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## Acid Catalysis

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# Triflic Acid-Catalyzed Dehydrative Amination of 2-Arylethanols with Weak *N*-Nucleophiles in Hexafluoroisopropanol

Max Van Hoof, Robert J. Mayer, Joseph Moran, and David Lebœuf\*

**Abstract:** The catalytic deoxyamination of readily available 2-arylethanols offers an appealing, simple, and straightforward means of accessing  $\beta$ -(hetero)arylethylamines of biological interest. Yet, it currently represents a great challenge to synthetic chemistry. In most cases, the alcohol has to be either pre-activated *in situ* or converted into a reactive carbonyl intermediate, limiting the substrate scope for some methods. Examples of direct dehydrative amination of 2-arylethanols are thus still scarce. Here, we describe a catalytic protocol based on the synergy of triflic acid and hexafluoroisopropanol, which enables the direct and stereospecific amination of a broad array of 2-arylethanols, and does *not* require any pre-activation of the alcohol. This approach yields high value-added products incorporating sulfonamide, amide, urea, and aniline functionalities. In addition, this approach was applied to the sulfidation of 2-arylethanols. Mechanistic experiments and DFT computations indicate the formation of phenonium ions as key intermediates in the reaction.

## Introduction

Direct dehydrative substitution of alcohols is among the most attractive synthetic methods for alkylation reactions.<sup>[1]</sup> Alcohols are abundant, inexpensive, easy to handle, and structurally diverse, while being either readily available or simple to prepare, if necessary, by reduction of common carboxylic acids. In addition, they only form water as a stoichiometric by-product. For those reasons, the ACS Green Chemistry Pharmaceutical Roundtable<sup>®</sup> identified the direct substitution of alcohols as a priority,<sup>[2]</sup> generating significant research interest in this challenging field.

However, because of the poor nucleofugality of the hydroxyl group, the direct substitution of aliphatic alcohols is an arduous task. Classic alcohol substitutions require a stoichiometric activation prior to the desired transformation, where the alcohol moiety is converted to a better leaving group. Examples include the preparation of halides or sulfonate esters or *in situ* activation through Mitsunobu reaction conditions, yet, generating significant amounts of organic waste (Scheme 1A). To address these issues, considerable efforts have been made in developing catalytic approaches (Scheme 1B), one of the most prominent ones relying on the use of Lewis or Brønsted acids. A major restraint is that these reactions are typically only effective with alcohols such as  $\pi$ -activated or tertiary ones, which are prone to generate relatively stable carbocation intermediates, thereby excluding common primary and secondary aliphatic ones.

To date, hydrogen borrowing strategies are arguably the most advanced methods for the direct catalytic dehydrative amination of primary and secondary alcohols, both in terms of efficacy and versatility (Scheme 1B).<sup>[3]</sup> These methods allow the introduction of a large range of amine nucleophiles, from alkylamines to more acidic sulfonamides. However, due to the possible enolization of arylacetaldehydes, 2-arylethanols remain challenging substrates and only yield products with few amines. Specifically, while alkylamines and anilines performed well for this reaction, examples with less nucleophilic amides and sulfonamides are scarce. A plausible explanation is that the self-condensation of the aldehyde intermediate outcompetes the condensation with less nucleophilic amines bearing electron-withdrawing groups. In addition, given the mechanisms involved, those reactions exclude tertiary aliphatic alcohols. Recently, the group of Denton reported a catalytic Mitsunobu reaction for the nucleophilic substitution of alcohols, which was applicable to C–N

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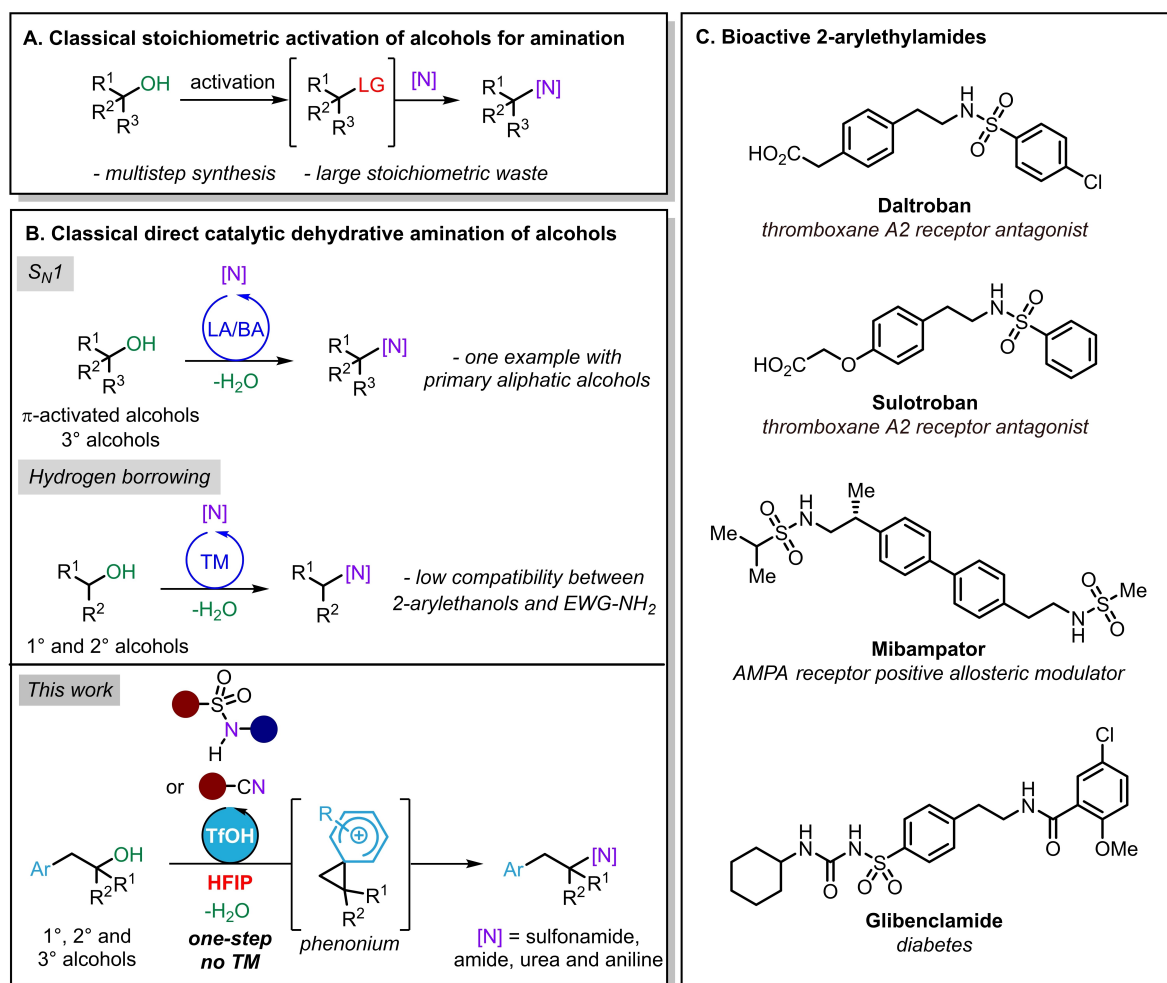
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**Scheme 1.** Traditional strategies for the deoxygenation of alcohols. LG = leaving group. TM = transition metal.

bond formation. However, only dibenzenesulfonamide, whose chemoselective deprotection is often difficult in the presence of various functional groups, was used as a *N*-nucleophile.<sup>[4]</sup> In turn, the group of MacMillan demonstrated that primary and secondary aliphatic alcohols could be activated *in situ* in the form of a NHC adduct.<sup>[5]</sup> Although efficient and mild, this transformation requires a promoter system featuring multiple catalysts, ligands, and additives. Regarding Lewis/Brønsted acid catalysis, a single example of direct deoxygenation of a primary aliphatic alcohol was reported by the group of Cook, relying on a Fe(III)/Ag(I) catalytic system.<sup>[6]</sup> Thus, a general and simple method for the catalytic deoxygenation of primary aliphatic alcohols, notably 2-arylethanol, remained unmet.

In this context, we set out to develop a complementary catalytic dehydrative amination of 2-arylethanol that would include electron-deficient amines. It would thus allow a rapid access to 2-arylethylamides, which are common structural motifs in bioactive molecules.<sup>[7]</sup> To achieve this take, we based our strategy on the generation of a phenonium ion intermediate with the assistance of the aryl-neighbor unit; then, due to its high electro-

philicity, nucleophilic addition of various weak *N*-nucleophiles could take place to provide the target compounds. While phenonium ions are well-established species in physical-organic studies,<sup>[8]</sup> their use in synthesis is still underexploited,<sup>[9]</sup> most of the time requiring tailored substrates with prone leaving groups such as halide or arylodonium ions. In this context, our starting point was our recent report on Brønsted acid-catalyzed dehydrative arylation of primary aliphatic alcohols,<sup>[10]</sup> which exclusively worked in hexafluoroisopropanol (HFIP) as a solvent,<sup>[11]</sup> with its role being to augment the overall Brønsted acidity of the catalyst.<sup>[12]</sup> However, the reaction proved only compatible with a narrow range of 2-arylethanol motifs and electron-rich arenes, limiting its synthetic utility.

Here, we describe a general method for the direct catalytic dehydrative amination of 2-arylethanol with sulfonamides and nitriles, directly yielding valuable *N*- $\beta$ -arylethylsulfonamides and *N*- $\beta$ -arylethylcarboxyamides, the structural motifs of many bioactive molecules (Scheme 1C). The transformation relies on the unique combination of triflic acid (TfOH) as a catalyst and HFIP as a solvent in a metal- and additive-free process. The reaction

tolerates a broad range of 2-arylethanol and *N*-nucleophiles bearing various functional groups. In addition, this set of reaction conditions was applied to the underexplored dehydrative sulfidation of 2-arylethanol. Mechanistic experiments were performed to gain insight into the reaction pathways and, combined with computations, were used to test the intermediacy of phenonium ions.

## Results and Discussion

We began our study by investigating the reactivity of 2-phenylethanol with *p*-toluenesulfonamide (4 equiv), using TfOH as a catalyst (10 mol%) and HFIP as a solvent (0.4 M) (Table 1). In these conditions, the target product **1** was obtained in a nearly quantitative yield (96%). Several classical solvents were tested as an alternative to HFIP, but none led to the formation of **1** (Entries 2–8). The only exception was trifluoroethanol; however, the yield was significantly inferior to that in HFIP (39%, Entry 9). Several Brønsted acids were also tested but did not improve the yields (Entries 10–15). In addition, we attempted to decrease the amount excess of *p*-toluenesulfonamide, resulting in a decreased yield (47%, Entry 16). Nevertheless, we do not consider the excess of *p*-toluenesulfonamide an issue since it was easily recovered by recrystallization in dichloromethane before purification. Lastly, the reaction was readily scaled up to 5 mmol, delivering **1** in 88% (1.21 g) within 48 h.

Next, we evaluated the scope of the reaction using *p*-toluenesulfonamide as a model nucleophile (Scheme 2). We first examined the reactivity of electronically diverse

2-arylethanol. The transformation tolerates various electron-donating and moderate electron-withdrawing groups at the *ortho*-, *meta*-, and *para*-position, including alkyl, free alcohol, ether, and halide, in yields ranging from 58 to 95% (**1–21**). It is noteworthy that, in the case of electron-donating groups (EDGs), the reaction temperature could be decreased to 80°C, while, in the case of moderate electron-withdrawing groups (EWGs), a temperature of 140°C was required to keep reasonable reaction times. Those observations are consistent with the respective ability of the corresponding aryl functionalities to form phenonium ions.<sup>[8]</sup> Gratifyingly, the reaction is also compatible with sterically hindered mesityl (**22**, 78%), naphthyl (**23**, 72%) and thienyl (**24**, 40%) groups. Not surprisingly, no product was observed with 4-nitrophenethyl alcohol (**6**), which is not apt at generating a stable phenonium intermediate,<sup>[7]</sup> and by using 2-(pyridin-3-yl)ethanol (**25**), which can easily trap the catalyst.

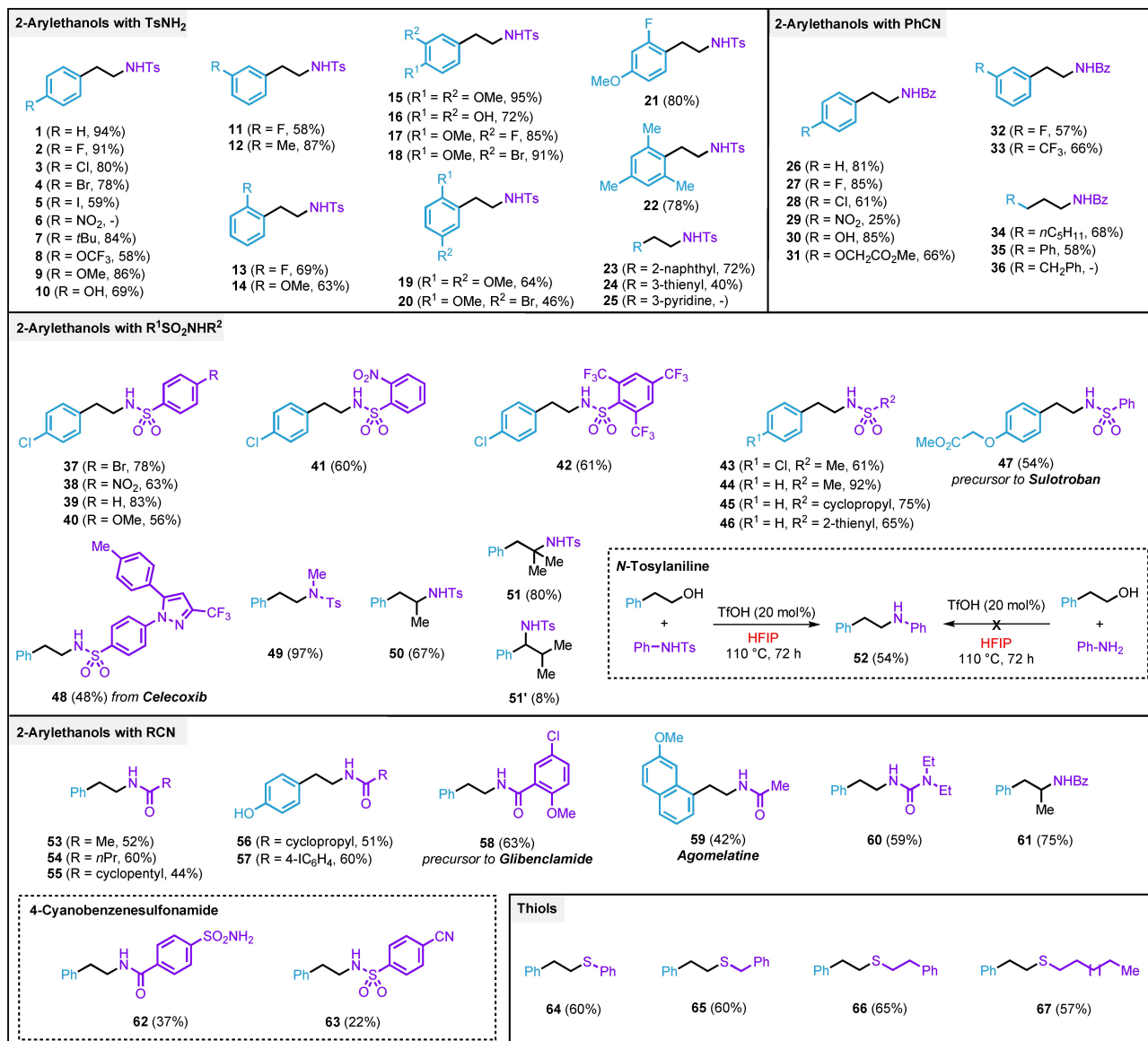
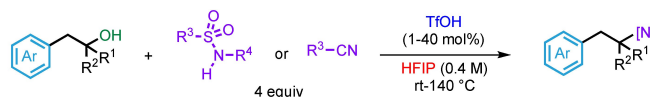
Based on these results, we questioned whether this methodology could be expanded to nitriles as nucleophiles in a Ritter reaction.<sup>[13]</sup> The reaction of 2-phenylethanol with benzonitrile afforded the corresponding amide **26** in 81% yield. However, larger amounts of TfOH (40 mol%) are required to achieve the transformation. This observation might be attributed to the higher Brønsted basicity of the amide than that of the sulfonamide, which could decrease the reaction rate because of a stronger interaction with the catalyst. In terms of reactivity of 2-arylethanol, similar results as with *p*-toluenesulfonamide were observed. A striking difference was that even highly deactivated 2-arylethanol (**29** and **33**) and linear primary aliphatic alcohols (**34** and **35**) were compatible with benzonitrile to provide the target compounds in moderate to good yields. On the other hand, 4-phenyl-1-butanol did not produce compound **36**, with the only product being 1,2,3,4-tetrahydronaphthalene (90%).

We then explored the influence of the substituent pattern on the sulfonamide. The transformation was compatible with a wide variety of sulfonamides, incorporating (hetero)aryl bearing EDGs and EWGs, alkyl, and cyclopropyl. In particular, the reaction accommodates the more synthetically flexible 2,4,6-tris(trifluoromethyl)benzenesulfonamide (**42**) than nosylamide, which was recently developed by the group of Maulide.<sup>[14]</sup> Importantly, our protocol could be applied to access the framework of bioactive molecules such as Sultroban (**47**, 54%) and to the late-stage functionalization of Celecoxib (**48**, 48%). Further, the reaction could be extended to secondary sulfonamides such as **49** (97% yield). In the same vein, the transformation was also used with secondary and tertiary alcohols to deliver products **50** and **51** in 67 and 80% yields, respectively. Of note, in the case of a tertiary alcohol, we observed the formation of the other regioisomer as a side product (**51'**, 8%). An unexpected result was obtained by using *N*-phenyl tosylamide as a nucleophile. During the monitoring of the reaction, we observed the complete cleavage of the tosyl group to afford aniline **52** in 54% yield, which was previously observed under acidic conditions.<sup>[15]</sup> On the other hand,

**Table 1:** Optimization studies.

Entry	Variation from standard conditions <sup>[a]</sup>	Yield <sup>[b]</sup> (%)
1	none	96
2	1,2-DCE instead of HFIP	NR
3	1,4-dioxane instead of HFIP	NR
4	MeCN instead of HFIP	NR
5	DMF instead of HFIP	NR
6	DMSO instead of HFIP	NR
7	<i>i</i> PrOH instead of HFIP	NR
8	MeNO <sub>2</sub> instead of HFIP	traces
9	TFE instead of HFIP	39
10	HCl (37% aq.) instead of TfOH	NR
11	HBr (48% aq.) instead of TfOH	NR
12	H <sub>2</sub> SO <sub>4</sub> instead of TfOH	55
13	TFA instead of TfOH	NR
14	<i>p</i> TsOH·H <sub>2</sub> O instead of TfOH	46
15	Tf <sub>2</sub> NH instead of TfOH	64
16	2.0 equiv. of TsNH <sub>2</sub> instead of 4.0 equiv	47

[a] Standard reaction conditions: 2-phenylethanol (0.40 mmol, 1.0 equiv) and TsNH<sub>2</sub> (1.6 mmol, 4.0 equiv) in the presence of TfOH (10 mol%) in HFIP (0.4 M) at 110°C for 24 h in a sealed pressure tube. [b] Isolated yield.



Scheme 2. Scope of the transformation.

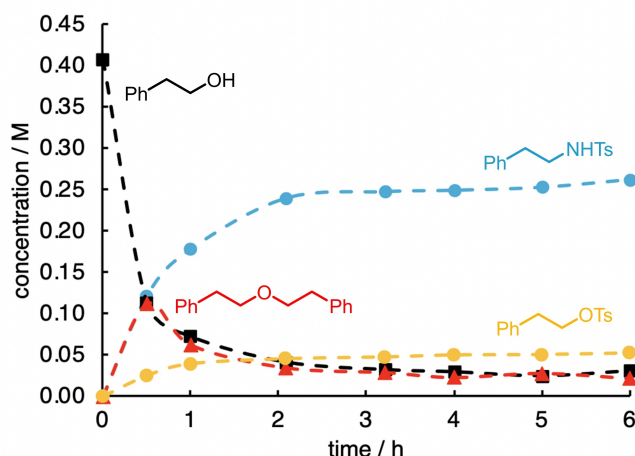
when starting from aniline, no reaction was observed, which might be explained by the fact that the corresponding anilinium formed in acidic conditions is unreactive under the reaction conditions. Consequently, another feature of our method is the possibility of employing a tosyl group as a decoy for a primary aniline. The possibility of cleaving the tosyl over a prolonged reaction time could be the reason why no product was obtained with deactivated 2-arylethanol and long-chain alcohols.

The transformation with nitriles exhibits a functional group compatibility similar to the one with sulfonamides. We were notably able to access a direct precursor for Glibenclamide (**58**, 63%) and to prepare Agomelatine

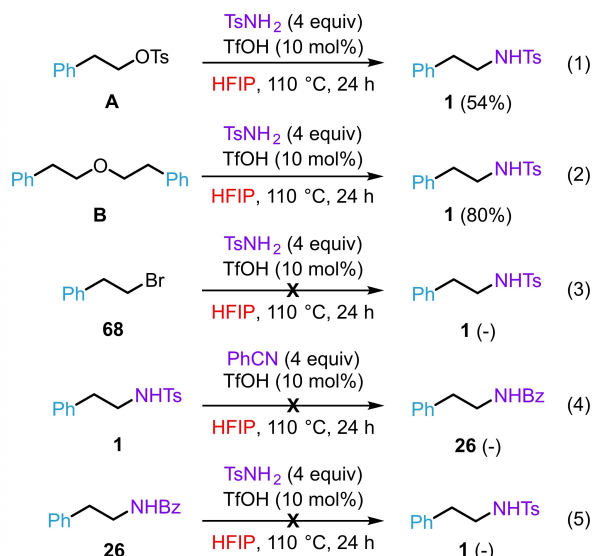
(**59**, 42%) in a single step. Importantly, cyanamides were also suitable reactants, affording urea **60** in 59% yield. Finally, we examined the competition between sulfonamide and nitriles to act as nucleophiles, which showed a moderate preference for the nitrile (**62**, 37%) over sulfonamide (**63**, 22%). We also demonstrated that our protocol was applicable to the less documented dehydrative sulfidation of 2-arylethanol (**64–67**, 57–65% yields).

Following the study of the scope of the reaction, we focused on the mechanistic understanding of the transformation, notably the putative involvement of a phenonium intermediate (Scheme 3). First, we measured the kinetic profile of the reaction of 2-phenylethanol with

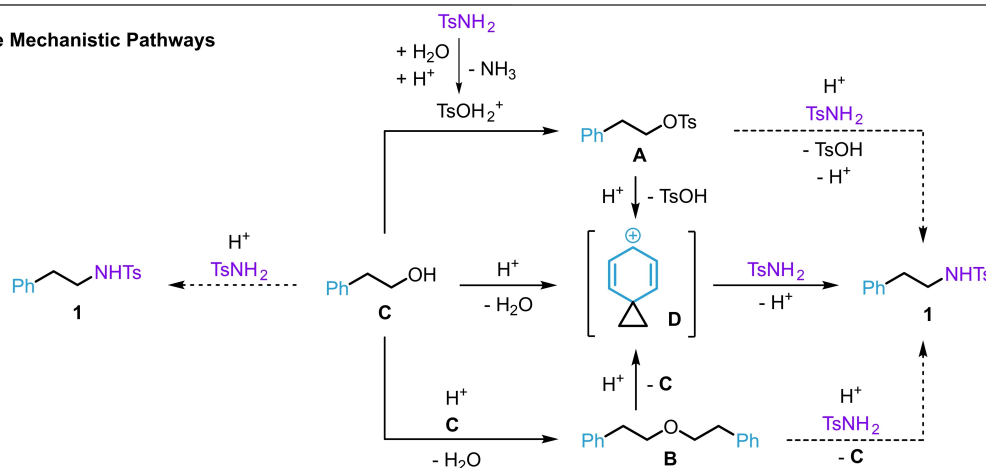
## A. Kinetic Profile



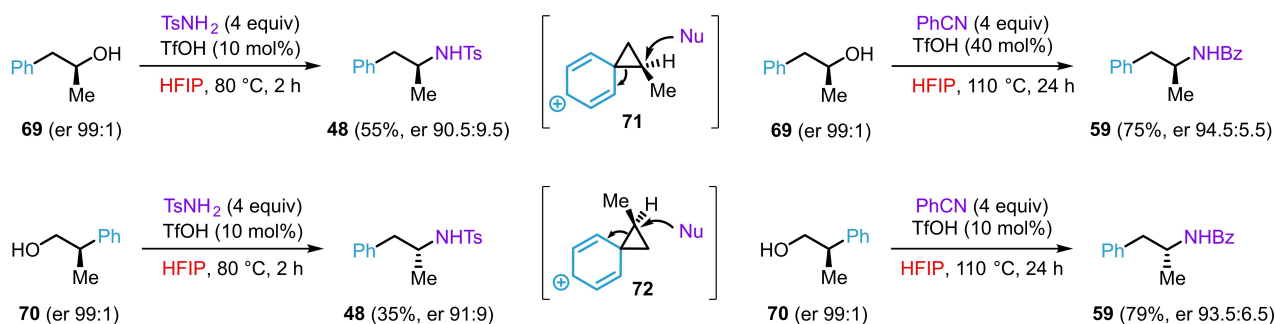
## B. Control Experiments



## C. Plausible Mechanistic Pathways



## D. Transfer of Chirality



**Scheme 3.** Control and mechanistic experiments regarding the elucidation of the mechanism. For the kinetic profile: 2-phenylethanol (0.40 mmol, 1.0 equiv) and TsNH<sub>2</sub> (1.6 mmol, 4.0 equiv) in the presence of TfOH (10 mol%) in HFIP (0.4 M) at 110 °C with aliquots taken at intervals of time.

TsNH<sub>2</sub> under our standard conditions, which allowed us to identify additional species, notably tosylate **A** and ether **B**. Those compounds were prepared independently and then subjected to the reaction conditions to deliver the target product in 54 and 80 % yields, respectively (Equations 1 and 2), suggesting that they are potentially competent reaction intermediates. Next, we studied the

importance of the oxygen functionality on the substrate, which proved critical as phenethyl bromide **68** did not provide compound **1** in our standard conditions (Equation 3). Finally, we looked at the reversibility of the transformation, which here did not take place from either sulfonamide **1** or amide **26** (Equations 4 and 5).

At this point, several mechanistic pathways were envisioned: Either a direct  $S_N2$  reaction or a nucleophilic addition to the phenonium ion, using either alcohol **C**, tosylate **A**, or ether **B** as reacting intermediates. To establish if the reaction occurs via a  $S_N2$  or phenonium intermediacy, we studied the transfer of chirality from compounds **69** and **70** in the presence of *p*-toluenesulfonamide and benzonitrile. With both **69** or **70** as the reactant, the same products (**48** or **59**) were obtained but as opposed enantiomers, which is consistent with the involvement of phenonium intermediates **71** and **72**.<sup>[16,17]</sup> The absolute configuration of the products was ascertained by comparison with literature data (see Supporting Information for details). However, we also noticed a slight erosion of the enantiomeric excess. These results show that while the nucleophilic attack at the phenonium intermediate is the preferred pathway, the involvement of a direct  $S_N2$  reaction might represent a plausible alternative pathway.

To obtain further insights into the reaction pathways, we next performed quantum-chemical calculations to compare the relative thermochemistry and key activation barriers for the different modes of attack (see the Supporting Information for details and full references). After exhaustive conformational sampling, structures were optimized at the SMD(HFIP)/B3LYP-D3BJ/def2-SVP level of theory, which were combined with further single-point calculations at the PWPB95-D4/def2-QZVP level. Starting from 2-phenylethanol, protonation and subsequent elimination of water (barrierless) leads to the corresponding phenonium ion (Scheme 4A). For this species, no open carbenium ion could be localized. The phenonium ion may react with any of the nucleophiles present in solution. Reaction with HFIP and tosylate (originating from hydrolysis of *p*-toluenesulfonamide) are kinetically least favorable and proceed via barriers of +64.6 and +64.8 kJ mol<sup>-1</sup>, respectively.<sup>[18]</sup> The protonated adducts are endergonic, but subsequent proton transfer to triflate yields species that are exergonic relative to 2-phenylethanol. Alternatively, the phenonium ion can react with 2-phenylethanol to yield the symmetric ether via a barrier of +25.4 kJ mol<sup>-1</sup> relative to the phenonium ion, affording the respective oxonium ion in a highly exergonic reaction (-64.0 kJ mol<sup>-1</sup>). The reaction with *p*-toluenesulfonamide proceeds without a distinct barrier and is significantly exergonic (-71.6 kJ mol<sup>-1</sup>) compared to the other potential nucleophiles. However, given the reaction conditions (110 °C, 24 h), kinetic barriers are unlikely to be a limiting factor in this reaction, and the product outcome can be rationalized purely based on the relative thermochemistry.

Of all potential nucleophiles, benzonitrile reacts with the phenonium ion via a distinct barrier (+58.2 kJ mol<sup>-1</sup>) to give the nitrilium ion in a highly exergonic step (-69.8 kJ mol<sup>-1</sup>). Given the high barrier for the attack of benzonitrile in comparison to, e.g., ether formation, it is thus not surprising that harsher reaction conditions (40 mol % of TfOH) are required to achieve sufficient conversion to the nitrilium ion and subsequent hydrolysis

(Curtin–Hammett scenario). Further hydrolysis, e.g., with the water that is liberated in the course of the reaction, yields the amide as end product (-116.2 kJ mol<sup>-1</sup>), rendering this pathway irreversible.<sup>[19]</sup>

Starting from protonated 2-phenylethanol, we additionally probed other mechanisms for the reaction with *p*-toluenesulfonamide (Scheme 4B) relative to the phenonium pathway. Direct substitution with TsNH<sub>2</sub> as a nucleophile via an  $S_N2$  pathway is energetically unfavorable ( $\Delta G^\ddagger = +97.7$  kJ mol<sup>-1</sup>; +119.9 kJ mol<sup>-1</sup> with explicit HFIP solvation). Similarly, the formation of the symmetric ether through an  $S_N2$  reaction followed by the elimination of phenyl alcohol to yield the phenonium ion seems unfeasible based on the activation barriers.

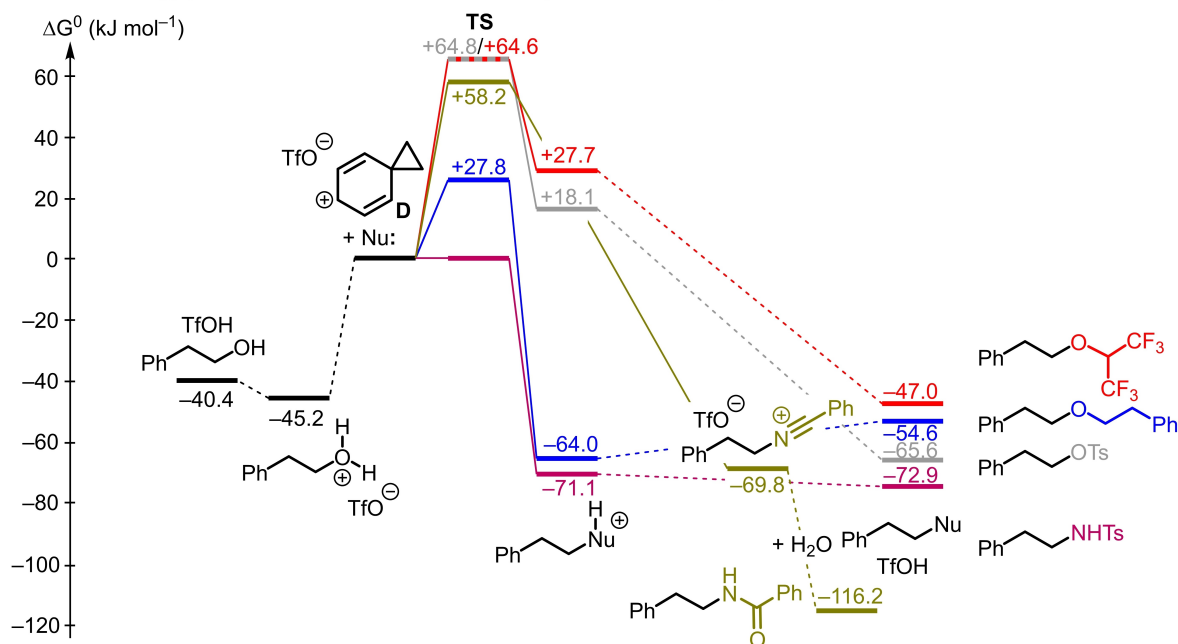
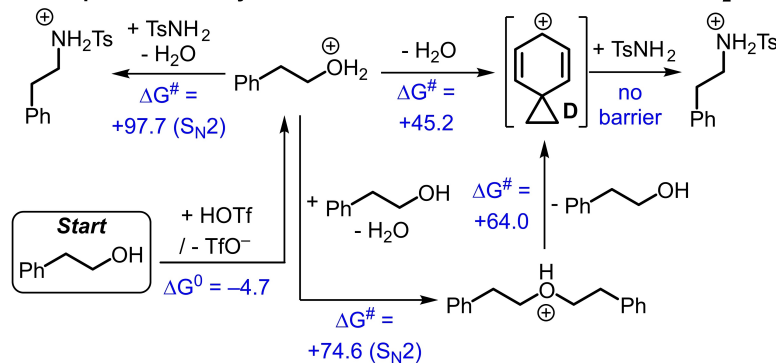
Lastly, we compared the thermochemistry for opening differently substituted phenonium ions at the two possible sites with water as a nucleophile (Scheme 4C).<sup>[8i]</sup> Without a substituent at the aryl ring, the phenonium ion form was computed to be more stable than the open carbenium ion in all cases (see the Supporting Information for details). Thermochemically, nucleophilic addition to the more substituted site of the phenonium ion is generally preferred, in line with the experimentally observed regioselectivities. With our computational method, nucleophilic attack at the higher substituted site further proceeds without a barrier, whereas the thermochemically less favorable attack at the unsubstituted site is also kinetically disfavored.

Analogously to the reaction of 2-phenylethanol, we tested the possibility of competing  $S_N1/S_N2$  reactions with substrates **69/70** (Scheme 4D). Whereas the formation of the phenonium ion from the oxonium ion is energetically slightly less favorable compared to the unsubstituted system (50.5 vs. 45.2 kJ mol<sup>-1</sup>), the addition of *p*-toluenesulfonamide is comparably exergonic (-75.5 vs. -71.1 kJ mol<sup>-1</sup>). Again, direct  $S_N2$  reaction with water acting as the leaving group is computed to be significantly less favorable (+96.0 kJ mol<sup>-1</sup>). Accordingly, the slight erosion of enantiomeric excess observed experimentally is unlikely to be the result of a direct  $S_N2$  attack of *p*-toluenesulfonamide, indicating that another mechanism is likely at play to account for the slight decrease of the enantiomeric excess. While not mentioned in the literature with respect to phenonium ions, we cannot rule out a mechanism involving a less common frontside  $S_N2$ , which would lead to an inversion of configuration at the alcohol.

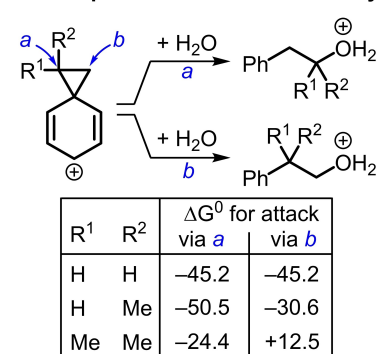
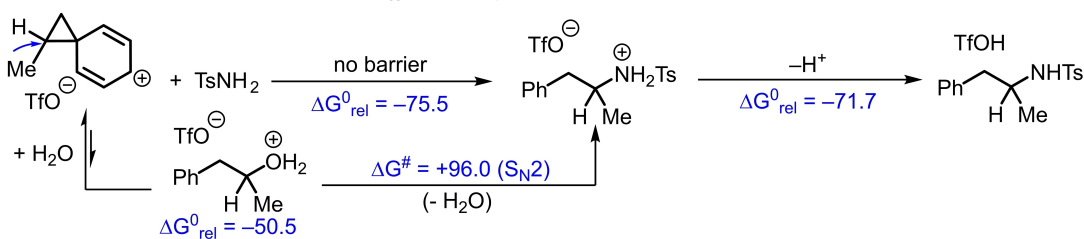
## Conclusions

In conclusion, we have developed a general method for the direct catalytic deoxygenation of 2-arylethanol relying on the combination of TfOH and HFIP. The scope and limitations of the reaction have been extensively studied (>60 examples), illustrating the tolerance of primary, secondary, and tertiary 2-arylethanol (as well as linear primary aliphatic alcohols), to enable the introduction of various weak *N*-nucleophiles such as sulfonamides, amides, ureas, and anilines. The reaction is operationally

## A. Gibbs energy profile for the substitution of OH by various nucleophiles

B. Computational analysis of mechanisms for the reaction with TsNH<sub>2</sub>

## C. Comparison of thermochemistry

D. Comparison of the phenonium vs. S<sub>N</sub>2 pathway with a substituted phenonium ion

**Scheme 4.** Results of the computational analysis at the SMD(HFIP)/PWPB95-D4/def2-QZVP//SMD(HFIP)/B3LYP-D3BJ/def2-SVP level of theory. (A) Gibbs energy profile for the reaction of the phenonium ion with different nucleophiles. (B) Computational analysis of different possible mechanisms for the reaction of 2-phenylethanol with *p*-toluenesulfonamide. (C) Computation analysis of the thermochemistry for opening of the phenonium ion with water. (D) Analysis of the opening of the methyl-substituted phenonium ion.

simple, does not necessitate a pre-activation of the alcohol, only produces water as a stoichiometric by-product, and is stereospecific. The utility of the transformation was also demonstrated by the preparation of bioactive molecules, advanced intermediates, as well as the late-stage functionalization of bioactive compounds. Lastly, our results have been rationalized through mecha-

nistic experiments and DFT computations, notably regarding the formation and ring-opening of phenonium ions. We anticipate that the advances made regarding the deoxygenation of primary aliphatic alcohols will reinvigorate the design of new transformations from these common and readily available precursors that will go beyond amination.



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## Conflict of Interest

The authors declare no conflict of interest.

## Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

**Keywords:** aliphatic alcohol · deoxyamination · hexafluoroisopropanol · Brønsted acid catalysis · phenonium ion

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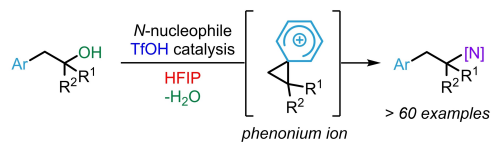
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## Research Article

## Acid Catalysis

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Triflic Acid-Catalyzed Dehydrative Amination of 2-Arylethanol with Weak *N*-Nucleophiles in Hexafluoroisopropanol



- [N] = sulfonamide, amide, urea and aniline
- Good functional group tolerance
- Phenonium intermediacy rationalized by mechanistic experiments and DFT computations
- Applicable to 1°, 2° and 3° alcohols
- Stereospecific

We report a catalytic deoxygenation of 2-arylethanol in hexafluoroisopropanol, which directly installs various amino groups, including sulfonamides, amides, ureas and anilines. The transformation

relies on the intermediacy of a phenonium ion, whose formation was rationalized by mechanistic experiments and DFT calculations.