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## One-Pot Arylative Epoxidation of Ketones Employing Amphoteric Bromoperfluoroarenes\*\*

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### Abstract

A one-pot cascade arylative epoxidation of enolizable ketones with bromopentafluorobenzene (PFPBr) and derivatives into perfluoroaryl oxiranes is reported. PFPBr is utilized as an equivalent of Br<sup>+</sup> and PFP<sup>-</sup> in this highly efficient, easily scaled up and diastereoselective epoxidation reaction, which produces synthetically useful polyfluoroaryl oxiranes.

### Keywords

bromopentafluorobenzene; polyfluoroarylepoxydes; cascade transformation

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

Our group has recently reported that alkynyl bromides and cyanogen bromide can act as equivalents of both Br<sup>+</sup> and alkynyl- or cyanide anions in a highly efficient one-pot conversion of ketones into fully substituted alkynyl or cyanoepoxydes.<sup>[4,5]</sup> Since the amphoteric reactivity of PFPBr as an equivalent of either Br<sup>+</sup> or PFP<sup>-</sup> has been reported (Scheme 1), we hypothesized that it may also serve as a competent reagent for the one-pot cascade epoxidation reaction of ketones (Scheme 2). It was expected that an enolate would abstract Br<sup>+</sup> from PFPBr to produce an  $\alpha$ -bromoketone **i** and a PFP anion. Following nucleophilic addition of the latter at the carbonyl group would generate an alkoxide **v**, which, upon intramolecular S<sub>N</sub>2 reaction would produce the oxirane **2**.

To test the above hypothesis, the reaction of isobutyrophenone (**1a**) and PFPBr (**3a**) has been examined (Table 1). Gratifyingly, it was found that employment of LiHMDS in THF

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led to 23% yield of the epoxide **2a** (entry 3)! Further brief optimization of the reaction conditions revealed that isobutyrophenone in the presence of NaHMDS in 1,4-dioxane almost quantitatively was converted into tetrasubstituted epoxide **2a** (entry 9). Under these reaction conditions, 1-bromoperfluorobutane and 1-iodoperfluorobutane did not undergo this cascade transformation.<sup>[6]</sup>

Next, the generality of the cascade transformation of different ketones with PFPBr was examined (Table 2). It was found that  $\alpha,\alpha$ -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 to the corresponding product **2e**. Diverse substituents at 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 ketone (**1j, j**) and *N*-tosyl-indole-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<sup>[4]</sup> and cyanogen bromide,<sup>[5]</sup> PFPBr smoothly reacted with propiophenone **1l** and butyrophenone **1m** producing the corresponding trisubstituted oxiranes (**2l, m**) in good yield and very high diastereoselectivity<sup>[7]</sup> (entries 12, 13). It should be mentioned that this reaction is easily scalable, as 10 mmol scale reaction of propiophenone **1l** with PFPBr resulted in outcome similar to that for 0.5 mmol reaction (entry 12).

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

The synthetic usefulness of the obtained polyfluorophenyl oxiranes was showcased by their further transformations. First, it was demonstrated that oxiranes **2b** and **2l** in the presence of stoichiometric amount of FeCl<sub>3</sub> undergo a facile semipinacol rearrangement<sup>[8]</sup> to produce the ring expansion product **4a** and a H-migration product **4b**, respectively, in good to excellent yields (Scheme 3). Secondly, it was shown that the obtained polyfluorophenyl oxiranes are excellent substrates for S<sub>N</sub>Ar reactions<sup>[9]</sup> (Scheme 4). Thus, **2l** underwent efficient substitution reaction with piperidine and sodium methylthiolate to produce the corresponding N- and S-containing products **5a** and **5b** in excellent yields with no oxirane ring opening<sup>[10]</sup> products detected.

In conclusion, we have demonstrated that amphoteric bromopolyfluoroarenes(heteroarenes) could serve as equivalents of both Br<sup>+</sup> and aryl(hetaryl) anions in the same cascade transformation. Thus, reaction of enolizable ketones with bromopolyfluoroarenes leads to a variety of valuable tri- and tetrasubstituted epoxides<sup>[11]</sup> in good to excellent yields and diastereoselectivity. A synthetic usefulness of the obtained polyfluorophenyl-containing oxiranes was further demonstrated in their transformations, including a semipinacol rearrangement and S<sub>N</sub>Ar reactions.

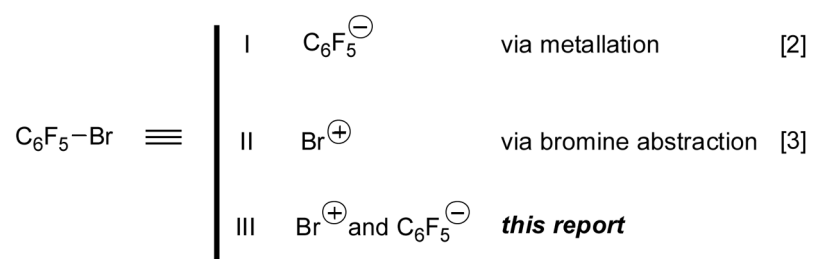
## Experimental Section

To an oven dried conical vial equipped with a magnetic stirring bar and a PTFE-topped screw cap, ketone (0.5 mmol) was added, and the vessel was evacuated and recharged by argon 3 times. Then anhydrous 1,4-dioxane (2.5 mL) was added dropwise and the reaction

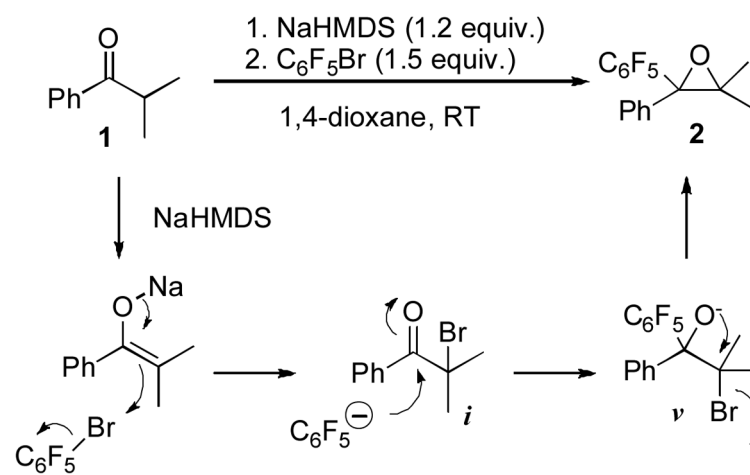
mixture was stirred until the ketone was completely dissolved. NaHMDS (0.6 mL, 1M in THF) was subsequently added to the solution of ketone aforementioned and the mixture was stirred for 5 minutes. Then PFPBr or other other arylbromide was added drop wise to the mixture and the reaction mixture was stirred for another 15 minutes and precipitation of NaBr was observed. Reaction mixture was filtered through a silica or zeolite pad, washed with 50 mL diethyl ether. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography of silica gel with hexane/ethyl acetate to obtain final product.

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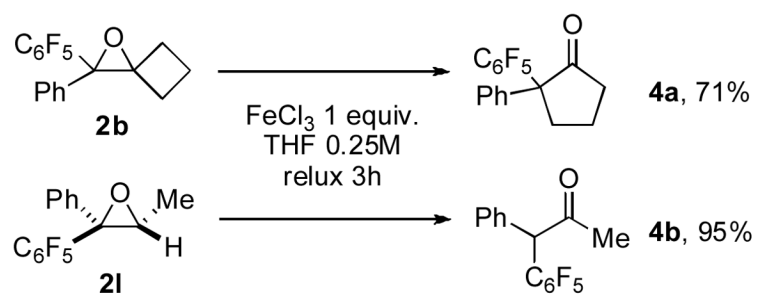
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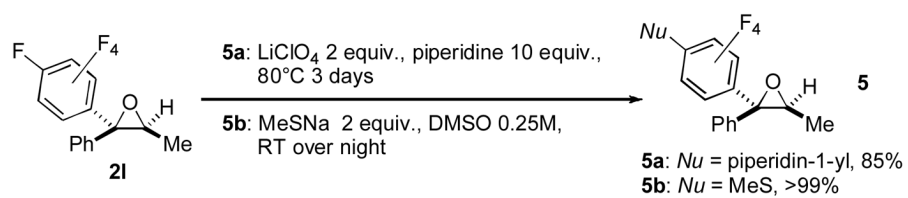
**Scheme 1.**  
Diverse Reactivity of PFPBr.

**Scheme 2.**

Proposed Reaction Path for Epoxidation of Ketones with PFPBr.



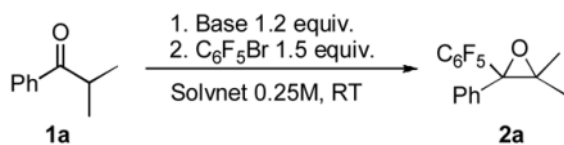
**Scheme 3.**  
Semipinacol Rearrangement of Oxiranes.



**Scheme 4.**  
S<sub>N</sub>Ar on Pentafluorophenyl Ring.

Table 1

Screening of Reaction Conditions.



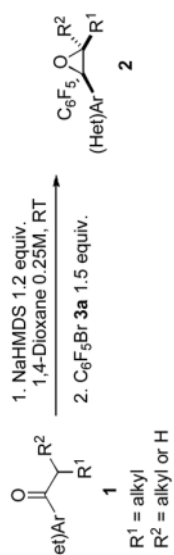
Entry	Base	Solvent	Result <sup>[a]</sup>
1	LiHMDS	DMF	trace
2	LiHMDS	Et <sub>2</sub> O	N.R.
3	LiHMDS	THF	23
4	LiHMDS	1,4-Dioxane	N.R.
5	LiO <sup>t</sup> Pr	THF	N.R.
6	LiO <sup>t</sup> Pr	1,4-Dioxane	N.R.
7	NaHMDS	THF	40%
8	NaHMDS	Et <sub>2</sub> O	75%
<b>9</b>	<b>NaHMDS</b>	<b>1,4-Dioxane</b>	<b>96%</b>
10	KO <sup>t</sup> Bu	THF	decomp
11	KO <sup>t</sup> Bu	1,4-Dioxane	decomp

<sup>[a]</sup>GC yields, using pentadecane as an internal standard.

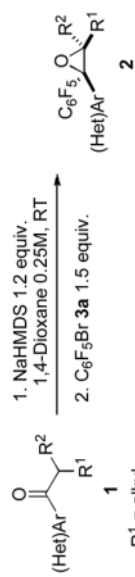


Table 2

Synthesis of Pentafluorophenyl Oxiranes.

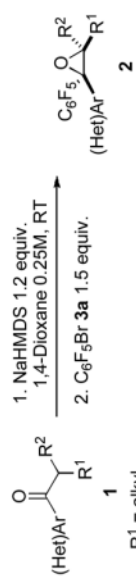


Entry	Ketone 1	Product 2	Yield, % <sup>[a]</sup> (dr)
1			92 90/ <sup>b</sup>
2			>99
3			74
4			70
5			66



R<sup>1</sup> = alkyl  
 R<sup>2</sup> = alkyl or H

Entry	Ketone 1	Product 2	Yield, %/dr
6	<b>1f</b> 	<b>2f</b> 	88
7	<b>1g</b> 	<b>2g</b> 	65
8	<b>1h</b> 	<b>2h</b> 	82
9	<b>1i</b> 	<b>2i</b> 	53
10	<b>1j</b> 	<b>2j</b> 	62



R<sup>1</sup> = alkyl  
 R<sup>2</sup> = alkyl or H

Entry	Ketone 1	Product 2	Yield, % <sup>[a]</sup> (dr)
11	 1k	 2k	60
12	 1l	 2l	81 (95:5) 90 (95:5) <sup>[c]</sup>
13	 1m	 2m	85 (93:7)

<sup>[a]</sup> Isolated yields of 0.5 mmol reactions.

<sup>[b]</sup> Reaction was in toluene medium.

<sup>[c]</sup> A 10 mmol reaction in toluene.

Table 3

## Synthesis of Polyfluoroaryl Oxiranes.

Entry	Ketone 1	Bromide 2	Product 3	Yield, % <sup>[a]</sup> (dr)
1				80
2	<b>1a</b>	<b>3b</b>	<b>2n</b>	84
3	<b>1a</b>	<b>3c</b>	<b>2o</b>	60
4	<b>1l</b>	<b>3b</b>	<b>2q</b>	86 (85:15)
5	<b>1m</b>	<b>3b</b>	<b>2r</b>	81 (77:23)

