Deoxygenative gem-difluoroolefination of carbonyl compounds with (chlorodifluoromethyl)trimethylsilane and triphenylphosphine

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Full Research Paper

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Abstract

**Background:** 1,1-Difluoroalkenes cannot only be used as valuable precursors for organic synthesis, but also act as bioisosteres for enzyme inhibitors. Among various methods for their preparation, the carbonyl olefination with difluoromethylene phosphonium ylide represents one of the most straightforward methods.

**Results:** The combination of (chlorodifluoromethyl)trimethylsilane (TMSCF$_2$Cl) and triphenylphosphine (PPh$_3$) can be used for the synthesis of gem-difluoroolefins from carbonyl compounds. Comparative experiments demonstrate that TMSCF$_2$Cl is superior to (bromodifluoromethyl)trimethylsilane (TMSCF$_2$Br) and (trifluoromethyl)trimethylsilane (TMSCF$_3$) in this reaction.

**Conclusion:** Similar to many other Wittig-type gem-difluoroolefination reactions in the presence of PPh$_3$, the reaction of TMSCF$_2$Cl with aldehydes and activated ketones is effective.

Introduction

The synthesis and application of selectively fluorinated organic molecules have attracted much interest from both organic chemists and biochemists because fluorine can endow these molecules with unique chemical, biological and physical properties [1-3]. 1,1-Difluoroalkenes have been frequently used in the design of potential enzyme inhibitors [4-6], since difluoromethylene functionality (CF$_2$) is known to be isosteric and isopolar to an oxygen atom [7-9], and the gem-difluorovinyl functionality is believed to be a bioisostere for a carbonyl group [10]. More commonly, 1,1-difluoroalkenes, which are highly electrophilic towards many nucleophiles at the terminal difluoromethylene carbon [11], are used as valuable precursors
of di- and trifluoromethyl compounds [10,12], monofluoroalkenes [13], monofluorinated heterocycles [14,15], carboxylic acids and esters [16]. Consequently, these relevant applications of 1,1-difluoroalkenes have led to many efforts to develop gem-difluoroolefination methods including β-elimination of functionalized difluoromethyl compounds, transition metal catalysed coupling reactions with gem-difluoroamination reagents, and deoxygenative gem-difluoroolefination of carbonyl compounds [17,18]. Among these methods, the latter one has been studied with several named reactions, for example Wittig, Horner–Wadsworth–Emmons, and Julia–Kocienski reactions.

In the Wittig gem-difluoroolefination, the reaction is believed to proceed via an undetected difluoromethylene phosphonium ylide, which can be generated in situ either by the transformation of a difluorinated phosphonium salt or by the reaction between difluorocarbene (:CF₂) and a phosphine (Scheme 1) [19-26]. In 1964, Fuqua and co-workers first reported the difluoromethylenation of aldehydes by using ClCF₂CO₂Na/PPh₃ [19]. In 1967, Burton and Herkes suggested that the ylide intermediate involved in the olefination process was more likely to be formed by the decarboxylation of a difluorinated phosphonium salt rather than the combination of :CF₂ and a phosphine (Scheme 1, reaction 1) [20]. Their suggestion is based on the accelerating effect of PPh₃ on the thermal decomposition of ClCF₂CO₂Na and the unsuccessful capture of :CF₂ with an alkene or alcohol during the olefination reaction [20]. Very recently, the successful preparation of (triphenylphosphonio)difluoracetate (Ph₃P’-CF₂-CO₂⁻) and its application in carbonyl gem-difluoroolefination by Xiao and co-workers [21] finally confirmed the mechanism proposed by Burton and others [19,20]. Burton and co-workers also developed another difluorocarbene-free approach using a 1:2 mixture of CF₂Br₂ and PPh₃ or P(NMe₂)₃ to prepare the ylide intermediate (Scheme 1, reaction 2) [22,23]. Although the difluorocarbene/phosphine procedure for Wittig olefination has been put forward by Fuqua et al. as early as 1964 [19], the formation of difluoromethylene phosphonium ylide in such a way is quite rare [24-26]. Established examples include using bis(trifluoromethyl)mercury (Hg(CF₃)₂) under the promotion of NaI (Scheme 1, reaction 3) [24] and using methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (MDFA) under the promotion of KI (Scheme 1, reaction 4) [25].

Our group has focused on the development and application of new difluorocarbene reagents [27-34]. The Prakash group and we have identified that (halodifluoromethyl)trimethylsilanes (TMSCFₓX, X = F, Cl, and Br) could serve as difluorocarbene sources under the activation of proper halide initiators or alkaline bases (Scheme 2) [31-34]. Recently, we have developed a relatively environmentally benign method to prepare TMSCF₂Br, which can be used as a general carbene source for
Scheme 2: Difluoromethylation of alkenes and alkynes and difluoromethylation of heteroatom nucleophiles with TMSCF₂X [31-34].

Scheme 3: Bromo–chloro exchange reaction using AgCl.

Results and Discussion

(Halodifluoromethyl)trimethylsilanes including TMSCF₃ (Ruppert–Prakash reagent), TMSCF₂Cl, and TMSCF₂Br are initially prepared by reductive silylation of ozone-depleting-substances bromotrifluoromethane (CF₃Br) [35], bromochlorodifluoromethane (CF₂BrCl) [36,37], and dibromodifluoromethane (CF₂Br₂) [36,37] with chlorotrimethylsilane (TMSCl).

In recent years, Prakash and co-workers have discovered two Freon-free methods for the synthesis of TMSCF₃ from fluoroform (CF₃H), which paved the way for the synthetic applications of TMSCF₃ [38,39]. Moreover, the preparation of TMSCF₂Br either by fluoro–bromo exchange reaction of TMSCF₃ [34] or by bromination of TMSCF₂H [34,40] has also been disclosed. To obtain TMSCF₂Cl, we tried the halogen exchange reaction of TMSCF₂Br. When a 1:10 mixture of TMSCF₂Br and TMSCI was heated in neat in the presence of 5 mol % of tetrabutylammonium chloride (TBAC) for 2 hours, ¹⁹F NMR spectroscopy analysis showed that the ratio of TMSCF₂Cl to TMSCF₂Br was 2.3:1, and prolonging reaction time could not improve the ratio. In view of the difficulty in separating TMSCF₂Cl from the reaction mixture because of the approximate boiling points of TMSCF₂Cl (~85 °C) [36,37] and TMSCF₂Br (~105 °C) [36,37], other chloride sources were tried to achieve a full conversion of TMSCF₂Br. Gratifyingly, when the reaction was performed in benzonitrile (bp ~190 °C) at 80 °C using a slight excess of silver chloride under the catalysis of TBAC, a full conversion of TMSCF₂Br afforded TMSCF₂Cl in 54% yield. Lowering the temperature to room temperature (rt) could improve the yield to 80% (Scheme 3). It is believed that the lower solubility of silver bromide than silver chloride in benzonitrile provides the driving force for this bromo–chloro exchange reaction.

At first, the olefination of 1-naphthaldehyde (1a) or benzaldehyde (1b) by using the combination of TMSCF₂Cl and PPh₃ was tried. Conceiving that the chloride ion might be necessary to promote the decomposition of TMSCF₂Cl to release CF₂ as reported, a catalytic amount of TBAC was used as the initiator. After heating a reaction mixture of aldehyde 1a, TMSCF₂Cl, PPh₃, and TBAC in THF at 100 °C for 8 h, ¹⁹F NMR spectroscopy analysis showed that difluorinated alkene 2a was formed in 69% yield (Table 1, entry 1). Surprisingly, it was found that in the absence of TBAC, PPh₃ could be used both to promote the fragmentation of TMSCF₂Cl and combine with the generated :CF₂ (Table 1, entry 2). A rough comparison of the reaction temperatures showed that a lower temperature (rt) is detrimental to the olefination process, although the decomposition of TMSCF₂Cl could occur to some extent (Table 1, entries 2 and 3).

Subsequently, the olefination of aldehyde 1b with TMSCF₂Br was examined. Unfortunately, the full consumption of
Table 1: Condition screening of gem-difluoroolefination with TMSCF₂X.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar</th>
<th>X</th>
<th>Initiator</th>
<th>Temp (°C)</th>
<th>t (h)</th>
<th>Conversion (%)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-naphthyl</td>
<td>Cl</td>
<td>TBAC (3 mol %)</td>
<td>100</td>
<td>8</td>
<td>100</td>
<td>69</td>
</tr>
<tr>
<td>2</td>
<td>1-naphthyl</td>
<td>Cl</td>
<td>none</td>
<td>70</td>
<td>10</td>
<td>100</td>
<td>59</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>Cl</td>
<td>none</td>
<td>rt</td>
<td>4</td>
<td>35</td>
<td>0</td>
</tr>
<tr>
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<td>Ph</td>
<td>Br</td>
<td>none</td>
<td>70</td>
<td>10</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>F</td>
<td>NaI (0.6 equiv)</td>
<td>70</td>
<td>10</td>
<td>&lt;5</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Ph</td>
<td>F</td>
<td>NaI (6.0 equiv)</td>
<td>110</td>
<td>10</td>
<td>&lt;5</td>
<td>0</td>
</tr>
</tbody>
</table>

*a Reactions were performed on 0.5 mmol scale in a pressure tube. b Conversion of TMSCF₂X and yields of 2 were determined by ¹⁹F NMR spectroscopy using PhCF₃ as an internal standard. c Isolated yield of 2a.

TMSCF₂Br did not afford any difluoroolefin 2b (Table 1, entry 4). As determined by ¹⁹F NMR, besides the side product (difluoromethyl)triphenylphosphonium bromide (δ = 127.9, 80 Hz, 2J_F-H = 47 Hz) as reported in the Wittig olefination with FSO₂CF₂CF₂Me [25], a new product which was assigned as difluorinated phosphonium salt 4 (δ = 88.8, 298 Hz, 2J_F-F = 298 Hz, 3J_P-F = 97 Hz, 3J_P-H = 106.6 Hz, 3F-H = 24 Hz) was detected as the major product (for details, see Supporting Information File 1). The formation of 4 is supposed to arise from a ready silylation of the addition intermediate betaine 3 by TMSBr. When TMSCF₂Cl was used, TMSCl is not reactive enough to trap the betaine 3, thus the oxaphosphetane 5 could be formed to give olefins and triphenylphosphine oxide (Scheme 4).

Finally, the olefination of aldehyde 1b with TMSCF₃ as the difluoromethylene source was tested. The results showed that no desired reaction took place when PPh₃ and either substoichiometric or stoichiometric amounts of NaI were used.

Scheme 4: Proposed different reaction pathways of the difluorinated ylide in the presence of TMSCI and TMSBr.
(Table 1, entries 5 and 6). Although it has been known that TMSCF$_3$ can be used in the difluoromethyleneation of alkenes and alkynes initiated by NaI [33], we could not give a reasonable explanation for the failure of the current reaction.

Using the conditions shown in Table 1, entry 2 as standard, the olefination of aldehydes with TMSCF$_2$Cl was investigated. As shown in Figure 1, a variety of structurally diverse aromatic aldehydes were successfully converted into gem-difluoro-

![Figure 1: gem-Difluoroolefination of aldehydes. Reactions were performed on 0.5 mmol scale in a pressure tube. a) Isolated yield. b) Yield was determined by $^{19}$F NMR spectroscopy using PhCF$_3$ as an internal standard.

![Figure 2: gem-Difluoroolefination of activated ketones. Reactions were performed on 0.5 mmol scale in a pressure tube. a) Yield was determined by $^{19}$F NMR spectroscopy using PhCF$_3$ as an internal standard. b) Isolated yield.](image-url)
slightly elevated temperature (80 °C) are shown in Figure 2. A range of aryl trifluoromethyl (6a–d) and chlorodifluoromethyl aromatic ketones (6e–g) were readily difluoromethylenated to give the corresponding olefins (7a–g) in moderate to good yields. It should be mentioned that in all cases, the formation of gem-difluoroolefins was accompanied by the formation of Ph₃PF₂ (δ −41.2, d, JPF = 668 Hz) [25], HCF₂Cl, fluorotrimethylsilane, and some unidentified byproducts in variable yields (for details, see Supporting Information File 1).

As previously reported, the key mechanistic issue of this Wittig-type reaction is the formation of the presumed difluoromethylene triphenylphosphonium ylide [19-25]. Initially it was speculated that it were trace amounts of nucleophilic impurities (such as chloride ions) that initiated the fragmentation of TMSCF₂Cl to release :CF₂ [31], which combined with PPh₃ to form the ylide. However, the experiment at room temperature showed that PPh₃ could significantly accelerate the decomposition of TMSCF₂Cl, which indicated that PPh₃ should have participated in the activation of TMSCF₂Cl. Consequently, two plausible mechanisms are proposed (Scheme 5): one is the initial activation of the C–Si bond by PPh₃ (Path A), the other is the initial activation of the C–Cl bond by PPh₃ (Path B). In Path A, PPh₃ firstly coordinates the silicon atom of TMSCF₂Cl to form activated penta-coordinated silicon species 8 [41] and activates both the C–Si and the C–Cl bond. Next, the release of CF₂ leads to silylphosphonium salt 9. Finally, the fragmentation of 9 occurs to give TMSCl with regeneration of PPh₃; meanwhile, the trapping of :CF₂ by PPh₃ gives the ylide. In Path B, a phosphonium salt 10, which is formed via a single-electron transfer (SET) mechanism, undergoes a chloride ion-promoted desilylation reaction to afford Ph₃P=CF₂ [42,43]. However, we could not rule out the possibility of chloride ion-activation in these processes due to the involvement of intermediates 9 and 10 in the proposed mechanisms.

**Conclusion**

In conclusion, a robust difluoromethylation reagent (chlorodifluoromethyltrimethylsilane (TMSCF₂Cl)) has been prepared via a relatively environmentally benign method and has been successfully used in the Wittig difluoroolefination. Similar as many other Wittig-type gem-difluoroolefination reactions in the presence of PPh₃, the reaction of TMSCF₂Cl with aldehydes and activated ketones is effective. Comparative reactions with TMSCF₂Br and TMSCF₃ under similar conditions failed to give the gem-difluorinated olefins, which indicate that the halo-

**Scheme 5**: Plausible mechanisms for the formation of difluoromethylene triphenylphosphonium ylide from TMSCF₂Cl and PPh₃.
fluorinated silanes in difluoromethylene transfer reactions. Further research on the synthetic application of TMSCF₂X (X = F, Cl, and Br) is currently underway.

Supporting Information

Full experimental details (difluoromethylation of O, S, and N-nucleophiles and gem-difluoroolefination of carbonyl compounds with TMSCF₂Cl) and compound characterization data are given.

Supporting Information File 1

Experimental procedures and characterization data.

[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-10-32-S1.pdf]

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References

32. For preliminary results on the difluoromethylation of O, S, and N-nucleophiles with TMSCF₂Cl under aqueous basic conditions, see Supporting Information File 1.

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