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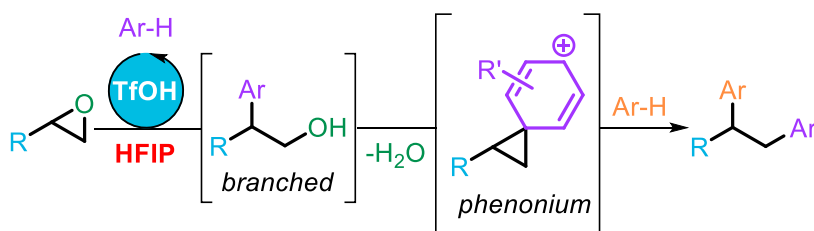


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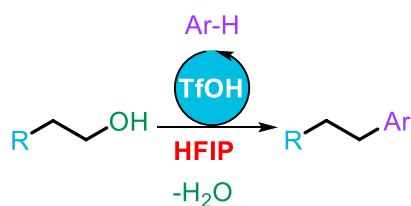
Article

Unlocking the Friedel-Crafts arylation of primary aliphatic alcohols and epoxides driven by hexafluoroisopropanol

A Brønsted acid-assisted Brønsted acid catalysis strategy for the arylation of epoxides and primary aliphatic alcohols



- Regioselective ring-opening arylation of epoxides
- Phenonium ions from alcohols without pre-activation



- Direct S_N2 Friedel-Crafts of primary aliphatic alcohols

> 150 examples of complex arylated compounds prepared under transition metal-free conditions

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Highlights

Access to a wide range of linear alcohols and arylated alkanes

Compatible with aliphatic and electronically deactivated epoxides

No pre-activation required for primary aliphatic alcohols

Hexafluoroisopropanol is key to the reactivity

We report catalytic conditions for the direct substitution of arenes with numerous classes of alcohols and epoxides that were not previously accessible—all without pre-activation of either reaction partner. Furthermore, since the products of epoxide substitution are alcohols, this discovery enables the direct substitution of epoxides with two different arenes in one pot. The key to the reactivity relies on the fluorinated solvent hexafluoroisopropanol, which dramatically lowers kinetic barriers.



Article

Unlocking the Friedel-Crafts arylation of primary aliphatic alcohols and epoxides driven by hexafluoroisopropanol

Shaofei Zhang,¹ Marie Vayer,¹ Florent Noël,¹ Vuk D. Vuković,¹ Andrei Golushko,¹ Nazanin Rezajooei,² Christopher N. Rowley,³ David Lebaeuf,^{1,*} and Joseph Moran^{1,4,*}

SUMMARY

Alcohols and epoxides are arguably ideal electrophiles for the Friedel-Crafts alkylation, since they are widely available, require no pre-activation, and produce no stoichiometric waste beyond water. However, neither primary aliphatic alcohols nor most classes of terminal epoxides are compatible with existing intermolecular Friedel-Crafts methodologies, and sequential Friedel-Crafts reactions starting from epoxides consequently remain underexplored. Here, we report that these limitations are easily overcome using Brønsted acid catalysis in hexafluoroisopropanol (HFIP) as a solvent. Electron-poor aromatic epoxides and aliphatic epoxides undergo stereospecific arylation to give an alcohol which, depending on the reaction conditions, can partake in a second nucleophilic substitution with a different arene in one pot. Phenyl ethanols react through a phenonium intermediate, whereas simple aliphatic alcohols participate in a rare intermolecular S_N2 Friedel-Crafts process, delivering linear products exclusively. This work provides an alternative to metal-catalyzed cross-couplings for accessing important scaffolds, widening the range of applications of the Friedel-Crafts reaction.

INTRODUCTION

Epoxides and primary aliphatic alcohols both represent important building blocks in synthetic chemistry,¹ the former especially serving as a gateway to densely functionalized molecules in medicinal chemistry, crop science, and material science.² In principle, the intermolecular Friedel-Crafts reaction would represent an ideal way to form C–C bonds between arenes and epoxides or primary aliphatic alcohols,^{3–6} since it would prevent pre-activation steps of the substrates and produce no stoichiometric waste beyond water, but this type of reactivity remains challenging in both cases:

- (1) Ring-opening Friedel-Crafts reactions of terminal epoxides, which give branched products, are mainly limited to electron-rich styrene oxides and arenes when Lewis or Brønsted acid promoters are employed (Scheme 1).^{7–9} Consequently, epoxide arylation strategies based on transition metal catalysis or photocatalysis have been developed but suffer from poor access to branched products,^{10–16} notably for alkyl epoxides.¹¹ For styrene oxides, more branch-selective arylation examples are known,^{14,15} but those bearing strong electron-withdrawing groups remain inaccessible.
- (2) Dehydrative Friedel-Crafts reactions of primary aliphatic alcohols are also undeveloped. Owing to their stability, only two low-yielding (<10%) examples of

The bigger picture

Substitution reactions are a common way to couple two molecular fragments at a sp^3 -hybridized carbon atom. The pre-activation of one or both coupling partners is typically required, which adds additional chemical steps and generates waste at each stage. Efforts to develop catalytic substitution reactions of arenes that bypass pre-activation, starting from common feedstocks, such as alcohols or epoxides, have been limited to specific structural subclasses.

We report the discovery of catalytic conditions for the direct substitution of arenes with numerous classes of alcohols and epoxides that were not previously accessible, allowing for one-step access to branched alcohols and complex arylated products. Furthermore, since the products of epoxide substitution are alcohols, this discovery enables the direct bis-substitution of epoxides with two different arenes in one pot.

Friedel-Crafts reactions of primary aliphatic alcohols longer than two carbons are known, both of which give complex mixtures of linear and branched products due to rearrangements.^{17,18} A few transition-metal-catalyzed methods have also been described, but they require the specific use of phenol derivatives as reaction partners.^{19–21} In general, to assemble such products, several strategies based on cross-coupling,^{22–31} hydrodefluorination³² or C–H functionalization^{33,34} have been devised, but they all require additional synthetic steps to pre-activate the alcohol and, in most cases, the arene coupling partner as well.

The development of a Friedel-Crafts reaction broadly applicable to both terminal epoxides and primary aliphatic alcohols would have an additional benefit: since the products of Friedel-Crafts ring-opening of epoxides are themselves primary aliphatic alcohols, sequential Friedel-Crafts reactions could then be envisaged where two distinct arenes can be installed in one pot to provide a straightforward access to 1,1,2-triarylethane frameworks, which have applications ranging from the life sciences to feedstock precursors. Existing strategies to access these compounds largely start from alkenes as precursors and ensure positional control of the C–C bond forming reaction. However, they require either multi-step preparation of different cross-coupling partners or substrates, the use of directing groups, or complex reaction conditions under inert atmosphere.^{35–49} Therefore, the direct and straightforward Friedel-Crafts strategy presented here offers a complementary alternative to current methods.

Herein, we describe the expansion of the Friedel-Crafts reaction to include most classes of terminal epoxides (ring-opening arylation), primary aliphatic alcohols (dehydroarylation), and a sequential dehydrodiarylation process stemming from their combination. The key to the reactivity is the use of the solvent hexafluoroisopropanol (HFIP)^{50–54} with triflic acid (TfOH) as a catalyst. Indeed, the association of Lewis or Brønsted acid catalysts with HFIP is known to trigger transformations with rather unreactive alcohols, alkenes, and cyclopropanes through the formation of highly reactive hydrogen-bond networks.^{55–60} Under these reaction conditions, the ring-opening Friedel-Crafts reaction of most epoxides is found to be stereospecific, and the resulting alcohols can react in a second Friedel-Crafts reaction through the intermediacy of a well-established^{61–69} but underexploited^{70–78} phenonium ion without pre-activation of the alcohol. Simple aliphatic alcohols can also undergo a Friedel-Crafts reaction through a rare intermolecular S_N2-type mechanism, as supported by density functional theory (DFT) calculations. This broad-reaching (>160 examples) expansion of the Friedel-Crafts reaction, thus, allows the user to re-evaluate the reactivity of primary aliphatic alcohols, epoxides, and related compounds toward new synthetic applications.

RESULTS AND DISCUSSION

Arylation of epoxides

Optimization studies for the ring-opening arylation of epoxides

We commenced our investigations by studying the monoarylation of highly electron-deficient styrene oxides, which are notoriously challenging to functionalize. Following a large survey of reaction conditions, notably Lewis and Brønsted acid catalysts (see Table S1), we observed that the reaction between (pentafluorophenyl) ethylene oxide and *m*-xylene (5 equiv) provided the target product **3** in 97% yield at room temperature in 6 h by conducting the reaction in HFIP (0.4 M) in the presence of TfOH (5 mol %) as a catalyst (Scheme 2). A similar reactivity was obtained by using the promoter system Bi(OTf)₃/*n*Bu₄NPF₆⁷⁹ instead of TfOH under otherwise

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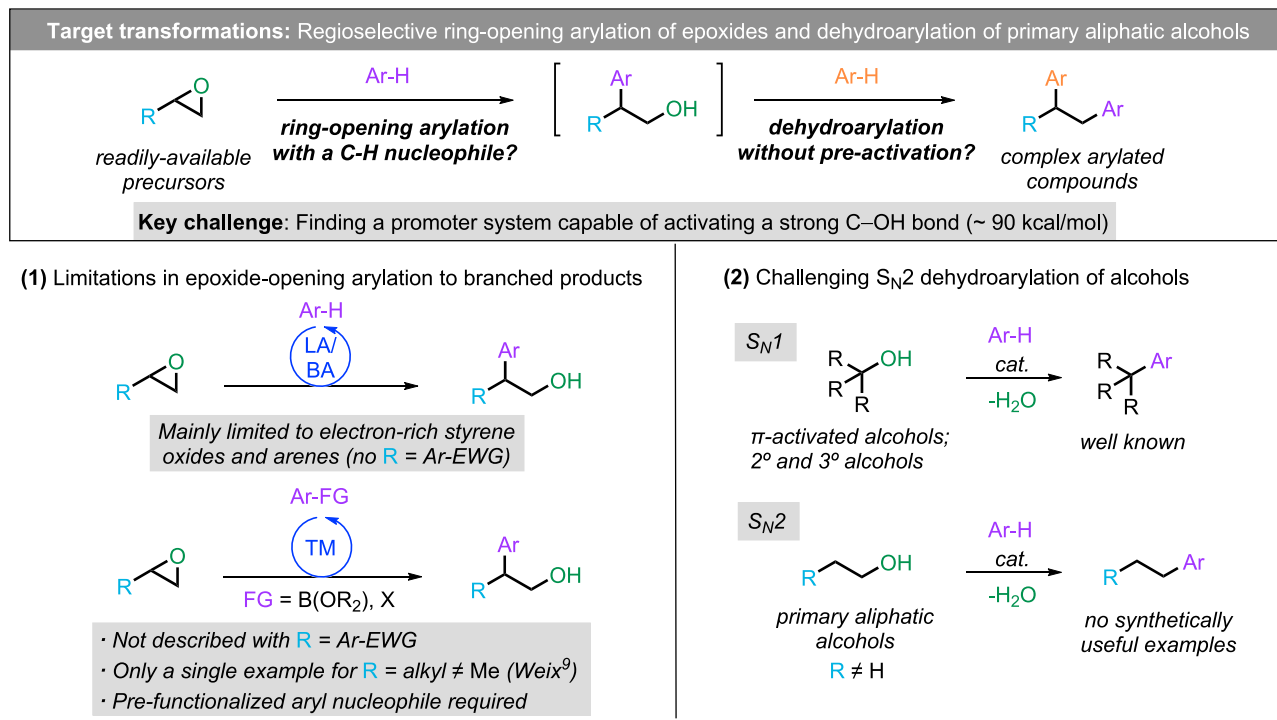
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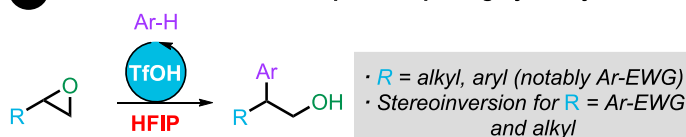
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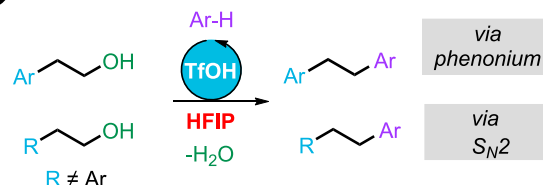


Our strategy

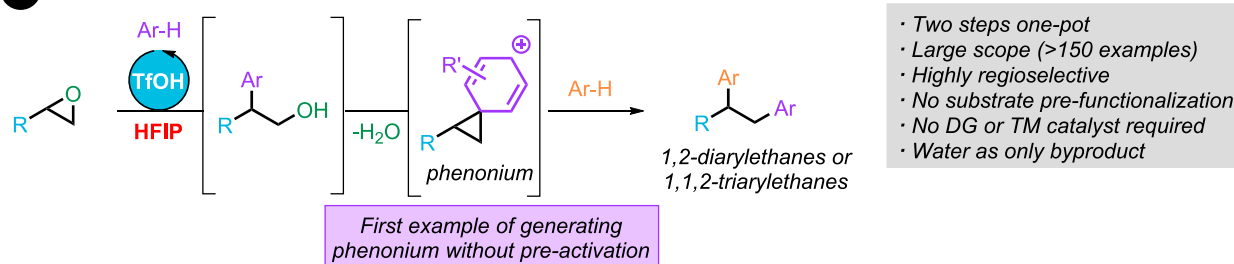
1 General branch-selective epoxide-opening hydroarylation



2 Dehydroarylation of primary aliphatic alcohols

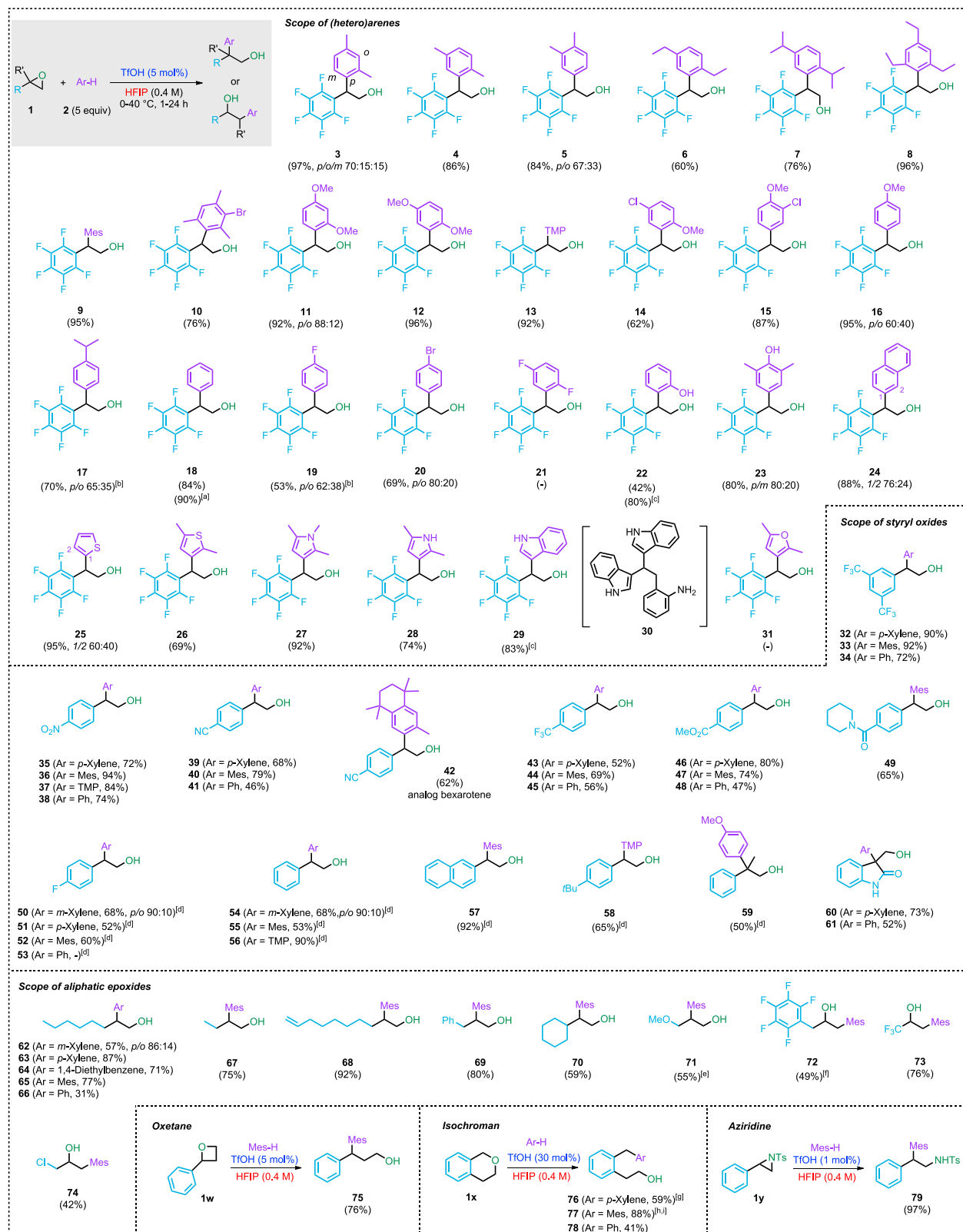


3 Dehydrodiarylation of epoxides



Scheme 1. Approaches toward the monoarylation and dehydrodiarylation of terminal epoxides and primary aliphatic alcohols

identical reaction conditions (96% yield). The reaction could also be performed at higher concentration (1 M), albeit with lower selectivity. More common solvents (dichloromethane, 1,2-dichloroethane, toluene, and nitromethane) led to a significant decrease in yield (<55%) because of the oligomerization of the substrate, highlighting the critical role of HFIP in the transformation. Of note, reducing the number of equivalents of *m*-xylene caused the ring-opening of the epoxide by HFIP to become a competitive side reaction.



Scheme 2. Monoarylation of epoxides

^a[1a] = 0.2 M.

^bRegioisomers were separated by flash column chromatography.

^cBi(OTf)₃/nBu₄NPF₆ (5 mol %) as the catalyst.

^dUsing TfOH (0.1 mol %).

^eDiarylated product detected but not isolated (22% yield determined by ¹H NMR using hexamethyldisiloxane as an external standard).

^fDiarylated product **107** isolated in 34% yield.

^gDiarylated product **120** isolated in 13% yield.

^h[1x] = 0.2 M. Diarylated product **121** isolated in 8% yield.

Mes = 1,3,5-trimethylphenyl. TMP = 1,3,5-trimethoxyphenyl.

Scope of arene nucleophiles

With optimized conditions in hand, we first explored the scope of (pentafluorophenyl) ethanol synthesis from styrene oxide **1a** using an array of aryl and heteroaryl nucleophiles. The transformation was compatible with a wide range of mono- to tetrasubstituted arenes, incorporating either electron-donating or electron-withdrawing substituents to afford the corresponding products **3–29** in 42%–97% yields. The steric hindrance exhibited by the various functional groups on the nucleophile did not hamper the reactivity, as nearly quantitative yields was achieved in most cases (up to 96%). Although the reaction with 1,3,5-triethylbenzene as a nucleophile produced a mixture of mono- and diarylated products **8** and **84** in a 1:1.25 ratio, conducting the reaction at 0°C enabled the selective formation of **8** in 96% yield. The same applied to mesitylene (**9**, 95%). Moreover, the reaction could be extended to less electron-rich nucleophiles, such as benzene (**18**), fluorobenzene (**19**), and bromobenzene (**20**), providing arylated compounds in 53%–84% yields. On the other hand, 1,4-difluorobenzene (**21**) was not sufficiently reactive due to its reduced nucleophilicity. In this case, the epoxide underwent oligomerization and nucleophilic ring-opening by HFIP. Lower reaction concentrations (0.2 M) improved the yield up to 90% in the case of benzene adduct **18**, in agreement with previous studies that identified the key role of H-bonded solvent clusters in Lewis and Brønsted acid-catalyzed reactions in HFIP.⁵³ Thus, the use of less nucleophilic arenes is compensated by activating the epoxide with a more acidic H-bond network. For reactions of some arenes, mixtures of regioisomers favoring the *para*-product were observed, typical of Friedel-Crafts alkylations. In the case of phenol, a mixture of *ortho*-C and O-alkylation products was obtained under TfOH catalysis, but the less acidic promoter Bi(OTf)₃/nBu₄NPF₆ exclusively furnished the *ortho*-C product (80%). Heteroarenes, such as thiophenes, pyrroles, and indoles were tolerated, furnishing compounds **25–29** in high yields. In the case of indole, lower catalyst loadings (0.1 mol %) prevented competitive hydroarylation, allowing **29** to form in 83% yield, with minimal amounts of by-product **30**. In turn, furans decomposed under the acidic reaction conditions.

Scope of styryl oxides

Next, we examined the influence of the styryl oxide substitution pattern, using arenes with different nucleophilicity, such as *p*-xylene, mesitylene, and benzene. Deactivated styrene oxides incorporating synthetically relevant electron-withdrawing groups (nitro, nitrile, trifluoromethyl, ester, and amide groups) furnished products in 46%–94% yields (**32–49**) regardless of the nucleophile employed. This transformation was also used to prepare an analog of bexarotene, an antineoplastic agent (**42**, 62%). When less electron-deficient styrene oxides were employed, such as 4-fluorostyrene oxide, styrene oxide, 2-(naphthalen-2-yl)oxirane, and 4-*tert*-butylstyrene oxide, the catalyst loading was decreased to 0.1 mol % to provide the target compounds in yields ranging from 52%–92% (**50–58**). These more reactive styrene oxides were not compatible with weak arene nucleophiles, such as benzene, due to the oligomerization of the former. The reaction was tolerant to 1,1-disubstituted epoxides (**59–61**), including those bearing the framework of interest indolin-2-one.

Scope of aliphatic epoxides

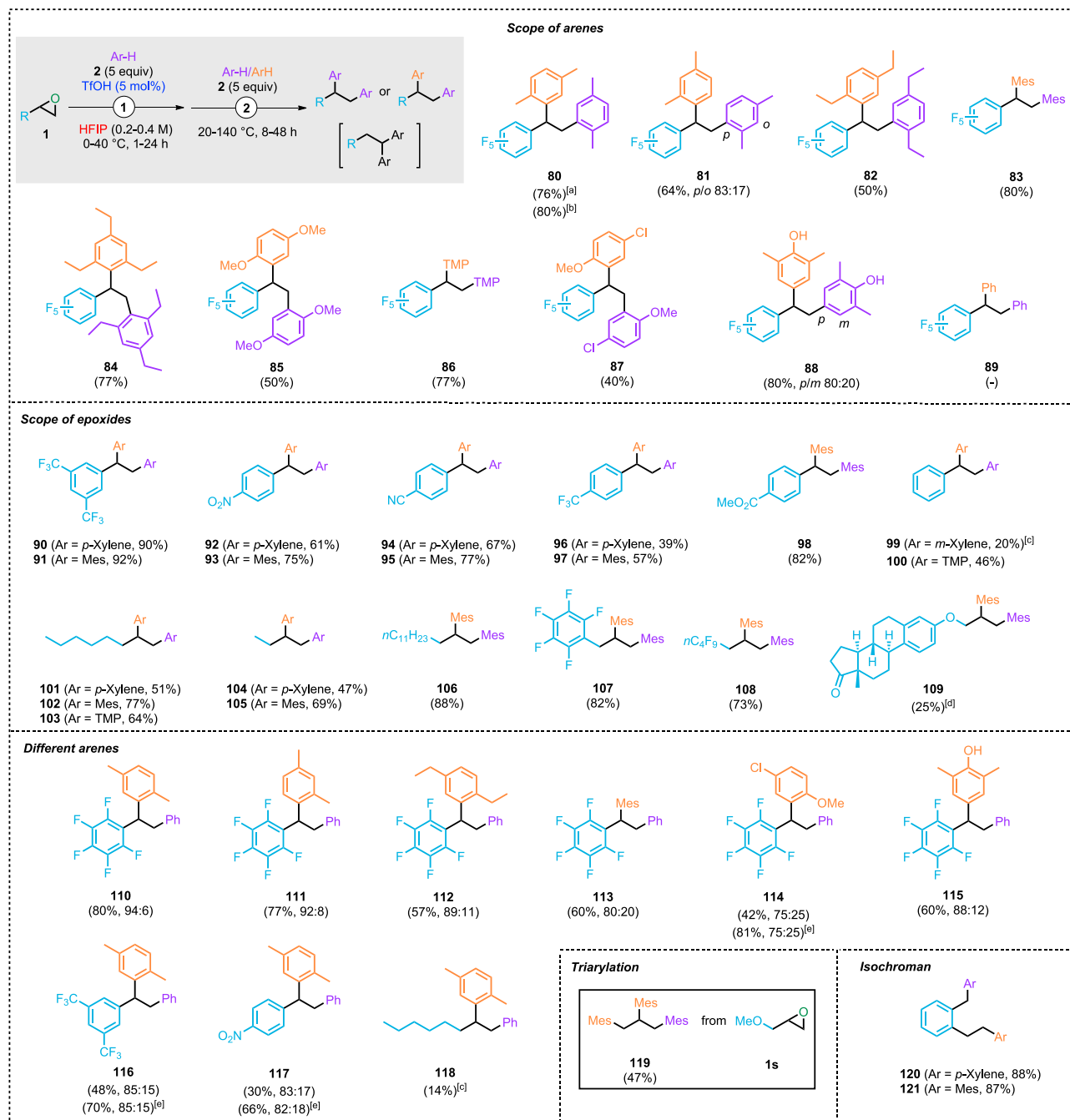
One of the strengths of this reaction system is its efficacy with alkyl-substituted oxiranes, selectively affording branched products in high yields (up to 92%, **62–71**). The transformation exhibits chemoselectivity in the presence of an alkene functionality, providing product **68** in 92% yield, and is tolerant of oxygen functionalities (**71**). In contrast with typical aliphatic epoxides, the presence of electron-withdrawing substituents near the oxirane renders the internal position less electrophilic and induces addition at the terminal position, furnishing secondary alcohols (**72–74**), in agreement with previous studies from Prakash et al.⁸⁰ This difference of regioselectivity is particularly striking in the case of **69** and **72**. Of note, using **1t** as a substrate yielded the diarylated adduct **107** as a minor product in 34% yield, showing that this change in regioselectivity does not preclude the dehydrodiarylation of epoxides.

Larger cyclic ethers and aziridines

Moving beyond epoxides as electrophiles, applying the reaction to 2-phenyloxetane and isochroman generated the corresponding phenyl propanol and ethanol derivatives **75–78** in 41%–88% yields. An increased catalyst loading of 30 mol % was required to enable the complete arylation of isochroman at the benzylic position. Of note, only one example of an arylative oxetane, as well as isochroman ring-opening was hitherto reported in the literature, both of which require pre-activated arene nucleophiles.^{81,82} The reaction was also compatible with aziridines to access phenylethylamine **79** in 97%.⁸

Scope of dehydrodiarylation of epoxides

Next, we turned our attention to the challenging one-pot dehydrodiarylation of epoxides (Scheme 3). To optimize the formation of 1,1,2-triarylethanes, we studied the reaction of (pentafluorophenyl)ethylene oxide with *m*-xylene, which would serve as a nucleophile for both steps. After completion of the first step at 20°C, we found that simply increasing the temperature to 80°C was sufficient to trigger the second arylation, affording the product **80** in 76% yield. Here, the control of the reaction temperature is essential as conducting the reaction at higher temperature (140°C) led to the formation of **80'** where both aryl groups are installed at the terminal position. A series of electron-rich arene nucleophiles bearing alkyl, methoxy, halide, and hydroxy functionalities was examined in reaction with styrene oxide **1a**, giving the target products in 40%–80% yields. (**80–88**) In some cases (**81** and **88**), a mixture of regioisomers was obtained, which results from the regioselectivity of the first arylation of the styrene oxide (see **3** and **23** in Scheme 1). Although weakly nucleophilic arenes, such as benzene, could be employed in the first step, they are not competent nucleophiles for the second step, as the phenyl ethanol intermediate remained intact even at reaction temperatures up to 140°C. Diversely substituted oxiranes (alkyl and aryl groups) also underwent the transformation to produce the corresponding 1,1,2-triarylethanes and 1,2-diarylethanes in high yields (**90–109**, up to 92%). On the other hand, reactions of simple styrene oxide led to products in lower yields (**99** and **100**). In this case, the alcohol intermediate appeared to rapidly dehydrate to generate the corresponding styrene, which subsequently oligomerized. In general, a comparison of Schemes 2 and 3 reveals that the yields obtained for the dehydrodiarylation are limited by the initial ring-opening arylation, with the subsequent dehydroarylation being highly efficient. In the case of alkyl-substituted oxiranes bearing electron-withdrawing groups, notably pentafluorobenzyl and perfluoroalkyl moieties, where the regioselectivity of the first step was inverted, the dehydrodiarylation was still achieved with 82% and 75% yields, respectively (**107** and **108**). Estrone glycidyl ether was subjected to the reaction conditions, delivering



Scheme 3. Dehydrodiarylation of terminal epoxides

^aAt 80°C, ratio 80:80' > 95:5.

^bAt 140°C, ratio 80:80' 83:17.

^cYield determined by ¹H NMR using hexamethyldisiloxane as an external standard.

^dTriarylated product 119 isolated in 11% yield.

^eYield over two steps.

Mes = 1,3,5-trimethylphenyl. TMP = 1,3,5-trimethoxyphenyl.

109 in 25% yield. The diarylation reaction was also extended to isochroman to give 120 and 121 in high yields (87%–88%). Even, triarylations are possible as methyl glycidyl ether 1s gave access to 1,2,3-triarylpropane 119 in 47% yield.

Reactions with two different nucleophiles

Two different arenes can be installed sequentially in a one-pot fashion by exploiting the difference between their nucleophilicity. For instance, by using benzene as nucleophile for the epoxide-opening and then adding a second more-nucleophilic arene, 1,1,2-triarylethanes were generated with three different aryl moieties in moderate to high yields (110–117). The arrangement of the aryl groups was ascertained through 2D HMBC (^1H - ^{13}C) NMR analyses in the case of 110. We also observed the formation of a minor regioisomer arising from nucleophilic addition at the terminal position, likely a consequence of steric hindrance in the phenonium intermediate. In cases where the yields were moderate (114, 116, and 117), we noticed that isolating the phenyl ethanol intermediate before re-engaging it in the reaction conditions significantly improved the yields (66%–81% yields over two steps). As anticipated, given the yield obtained for the ring-opening of 1,2-epoxyoctane with benzene (66, 31%), 1,2-diarylethane 118 was generated in a low yield (14%) for the reaction sequence.

Stereochemical studies on the reactivity of epoxides

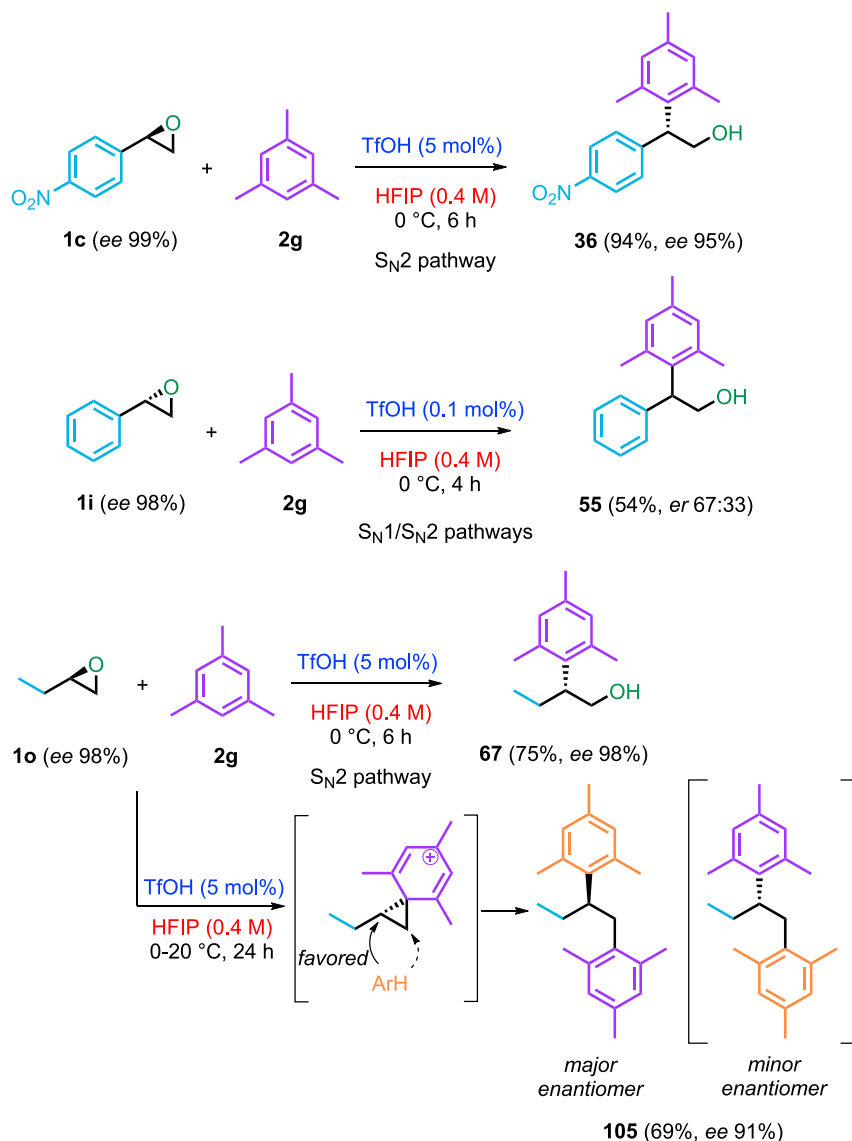
To establish whether the ring-opening monoarylation of epoxides occurs through a $\text{S}_{\text{N}}1$ or $\text{S}_{\text{N}}2$ process, we examined the reactivity of three representative enantioenriched chiral epoxides: 4-nitrostyrene oxide 1c, styrene oxide 1i, and alkyl epoxide 1o (Scheme 4). In the case of 1c (99% ee) and 1o (98% ee), the chiral information was nearly completely transferred to the alcohols 36 (95% ee) and 67 (98% ee), respectively, through a stereoinvertive arylation of the epoxide.^{7,83–86} In contrast, in the case of 1i, significant erosion of the enantiomeric excess from 98% ee to an er of 67:33 was observed. Thus, the results are consistent with the scenario where electron-poor styrene oxides and aliphatic epoxides undergo a highly stereospecific $\text{S}_{\text{N}}2$ Friedel-Crafts alkylation, whereas more electron-rich styrene oxides proceed through competitive $\text{S}_{\text{N}}1$ and $\text{S}_{\text{N}}2$ mechanisms. In the same vein, we determined the ee of the diarylated product 105, which diminished from 98% to 91%, being consistent with the intermediacy of a phenonium intermediate. The slight decrease of ee can be attributed to competing nucleophilic addition on the phenonium intermediate at either the internal (major) or terminal (minor) carbons, as mentioned previously.

Friedel-Crafts alkylation of primary aliphatic alcohols

Primary aliphatic alcohols generally do not undergo Friedel-Crafts reactions,^{3–6} except for some examples with methanol and ethanol under extreme conditions, e.g., using high temperatures (300°C–400°C) with zeolites as promoters.^{87,88} However, the reactivity with epoxides clearly indicates this is possible using the TfOH/HFIP reaction system.

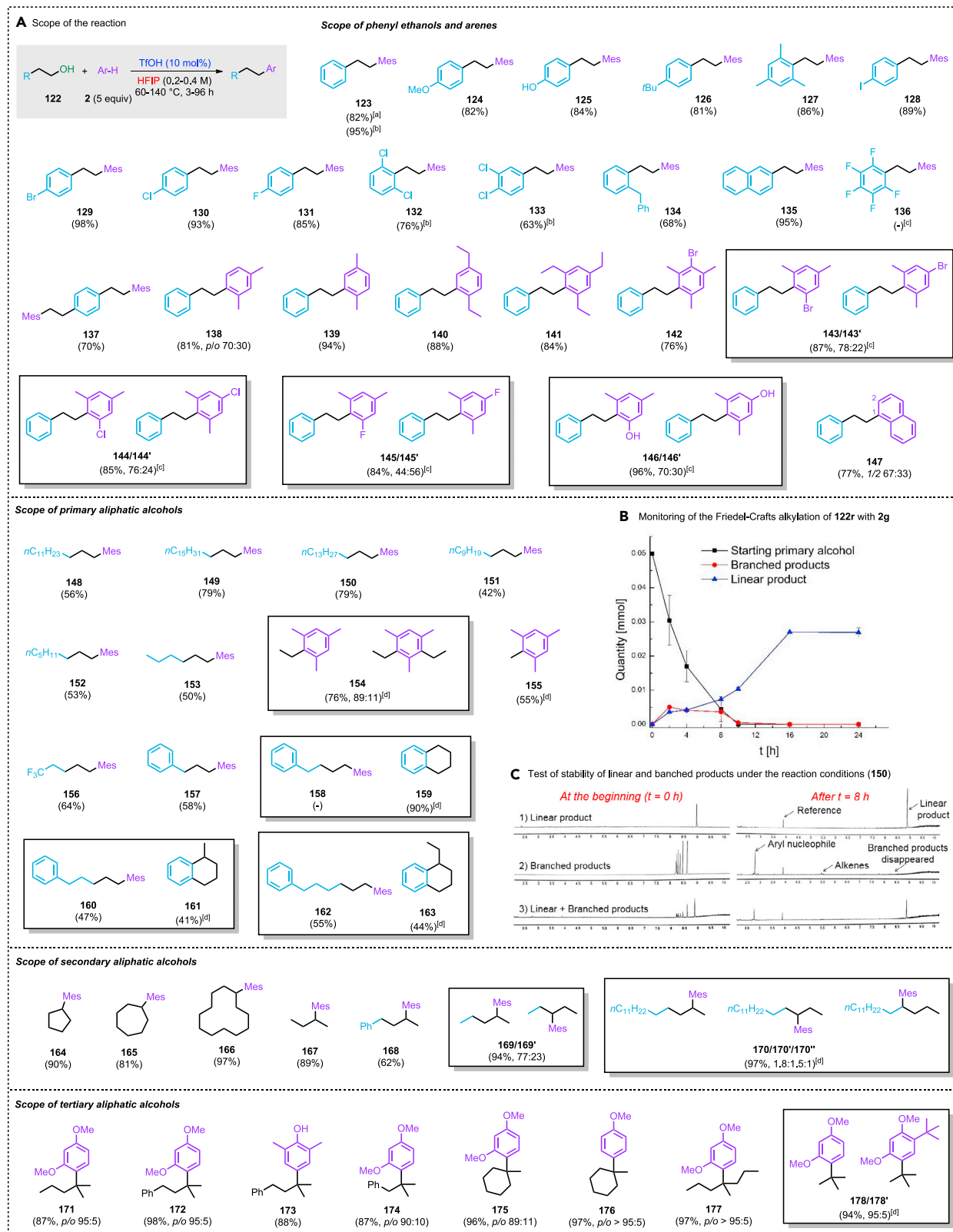
Scope of phenyl ethanols and arene nucleophiles

Therefore, we explored the reactivity of common phenyl ethanol precursors to rapidly access 1,2-diarylethanes as a complementary method to the arylation of epoxides (Scheme 5A). Starting with mesitylene as a nucleophile, we surveyed an array of diversely substituted phenyl ethanol derivatives. In the case of phenyl ethanol, the reaction gave the 1,2-diarylethane 123 in 82% yield at 80°C, which was increased to 95% at 120°C (see Table S2). The transformation was compatible with the presence of electron-donating, -withdrawing, or naphthyl groups, giving the products in high yields (63%–98%). Higher temperatures (120°C) were required for phenyl ethanols bearing electron-deficient arenes, most likely because the resulting phenonium ion intermediate is less stabilized (132 and 133). However, this reactivity is notable, as reactions that proceed through electron-deficient phenonium intermediates, with



Scheme 4. Stereochemical studies

rare exceptions,⁷⁸ require their generation from a hypernucleofuge via the use of hypervalent iodine.^{71,76,77} Only in the case of a phenyl ethanol bearing a more strongly deactivated arene, such as pentafluorophenyl, was the reactivity precluded (**136**). A benzyl group was tolerated in the *ortho*-position of phenyl ethanol substrate to afford compound **134** (68%). A symmetric diol underwent bidirectional Friedel-Crafts reactions to deliver diarylated adduct **137** in 70% yield. Electron-rich arene nucleophiles were tolerated (48%–94%), including the sterically hindered 1,3,5-triethylbenzene (**141**, 84%). Less nucleophilic arenes, such as xylenes, delivered the products **138** and **139** in high yields (81% and 94%, respectively). Halogenated arene nucleophiles, as well as phenols coupled with phenyl ethanol to furnish two regioisomers, which were separated by flash column chromatography (84%–96% combined yields, **143**–**146** and **143'**–**146'**). On the other hand, the reaction was not compatible with heteroarenes (pyrrole, thiophene, and indole), leading only to the decomposition of the substrates under the reaction conditions.



Scheme 5. Friedel-Crafts alkylation of primary aliphatic alcohols

^aAt 80°C.

^bAt 120°C.

^cRegioisomers were separated by flash column chromatography.

^dYield determined by ¹H NMR using hexamethyldisiloxane as an external standard.

Mes = 1,3,5-trimethylphenyl.

The observation that phenyl ethanols bearing deactivated arene moieties undergo Friedel-Crafts alkylation, although they benefit little from phenonium ion stabilization, led us to explore whether purely aliphatic primary alcohols could be used as coupling partners. By raising the temperature to 140°C under otherwise standard conditions (10 mol % TfOH in HFIP, 0.2 M), the reaction of 1-tetradecanol with mesitylene gave linear Friedel-Crafts alkylation product **148** in 56% yield (see Table S3).

Scope of primary aliphatic alcohols

The scope of the transformation was explored for various primary aliphatic alcohols under the optimized reaction conditions. In general, the desired products were obtained in yields ranging from 42% to 79%. In general, higher yields were achieved with alcohols bearing longer aliphatic chains, which might be ascribed to stronger intermolecular dispersion interactions between longer alkyl groups, hindering elimination to the alkene and the eventual formation of branched products and oligomers. Primary aliphatic alcohols with a short alkyl chain, such as ethanol and methanol, furnished the corresponding products **154** and **155** in relatively high yield (76% and 55%, respectively); nevertheless, because of ethanol's limited steric bulk, a mixture of *mono*- and *bis*-alkylated products was obtained in this case. When phenyl-substituted primary aliphatic alcohols were employed, stable tetralin derivatives were formed as by-products (**159**, **161**, and **163**), which likely results from the formation of alkene by-products during the reaction.

Origin of linear selectivity

No branched products were detected at the end of the reaction for most substrates. To understand this unusual result, the reaction was monitored over time by GC-MS (Scheme 5B). The concentration of the major, linear product **150** increased consistently over the first 16 h. In contrast, the concentration of the minor branched products increased for 2 h and then decreased. At the same time, the concentration of hexadecenes increased, suggesting the decomposition of the branched products during the reaction. However, the exact concentration of hexadecenes could not be determined with certainty due to their low response factors by GC-MS. Our hypothesis was confirmed upon testing the stability of the linear and branched products under the standard reaction conditions in three experiments with (1) the linear product, (2) the mixture of branched products, and (3) the mixture of linear and branched products (Scheme 5C). In all cases, only the linear product remained intact after 8 h, and the branched products decomposed into alkenes and mesitylene. A mechanistic interpretation of these results is that, in the case of branched products, retro-hydroarylation, produces an alkene that oligomerizes over time. Indeed, in a previous study,⁵⁷ we demonstrated that arenes could be protonated under our standard reaction conditions to generate the corresponding arenium (see Scheme S1), which could lead to alkenes following a β -elimination. In contrast, we suspect that the retro-hydroarylation from the linear product might end up being less favored.

Scope of secondary and tertiary aliphatic alcohols

Lastly, we evaluated if our standard reaction conditions could be used with secondary and tertiary aliphatic alcohols. Although the Friedel-Crafts arylation of tertiary

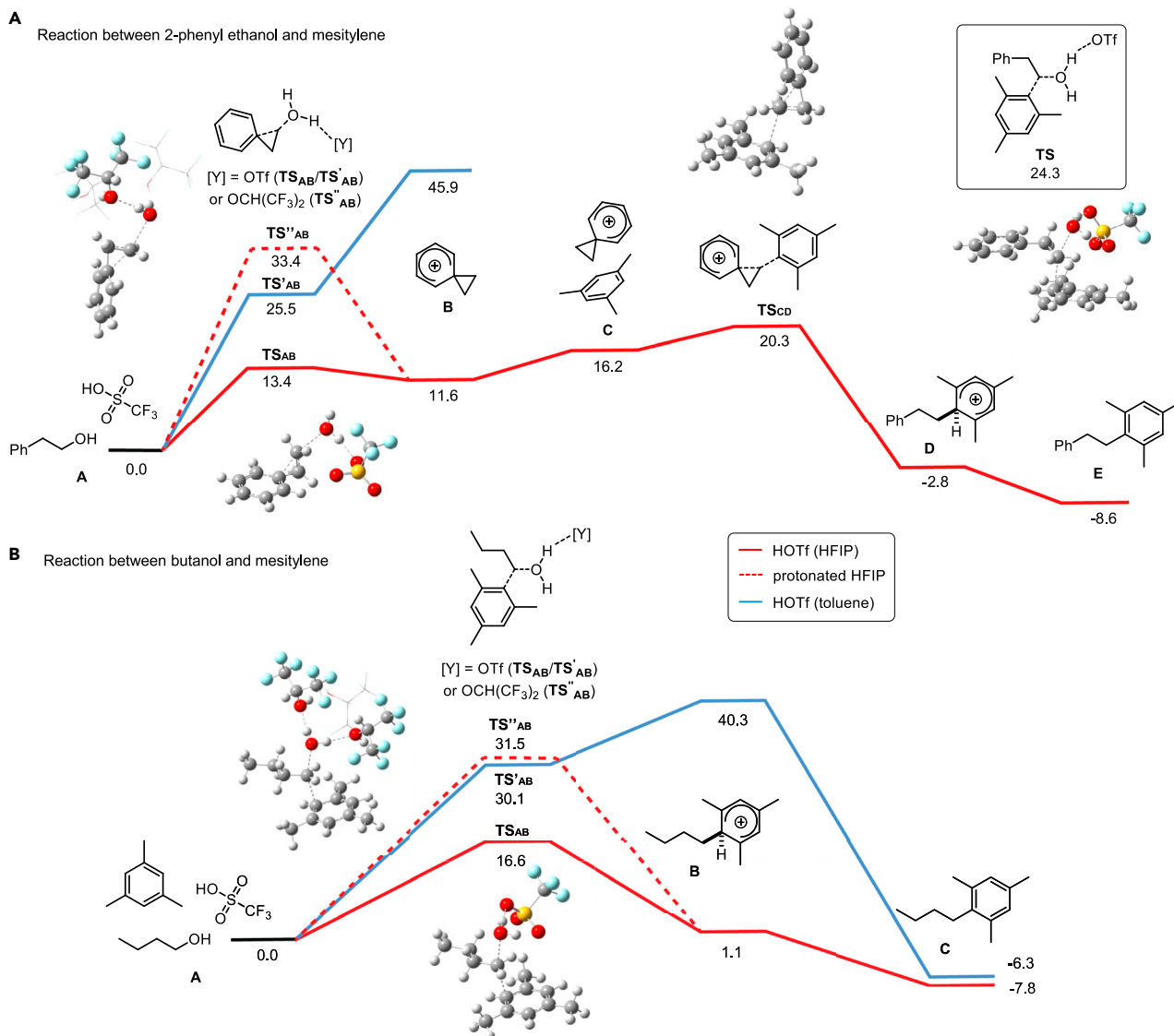
aliphatic alcohols is a well-established process, few examples of catalytic Friedel-Crafts reactions of secondary aliphatic alcohols have been described in the literature beyond isopropanol.^{89,90} Using mesitylene as a nucleophile, the transformation was successfully applied to cyclic alcohols (**164–166**), yielding the target products in 81%–97%. When compared with primary aliphatic alcohols, the reaction temperature could be lowered to 50°C. The reaction was also highly efficient with linear secondary alcohols, such as 2-pentanol, but led to a mixture of two regioisomers **169** and **169'**, which is consistent with the above-mentioned findings with primary aliphatic alcohols. It is noteworthy that the ratio between the two regioisomers changed over time to finally attain an equilibrium after 24 h (from 70:30 after 6 h to 77:23 after 24 h). The reaction was then extended to tertiary aliphatic alcohols, notably *tert*-butanol, only requiring 3 equivalents of nucleophile and 5 mol % of TfOH at a concentration of 1 M in HFIP. However, the reaction required electron-rich arenes, such as 1,3-dimethoxybenzene, anisole, or 2,6-dimethylphenol, to obtain high yields (up to 98%). In the case of mesitylene, the oligomerization of the substrate was the main outcome.

Mechanistic aspects through DFT calculations

To achieve a deeper understanding of the Friedel-Crafts reaction of primary aliphatic alcohols in HFIP, we used DFT calculations to model the potential reaction mechanisms involved for 2-phenyl ethanol and butanol. All calculations were performed using Gaussian 16.⁹¹ The B3LYP exchange correlation was used with the def2-TZVP basis set.⁹² The Grimme D3 correction for dispersion was employed with the Becke-Johnson damping function.⁹³ The solventmodel density (SMD) continuum solvation model was applied to HFIP and toluene solvents. The cartesian coordinates for the optimized structures are provided in the [supplemental information](#)

The much lower reaction temperatures required for Friedel-Crafts reactions of phenyl ethanol compared with simple primary aliphatic alcohols suggests that the former react through a different mechanism, which would be consistent with the formation of a stable phenonium intermediate. We identified a concerted mechanism where TfOH transfers a proton to the hydroxyl group of phenyl ethanol while a C–C bond is formed between the α -carbon and the *ipso* carbon of the phenyl ring. At the transition state, the proton transfer is effectively complete, forming a structure where the nascent water molecule acts as a Lewis base for the carbocation. Once formed, the phenonium ion undergoes nucleophilic addition with mesitylene to form a Wheland intermediate. Deprotonation of this Wheland intermediate yields the product. The Gibbs energy profile for this mechanism is presented in [Scheme 6A](#). Comparing the calculations in toluene versus HFIP, the importance of solvent becomes evident. In a continuum solvent model for toluene, the phenonium is a high-energy species (45.9 kcal/mol), due to the lack of stabilizing electrostatic interactions with the apolar solvent. In a continuum model for HFIP, the phenonium is far more stable (11.6 kcal/mol), consistent with the stabilization of ionic intermediates by the higher dielectric constant of HFIP. As a potential alternative mechanism that avoids a phenonium ion, we also considered a pathway in which the attack by mesitylene is concerted with the proton transfer from TfOH to the alcohol. However, the activation energy for this pathway (24.3 kcal/mol) is higher than the one proceeding through the phenonium ion intermediate.

Our previous studies on Friedel-Crafts alkylation and hydroarylation processes in HFIP^{55,56} suggest that a protonated cluster of HFIP directly acts as the Brønsted acid in these reactions, rather than TfOH itself. Therefore, we identified a transition state where the excess proton is stabilized by a cluster of four H-bonded HFIP molecules



Scheme 6. Gibbs energy profiles (ΔG , kcal mol⁻¹) for the addition of mesitylene to phenyl ethanol and to butanol

within a continuum model for the bulk HFIP solvent. This transition state is similar to the one described above, but the activation energy is predicted to be 33.4 kcal/mol.

Simple primary aliphatic alcohols, such as butanol, cannot form a phenonium intermediate; therefore, these substrates must react through a different mechanism. In this case, we have identified transition states where the protonation of butanol occurs in concert with the formation of the C–C bond with mesitylene (Scheme 6B). These were modeled for two Brønsted acids: (1) TfOH stabilized by H-bonds with HFIP molecules and (2) a protonated cluster of HFIP. Both mechanisms are modeled with a continuum representation for the HFIP solvent in addition to those modeled explicitly. In both cases, the proton transfer is complete before the formation of the C–C bond. The dissociating H₂O engages in hydrogen bonding interactions with the HFIP/triflate and simultaneously serves as a Lewis base to the carbocation, which stabilizes the transition state. The reactions promoted by TfOH or protonated-HFIP cluster are predicted

to have barriers of 16.8 and 32.2 kcal/mol, respectively. When toluene is used as a solvent, the Wheland intermediate is unstable (40.3 kcal/mol); therefore, the alkylation pathway is much higher energy than when the solvent is HFIP.

Although the direct protonation by TfOH in HFIP has a lower barrier in both cases (butanol and phenyl ethanol), the significance of the mechanisms proposed will depend on the relative concentration of TfOH versus protonated HFIP in solution. It is also possible that many more molecules of HFIP could be involved in the reaction, but our calculations reveal that, from a qualitative standpoint, both mechanisms are viable.

Conclusion

In summary, HFIP enables a significant expansion of the Friedel-Crafts reaction to now include simple primary aliphatic alcohols (as well as secondary and tertiary alcohols), phenyl ethanol, most classes of terminal epoxides, oxetanes, isochromans, and aziridines as electrophiles. For most of the epoxides, the reactions are stereospecific, which should be useful for stereoselective synthesis. As Friedel-Crafts reactions featuring epoxides produce primary aliphatic alcohols, we have described the dehydroarylation of epoxides, where two of the same arenes or two different arenes can be introduced in one pot. This method opens direct access to phenonium ions from phenyl ethanol, which should reach beyond the Friedel-Crafts reaction, allowing new ionic transformations to be developed. Mechanistic studies suggest that simple primary aliphatic alcohols react through a S_N2 -type mechanism, which is rare for intermolecular Friedel-Crafts reactions involving alcohols. Finally, all the reactions described herein start directly from readily available precursors without pre-activation steps and produce no stoichiometric waste beyond water.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Joseph Moran (moran@unistra.fr).

Materials availability

All materials generated in this study are available from the lead contact without restriction.

Data and code availability

This study did not generate any datasets.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at <https://doi.org/10.1016/j.chempr.2021.10.023>.

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AUTHOR CONTRIBUTIONS

Conceptualization, D.L. and J.M.; methodology, D.L. and J.M.; investigation, S.Z., M.V., F.N., V.D.V., A.G., N.R., and C.N.R.; writing – original draft, D.L. and J.M.; writing – review & editing, D.L. and J.M.; funding acquisition, J.M.; supervision, D.L. and J.M.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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