Difluoromethylation and gem-difluorocyclopropenation with difluorocarbene generated by decarboxylation†

Xiao-Yun Deng, Jin-Hong Lin, Jian Zheng and Ji-Chang Xiao*

Difluoromethylation of the 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 (Ph3P+CF2CO2−) by decarboxylation occurred smoothly without the presence of any base or other additives.

As fluorinated moieties usually show 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 in 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 a 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,3d difluoromethylation of the X–H bond (X = N, O, S, etc.),3b,c [19F]-trifluoromethylation,5 and coordination with transition metals.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 a strong base or additive, and some reagents are volatile or highly hygroscopic.7–13 Previously, we have shown that difluoromethylene phosphobetaine (Ph3P+CF2CO2−, 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 the difluoromethylation of the 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 the activated X–H bond (X = N, O and S), such as ClCF2CO2Na,12 FSO2CF2CO2TMS16a, TMSCF2Br7 and HCF3S(O)(NTs)Ph17. However, basic conditions are required in these reactions, limiting their wide applicability. The two exceptions are the N-difluoromethylation of imidazoles and benzimidazoles with TMSCF2N7,16b and N-difluoromethylation of N-[pyridin-2-y]acetamide with ClCF2CO2Na,12 which can proceed under neutral conditions. But the methods suffer from a high reaction temperature, and/or are applicable only 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 a base.

Although S-difluoromethylation with difluorocarbene is a straightforward protocol to incorporate the SCF2H 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 TMSCF2Br8 and HCF3S(O)(NTs)Ph17 can be used to achieve the 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 BrCF2CO2Na13, FSO2CF2CO2TMS16b and (CF3)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 TMSCF3,7,16c TMSCF3Cl8 and TMSCF2Br9 are versatile difluorocarbene precursors and effective for gem-difluorocyclopropenation, the reagents are highly volatile and the reaction requires the presence of an 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.

In our previous study, it was found that low-polarity solvents such as cyclohexane and p-xylene favor the dissociation of PDFA into difluorocarbene. For the difluoromethylation of aromatic carboxylic acids 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).

With the optimal reaction conditions in hand (entry 7, Table 1), we then investigated the substrate scope for the difluoromethylation of the activated X–H bond (Table 2). For the difluoromethylation of the 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 difluorocarbene. The products in high yields (3f–3g). N-heterocycles are key structural units prevalent in biological systems. The incorporation of the difluoromethyl group is of great interest in synthetic and medicinal chemistry. Fortunately, the N-difluoromethylation of heterocycles with PDFA proceeded very well to afford the desired products (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 neutralization of the substrates by base (2).

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 very 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 cannot increase the yield (entries 8–12). Increasing the loading of PDFA from 1 equiv. to 2 equiv. led to a dramatic improvement in the yield from 44% to 66% (entry 14 vs. entry 7). Further increasing its amount had no effect on the yield (entry 15).

The reaction can be applied to a variety of aliphatic thiols (Table 4). In the case of benzyl aliphatic thiol, a 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, for which strong basic conditions are required, our method seems more attractive.

The successful difluoromethylation prompted us to investigate the gem-difluorocycloprenation. Our initial attempts at the reaction of alkynyl 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 and 10), but higher temperature did not give better results (entries 11–13). Using 2 equiv. of PDFA, the yield was

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### Table 1 Screening reaction conditions for the difluoromethylation of the activated X–H bond

| Entry | Solvent | Temp. (°C) | Molar ratio (1:2a) | Yield (%) |
|-------|---------|------------|--------------------|-----------|
| 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.

### Table 2 Difluoromethylation of the activated X–H bond

| Entry | Solvent | Temp. (°C) | Molar ratio (1:2) | Yield (%) |
|-------|---------|------------|--------------------|-----------|
| 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                | 12        |
| 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: 2a (0.6 mmol) and 1 (1.2 mmol) in p-xylene (3 mL) for 2 h at 90 °C.

### Table 3 Screening reaction conditions for the difluoromethylation of aliphatic thiols

| Entry | Solvent | Temp. (°C) | Molar ratio (1:4a) | Yield (%) |
|-------|---------|------------|--------------------|-----------|
| 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                | 12        |
| 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.
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).

We then explored the substrate scope for the gem-difluorocyclopropenation of alkynes with PDFA under these 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 substrates substituted by electron-withdrawing groups, low yield was afforded (7k). The reaction of aliphatic alkynes was also successful in affording the products in moderate yields (7l). Besides terminal alkynes, internal alkynes are also suitable for this conversion (7m–7n).

On the basis of the above results and related reports, we propose that the reaction mechanism as shown in Scheme 1 is plausible. Decarboxylation of PDFA generates phosphonium ylide A, the further dissociation of which produces difluorocarbene. Difluorocarbene can be readily trapped by the X-H group (X = N, O or S) to give intermediate B, which undergoes a 1,2-hydride migration to afford the final difluoromethylation product.

For the gem-difluorocyclopropenation reaction, the direct cyclization of difluorocarbene with alkyne furnishes the desired product.

In summary, difluoromethylene phosphobetaine (Ph₃P⁺CF₂CO₂⁻, PDFA) has been found to be an efficient difluorocarbene precursor in the difluoromethylation of the 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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