Friedel–Crafts alkylation of arenes with epoxides promoted by fluorinated alcohols or water†

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The stereoselective intra- and intermolecular Friedel–Crafts alkylation of electron-rich arenes with epoxides can take place in refluxing 1,1,1,3,3,3-hexafluoroisopropanol owing to its weak acidity and high ionizing power.

The regio- and stereoselective Friedel–Crafts alkylation of arenes with epoxides is important in organic synthesis. These reactions are regularly catalyzed by Lewis acids which activate epoxides towards electrophilic substitution.[1] However, sometimes degradation and polymerization of epoxides occur before electrophilic substitution in the presence of strong Lewis acids. In 2004, He's research group reported that $AuCl_3$/3AgOTf could catalyze the cyclialkylation of arenes with tethered epoxides in moderate to good yields.[2] Recently, Pericàs's research group reported that the cyclialkylation of arenes with tethered epoxides could be efficiently catalyzed by common Lewis acids such as $BF_3{\cdot}Et_2O$ or $FeBr_3$ with the reaction catalyzed by $FeBr_3$/3AgOTf giving the highest yield.[3] We recently reported that water (60–100 °C) could promote the ring-opening of epoxides and aziridines with heteroatom nucleophiles. Mechanistic studies showed that water acted as a mild acid catalyst at elevated temperature.[4] This stimulated us to check if water can replace Lewis acids in more important carbon–carbon bond formation reactions. Herein we report that the intra- and intermolecular Friedel–Crafts alkylation of electron-rich arenes with epoxides can take place in water and fluorinated alcohols without additional catalyst.

The cyclialkylation of (2*R*,3*R*)-2-((3,5-dimethoxyphenoxy)-methyl)-3-phenyloxirane (**1a**) produces 3-chromanol which is the core structure of many natural products. Lewis acid catalyzed cyclialkylation using $AuCl_3$/3AgOTf (2.5 mol%), $FeBr_3$ (10 mol%) or $BF_3{\cdot}Et_2O$ (30 mol%) gave **2a** in 76%, 92%, and 79% yields respectively.[2,3] The cyclialkylation of **1a** was firstly tested in refluxing water without any additive. Although diol from the hydrolysis of epoxide was produced in 45% yield, the reaction indeed gave the desired cyclialkylation product **2a** in 55% yield (Table 1, entry 5).[5] In toluene, acetone or acetonitrile, cyclialkylation did not occur, even after prolonged refluxing. The reaction proceeded slowly in methanol and 18% yield was obtained after 26 h. These experiments clearly indicate that water at refluxing temperature can activate epoxides. We reason that more acidic but less nucleophilic solvents should perform better than water.

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Table 1 Intramolecular cyclialkylation of epoxide **1a**[a]

Entry	Solvent	Condition	Time	Yield (%)[b]
1	Toluene	Reflux	26 h	N.R.
2	Acetone	Reflux	26 h	N.R.
3	CH_3CN	Reflux	26 h	N.R.
4	MeOH	Reflux	26 h	18
5	H_2O	Reflux	10 h	55[c]
6	TFE	r.t.	48 h	96
7	HFIP	r.t.	4 h	99
8	TFE	Reflux (74 °C)	4.5 h	99
9	HFIP	Reflux (59 °C)	5 min	99
10[d]	Phenol (20 mol%) in H_2O	Reflux	19 h	77[c]
11[d]	4-Nitrophenol (20 mol%) in H_2O	Reflux	3.5 h	41[c]
12[d]	AcOH (20 mol%) in H_2O	Reflux	40 min	12[c]

[a] The reaction was conducted with 0.15 mmol of **1a** in 5 mL of the indicated solvent. [b] Isolated yield. [c] The conversion of **1a** was 100% and the only by-product was diol from the hydrolysis of epoxide. [d] The amount of additive is the mole percent relative to the amount of substrate.

Fluorinated alcohols are known for their acidic properties and can promote the ring-opening of epoxides with aromatic amines.[6] Treatment of **1a** in 2,2,2-trifluoroethanol (TFE) at room temperature for 48 h provided **2a** in 96% yield. Replacing TFE with more acidic 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) shortened the reaction time to 4h. When the reaction was carried out in refluxing HFIP, the cyclialkylation finished within 5 min and gave quantitative yield of **2a**. The reaction is regio- and stereocontrolled because only *endo* cyclization with an S_N2-like inversion of the chiral center is observed and the isolated product is enantiomerically pure (>99% ee). Phenol is more acidic and less nucleophilic than water and was reported to catalyze the epoxide-opening with amines.[7] By using water containing 0.2 equiv. of phenol as reaction medium, cyclialkylation product **2a** was obtained in a better yield than that operated in pure water (entry 10). However, on replacing phenol with more acidic 4-nitrophenol, the yield of diol increased (entry 11). If water containing 0.2 equiv. of acetic acid was used as the reaction medium, the amount of diol further increased and the yield of cyclialkylation product **2a** decreased to 12% (entry 12). This indicates the importance of using a weak acid to ensure the cyclialkylation, in which the arene acts as the nucleophile. Activation of epoxides by a strong proton acid mainly provides the solvolysis product diol.

In 2008, Mayr's research group reported that the intermolecular ring-opening of epoxides with electron-rich

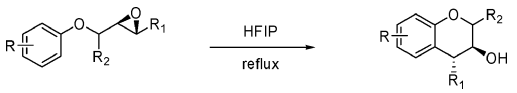
heteroarenes such as indoles and pyrroles could take place in refluxing TFE without additional catalyst. The reactions gave moderate to excellent yields and excellent stereoselectivities.[8] The ring-opening of epoxides with arenes is more important and of general interest, but carrying out these reactions in fluorinated alcohols has not been systematically studied.[9] Encouraged by the high efficiency of the non-metal-mediated cyclialkylation of **1a** in refluxing HFIP, the scope of this method was studied by varying the substituted groups on the phenyl ring and the oxirane. Methoxy-substituted, *tert*-butyl-substituted, unsubstituted, and halogen-substituted phenyl rings were all good nucleophiles to react with the phenyl substituted epoxides **1b–1f** (Table 2, entries 1–6). Naphthalene and halogen-substituted naphthalene **1g** and **1h** (entries 7 and 8) were also good nucleophiles, providing high yields of cyclialkylation products selectively at the α-position of naphthalene. The cyclialkylations of enantiopure substrates **1b**, **1c**, **1d**, and **1f** were found to be stereospecific by comparing the products' optical rotation values with the reported data. The cyclialkylations of enantiopure substrates **1e**, **1g**, and **1h** were also stereospecific since 99% enantiopure product was formed as detected by chiral HPLC. The cyclialkylation of 2-[(3,5-dimethoxyphenoxy)phenylmethyl]oxirane **1i** (entry 9) is useful in particular because the reaction generates the core structure of naturally occurring catechins.[10] In previous research, the combination of $AuCl_3$/3AgOTf was too harsh for this substrate and an improved catalytic system containing thiourea/$AuCl_3$/AgOTf was used to construct **2i** in 65% yield.[11] The annulation of **1i** in refluxing HFIP was slow but clean due to the weak acidity of HFIP. Compound **2i** was obtained in 96% yield based on 53% conversion of the starting material. Microwave irradiation was applied to this reaction, but no positive effect was observed. This provides an alternative process for synthesizing the biologically active catechins. The dimethyl substituted epoxide **1j** (entry 10) reacted faster and gave a similar yield comparing with the terminal dihydrogen substituted epoxide **1i** (entry 9).

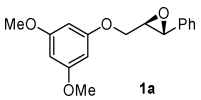
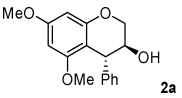
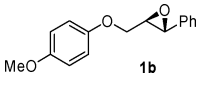
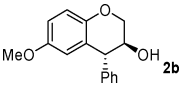
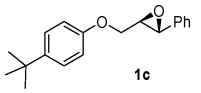
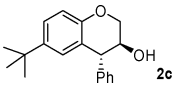
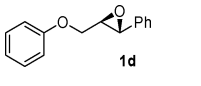
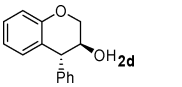
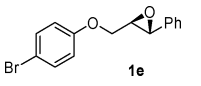
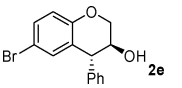
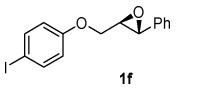
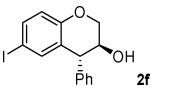
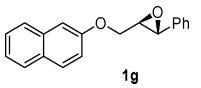
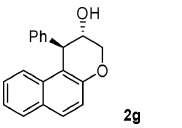
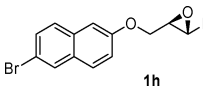
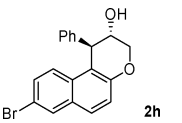
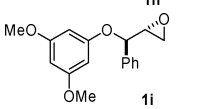
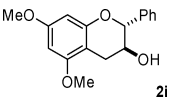
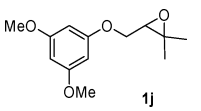
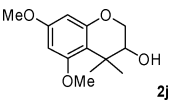
$AuCl_3$/3AgOTf (5 mol%) or $FeBr_3$/3AgOTf (10 mol%) can also catalyze the intermolecular reaction between electron-rich arenes and epoxides but only moderate yields can be obtained.[2,3] Mayr's research group formerly tried the intermolecular reaction between anisole and styrene oxide in refluxing TFE and isolated only solvent addition product.[8] To test whether intermolecular Friedel–Crafts alkylation can take place under these reaction conditions, we attempted the reaction between 1,3,5-trimethoxybenzene and (*R*)-styrene oxide in refluxing HFIP (Table 3). The reaction proceeded quickly at the benzylic position of styrene oxide and gave 61% yield of alkylation product **3a** accompanied by 30% of HFIP addition product (also at the benzylic position of styrene oxide). The intermolecular reaction was also stereospecific judged from the chiral HPLC analysis. When the above intermolecular reaction was carried out in water, only 5% alkylation product was formed along with 95% of diol.

When the nucleophilicity of the arene declines, the yield of alkylation product decreases while the yield of solvolysis product increases. 1,4-Dimethoxybenzene reacted with styrene oxide, providing 35% of alkylation product **3c** and 60% of solvolysis product. For the reaction between anisole and styrene oxide, only 15% of alkylation product **3d** was obtained. The reaction between 1,3,5-trimethoxybenzene and aliphatic propylene oxide proceeded slowly at the less-substituted position of the epoxide and the conversion-based yield of **3e** was 96% after 48 h.

Water and fluorinated alcohols possess various special properties (acid/base character, hydrogen bond forming ability, high polarity, and high ionizing power) and thus the contribution of each property to the reaction is worth discussing. In the study of reactions between indoles and epoxides in refluxing TFE, it was suggested that heterolytic cleavage of the C–O bond was facilitated by electrophilic solvent assistance (ESA) from the protic solvent TFE.[8,12] This report also emphasized the beneficial solvent effect of fluorinated alcohols in respect to their high ionizing power and low nucleophilicity. We also found that the reactions did not work in solutions of

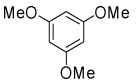
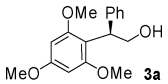
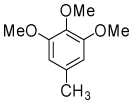
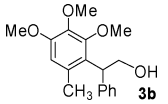
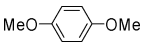
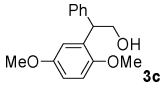
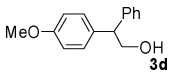
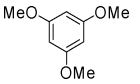
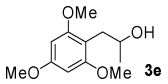
Table 2 HFIP-promoted intramolecular cyclialkylation[a]



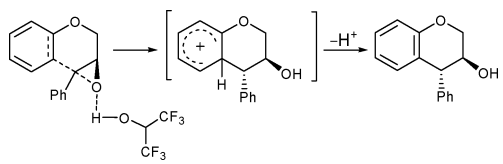
Entry	Substrate	Product	Time	Yield (%)
1	 **1a**	 **2a**	5 min	99
2	 **1b**	 **2b**	30 min	96
3	 **1c**	 **2c**	30 min	99
4	 **1d**	 **2d**	1 h	88
5	 **1e**	 **2e**	6 h	87
6	 **1f**	 **2f**	4.5 h	88
7	 **1g**	 **2g**	15 min	91
8	 **1h**	 **2h**	20 min	96
9	 **1i**	 **2i**	72 h	51
10	 **1j**	 **2j**	48 h	52

[a] All reactions were conducted with 0.15 mmol of substrate in 5 mL of refluxing HFIP; isolated yield.

Table 3 HFIP-promoted intermolecular Friedel–Crafts alkylation[a]

Nucleophile	Epoxide	Product	Time/h	Yield (%)
		 **3a**	0.5	61 (>99% ee)
		 **3b**	0.5	50[b]
		 **3c**	0.5	35[b]
		 **3d**	0.5	15[b]
		 **3e**	48	96[c]

[a] The reactions were conducted with nucleophiles (2.5 mmol) and epoxides (0.5 mmol) in 2.5 mL of refluxing HFIP; isolated yield. [b] Racemic styrene oxide was used; the conversion of the reaction was 100% and the major by-product was hexafluoroisopropyl ether. [c] The ratio of propene oxide and 1,3,5-trimethoxybenzene was 1 : 1; 30% conversion.



Scheme 1 Concerted addition of arene to the proton activated oxirane.

dichloromethane containing one equivalent of water or HFIP, which suggested that the high polar and high ionizing reaction medium was crucial.

Water, fluorinated alcohols and phenol have a common property in their acidic nature. The cyclialkylation of **1a** is more efficient in more acidic HFIP (pK_a = 9.3) than in TFE (pK_a = 12.4). Similarly, a better result is obtained after the addition of 20 mol% of phenol (pK_a = 9.95) in water (pK_a = 15.7). We presume that the reactions carried out in aqueous solution or fluorinated alcohols are acid-catalyzed. We noticed that hydrogen bond forming mechanisms have been proposed in other HFIP-promoted reactions.[13] But in the present studies, maximum reaction rates were reached in refluxing water or refluxing fluorinated alcohols. Actually the hydrogen bond donating ability of these solvents drops as temperature rises owing to the fact that hydrogen-bond formation is exothermic.[14] Although HFIP is known to have a remarkable stabilizing effect for cationic species due to its high polarizability and low nucleophilicity,[15] the epoxide ring-opening does not go through a discrete carbocation intermediate because both intra- and intermolecular alkylation take place with high stereocontrol and a total S_N2 inversion is observed. We assumed that water, fluorinated alcohols and phenol are capable of activating epoxides by protonation (Scheme 1). The cleavage of the C–O bond and the formation of the new carbon–carbon bond are concerted.[16] The polar transition state of the reaction could be stabilized well by the high ionizing solvent HFIP.

In conclusion, 1,1,1,3,3,3-hexafluoroisopropanol can efficiently promote the electrophilic aromatic substitution between arenes and epoxides with high regio- and stereocontrol. This non-metal-mediated Friedel–Crafts alkylation does not need strict anhydrous conditions which are usually required for Lewis acid catalyzed reactions. Removing low boiling point (b.p. = 59 °C) and low viscosity HFIP by distillation affords the product and HFIP can be recovered and reused. Water can also promote the Friedel–Crafts alkylation although the diol by-product is also formed, especially in the intermolecular reactions. We believe that the unique catalytic effects of HFIP and water demonstrated here will enable their further usage in other Lewis acid catalyzed reactions.

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