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Rapid and Mild Metal-Free Reduction of Epoxides to Primary Alcohols Mediated by HFIP.

Marie Vayer, Shaofei Zhang, Joseph Moran* and David Lebeuf*

KEYWORDS epoxides, hydrogenolysis, hexafluoroisopropanol, Brønsted acid, (hetero)cycles.

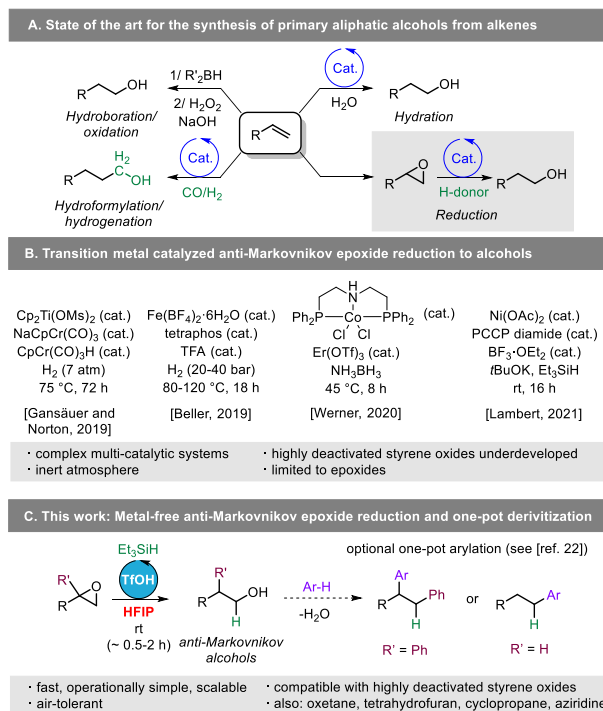
ABSTRACT: The reduction of epoxides is a powerful tool to access anti-Markovnikov alcohols, but reported methods are poorly compatible with strongly electronically deactivated substrates. Here, we describe a general method for the linear-selective reduction of styryl oxides incorporating strong electron-withdrawing groups. The method remains compatible with more traditional epoxide motifs, such as aliphatic and electron-rich styrene oxides. Other (hetero)cycles such as oxetanes, tetrahydrofurans, aziridines and cyclopropanes can also be reductively opened. This user-friendly reaction relies on the combination of a Brønsted acid catalyst and hexafluoroisopropanol as a solvent and thus, in contrast to existing epoxide reduction methods, does not require anhydrous reagents or an inert atmosphere. The generated primary alcohols can be conveniently functionalized in situ by a dehydrative Friedel-Crafts arylation without pre-activation.

Primary aliphatic alcohols are ubiquitous functional groups in natural products, pharmaceuticals, agrochemicals, fragrances, and materials.¹ As synthetic building blocks that can be rapidly functionalized, their efficient, practical and regioselective preparation is highly coveted. Strategies for their synthesis from readily available olefins is summarized in Scheme 1A. Industrially, primary aliphatic alcohols are mainly synthesized in two steps by a hydroformylation/hydrogenation sequence.^{2,3} In the laboratory, two-step hydroboration/oxidation sequences prevail.⁴ Notwithstanding their undeniable utility and wide scope, these methods suffer either from regioselectivity issues or from functional group tolerance. To circumvent those issues, the direct hydration of alkenes has been described,⁵ featuring, for instance, triple relay catalysis,⁶ visible-light-mediated protocols,⁷ and metal-oxo enzymes.⁸ However, these methods are mostly limited to terminal styrene oxides.

The catalytic reduction of epoxides has recently emerged as a complementary alternative to access primary aliphatic alcohols (Scheme 1B).⁹ The preparation of epoxides from olefins or carbonyl derivatives is straightforward and allows the pre-installation of the key oxygen functionality.¹⁰ Until recently, this strategy was held back by difficult regiocontrol between linear and branched alcohols, except for carefully designed substrates.⁹ In 2019, a significant advance was made by Gansäuer and Norton who reported a strategy based on the radical reduction of epoxides using a Ti/Cr cooperative catalytic system.^{11,12} Although this approach was atom-economical, the reaction led to the formation of by-products (e.g. allylic alcohols) and a single example of a monosubstituted epoxide was described in moderate yield. Nearly simultaneously, Beller disclosed an iron-catalyzed regioselective hydrogenation of terminal epoxides in the presence of a Brønsted acid,¹³ which was later extended to internal epoxides.¹⁴ However, the reaction occurs under harsh conditions (80-120 °C, 20-40 bar H₂) and was not compatible with substrates incorporating key functional groups (nitro-, cyano- and aziridines). Approaches relying on multiple catalysts to produce anti-Markovnikov alcohols were also described by Werner (pincer-ligated cobalt complex/Er)¹⁵ and by Lambert (Ni/B).^{16,17} Although the overall reaction scope

of these methods was broad, neither were reported to be compatible with highly deactivated styrene oxides bearing an electron-withdrawing group stronger than a trifluoromethyl¹⁸ nor to reduce (hetero)cycles beyond epoxides. Lambert's method operates under mild conditions (ambient temperature and pressure), but regiocontrol is incomplete in the case of aliphatic epoxides. Recently, an elegant and mild

Scheme 1. Approaches toward the synthesis of primary aliphatic alcohols.



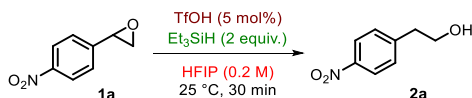
electroreduction of epoxides was reported by Qi and Lu.¹⁹ However, this method only provided moderate yields (41-51%) for deactivated styrene oxides, while aliphatic epoxides exclusively led to Markovnikov alcohols. In summary, while several protocols have been developed, each with their own

advantages and limitations, a general and user-friendly method for epoxide reduction is still missing.

In hexafluoroisopropanol (HFIP), a solvent known for its H-bond donating ability,²⁰ the strength of catalytic Brønsted acids is drastically increased, rendering electronically deactivated substrates more reactive.²¹ We recently reported an efficient, practical, and broadly applicable Friedel-Crafts arylation of epoxides, including highly deactivated styrene oxides, using catalytic triflic acid (TfOH) in HFIP.^{22,23} The formed alcohols could undergo a second arylation to access diaryl- and triarylalkanes without pre-activation,²⁴ although this is less efficient when two different nucleophiles were employed. Herein, we demonstrate that this simple catalytic system can be applied to the reduction of epoxides, including electronically deactivated substrates, to rapidly afford the corresponding anti-Markovnikov alcohols at room temperature (Scheme 1C). This practical transformation exhibits broad functional group tolerance, notably towards strong electron-withdrawing groups, and can also be applied to the reductive ring-opening of other (hetero)cycles, such as oxetanes, cyclopropanes and aziridines. Moreover, by coupling epoxide reduction to Friedel-Crafts reactions in the same pot, this work overcomes existing limitations in the dehydrodiarylation of epoxides.

Our optimization studies started with *para*-nitrostyrene oxide **1a** as a model substrate using TfOH as a catalyst (5 mol%) in HFIP (0.2 M) as a solvent (Table 1, see also the Supporting Information for full details). Triethylsilane (Et₃SiH) was initially chosen as a hydrogen donor due to its compatibility with HFIP in hydrosilylation reactions²⁵ and, more generally, in acidic media.²⁶ Using an excess of Et₃SiH (2 equiv), the target product **2a** was obtained in 86% yield within 30 minutes at ambient temperature (entry 1). Other hydrogen donors such as H₂ and pinacol borane (HBPin) were tested but did not generate **2a** (entries 2 and 3). The catalyst loading could be reduced to 1 mol% or even 0.1 mol% without any drop in yields (entries 4 and 5). However, at 0.1 mol% loading, a prolonged reaction time (2 h) was required to fully convert the silyl-protected intermediate into **2a**. Increasing the concentration proved to be detrimental to the yields (entries 6 and 7). The combination of 1 mol% TfOH and 1.5 equiv. of Et₃SiH was optimal in terms of efficacy (91%) and reaction time (30 min) (entry 8). Of note, the reaction was accomplished on a larger scale (7.5 mmol) to deliver **2a** in 88% yield (1.1 g).²⁷ Common solvents (CH₂Cl₂, MeNO₂ and toluene) and *O*-methyl hexafluoroisopropanol (HFIPMe) were also examined but did not provide **2a** in synthetically useful yields (entries 9-12), highlighting the critical role of HFIP in this reaction. Lastly, a control experiment was performed in the absence of TfOH and no product was observed (entry 13).

Table 1. Optimization of reaction conditions for the formation of phenylethanol **2a**.



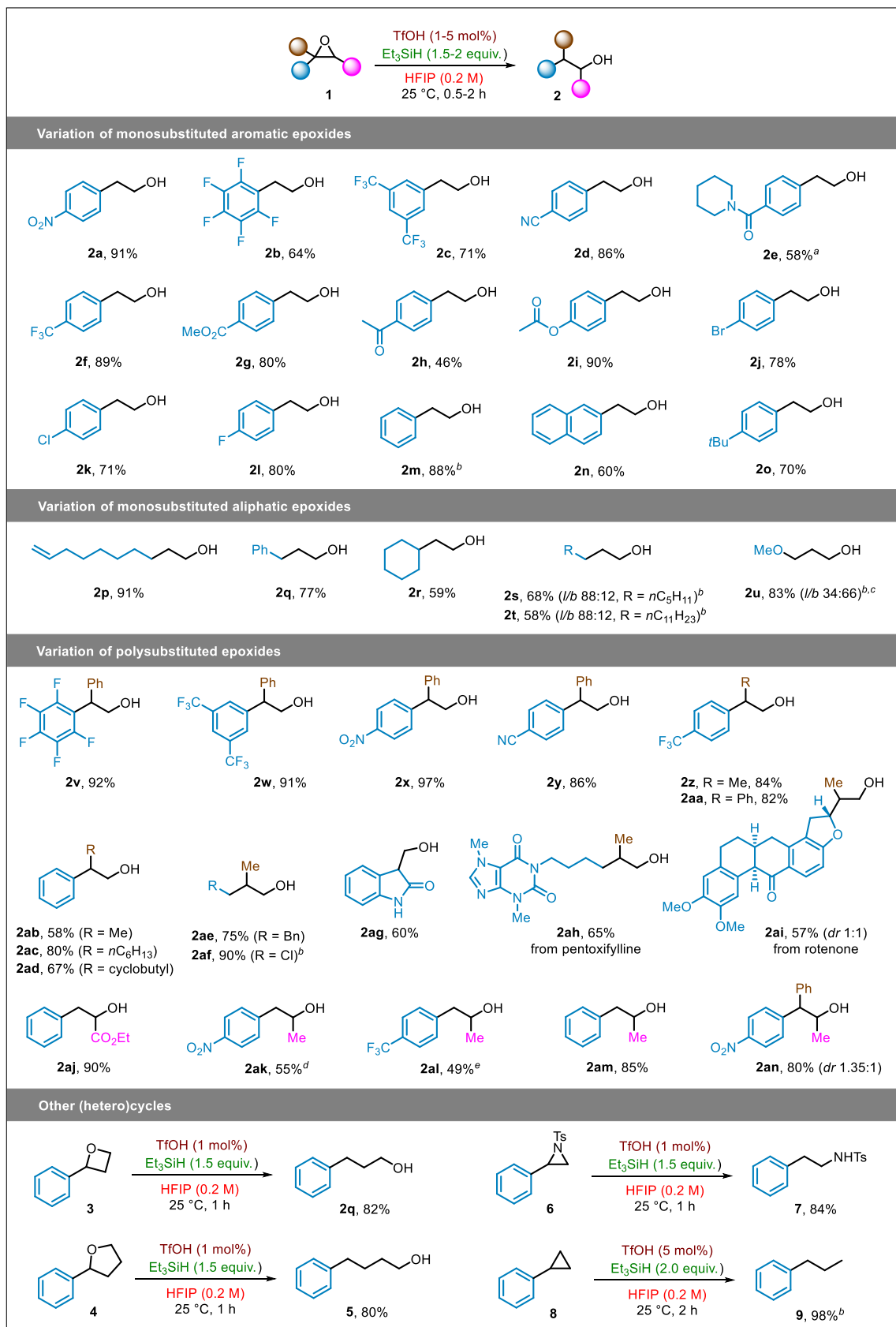
Entry	Variation from standard conditions ^a	Yield (%)
1	none	86
2	H ₂ (20 bar) instead of Et ₃ SiH	-
3	HBPin instead of Et ₃ SiH	-
4	1 mol% of TfOH instead of 5 mol%	83

5	0.1 mol% of TfOH instead of 5 mol%	92b
6	0.4 M instead of 0.2 M	79
7	1.0 M instead of 0.2 M	54
8	1 mol% TfOH and 1.5 eq of Et₃SiH	91 (88)^c
9	CH ₂ Cl ₂ instead of HFIP	n.r.
10	MeNO ₂ instead of HFIP	17
11	toluene instead of HFIP	traces
12	HFIPMe instead of HFIP	traces
13	without TfOH	n.r.

^a Reactions performed in a sealed tube. ^b 2 h reaction time. ^c 7.5 mmol scale.

With optimized conditions in hand, we explored the scope of the reaction using a large variety of epoxides (Scheme 2). Monosubstituted styrene oxides were smoothly converted into the target primary aliphatic alcohols in high yields (up to 91%). In particular, the reaction was compatible with highly electronically deactivated styrene oxides containing perfluoro, trifluoromethyl, cyano, amide, ester, and ketone groups. In the latter case, a product resulting from the reduction of the ketone in the alkane was nonetheless observed in 20% yield. The transformation was also extended to aliphatic epoxides to provide the anti-Markovnikov alcohols in good yields (51-91%). In a limited number of cases (**2s** and **2t**), some amounts of Markovnikov alcohols were detected. On the other hand, one limitation of our method concerns the reactivity of glycidyl ether derivatives, whose reduction led mainly to the branched alcohol (**2u**). This might be explained by the coordination of the promoter system to both oxygen functionalities, favoring the direct addition of the silane to the epoxide at the less sterically hindered position. The reaction was also compatible with 1,1-disubstituted epoxides (aryl-alkyl and alkyl-alkyl substituents) to exclusively afford primary alcohols in yields up to 92% (**2v-2ai**). The methodology was successfully applied to derivatives of bioactive molecules such as pentoxifylline (**2ah**, 65%) and rotenone (**2ai**, 57%). 1,2-Disubstituted and 1,1,2-trisubstituted epoxides were amenable to this process to provide the corresponding secondary alcohols in 55-85% yields (**2aj-2an**). During those investigations, we noticed, the formation of a side product resulting from a 1,2-Me shift, which was directly correlated to the substitution pattern of the styrene oxide. This type of rearrangement could be suppressed with less electron-deficient 1-phenylpropylene oxide (**2am**) as well

Scheme 2. Scope of the reaction.

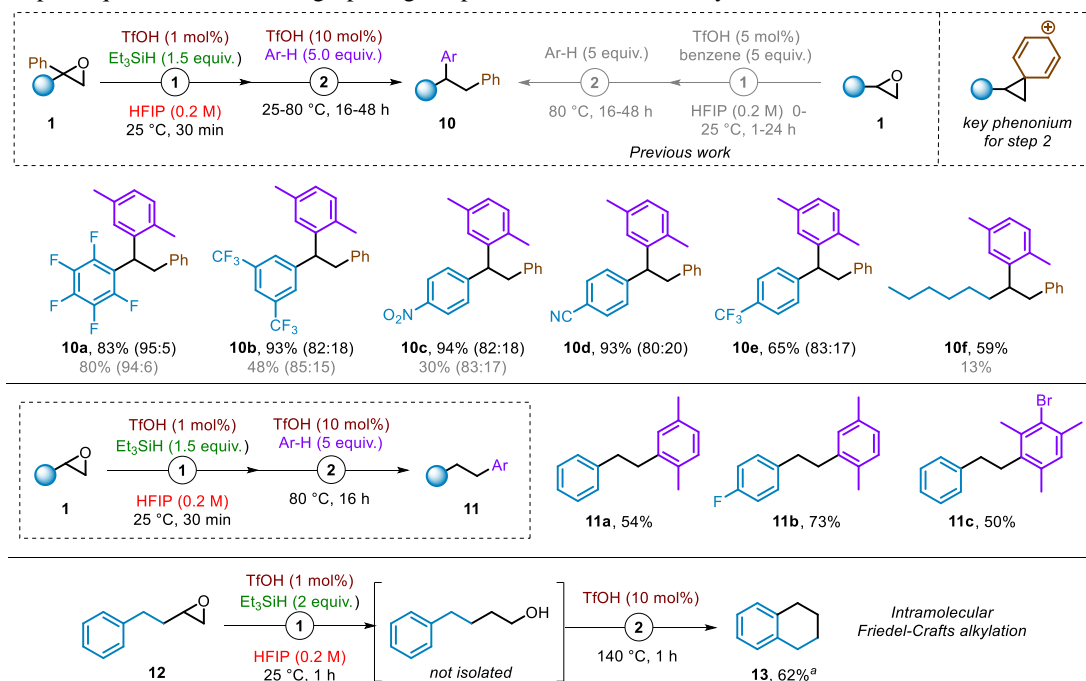


^a TfOH (20 mol%) and Et₃SiH (3 equiv). ^b Yield determined by ¹H NMR using mesitylene as an external standard. ^c 16 h. ^d Side product arising from a 1,2-Me shift obtained in 20% yield. ^e Side product arising from a 1,2-Me shift obtained in 7% yield.

as with trisubstituted epoxides (**2an**). Moving beyond epoxides, the method served as a rare metal-free protocol for the reduction of related but underdeveloped aryl-substituted (hetero)cycles such as oxetanes (**2q**),^{19,28} tetrahydrofurans (**5**),^{19,29} aziridines (**7**),³⁰ and cyclopropanes (**9**),³¹ generating the corresponding ring-opening products in high yields (80-98%).

Since primary alcohols were successfully produced with our strategy and based on our previous work on the Friedel-Crafts arylation of primary aliphatic alcohols,²² we next examined a one pot method for the reductive ring-opening arylation of epoxides (Scheme 3). Due to the importance of the 1,1,2-triarylethane and 1,2-diarylethane motifs in life sciences,³² the reactivity of 1,1-disubstituted epoxides was initially studied using *p*-xylene as an arene nucleophile for the second step. First, the reaction was conducted under the conditions designed for the reductive ring-opening. After the reaction was completed, 10 mol% TfOH and 5 equivalents of *p*-xylene were added to the reaction mixture, which was typically heated to 80 °C for 48 h. The target products were thus obtained in 59 to 94% yields (**10a-10f**) via a phenonium ion intermediate. The formation of regioisomers was observed as the nucleophile can attack at either the internal (major product) or the terminal position (minor product) of the phenonium ion intermediate. The major advantage of this reaction sequence is that it overcomes the limitations encountered with our previous work on the dehydrodiarylation of epoxides, where yields were modest, or even low in the case of aliphatic epoxides, when two different nucleophiles were used. The reaction was also found to be compatible with mono-substituted styryl oxides, giving access to the corresponding products **11a-11c** in good yields (50-73%). Lastly, we demonstrated that an intramolecular Friedel-Crafts alkylation could be accomplished following the reduction of epoxide **12**, affording tetrahydronaphthalene **13** in 62% yield.

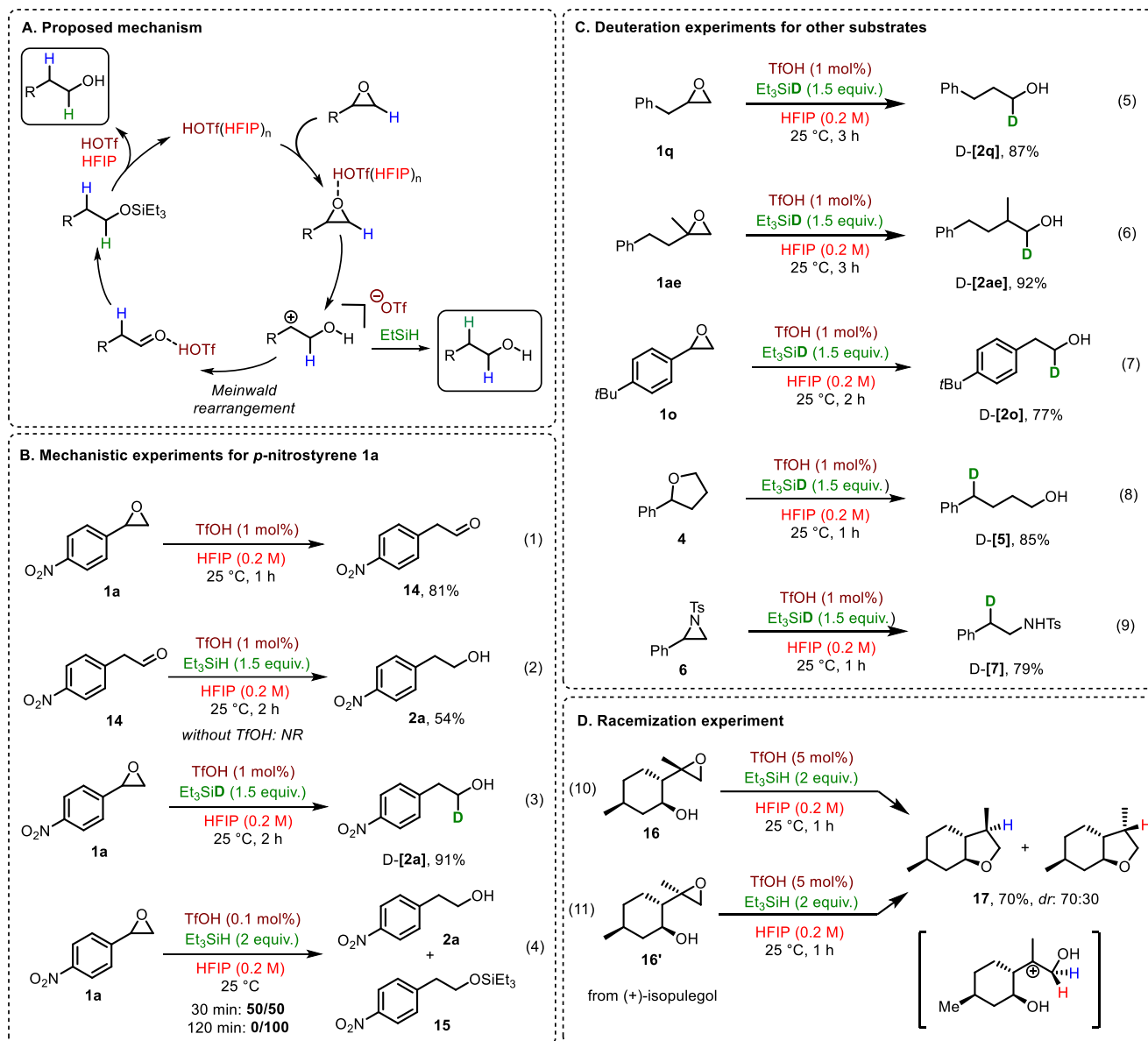
Scheme 3. One pot sequential reductive ring-opening of epoxides/Friedel-Crafts arylation reaction



^a Yield determined by ¹H NMR using mesitylene as an external standard.

Scheme 4. Mechanistic investigations

We then investigated the mechanism of this transformation (Scheme 4). Based on the reactivity of epoxides with Brønsted acids,³³ we hypothesized that deactivated styrene oxide **1a** is first protonated by TfOH, whose acidity is augmented through its coordination to HFIP. This increase in acidity promotes the Meinwald rearrangement of the epoxide to the corresponding aldehyde **14**. This aldehyde would be further reduced by the silane to access silyl ether **15**, which would be deprotected *in situ* to deliver phenylethanol **2a** under our acidic reaction conditions. A series of experiments was carried out to evaluate this proposal (Scheme 5B). In the absence of triethylsilane, aldehyde **14** was obtained as sole product in 81% yield (Eq. 1). When subjected to our standard conditions, **14** yielded the target alcohol **2a** (Eq. 2). Of note, the reduction step did not work without TfOH, showing its importance for each step. The reaction in the presence of deuterated triethylsilane (Et₃SiD) furnished the corresponding product [D]-**2a**, which is consistent with aldehyde **14** being a crucial intermediate (Eq. 3). Lowering the loading of TfOH to 0.1 mol% allowed us to observe the formation of silyl ether **15** in a 1:1 mixture with **2a** after 30 min before it fully converted into **2a** after 2 h (Eq. 4). The reaction was also performed with other representative epoxides (electron-rich styrene oxide, 1,1-disubstituted epoxide and mono-substituted alkyl epoxide) in the presence of Et₃SiD to evaluate whether the substitution pattern has an influence on the reaction pathway (Scheme 5.C). In the case of **1q** and **1ae**, the reaction led to similar results as **1a** (Eq. 5 and Eq.6), which is consistent with a Meinwald rearrangement. On the other hand, in the case of electron-rich styrene oxide (**1o**), deuteration was observed at the benzylic position ([D]-**2o**), suggesting that the stabilized carbocation intermediate underwent a direct reduction. In parallel, we conducted a similar experiment with oxetane **3**, tetrahydrofuran **4** and



aziridine **6**. In the case of **4** and **6**, we observed deuteration exclusively at the benzylic position, in the same vein as with **1o**. In turn, a mixture of several products was obtained with **3**, making it difficult to identify a clear mechanism. Lastly, to determine whether the Meinwald rearrangement occurred through a concerted mechanism or a carbocation, we compared the reactivity of diastereomeric derivatives of (+)-isopulegol (Eq. 10 and Eq. 11). In both cases, 3,6-dimethyloctahydrobenzofuran **17**, resulting from the cyclization of the reaction intermediate, was obtained with a similar *dr*, consistent with the formation of a carbocation during the first step of the Meinwald rearrangement.

In conclusion, we have developed a practical strategy to selectively access anti-Markovnikov alcohols *via* a reductive ring-opening of epoxides. The mechanistic studies suggest an isomerization/hydrosilylation process promoted by the association of TfOH/HFIP in the presence of triethylsilane. This transformation occurs under mild conditions and exhibits a broad substrate scope, including aryl epoxides containing strong electron-withdrawing groups and derivatives of bioactive molecules. In addition, the reaction was extended to oxetane, tetrahydrofuran, aziridine and cyclopropane as

electrophiles. Finally, a one-pot epoxide reduction/dehydroarylation sequence was disclosed, leading to the rapid preparation of complex arylated products.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge via the Internet at <http://pubs.acs.org>.

Experimental procedures, optimizations studies, mechanistic studies, characterization data; copies of NMR spectra (PDF)

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Author Contributions

The manuscript was written through contributions of all authors.

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Notes

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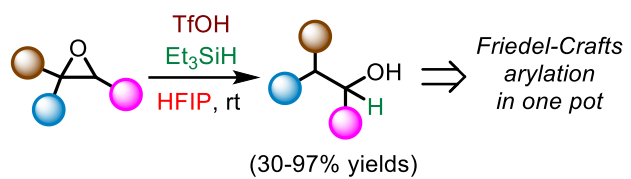
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