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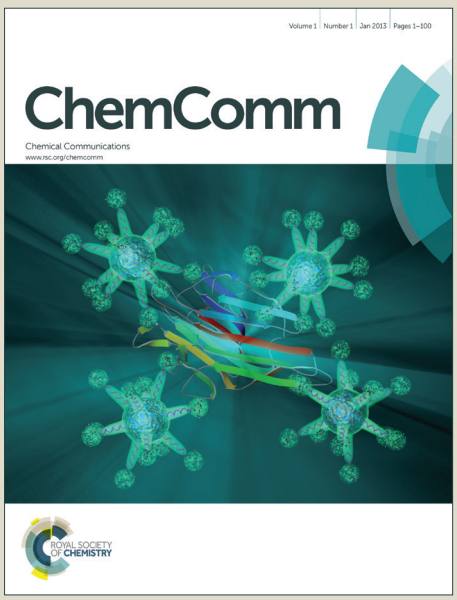

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Difluoromethylation and *gem*-difluorocyclopropenation with difluorocarbene generated by decarboxylation

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The difluoromethylation of activated X-H bond (X = N, O and S) and aliphatic thiols, and *gem*-difluorocyclopropenation of alkynes with difluorocarbene generated in situ from difluoromethylene phosphobetaine ($Ph_3P^+CF_2CO_2^-$) by decarboxylation occured smoothly without the presence of any base or other additives.

As fluorinated moieties usually shows profound effects on the physical, chemical, and biological properties of the target molecules, fluorine has been considered as the "second-favorite heteroatom" after nitrogen in drug design. The number of fluorine-containing pharmaceuticals and agrochemicals has been increasing rapidly for the past decades.[1] Consequently, determined efforts have been devoted to the exploration of applicable protocols for the incorporation of fluorine-containing groups.[2] Difluorocarbene has proved to be highly valuable intermediate, not only from the perspective of theoretical investigation, but also from its synthetic utilities as the transformation of difluorocarbene can incorporate the difluoromethylene group into various organic molecules.[3] The transformation of difluorocarbene include homocoupling to produce tetrafluoroethylene,[4] [2+1] cycloaddition with alkenes or alkynes,[3a] difluoromethylation of X–H bond (X = N, O, S, etc),[3a] [^{18}F]-trifluoromethylation,[5] and coordination with transition metal.[6] Although a number of difluorocarbene reagents have been developed to realize a variety of reactions due to the increasing research interest in this chemistry, these reactions usually require the addition of strong base or additive,[7-10] and some reagents are volatile or highly hygroscopic.[11-13] Previously, we have shown that difluoromethylene phosphobetaine ($Ph_3P^+CF_2CO_2^-$, PDFA), an efficient phosphonium ylide reagent,[14] can readily generate difluorocarbene simply via decarboxylation.[15] We have now investigated the use of this difluorocarbene precursor in difluoromethylation of activated X-H bond (X = N, O and S), difluoromethylation of aliphatic thiols, and *gem*-difluorocyclopropenation of alkynes.

Many difluorocarbene precursors can be successfully applied to the difluoromethylation of activated X-H bond (X = N, O and S), such as $ClCF_2CO_2Na$,[12d] $FSO_2CF_2CO_2TMS$,[16a] $TMSCF_2Br$[9] and $HCF_2S(O)(NTs)Ph$.[17] However, basic conditions are required in these reactions, limiting their wide applicability. The two exceptions were the *N*-difluoromethylation of imidazoles and benzimidazoles with $TMSCF_3$,[7c] and *N*-difluoromethylation of *N*-(pyridin-2-yl)acetamide with $ClCF_2CO_2Na$,[12c] which can proceed under neutral conditions. But the methods suffer from the high reaction temperature, and/or are only applicable to *N*-difluoromethylation. In sharp contrast, we found that all of *N*-, *O*- and *S*-difluoromethylation with PDFA can occur smoothly under mild conditions without the presence of base.

Although *S*-difluoromethylation with difluorocarbene is a straightforward protocol to incorporate SCF_2H group, which is a valuable moiety in medicinal chemistry and agrochemistry, it has thus far been limited to isolated examples.[9,12d,17-19] Especially for the aliphatic S-H difluoromethylation, only two reports have been published. Hu disclosed that both $TMSCF_2Br$[9] and $HCF_2S(O)(NTs)Ph$[17] can be used to achieve difluoromethylation of aliphatic thiols. But in both protocols, strong basic conditions are unavoidable.

The difluorocarbene reagents previously used for *gem*-difluorocyclopropenation to afford *gem*-difluorocyclopropenes, which have received much attention in synthetic chemistry, include $BrCF_2CO_2Na$,[13] $FSO_2CF_2CO_2TMS$,[16b] and $(CF_3)_2Cd$.[20] Most of these methods still lack generality due to such disadvantages as harsh reaction conditions, the use of highly toxic reagents, low product yields or inconvenient operations. Although $TMSCF_3$[7a] and $TMSCF_2Cl$,[8] $TMSCF_2Br$[9] are versatile difluorocarbene precursors and effective for *gem*-difluorocyclopropenation, the reagents are highly volatile and the reaction requires the presence of initiator for the generation of difluorocarbene.

In this work, PDFA was found to be an efficient difluorocarbene reagent for difluoromethylation and *gem*-difluorocyclopropenation via decarboxylation under neutral conditions. The attractive decarboxylative protocol is worthy of attention due to its operational convenience and mild reaction conditions.

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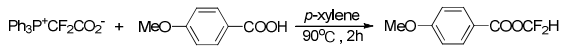
In our previous study, it was found that low-polarity solvent such as cyclohexane and *p*-xylene favors the dissociation of PDFA into difluorocarbene.[15] For the difluoromethylation of aromatic carboxylic acid with PDFA, *p*-xylene proved to be a suitable solvent (entries 1-4, Table 1). Elevating the reaction temperature to 90 °C in *p*-xylene improved the yield to 47 % (entry 6). The reaction was quite sensitive to the loading of PDFA. Increasing its amount to 2 equiv. led to a significant increase in the yield (entry 7).

Table 1 Screening reaction conditions for the difluoromethylation of activated X-H bond[a]



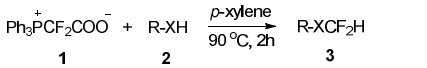
1 2a 3a

Entry	Solvent	Temp (°C)	Molar Ratio (**1**:**2a**)	Yield (%)[b]
1	Cyclohexane	60	1:1	5
2	*p*-Xylene	60	1:1	18
3	DMF	60	1:1	7
4	THF	60	1:1	11
5	*p*-Xylene	80	1:1	31
6	*p*-Xylene	90	1:1	47
7	*p*-Xylene	90	2:1	84

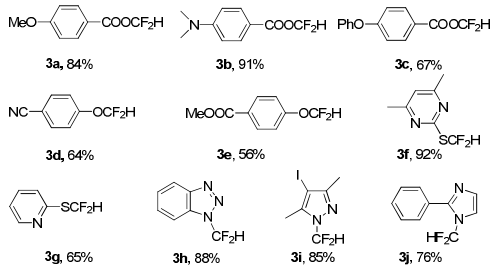
[a]Reaction conditions: **2a** (0.6 mmol) and **1** in solvent (3 mL). [b]Determined by ^{19}F NMR with trifluoromethylbenzene as the internal standard.

With the optimal reaction conditions in hand (entry 7, Table 1), we then investigated the substrate scope for the difluoromethylation of activated X-H bond (Scheme 2). For the difluoromethylation of O-H bond, the hydroxyl group in both carboxylic acids (**3a**-**3c**) and phenols (**3d**-**3e**) is reactive, and the carboxylic acids seem more reactive compared with phenols. The aromatic thiols can also be converted smoothly into the desired products (**3f**-**3g**). *N*-heterocycles are key structural units and prevalent in biological systems. The incorporation of difluoromethyl group is of great interest in synthetic and medicinal chemistry. Fortunately, *N*-difluoromethylation of heterocycles with PDFA proceeded very well to afford the products in high yields (**3h**-**3j**). It is worth noting that no additive or base is required to generate difluorocarbene from PDFA, and the reaction can occur directly without neutralizing the substrates by base.

Table 2 Difluoromethylation of activated X-H bond[a]



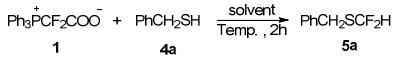
1 2 3



[a]Reaction conditions: **2** (0.6 mmol), **1** (1.2 mmol) in *p*-xylene (3 mL) for 2 h at 90 °C.

However, the above reaction conditions (entry 7 , Table 1) are not effective for the difluoromethylation of alcohols or aliphatic thiols. We have screened many conditions for the difluoromethylation of alcohols, but no condition can afford the desired product over 30 % yield. To our delight, the difluoromethylation of aliphatic thiols seems to be much promising. For the reaction of benzyl thiol **4a** with PDFA, 1,4-dioxane was found to be a suitable solvent instead of *p*-xylene. At 60 °C, the reaction furnished the desired product in 44 % yield (entry 7, Table 3). Lowering or elevating the reaction temperature can't increase the yield (entries 8-12). Increasing the loading of PDFA from 1 equiv. to 2 equiv. led to a dramatic improvement of the yield from 44 % to 66 % (entry 14 vs. entry 7). Further increasing its amount had no effect on the yield (entry 15).

Table 3 Screening reaction conditions for the difluoromethylation of aliphatic thiols[a]



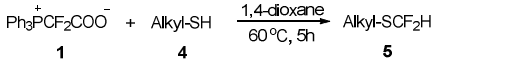
1 4a 5a

Entry	Solvent	Temp (°C)	Molar Ratio (**1**:**4a**)	Yield (%)[b]
1	*p*-Xylene	60	1:1	26
2	Toluene	60	1:1	28
3	DMF	60	1:1	5
4	DCE	60	1:1	trace
5	Cyanobenzene	60	1:1	16
6	THF	60	1:1	40
7	1,4-Dioxane	60	1:1	44
8	1,4-Dioxane	50	1:1	23
9	1,4-Dioxane	70	1:1	43
10	1,4-Dioxane	80	1:1	43
11	1,4-Dioxane	90	1:1	44
12	1,4-Dioxane	100	1:1	44
13	1,4-Dioxane	60	1.5:1	61
14	1,4-Dioxane	60	2:1	66
15	1,4-Dioxane	60	3:1	65

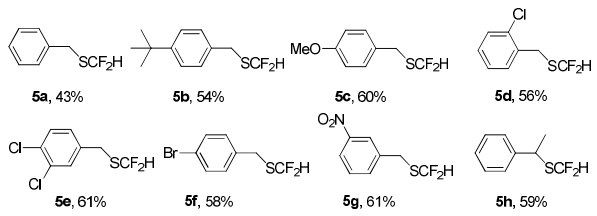
[a]Reaction conditions: compound **4a** (0.6 mmol) and **1** in solvent (3 mL). [b]Determined by ^{19}F NMR with trifluoromethylbenzene as the internal standard.

The reaction can be applied to a variety of aliphatic thiols (Table 4). In the case of benzyl aliphatic thiol, low isolated yield was obtained due to the high volatility of the product (**5a**). Irrespective of whether the aryl group is substituted by an electron-withdrawing or -donating group, the products were obtained in good yields, indicating that the transformation is not sensitive to the electronic effects (**5a**-**5h**). The conversion is not only applicable for primary thiols, but also for secondary thiol (**5h**). Compared with the reported methods,[9,17] for which strong basic conditions are required, our method seems more attractive.

Table 4 Difluoromethylation of aliphatic thiols[a]



1 4 5



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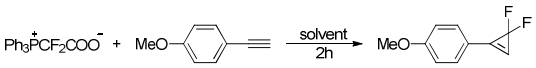
[a]Reaction conditions: **4** (0.6 mmol), **1** (1.2 mmol) in *p*-xylene (3 mL) for 5 h at 60 °C.

The successful difluoromethylation prompted us to investigate the *gem*-difluorocyclopropenation. Our initial attempts at the reaction of alkyne **6a** with PDFA in *p*-xylene at 80 °C gave the expected products in 63 % yield (entry 1, Table 5). The examination of other solvents suggested that *p*-xylene was the suitable solvent for this transformation (entries 2-8 vs. entry 1). Elevating the reaction temperature to 110 °C improved the yield slightly (entries 9-10), but higher temperature didn't give better results (entries 11-13). With the use of 2 equiv. of PDFA, the yield was increased significantly (entry 14). The concentration of the substrates had no obvious effect on the yield, as evidenced by the observation that the reaction in 3 mL of *p*-xylene instead of 2 mL gave the desired product in almost the same yield (entry 15).

Table 5 Screening reaction conditions for *gem*-difluorocyclopropenenation[a]



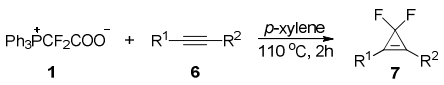
1 **6a** **7a**

Entry	Solvent	Temp (°C)	Molar Ratio (**1**:**6a**)	Yield (%)[b]
1	*p*-Xylene	80	1:1	63
2	Cyclohexane	80	1:1	39
3	Toluene	80	1:1	45
4	DMF	80	1:1	5
5	DG	80	1:1	19
6	Cyanobenzene	80	1:1	20
7	THF	80	1:1	31
8	1,4-Dioxane	80	1:1	39
9	*p*-Xylene	90	1:1	67
10	*p*-Xylene	110	1:1	73
11	*p*-Xylene	120	1:1	70
12	*p*-Xylene	130	1:1	71
13	*p*-Xylene	140	1:1	70
14	*p*-Xylene	110	2:1	96
15[c]	*p*-Xylene	110	2:1	98

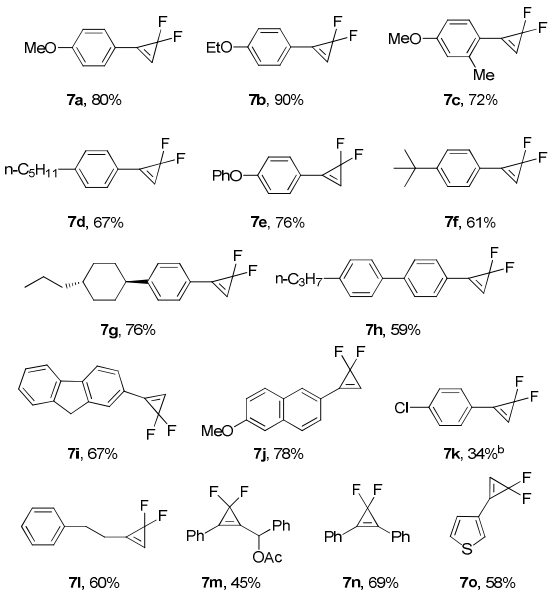
[a]Reaction conditions: compound **6a** (0.6 mmol) and **1** in solvent (2 mL). [b]Determined by ^{19}F NMR with trifluoromethylbenzene as the internal standard. [c]3 mL of *p*-xylene was used.

We then explored the substrate scope for the *gem*-difluorocyclopropenation of alkynes with PDFA under this optimal reaction conditions (Table 6). The electronic effects are important for the transformation. The substrates substituted by electron-donating groups on the phenyl ring can be converted well into the expected products in good yields (**7a**-**7j**), but in the case of substrate substituted by an electron-withdrawing group, low yield was afforded (**7k**). The reaction of aliphatic alkynes was also successful to give the product in moderate yield (**7l**). Besides terminal alkynes, internal alknyes are also suitable for this conversion (**7m**-**7n**).

Table 6 *gem*-Difluorocyclopropenation of alkynes[a]



1 **6** **7**



7a, 80% **7b**, 90% **7c**, 72%

7d, 67% **7e**, 76% **7f**, 61%

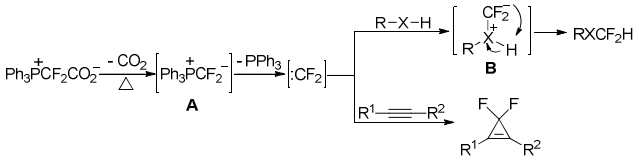
7g, 76% **7h**, 59%

7i, 67% **7j**, 78% **7k**, 34%[b]

7l, 60% **7m**, 45% **7n**, 69% **7o**, 58%

[a]Reaction conditions: **1** (1.2 mmol) and alkynes (0.6 mmol) in *p*-xylene (3 mL) at 110 °C for 2 h. Isolated yields. [b]Determined by ^{19}F NMR with trifluoromethylbenzene as the internal standard.

On the basis of the above results and related reports,[14a,15a] we propose that the reaction mechanism as shown in Scheme 1 is plausible. Decarboxylation of PDFA generates phosphonium ylide **A**,[14a] the further dissociation of which produces difluorocarbene.[15a] Difluorocarbene can be readily trapped by X-H group (X = N, O or S) to give intermediate **B**, which undergo a 1,2-hydride migration to affrod the final difluoromethylation product. For the *gem*-difluorocyclopropenation reaction, the direct cyclization of difluorocarbene with alkyne furnishes the desired product.



Scheme 1 Proposed reaction mechanism

In summary, the difluoromethylene phosphobetaine ($Ph_3P^+CF_2CO_2^-$, PDFA) has been found to be an efficient difluorocarbene precursor in the difluoromethylation of activated X-H bond (X = N, O, S) and aliphatic thiols, and *gem*-difluorocyclopropenation of alkynes. All of these reactions proceeded smoothly under neutral conditions without the addition of any other additive or base. This decarboxylative protocol represents an efficient method for the transformation of difluorocarbene due to the operational convenience and the high stability of PDFA.

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