Preprint Title	Synthesis and synthetic applications of (4-hydroxyphenyl)perfluoroalkylmethanols
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Publication Date	01 Juni 2021
Article Type	Full Research Paper
Supporting Information File 1	SI.pdf; 3.1 MB
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Synthesis and synthetic applications of (4-hydroxyphenyl)perfluoroalkyl-methanols

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Abstract

Development of the convenient method for the synthesis of (hydroxyphenyl)perfluoro-alkylmethanols was achieved by the Meerwein-Ponndorf-Verley (MPV) type reduction of the *in situ*-generated perfluoroalkylated ketones as the key step, and the benzylic OH group of the resultant alcohols was converted to H or $Rf(CH_2)_nO$ by way of the corresponding chlorides whose transformation was not easy by any other methods.

Keywords

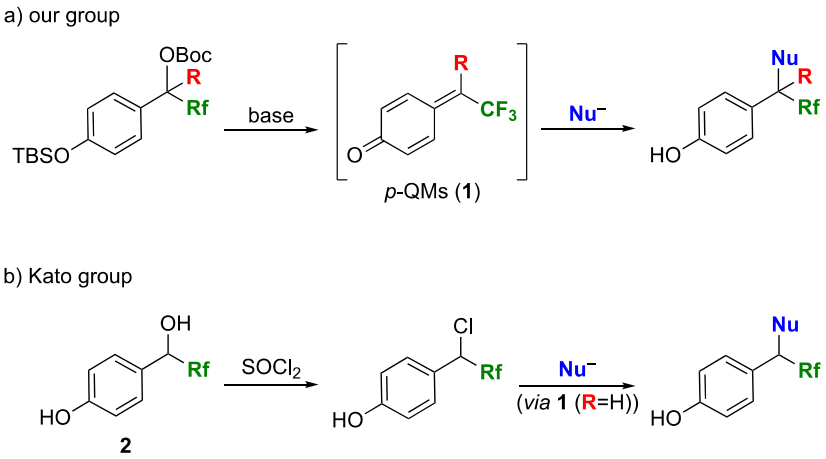
perfluoroalkyl; reduction; *p*-quinone methide

Introduction

p-Quinone methides (*p*-QMs, **1**) are recognized as one of the most interesting reactive intermediates [1–3] which demonstrate strong electrophilicity towards a variety of nucleophilic species where aromaticity restoration acts as the major driving force. Effective application of their feature recently allowed us to open new routes to construct quaternary [4,5] and tetrasubstituted [6] carbon centers with one of the substituents being a CF_3 group (Scheme 1a). As a clear advantage to the other *p*QM applications

[1–3] including fluorine-containing ones [7–10], our adequately designed substrates enabled the employment of only a catalytic amount of a base for promotion of the reactions with various nucleophiles.

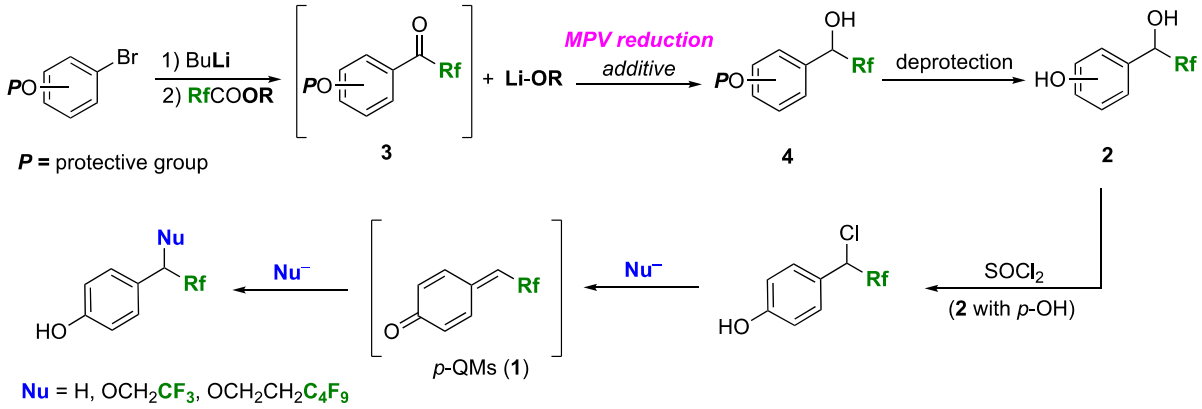
Among a large number of articles on *p*-QMs, one interesting report from the Kato group [8] has drawn our attention, which dealt with the introduction of Nu moieties by treatment of the alcohol **2** (Rf: CF_3) with appropriate Grignard reagents, $NaBH_4$ [8], or a variety of carbanionic species [10,11] by way of the corresponding benzylic chloride (Scheme 1b).



Scheme 1: Previous synthetic routes to (4-hydroxyphenyl)perfluoroalkylmethanols **2**.

Thus, this process readily realizes the net substitution at the CF_3-attached carbon atom which is considered to be difficult *via* S_N1 [12,13] or S_N2 [14–16] reactions from the standpoint of the steric and electrostatic nature of this group. However, strongly acidic conditions are known to exceptionally facilitate this type of conversion [17,18]. Our another interest stems from the fact that the compounds like **2** are easily accessible from the *O*-protected bromobenzenes after their conversion to the corresponding organometallic species, followed by the reaction with $RfCO_2R$ leading to the formation of the desired **2** by way of the Meervein-Ponndorf-Verley (MPV) reduction by the *in situ*-generated metal alkoxide which was independently reported by us [19] as well as other groups [20,21]. In spite of straightforward construction of **2** by the convenient Friedel-Crafts type reactions [22,23], this process is known to be suffered from the contamination by the undesired *o*-regioisomers as well as multiply substituted products [23]. Because of these reasons, we investigated the construction of benzylic alcohols with alkoxy moieties at *o*- or *p*- as well as *m*-positions of the benzene ring and Rf groups such as CF_3, C_3F_7, C_4F_9, and C_6F_{13} because, to the best of our knowledge, there is only one report dealing with *p*-QMs with Rf groups other than CF_3 [9]. Moreover, thus obtained compounds **2** were employed for the net

substitution of the benzylic OH group for hydrogen or fluorine-containing alkoxy groups, the latter of which were not easily accessible by the usual alkylation technique to the original benzylic OH group (Scheme 2).



Scheme 2: Synthetic routes to (hydroxyphenyl)perfluoroalkylmethanols **2** and its derivatization by way of *p*-QMs.

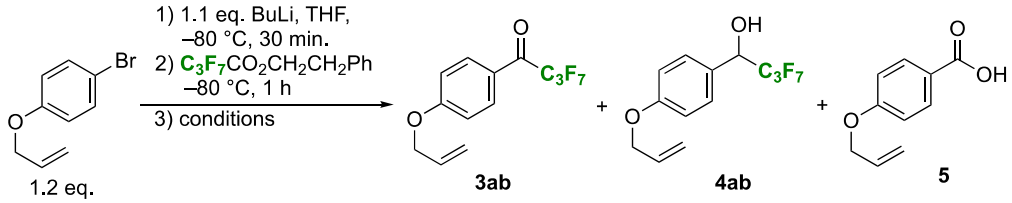
Results and Discussion

Reduction of ketones containing Rf groups by metal alkoxides

First of all, we have initiated our research from the MPV reduction of the *in situ*-constructed ketone **3ab** obtained by the reaction of 2-phenylethyl heptafluorobutyrate and the lithiated species from 4-(allyloxy)phenyl bromide. This allyl protective group was selected on the basis of its good resistance both for acidic and basic conditions as well as ready removal by a combination of TMSCl and NaI [24].

As described by us [19] as well as other groups [20,21], the MPV reduction of the fluorinated ketone **3ab** was affected by the lithium alkoxide generated *in situ*, but the desired reaction was found to proceed only partially possibly because of the lower reduction ability of the resultant $PhCH_2CH_2OLi$ (Table1, Entries 1 and 2). In these cases, a small amount of the byproduct was noticed which was considered to be the carboxylic acid **5** possibly formed as a result of the haloform type sequence [20,25–27]. Validity of the *i*-PrOH addition to this system [19] was noticed to nicely constitute an equilibrium with $LiOCH_2CH_2Ph$ which afforded *i*-PrOLi with the higher MPV reduction ability, resulting in formation of **3ab** in 60% yield (Entry 3). Although an excess amount of *i*-PrOH was not effective at all for the chemical yield of **3ab** (Entry 4), the reduction was completed in an hour at the elevated temperature, in particular under reflux in THF to attain the better result in much shorter reaction time (Entries 5

Table 1. Optimization of MPV reduction of 4-(allyloxy)bromobenzene.



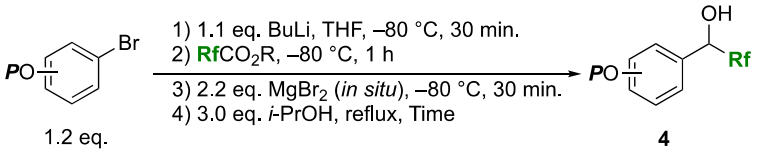
Entry	Conditions	Isolated yield[a] (%)	
		3ab	**4ab**
1[b]	r.t., 12 h	(28)	(34)
2[b]	reflux, 1 h	(24)	40
3	3.0 eq. *i*-PrOH, r.t., 12 h	0	60
4	30 eq. *i*-PrOH, r.t., 12 h	0	57
5	3.0 eq. *i*-PrOH, 50 °C, 1 h	0	66
6	3.0 eq. *i*-PrOH, reflux, 1 h	0	69
7	1.1 eq. $MgBr_2$[c], –80 °C, 30 min. then 3.0 eq. *i*-PrOH, reflux, 1 h	0	89
8	1.1 eq. $MgBr_2$[d], –80 °C, 30 min. then 3.0 eq. *i*-PrOH, reflux, 1 h	0	77
9	2.2 eq. $MgBr_2$[d], –80 °C, 30 min. then 3.0 eq. *i*-PrOH, reflux, 1 h	0	89

[a]In the parenthesis were shown the yields determined by ^{19}F NMR. [b]Formation of **5** as a byproduct was noticed in both cases. [c]Commercially available $MgBr_2$ was employed. d) *In situ* generated $MgBr_2$ was employed.

and 6). Introduction of commercially available $MgBr_2$ to a mixture was quite effective for the promotion of this procedure, and the desired alcohol **4ab** was obtained in 89% yield (Entry 7). *In situ* prepared $MgBr_2$ from Mg and 1,2-dibromoethane also worked nicely to give the same level of the yields (Entries 8 and 9).

With the optimal reaction conditions in hand (Entries 7 and 9 in Table 1), we next examined the substrate scope for this reaction whose results were summarized in Table 2. When brominated phenols protected by an allyl group were used, the corresponding alcohols with a C_3F_7 moiety were obtained in high yields irrespective of the substitution position (Entries 2, 5 and 7). Moreover, the esters with shorter (CF_3) or longer (C_6F_{13}) Rf chains were found to be applicable and construction of the desired products were nicely realized in good yields (Entries 1 and 3). Employment of other

Table 2 Synthesis of various alcohols **4** by way of the MPV reduction.[a]



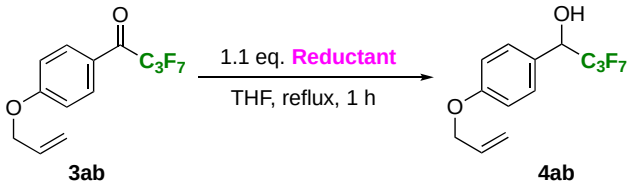
Entry	***P*O group**	**Rf**CO_2R	Time (h)	Isolated yield (%)
1	*p*-allyl-O-	**CF_3**CO_2Et	6	65 **(4aa)**
2	*p*-allyl-O-	**C_3F_7**CO_2Et	1	89 **(4ab)**
3	*p*-allyl-O-	**C_6F_{13}**CO_2Me	12	65 **(4ad)**
4	*m*-allyl-O-	**CF_3**CO_2Et	6	68 **(4ba)**
5	*m*-allyl-O-	**C_3F_7**CO_2Et	1	86 **(4bb)**
6	*o*-allyl-O-	**CF_3**CO_2Et	18	74 **(4ca)**
7	*o*-allyl-O-	**C_3F_7**CO_2Et	18	80 **(4cb)**
8	*p*-Me-O-	**CF_3**CO_2Et	6	66 **(4da)**
9	*p*-Me-O-	**C_3F_7**CO_2Et	1	79 **(4db)**
10	*o*-Me-O-	**CF_3**CO_2Et	18	65 **(4ea)**
11	*o*-Me-O-	**C_3F_7**CO_2Et	18	82 **(4eb)**
12	*p*-THP-O-	**C_3F_7**CO_2Et	1	80 **(4fb)**
13[b]	*p*-THP-O-	**C_3F_7**CO_2Et	1	75 **(4fb)**
14[b]	*p*-THP-O-	**C_6F_{13}**CO_2Me	1	75 **(4fd)**

[a]Reaction was carried out by using 1 mmol of **Rf**CO_2**R**. [b]5 mmol of **Rf**CO_2**R** was used.

protective groups like Me or THP (tetrahydropyranyl) also allowed to furnish results similar to the case of the allylic protection. In particular, it was revealed that the gram scale process with the THP-protected substrate at the *p*-position led toformation of nice solid products whose convenient purification required just washing the crude material by a mixture of CH_2Cl_2 and hexane, affording the desired products **4fb** and **4fd** with satisfactory purity for further steps (Entries 12–14).

The effect of $MgBr_2$ for the present reduction was briefly examined for the reaction of the ketone **3ab** and metal alkoxides (Table 3). In agreement with our previous report, *i*-PrOMgBr was very suitable for the MPV reduction (Entry 1), but this is not the case for *i*-PrOLi only afforded the same product **4ab** in lower yield (Entry 2). It is interesting to note that the addition of $MgBr_2$ to this lithium-based alkoxide dramatically improved the situation and almost the same result to the case of Entry 1 was attained (Entry 3). This was considered as the consequence of the metal exchange of *i*-PrOLi and $MgBr_2$ judging from the bond dissociation energy (Li-O: 341 kJ/mol, Li-Br: 423 kJ/mol, Mg-O:

Table 3 The effect of $MgBr_2$.



3ab **4ab**

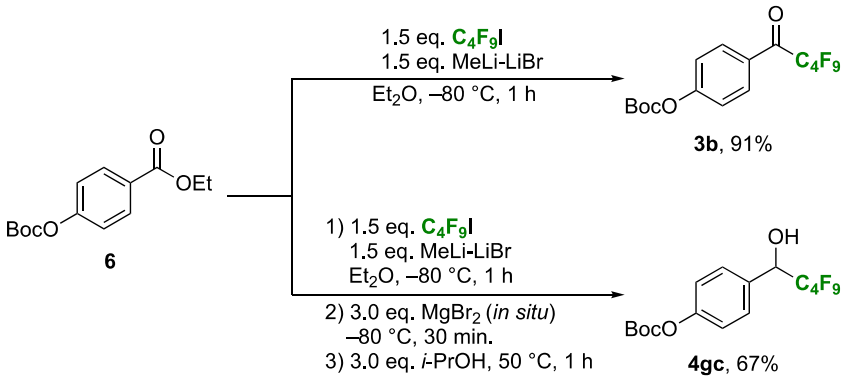
Entry	Reductant	Isolated yield (%)
1	*i*-PrOMgBr	94
2[a]	*i*-PrOLi	53
3	*i*-PrOLi + $MgBr_2$	88
4[b]	$NaBH_4$	91

[a]Formation of **5** as a byproduct was noticed.
[b]The reaction was conducted at r.t. for 1 h.

394 kJ/mol, Mg-Br: 297 kJ/mol) [28], furnishing the better reductant *i*-PrOMgBr *in situ*. Moreover, this Table clearly indicated the analogous power of *i*-PrOMgBr to the well-known reductant, $NaBH_4$, and thus, this MPV reduction was recognized as the alternative as well as reliable method for the preparation of this type of Rf-possessing alcohols **4**.

Next, the alternative protocol was investigated to get access to our target by using Rf-I as the perfluoroalkyl source. After some screening, we have found out the optimal conditions providing the ketone **3b** starting from ethyl *p*-hydroxybenzoate **6** whose OH moiety was protected by the Boc group. After confirmation of this ketone **3b** production by TLC, introduction of both $MgBr_2$ and *i*-PrOH to the reaction mixture affected the desired protocol to afford the corresponding alcohol **4gc** in good overall yield in a one pot manner (Scheme 3).

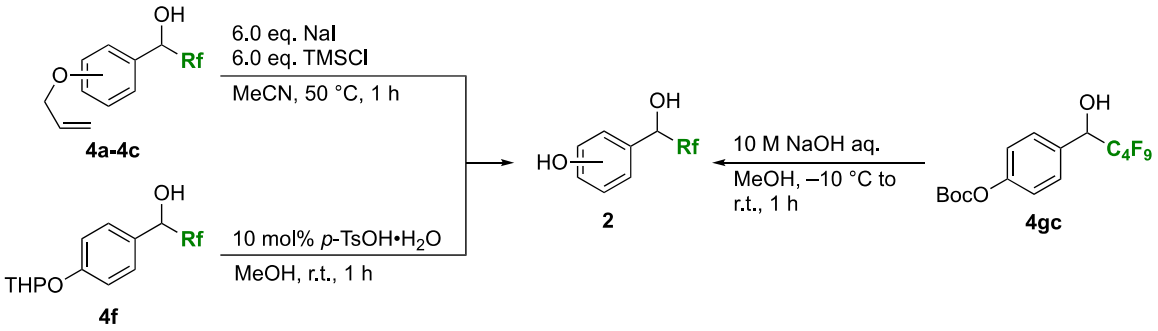
In Table 4 was depicted the condition for the deprotection of **4**. The allyl group in



Scheme 3: Synthesis of the ketone **3b** and the corresponding alcohol **4gc** from **6**.

4aa-4ac was efficiently removed by the combination of TMSCl and NaI regardless of the length of Rf chains (Entries 1 to 4). However, the steric congestion was considered to be the major reason why the compound **4cb** recorded a lower yield along with some unidentified byproducts (Entry 5). On the other hand, the THP moiety was smoothly eliminated by the action of a catalytic amount of *p*-TsOH in methanol (Entries 6 and 7), and cleavage of the Boc group in **4gc** was readily attained by aqueous NaOH to quantitatively afford the corresponding phenol product **2ac**.

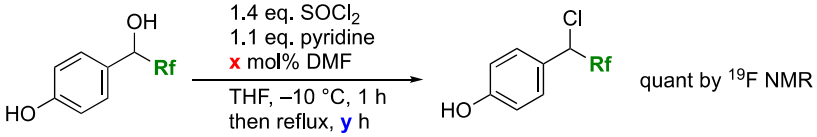
Table 4 Deprotection of **4**.



Entry	Substrates	Rf	Isolated yield of **2** (%)
1	**4aa**	CF_3	72 (**2aa**)
2	**4ab**	C_3F_7	73 (**2ab**)
3	**4ad**	C_6F_{13}	70 (**2ad**)
4	**4bb**	C_3F_7	89 (**2bb**)
5	**4cb**	C_3F_7	41 (**2cb**)
6	**4fb**	C_3F_7	95 (**2ab**)
7	**4fd**	C_6F_{13}	95 (**2ad**)
8	**4gc**	C_4F_9	99 (**2ac**)

Conversion of the OH group at the benzylic position

Next, by way of *in situ* generation of *p*-quinone methides **1**, the efficient



2ab (Rf = C_3F_7)
2ac (Rf = C_4F_9)
2ad (Rf = C_6F_{13})

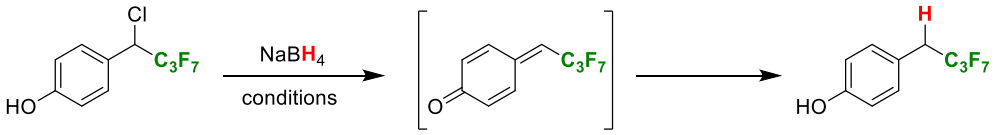
7b: x = 10, y = 2 (Rf = C_3F_7)
7c: x = 20, y = 3 (Rf = C_4F_9)
7d: x = 50, y = 6 (Rf = C_6F_{13})

Scheme 4: Chlorination of **2** at the benzylic position.

conversion of the OH group at the benzylic position of **2** was performed. At first, chlorination of **2** was conveniently carried out without any protection at the phenolic hydroxy group under the reported conditions [8], but this method met low reproducibility possibly because of low solubility of these phenols in the original solvent, toluene. After examination of other solvents, THF was found to be suitable for realization of the almost quantitative conversion of **2** to **7** in the presence of the additive DMF whose amount was required to be proportionally increased by the chain length of the Rf group (Scheme 4).

Reductive removal of the C-Cl in **7b** without further purification was performed by the treatment with $NaBH_4$ in THF at room temperature, which produced the desired **8b**. However, this product was suffered from contamination with byproducts whose separation was difficult (Entry 1 in Table 5). Increase of the equivalent of $NaBH_4$ dramatically improved this problematic situation but failed in complete suppression of byproducts (Entry 2). DME recorded a similar result to the case of THF, and Et_2O was found to be inadequate (Entries 3 and 4). Finally, it was clarified that raising the

Table 5: Investigation of the reduction of OH at the benzylic position in **7**.



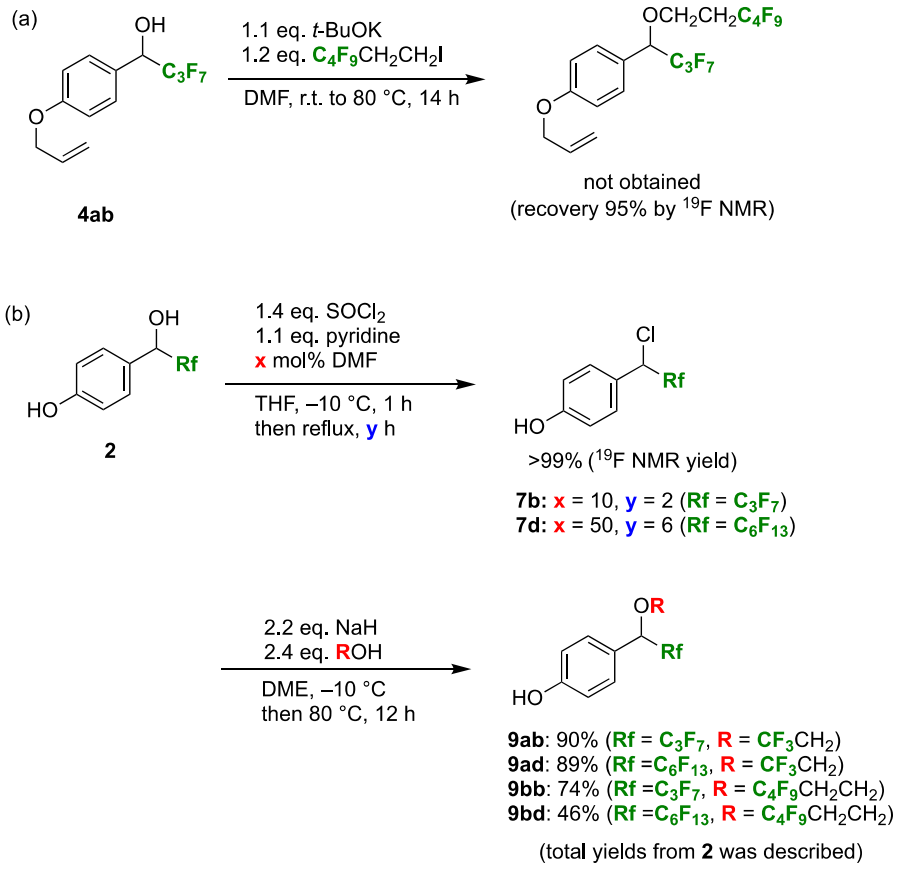
7b **1b** **8b**

Entry	Substrate	$NaBH_4$ (eq.)	Conditions	^{19}F NMR yield[a,b] (%)	
1	**7b**	1.5	THF, –10 ºC, 30 min., then r.t. 12 h	52	[43]
2	**7b**	3.0	THF, –10 ºC, 30 min., then r.t. 12 h	93	
3	**7b**	3.0	DME, –10 ºC, 30 min., then r.t. 12 h	>95	
4	**7b**	3.0	Et_2O, –10 ºC, 30 min., then r.t. 12 h	3	
5	**7b**	3.0	THF, reflux, 12 h	>99	
6	**7b**	3.0	THF, reflux, 1 h	>99	
7	**7b**	2.0	THF, reflux, 1 h	>99	[93]
8	**7b**	1.5	THF, reflux, 1 h	80	
9	**7c**	2.0	THF, reflux, 1 h		[97]
10	**7d**	2.0	THF, reflux, 1 h		[89]

[a]2-Step total yield from **2**. [b]In the brackets were shown the 2-step yield after isolation. [c]Recovery 85% (determined by ^{19}F NMR).

reaction temperature was crucial to lead to the quantitative conversion of **7b** to the desired product **8b** just in an hour (Entries 5 and 6), and 2.0 eq. of $NaBH_4$ was found to be suffice (Entries 7 and 8). The optimized condition depicted in Entry 7 was also applicable to **7c** and **7d** to furnish the corresponding products **8c** and **8d** in excellent yields (Entries 9 and 10), respectively. Transformation of the benzylic OH group to H was usually performed by way of the Bu_3SnH-mediated radical reduction of the corresponding esters [29–32] or the corresponding halide [33]. However, it is quite interesting to note that the presence of a phenolic OH group at the *p*-position strongly facilitated this process just by the treatment with such a convenient and safe reagent as $NaBH_4$.

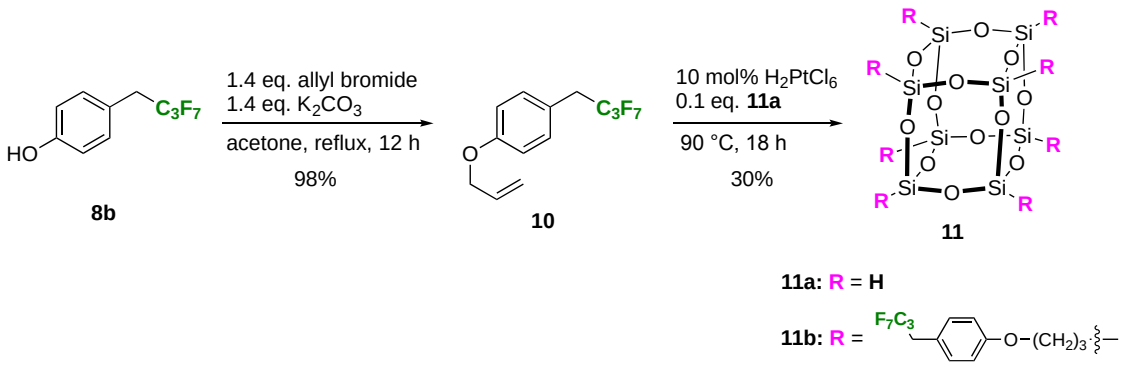
This Cl atom was also effective for the net substitution by polyfluorinated alcohols whose products were usually difficult to be prepared by way of the *O*-alkylation of **2**. For example, as shown in Scheme 5a, alkylation of **4ab** by $C_4F_9CH_2CH_2I$ after the conversion to the corresponding alkoxide only led to the recovery of **4ab** because this



Scheme 5: Transformation to the perfluorinated ethers (total yields from **1** was described).

alkoxide only acted as a base to abstract an acidic proton next to the C_4F_9 moiety. Construction of **9ab** or **9ad** from **2** was also problematic due to the reluctance of CF_3CH_2I to accept nucleophilic attack by alkoxides. Thus, introduction ofpolyfluorinated alkoxides at the benzylic position was quite rare until now [6].

Two representative compounds **2ab** (Rf: C_3F_7) and **2ad** (Rf: C_6F_{13}) were employed here for the reaction with CF_3CH_2ONa and $C_4F_9CH_2CH_2ONa$ and four types of **9** were constructed in good to excellent yields irrespective of the Rf chain length in **2** as well as the structures of the nucleophilic polyfluorinated alkoxides (Scheme 6).



Scheme 6: Synthesis of Fluorine-containing POSS **11b**.

Polyhedral oligomeric silsesquioxane (POSS) recently attracted significant attention as a variety of organic-inorganic hybrid nanomaterials [34,35] while there have appeared only a few reports on the corresponding fluoroalkyl-containing counterparts [36–40]. Thus, the synthesis of POSS was carried out for demonstration of the synthetic utility of **8** (Scheme 6). Allylation at the phenolic hydroxy group of **8b** proceeded in smooth as well as semi-quantitative manners, and hydrosilylation of the resultant **10** with **11a** was realized in the presence of a catalytic amount of H_2PtCl_6 to furnish the desired POSS **11b** whose structure was fully confirmed by NMR (^1H, ^{13}C, ^{19}F) spectra and the elemental analysis.

Conclusion

In conclusion, we have developed a new synthetic method to get access to a variety of Rf-possessing benzylic alcohols **2** by way of the convenient MPV reductions which were realized on the basis of a byproduct ROLi without addition of the usual hydride reductants. Moreover, the facile conversion of the benzylic OH group on the carbon possessing an Rf group was accomplished by utilization of the characteristics of *p*QMs generated *in situ*, although substitution at this site is usually known to be

extremely difficult. In spite of a structural limitation for the substrates applicable, we believe that this method opens a new avenue to construct unique structures like **8** and **9**, which have been barely reported thus far.

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