Cascade Reactions

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One-Pot Arylative Epoxidation of Ketones by Employing Amphoteric Bromoperfluoroarenes**

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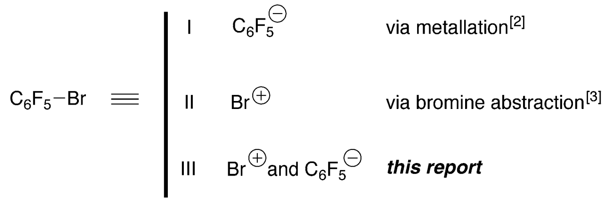
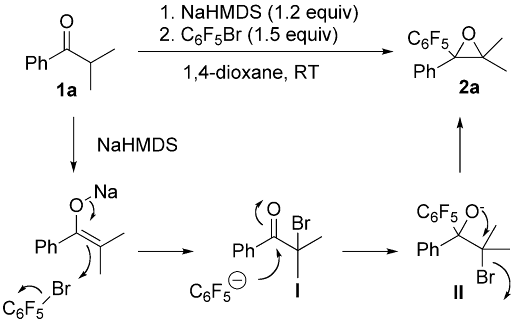
Bromopentafluorobenzene (PFPBr) is an important building block for the preparation of polyfluorophenyl-containing compounds;[1] the PFP-Br bond can be cleaved under a variety of conditions (Scheme 1). Through metalation reactions with alkali metals, alkyl lithium reagents, or oxidative additions to Pd^0, PFPBr serves as an equivalent of the PFP anion[2] (mode I), which participates in reactions with diverse electrophiles or in cross-coupling reactions. On the other hand, there have been reports on Br$^+$ abstraction from PFPBr by nucleophiles (mode II).[3] Herein, we present an unprecedented mode III, in which PFPBr functions as an equivalent of both Br$^+$ and PFP$^-$ in the same transformation: a one-pot arylative epoxidation of ketones into pentafluorophenyloxiranes.



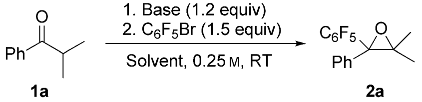
Scheme 1. Diverse reactivity of PFPBr.

Our group has recently reported that alkynyl bromides and cyanogen bromide can act as equivalents of both Br$^+$ and alkynyl- or cyanide anions in a highly efficient one-pot conversion of ketones into fully substituted alkynyl or cyanoepoxides.[4,5] As the amphoteric reactivity of PFPBr, as an equivalent of either Br$^+$ or PFP$^-$ has been established (Scheme 1), we hypothesized that it may also serve as a competent reagent for the one-pot cascade epoxidation of ketones (Scheme 2). It was expected that an enolate would abstract Br$^+$ from PFPBr to produce α-bromoketone **I** and a PFP anion. Nucleophilic addition of the latter at the carbonyl group would generate alkoxide **II**, which, upon intramolecular S_N2 reaction, would produce oxirane **2a**.



Scheme 2. Proposed reaction path for the epoxidation of ketones with PFPBr. NaHMDS = sodium hexamethyldisilazide.

Table 1: Screening of reaction conditions.



Entry	Base	Solvent	Result[a]
1	LiHMDS	DMF	trace
2	LiHMDS	Et_2O	N.R.
3	LiHMDS	THF	23
4	LiHMDS	1,4-dioxane	N.R.
5	LiO*i*Pr	THF	N.R.
6	LiO*i*Pr	1,4-dioxane	N.R.
7	NaHMDS	THF	40%
8	NaHMDS	Et_2O	75%
9	**NaHMDS**	**1,4-dioxane**	**96%**
10	KO*t*Bu	THF	decomp
11	KO*t*Bu	1,4-Dioxane	decomp

[a] Yields determined by GC, using pentadecane as an internal standard.

To test the above hypothesis, the reaction of isobutyrophenone (**1a**) and PFPBr (**3a**) was examined (Table 1). Gratifyingly, it was found that employing LiHMDS in THF led to a 23% yield of tetrasubstituted epoxide **2a** (entry 3). Brief optimization of the reaction conditions revealed that isobutyrophenone in the presence of NaHMDS in 1,4-dioxane was almost quantitatively converted into epoxide **2a** (entry 9). However, under these reaction conditions, 1-bromoperfluorobutane and 1-iodoperfluorobutane did not undergo this cascade transformation.[6]

Next, the generality of the cascade transformation of various ketones with PFPBr was examined (Table 2). It was found that α,α-disubstituted methyl aryl ketones are suitable substrates for this transformation. Thus, isopropyl, cyclobutyl, cyclopentyl, and cyclohexyl phenyl ketones **1a–d** smoothly reacted with PFPBr to produce epoxides **2a–d** in good to excellent yields. Pyran-4-yl ketone **1e** was also successfully converted into the corresponding product **2e**. Diverse substituents on the phenyl ring, such as 4-methoxy **1f** and 4-cyano **1g,h**, were tolerated in this reaction (entries 6–8). Moreover, different heteroaryl ketones, including pyridin-3-yl

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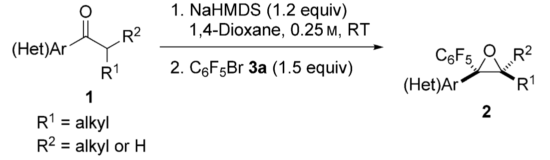
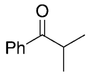
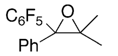
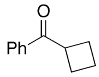
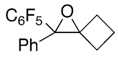
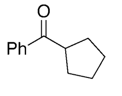
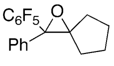
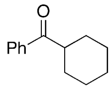
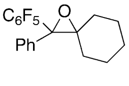
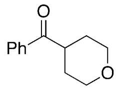
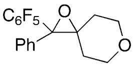
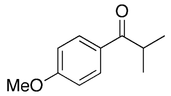
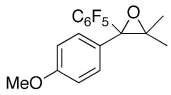
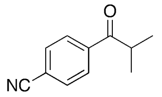
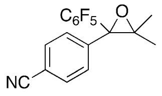
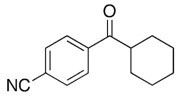
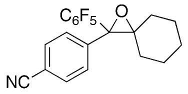
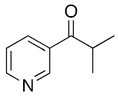
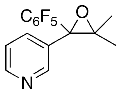
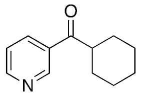
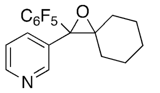
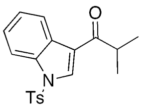
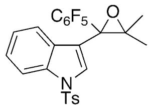
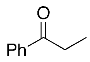
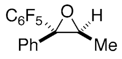
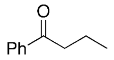
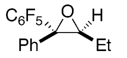
Table 2: Synthesis of pentafluorophenyloxiranes.



Entry	Ketone **1**		Product **2**		Yield [%][a] (d.r.)
1	**1a**		**2a**		92 90[b]
2	**1b**		**2b**		>99
3	**1c**		**2c**		74
4	**1d**		**2d**		70
5	**1e**		**2e**		66
6	**1f**		**2f**		88
7	**1g**		**2g**		65
8	**1h**		**2h**		82
9	**1i**		**2i**		53
10	**1j**		**2j**		62
11	**1k**		**2k**		60
12	**1l**		**2l**		81 (95:5) 90 (95:5)[c]
13	**1m**		**2m**		85 (93:7)

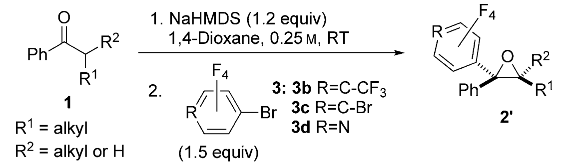
[a] Yields of product isolated from 0.5 mmol reactions. [b] Reaction was conducted in toluene. [c] A 10 mmol reaction in toluene.

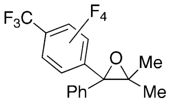
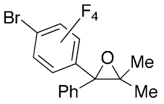
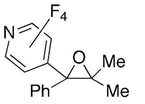
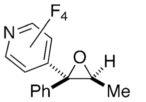
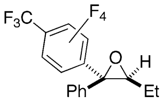
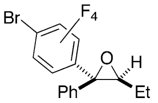
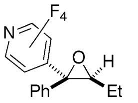
ketones **1i,j** and *N*-tosylindole-3-yl ketone **1k**, were converted into the corresponding epoxides **2i–k** in good yields (entries 9–11). Importantly, in contrast to the epoxidation reaction with alkynyl bromides[4] and cyanogen bromide,[5] PFPBr smoothly reacted with propiophenone **1l** and butyrophenone **1m**, producing the corresponding trisubstituted oxiranes **2l,m** in good yields and very high diastereoselectivities[7] (entries 12 and 13). It should be mentioned that this reaction is easily scalable, as a 10 mmol scale reaction of propiophenone **1l** with PFPBr resulted in an outcome similar to that for the 0.5 mmol reaction (entry 12).

Next, the scope of bromopolyfluroarenes was tested. It was found that 1-bromo-4-trifluoromethyltetrafluorolbenzene **3b**, 1,4-dibromotetrafluorobenzne **3c**, and 4-bromotetrafluoropyridine **3d** were all competent reactants in this cascade transformation, producing the corresponding polyfluoroaryl (hetaryl) epoxides in good yields (**2′n–t**). Although the reactions of **3b–d** with propiophenone and butyrophenone produced good yields of the trisubstituted epoxides **2′q–t**, the diastereoselectivity was lower (Table 3, entries 4–7) than that of the analogous reactions with PFPBr (Table 1, entries 12 and 13).

The synthetic utility of the polyfluorophenyloxirane products was showcased by their further transformation. First, it was demonstrated that oxiranes **2b** and **2l**, in the presence of a stoichiometric amount of $FeCl_3$, undergo a facile semipinacol rearrangement[8] to produce both ring expansion product **4a** and a H-migration product **4b** in good to excellent

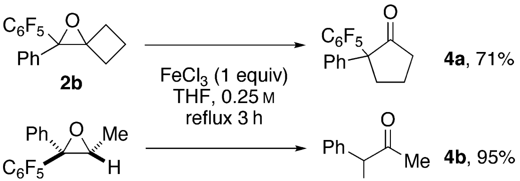
Table 3: Synthesis of polyfluoroaryloxiranes.



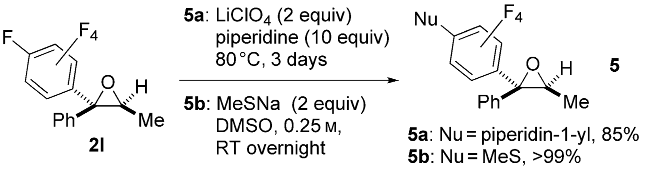
Entry	Ketone **1**	Bromide **3**	Product **2′**		Yield [%][a] (d.r.)
1	**1a**	**3b**	**2′n**		80
2	**1a**	**3c**	**2′o**		84
3	**1a**	**3d**	**2′p**		60
4	**1l**	**3b**	**2′q**		86 (85:15)
5	**1m**	**3b**	**2′r**		81 (77:23)
6	**1m**	**3c**	**2′s**		75 (90:10)
7	**1m**	**3d**	**2′t**		77 (90:10)

[a] Yields of product isolated from 0.5 mmol reactions.

yields (Scheme 3). Second, it was shown that polyfluorophenyl oxiranes are excellent substrates for $\mathrm{S_NAr}$ reactions[9] (Scheme 4). Thus, **2l** underwent an efficient substitution reaction with piperidine and sodium methylthiolate to produce the corresponding N- and S-containing products **5a** and **5b**, respectively, in excellent yields and with no oxirane ring-opening[10] products detected.



Scheme 3. Semipinacol rearrangement of oxiranes.



Scheme 4. $\mathrm{S_NAr}$ on a pentafluorophenyl ring.

In conclusion, we have demonstrated that amphoteric bromopolyfluoroarenes (or heteroarenes) can serve as equivalents of both Br$^+$ and aryl (or hetaryl) anions in the same cascade transformation. The reaction of enolizable ketones with bromopolyfluoroarenes leads to a variety of valuable tri- and tetrasubstituted epoxides[11] in good to excellent yields and diastereoselectivities. The synthetic utility of the polyfluorophenyl-containing oxirane products was demonstrated by their further transformation, including a semi-pinacol rearrangement and $\mathrm{S_NAr}$ reactions.

Experimental Section

Ketone (0.5 mmol) was added to an oven-dried, conical vial equipped with a magnetic stir bar and a PTFE-topped screw cap. The vessel was then evacuated and recharged three times with argon. Anhydrous 1,4-dioxane (2.5 mL) was added dropwise and the reaction mixture was stirred until the ketone was completely dissolved. NaHMDS (0.6 mL, 1 M in THF) was subsequently added to the solution and the resulting mixture was stirred for 5 min. PFPBr, or another aryl bromide, was then added dropwise to this mixture and stirred for another 15 min, at which time precipitation of NaBr was observed. The reaction mixture was filtered through a silica or zeolite pad and washed with 50 mL of diethyl ether. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel with a gradient from pure hexanes to 20:1 (v/v) hexanes/ethyl acetate to obtain the final product.

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Keywords: bromopentafluorobenzene · cascade transformations · epoxidation · perfluorinated compounds · perfluoroarylepoxides

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