
	6g: 27%[b] (75% ee, 76% es)		**6h:** 46% (76% ee, 81% es)
5i			
	6i: 60%[c] (70% ee, 74% es)		

[a] Isolated yields. Enantiomeric excess determined by chiral HPLC analysis. [b] Reaction run in (5:1) toluene:DCE. [c] Phenol of **5i** is protected with TBS. Reaction yielded a mixture of TBS protected and deprotected phenol. Mixture converted to the **6i** with TBAF (1 equiv).

To determine whether the reaction proceeds with inversion of stereochemistry, the absolute configuration of enantioenriched alcohol **3i** and the resulting indoline ring **4i** were assigned by X-ray crystallography (Scheme 2a). Alcohol **3i** crystalized readily and assigned the (*R*) configuration. Pentabromophenol-derived indoline **7**, however, had the (*S*) configuration, thereby confirming that the intramolecular substitution of secondary alcohols proceeds with stereoinversion. For the intramolecular substitution of tertiary alcohols, our model predicts stereoinversion. The departing iron-hydroxide would block the front face of the carbocation favoring rapid attack of nitrogen from the opposite face (Scheme 2b). The stereochemistry of tertiary alcohol **5a** was confirmed (*R*)- configuration by X-ray crystallography. However, since an X-ray-suitable crystal for indoline product **6a** remains

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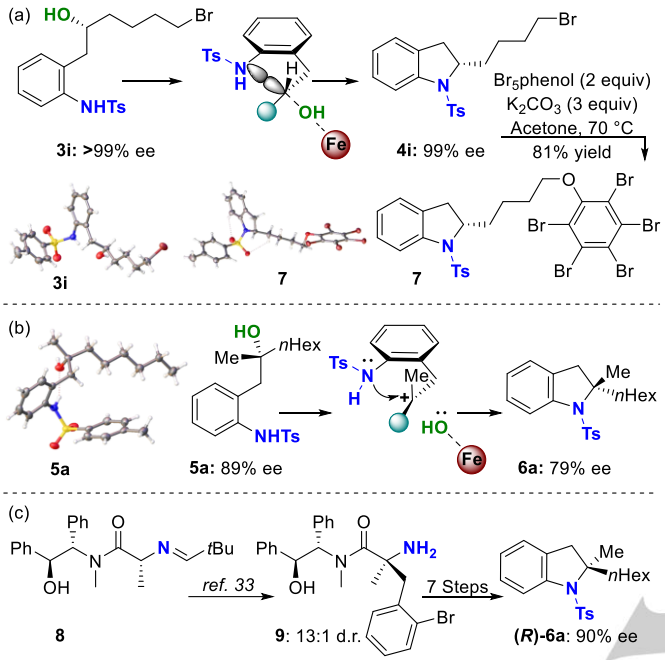
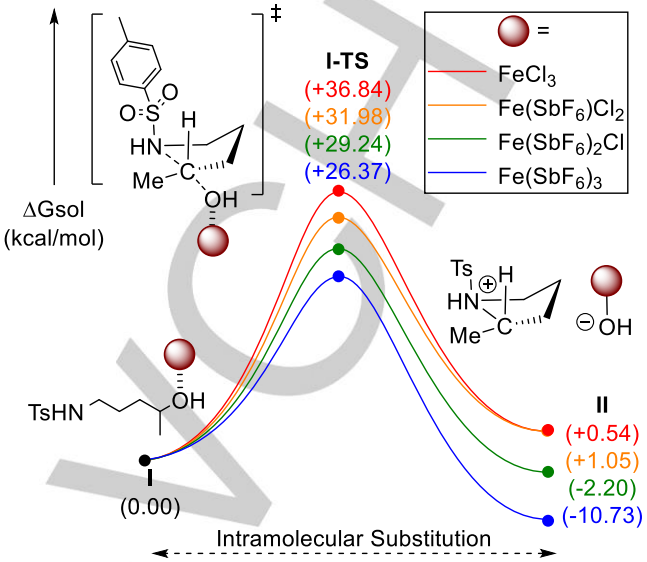
unrealized, an asymmetric benzylation of *D*-alanine derivative **8** followed by a seven-step sequence produced ***(R)*-6a** (Scheme 2c and SI),[33] a testament to the limitations of current methods to prepare α-tertiary chiral amines. Indoline product **6a** was determined to be in the (*S*) configuration, thereby confirming the intramolecular substitution of tertiary alcohols also proceeds with stereoinversion.



Scheme 2. Stereochemical model and absolute configuration for the intramolecular substitution of (a) secondary alcohols (b) tertiary alcohols. (c) Absolution configuration determination for indoline product **6a** via an asymmetric benzylation of *D*-alanine derivative **8**.

To help elucidate whether $Fe(SbF_6)_3$ is the active iron catalyst, we employed density functional theory calculations (Scheme 3 and SI). We focused on the stereoinversion step for **3a** with the alcohol bound to $FeCl_3$, $Fe(SbF_6)Cl_2$, $Fe(SbF_6)_2Cl$, and $Fe(SbF_6)_3$. The lowest barrier for C–N bond formation (**I-TS**) was 26.4 kcal/mol with $Fe(SbF_6)_3$. This finding is consistent with our experimental data—where no reaction occurs in the absence of $AgSbF_6$, and the best yields were obtained with three equivalents relative to Fe (see SI). These calculations show that the residual reactivity observed with fewer than three equivalents of $AgSbF_6$ is likely due to an equilibrium that includes $Fe(SbF_6)_3$—the relevant, active catalyst.

In conclusion, we have developed a mild and efficient iron-catalyzed substitution of unactivated alcohols with sulfonamide nucleophiles. This methodology allows efficient access to secondary and tertiary alkyl sulfonamides from readily available alcohols. Furthermore, the intramolecular variant of the reaction proceeds with inversion of stereochemistry. By employing the concept of tight-ion pairing as a solution to cation facial selectivity, this method represents a rare example where secondary and even *tertiary alcohols* react with an achiral catalyst to transfer the chiral information to the products under non-solvolytic conditions. This method enables efficient access to enantioenriched 2,2-disubstiuted indoline products in far fewer steps than current technology allows. By rapidly intercepting ion pairs, we have leveraged an unconventional tactic to form the Csp^3–N bond with predictable stereochemical outcomes.



Scheme 3. Computed Free-Energy Diagram for the Intramolecular Substitution of **3a**.

Acknowledgements

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Conflicts of Interest

The authors declair no conflicts of interest.

Keywords: Alcohol Substitution • Indoline • Iron • Asymmetric • Sulfonamide

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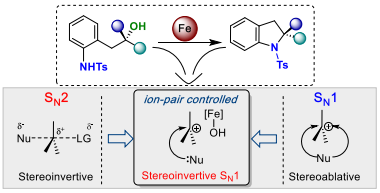
Layout 1:

COMMUNICATION

Employing a simple iron catalyst, the direct conversion of secondary and tertiary alcohols to sulfonamides is reported. Starting from enantioenriched alcohols, the intramolecular variant proceeds with stereoinversion to produce enantioenriched 2- and 2,2-subsituted pyrrolidines and indolines—without prior derivatization of the alcohol or solvolytic conditions.



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