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Facile double *O*-difluoromethylations of diphenols with $TMSCF_2Br$

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ABSTRACT

A simple and highly efficient method for the double *O*-difluoromethylations of diphenols in 10 min is described, using $TMSCF_2Br$ as a difluorocarbene reagent. The reactivity order of different diphenols is *o*-diphenol > *m*-diphenol > *p*-diphenol in the two-phase difluoromethylation reaction, which can be explained by the different lipophilicities of these different diphenols.

Introduction

Fluoroorganic compounds have received extensive attention in advanced materials [1], pharmaceuticals [2] and agrochemicals [3], among others [4]. Among various fluorine-containing moieties, the difluoromethoxyl group (OCF_2H) frequently exists in many drugs. For example, Roflumilast, Pantoprazole, and Garenoxacin contain one OCF_2H unit [5], and Seviteronel and the precursor of Antifibrotic agent contain two OCF_2H units (Scheme 1a) [6]. Their applications in medicines are attributed to the unique properties of the CF_2H group [7], especially as a lipophilic hydrogen bond donor [8].

Due to the wide applications of aryl difluoromethyl ethers in biomedicine, the access to aryl difluoromethyl ethers from the difluoromethylation of phenols with a series of difluorocarbene reagents have been extensively documented (Scheme 1b) [9]. However, only few examples for the synthesis of bis-difluoromethoxylated compounds have been reported (Scheme 1c), including double *O*-difluoromethylations of diphenols with HCF_2Cl, CF_3CO_2Na, $BrCF_2CO_2Et$, $ClCF_2CO_2Na$, $ClCF_2CO_2Me$ or $BrCF_2P(O)(OEt)_2$ as the difluorocarbene source at high temperatures (60–110 °C) in 3 to 48 h [6,10–13]. These methods suffer from drawbacks such as high reaction temperature, long reaction time, poor tolerance of functional groups, and narrow substrate scope, which limits the wide application of these double *O*-difluoromethylation methods. Therefore, the development of new efficient and mild methods for double *O*-difluoromethylations of diphenols is highly desirable.

Based on our group's previous study on *O*-difluoromethylation, we decided to examine the double *O*-difluoromethylations of diphenols with $TMSCF_2Br$ as the privileged difluorocarbene reagent [14]. $TMSCF_2Br$, a difluorocarbene reagent initially developed by our group, is now commercially available and frequently applied in organic synthesis [14j,15a]. It could react with a wide range of compounds, such as reactions with (thio)phenols to form difluoromethylated compounds, with aldehydes or diazo compounds to form difluoroalkenes, with alkenes (alkynes) to form difluorocyclopropanes (difluorocyclopropenes) [14,15].

Results and discussion

Initially, we chose pyrocatechol (**1a**) as a model substrate, and the reaction was carried out following the previously reported conditions (Table 1, entry 1) [14g]. However, only a 16 % yield of product **3a** was afforded (entry 1). Considering that the reaction is a two-phase system, the phase-transfer catalyst *n*-Bu_4NBr (TBAB) was applied to improve the reaction yield (entry 2). Gratifyingly, adding 0.5 equivalent of TBAB could increase the yield of **3a** to 61 %. It was found that the present reaction was not sensitive to temperature (entries 2–5), thus room temperature was chosen for convenience (entry 3). Similar phase-transfer catalysts such as TMABr, TBAC, and TBAI were tested (entries 6–8), which were found to be less efficient than TBAB. Besides KOH, other bases including LiOH and CsOH gave product **3a** with 9 % and 19 % yields, respectively (entries 9–10). Final optimization of the amount of TBAB (entries 11–12) and reaction time (entry 13) demonstrated that

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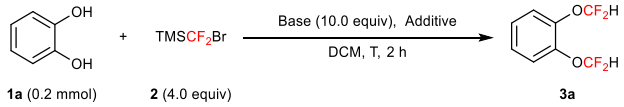
a 75 % yield of **3a** could be obtained from the reaction of 0.2 mmol of **1a** and 4.0 equivalents of **2** in the presence of 0.9 equivalent of TBAB and 10.0 equivalent of 20 wt% aqueous KOH in DCM at room temperature for 10 min.

Under the optimized reaction conditions, the substrate scope of the reaction was explored (Table 2). The double difluoromethylation reactions of *o*-diphenols proceeded smoothly, and the corresponding aryl difluoromethyl ethers were obtained in moderate to good yields (Table 2A). The reaction has good compatibility with various functional groups, such as methyl (**1d**, **1e**), methoxy (**1g**), halogen (**1j-o**), carbonyl (**1p**, **1r**), cyano (**1u**, **1v**), and trifluoromethyl groups (**1x**). Generally, substrates with electron-donor groups have slightly lower yields than substrates with electron-withdrawing groups. The present transformation was not sensitive to the position of the substituents of **1**. A loss in isolated yields was observed, probably owing to the volatility of the double difluoromethylated products. Subsequently, *m*- diphenol and *p*-diphenol substrates under the conditions A were investigated. Notably, the yields of double difluoromethylations of resorcinol (**1ae**) and hydroquinone (**1ag**) were dramatically decreased compare to catechol (**1a**) (Table 2B). The poor reactivity could be improved by the corporation of a phenyl or naphthyl group into *m*-diphenols or *p*-diphenols, generating the corresponding products **3y-3ad** in 27–64 % yields (Table 2C and D).

During the expansion of substrate scope, we found that similar double difluoromethylations of unsubstituted *m*-diphenol (**1ae**) and *p*-diphenol (**1ag**) only gave poor yields of corresponding products **3ae** (16 %) and **3ag** (15 %), respectively (see Table 2B). We quickly found that both diphenols **1ae** and **1ag** are dissolved mainly in aqueous phase, and $TMSCF_2Br$ is dissolved in organic phase (DCM). Therefore, we envisioned that the yield of the reaction is related to the distribution of substrates in the organic/aqueous two-phase system; that is, substrates with better water solubility could hardly enter the organic phase to react with difluorocarbene. To test our hypothesis, the relationship between the yield and lipophilicity (logP) of *o*-diphenols, *m*-diphenols, and *p*-diphenols in difluoromethylation reactions under conditions A was studied (Table 3). It was found that comparing with o-diphenol (1a, logP

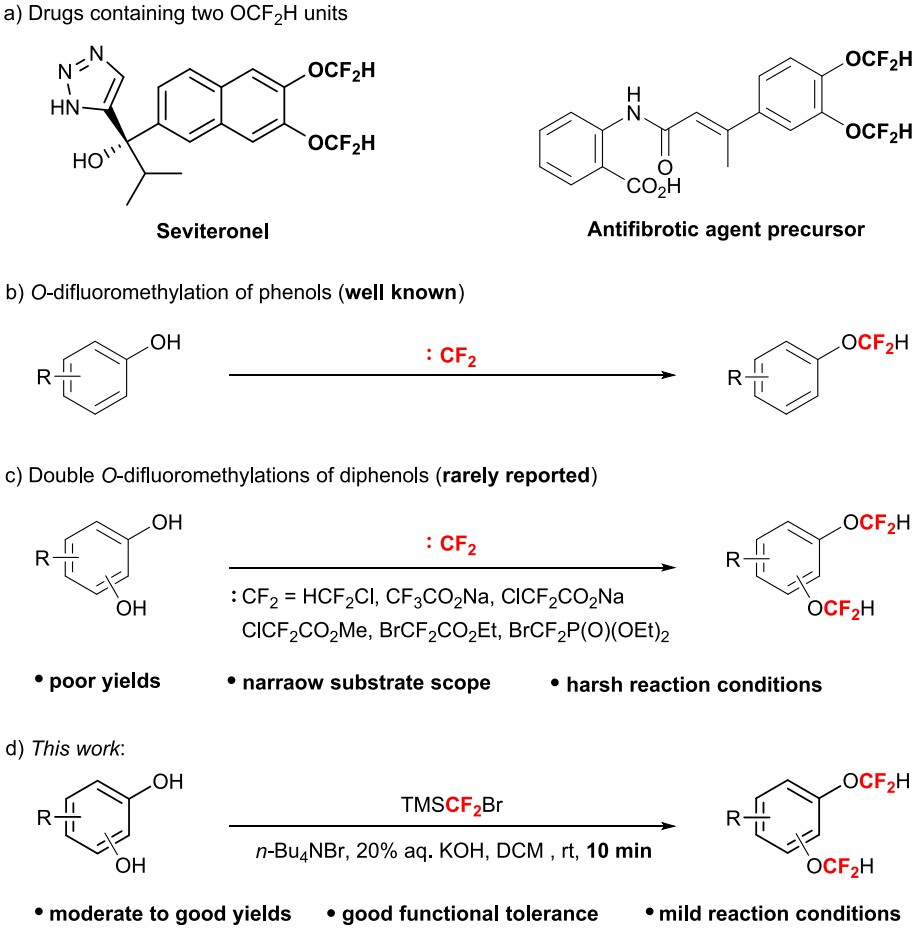
Table 1
Optimization of the reaction conditions.[a]



1a (0.2 mmol) **2** (4.0 equiv) **3a**

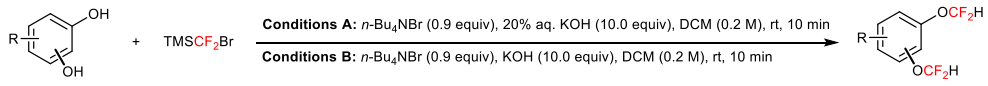
Entry	Base	Additive (equiv)	T (^{0}C)	Yield (%)[a]
1	20 % aq. KOH	none	0	16
2	20 % aq. KOH	TBAB (0.5)	0	61
3	20 % aq. KOH	TBAB (0.5)	rt	60
4	20 % aq. KOH	TBAB (0.5)	50	63
5	20 % aq. KOH	TBAB (0.5)	80	61
6	20 % aq. KOH	TMABr (0.5)	rt	20
7	20 % aq. KOH	TBAC (0.5)	rt	21
8	20 % aq. KOH	TBAI (0.5)	rt	45
9[b]	LiOH	TBAB (0.5)	rt	9
10	$CsOH·H_2O$	TBAB (0.5)	rt	19
11	20 % aq. KOH	TBAB (0.3)	rt	58
12	20 % aq. KOH	TBAB (1.0)	rt	70
13[c]	**20 % aq. KOH**	**TBAB (0.9)**	**rt**	**75**

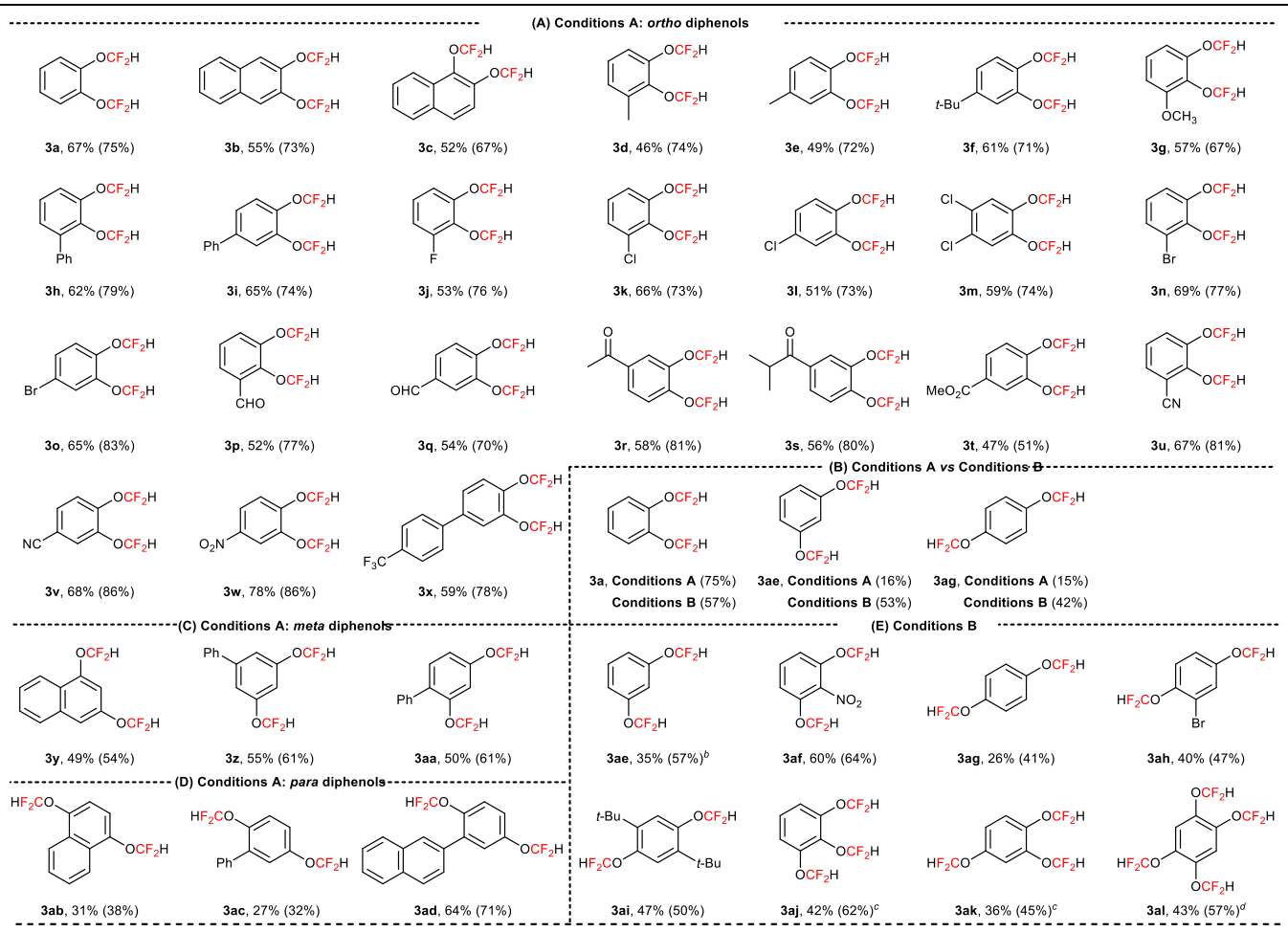
[a]Yields were determined by ^{19}F NMR using $PhCF_3$ as an internal standard.
[b] Add 0.5 mL of H_2O as a co-solvent.
[c] The reaction was performed for 10 min.



Scheme 1. Difluoromethylation of phenols with difluorocarbene reagents.

Table 2
Scope of diphenols for $TMSCF_2Br$-mediated difluoromethylations.[a]





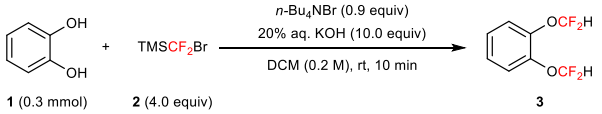
[a]Isolated yields. Yields in parentheses were determined by ^{19}F NMR using $PhCF_3$ as an internal standard.
[b]Reactions were conducted on a 0.5 mmol scale.
[c]Using 6.0 equivalents of $TMSCF_2Br$.
[d]Using 8.0 equivalents of $TMSCF_2Br$, DCM (0.1 M).

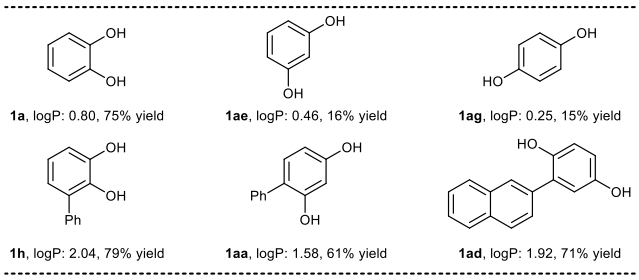
= 0.8), both m-diphenol (1ae) and p-diphenol (1ag) possess smaller logP values (0.46 for 1ae and 0.25 for 1ag), which may account for the low yields in the difluoromethylation reactions with 1ae and 1ag (Table 3). On the other hand, the difluoromethylations with substrates bearing a lipophilic group such as phenyl (**1aa**, logP 1.58) or naphthyl group (**1ad**, logP 1.92) affords the **3aa** and **3ad** in 61 % and 71 % NMR yields, respectively. These experimental results support our hypothesis that the yield of the reaction is related yield of the reaction is related to the distribution of substrates in the organic/aqueous two-phase system. In other words, the substrates with higher logP values generally give better yields in the double *O*-difluoromethylation reactions.

Inspired by the afore-mentioned insight, we attempted to perform the difluoromethylation under water-free conditions. As shown in Table 2E, when anhydrous KOH was used instead of 20 wt% aqueous KOH solution, the yields of the reactions with *m*-diphenol (**1ae**) and *p*-diphenol (**1ag**) were successfully improved from 16 % and 15 % to 53 % and 42 %, respectively (Table 2B). Under anhydrous conditions, there was little difference in the yields of the reactions with three diphenols, which further supports our hypothesis. It is noteworthy that for most lipophilic phenols and diphenols, organic/aqueous biphase reaction system [such as DCM/H_2O(KOH)] is preferred, because the base (such as KOH) dissolves in water phase and avoids rapid reactions with difluorocarbene (dissolves in organic phase). Therefore, for substituted *m*-diphenols and *p*-diphenols with high lipophilicity, the biphase reaction system (Conditions A) is preferred. However, for the substrates with high hydrophilicity, the anhydrous reaction medium (organic monophase) is preferred. Thus, the substrate scope was further extended to a wide range of *m*-diphenols or *p*-diphenols with an electron-withdrawing group (**1af**), a halogen atom (**1ah**), electron-donor groups (**1ai**), as well as polyphenols (**1aj-1al**) (Table 2E).

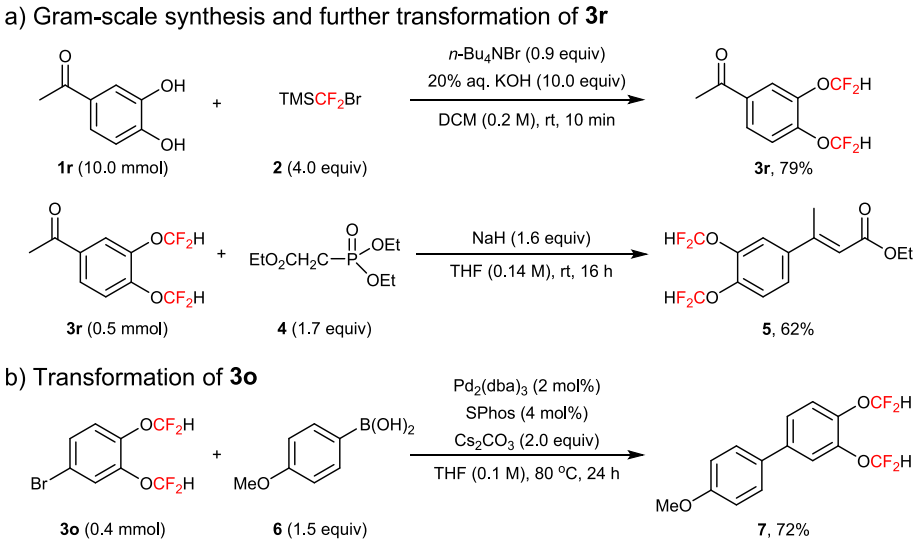
To further showcase the practicability of this method, we carried out gram-scale synthesis as well as other synthetic applications of aryldifluoromethoxyl ethers (Scheme 2). **3r** was easily scaled up to 10.0 mmol with only a slight decrease in yield (1.99 g, 79 %). Horner-Wadsworth-

Table 3
Relationship between the difluoromethylation yields and logP of diphenols.[a]





[a] Reactions were conducted on a 0.3 mmol scale, and the yields were determined by using $PhCF_3$ as an internal standard.



Scheme 2. Gram-scale synthesis and synthetic applications of **3.**

Emmons olefination of **3r** was further examined and afforded product (**5**) in 62 % yield. Moreover, a Suzuki coupling of **3o** with (4-methoxyphenyl)boronic acid (**4**) catalyzed by $Pd_2(dba)_3$ and SPhos provided **7** in 72 % yield.

Conclusions

In summary, we have developed an efficient and mild access to bis-difluoromethoxylated compounds via double *O*- difluoromethylations of diphenols, which features short reaction time (10 min), good reaction yields, and good functional group compatibility. It was found that different reaction behaviors of *o*-, *m*- and *p*-diphenols in the present two-phase system are related to their different lipophilicities. For liphophilic biphenols, biphase reaction system (Conditions A) is preferred; however, for hydrophilic biphenols, anhydrous reaction medium (Conditions B) usually gives better yields. Not only does this work provide an improved synthetic method for double *O*-difluoromethylations of diphenols, it also gives new insights into the difluorocarbene-involved difluoromethylations with hydrophilic or lipophilic substrates.

CRediT authorship contribution statement

Fanwen Kong: Writing – original draft, Investigation. **Rongyi Zhang:** Methodology. **Xiu Wang:** Writing – original draft, Methodology, Formal analysis. **Chuanfa Ni:** Formal analysis, Data curation. **Jinbo Hu:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2024.155335.

Data availability

Experimental details and spectral analysis are available free of charge from the ESI available with this article.

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