Beilstein Journal of Organic Chemistry

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

Fei Wang, Lingchun Li, Chuanfa Ni and Jinbo Hu*

Full Research Paper

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Address:
Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Ling-Ling Road, Shanghai 200032, China

Email:
Jinbo Hu* - jinbohu@sioc.ac.cn

* Corresponding author

Keywords:
(chlorodifluoromethyl)trimethylsilane; difluorocarbene; *gem*-difluoroolefin; organo-fluorine; Wittig reaction; ylide

Beilstein J. Org. Chem. **2014,** *10,* 344–351.
doi:10.3762/bjoc.10.32

Received: 16 September 2013
Accepted: 14 January 2014
Published: 06 February 2014

This article is part of the Thematic Series "Organo-fluorine chemistry III".

Guest Editor: D. O'Hagan

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 ($TMSCF_2Cl$) and triphenylphosphine (PPh_3) can be used for the synthesis of *gem*-difluoroolefins from carbonyl compounds. Comparative experiments demonstrate that $TMSCF_2Cl$ is superior to (bromodifluoromethyl)trimethylsilane ($TMSCF_2Br$) 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 $TMSCF_2Cl$ with aldehydes and activated ketones is effective.

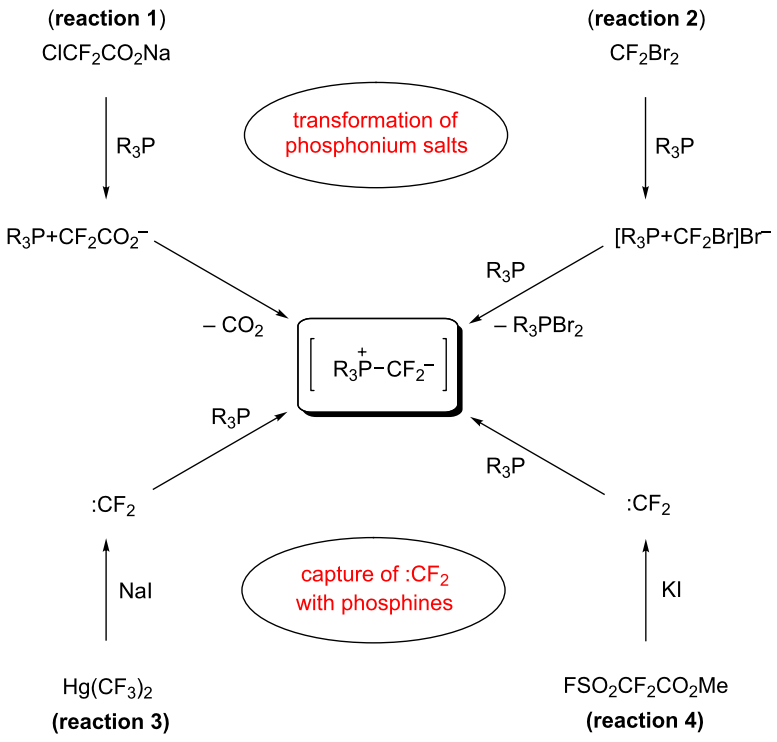
Introduction

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

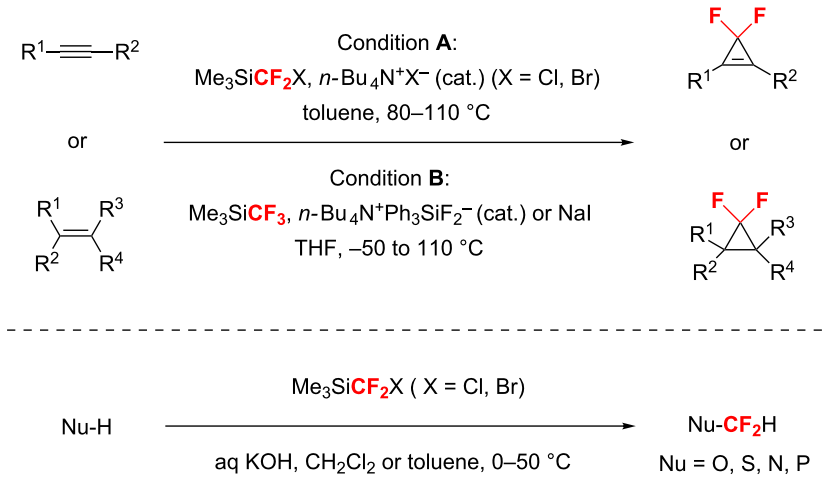
of di- and trifluoromethyl compounds [10,12], monofluoroalkenes [13], monofluorinated heterocycles [14,15], carboxylic acids and esters [16]. Consequently, these relevant applications of 1,1-difluoroalkenes have led to many efforts to develop *gem*-difluoroolefination methods including β-elimination of functionalized difluoromethyl compounds, transition metal catalysed coupling reactions with *gem*-difluorovinylation 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 ($:CF_2$) and a phosphine (Scheme 1) [19-26]. In 1964, Fuqua and co-workers first reported the difluoromethylenation of aldehydes by using $ClCF_2CO_2Na/PPh_3$ [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 $:CF_2$ and a phosphine (Scheme 1, reaction 1) [20]. Their suggestion is based on the accelerating effect of PPh_3 on the thermal decomposition of $ClCF_2CO_2Na$ and the unsuccessful capture of $:CF_2$ with an alkene or alcohol during the olefination reaction [20]. Very recently, the successful preparation of (triphenylphosphonio)difluoroacetate ($Ph_3P^+CF_2CO_2^-$) 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 CF_2Br_2 and PPh_3 or $P(NMe_2)_3$ 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 ($Hg(CF_3)_2$) 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 ($TMSCF_2X$, 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 $TMSCF_2Br$, which can be used as a general carbene source for



Scheme 1: Various procedures for the generation of difluoromethylene phosphonium ylide [19-25].

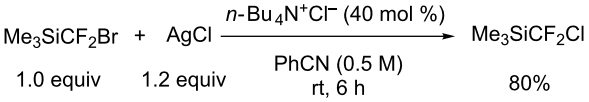


Scheme 2: Difluoromethylenation of alkenes and alkynes and difluoromethylation of heteroatom nucleophiles with $TMSCF_2X$ [31-34].

the difluoromethylenation of alkynes and alkenes and difluoromethylation of heteroatom nucleophiles [34]. In this paper, the novel preparation of $TMSCF_2Cl$ from $TMSCF_2Br$ and the application of the former in deoxygenative *gem*-difluoroolefination of carbonyl compounds via Wittig-type reaction are reported.

Results and Discussion

(Halodifluoromethyl)trimethylsilanes including $TMSCF_3$ (Ruppert–Prakash reagent), $TMSCF_2Cl$, and $TMSCF_2Br$ are initially prepared by reductive silylation of ozone-depleting-substances bromotrifluoromethane (CF_3Br) [35], bromochlorodifluoromethane (CF_2BrCl) [36,37], and dibromodifluoromethane (CF_2Br_2) [36,37] with chlorotrimethylsilane (TMSCl). In recent years, Prakash and co-workers have discovered two Freon-free methods for the synthesis of $TMSCF_3$ from fluoroform (CF_3H), which paved the way for the synthetic applications of $TMSCF_3$ [38,39]. Moreover, the preparation of $TMSCF_2Br$ either by fluoro–bromo exchange reaction of $TMSCF_3$ [34] or by bromination of $TMSCF_2H$ [34,40] has also been disclosed. To obtain $TMSCF_2Cl$, we tried the halogen exchange reaction of $TMSCF_2Br$. When a 1:10 mixture of $TMSCF_2Br$ and TMSCl was heated in neat in the presence of 5 mol % of tetrabutylammonium chloride (TBAC) for 2 hours, ^{19}F NMR spectroscopy analysis showed that the ratio of $TMSCF_2Cl$ to $TMSCF_2Br$ was 2.3:1, and prolonging reaction time could not improve the ratio. In view of the difficulty in separating $TMSCF_2Cl$ from the reaction mixture because of the approximate boiling points of $TMSCF_2Cl$ (~85 °C) [36,37] and $TMSCF_2Br$ (~105 °C) [36,37], other chloride sources were tried to achieve a full conversion of $TMSCF_2Br$. 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 $TMSCF_2Br$ afforded $TMSCF_2Cl$ 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.

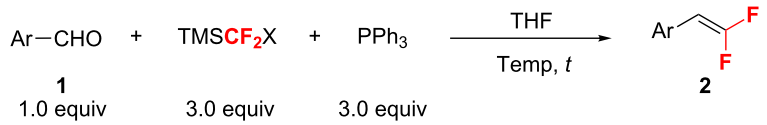


Scheme 3: Bromo–chloro exchange reaction using AgCl.

At first, the olefination of 1-naphthaldehyde (**1a**) or benzaldehyde (**1b**) by using the combination of $TMSCF_2Cl$ and PPh_3 was tried. Conceiving that the chloride ion might be necessary to promote the decomposition of $TMSCF_2Cl$ to release CF_2 as reported, a catalytic amount of TBAC was used as the initiator. After heating a reaction mixture of aldehyde **1a**, $TMSCF_2Cl$, PPh_3, and TBAC in THF at 100 °C for 8 h, ^{19}F 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, PPh_3 could be used both to promote the fragmentation of $TMSCF_2Cl$ and combine with the generated $:CF_2$ (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 $TMSCF_2Cl$ could occur to some extent (Table 1, entries 2 and 3).

Subsequently, the olefination of aldehyde **1b** with $TMSCF_2Br$ was examined. Unfortunately, the full consumption of

Table 1: Condition screening of *gem*-difluoroolefination with $TMSCF_2X$.

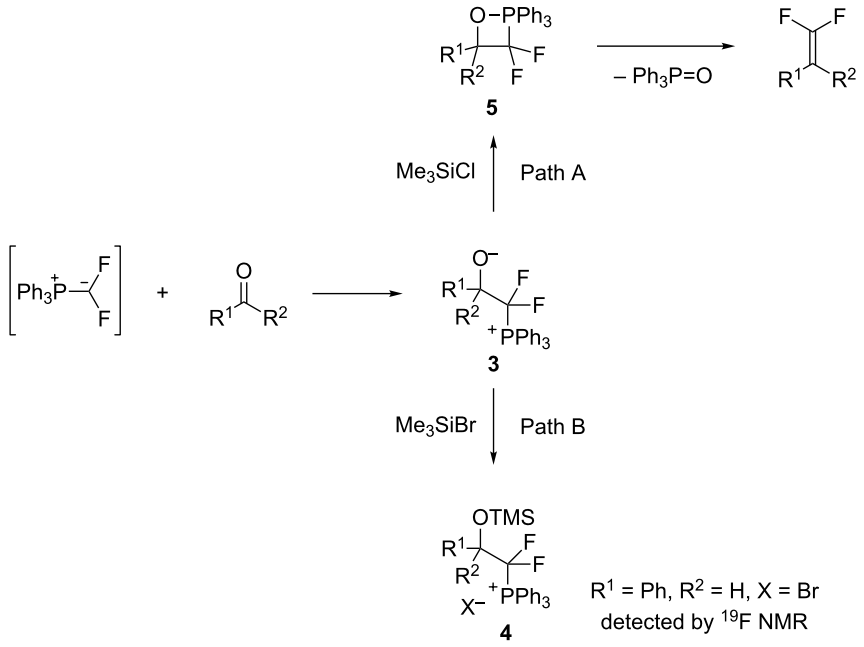


Entry[a]	Ar	X	Initiator	Temp (°C)	*t* (h)	Conversion (%)[b]	Yield (%)[b]
1	1-naphthyl	Cl	TBAC (3 mol %)	100	8	100	69
2	1-naphthyl	Cl	none	70	10	100	59[c]
3	Ph	Cl	none	rt	4	35	0
4	Ph	Br	none	70	10	100	0
5	Ph	F	NaI (0.6 equiv)	70	10	<5	0
6	Ph	F	NaI (6.0 equiv)	110	10	<5	0

[a]Reactions were performed on 0.5 mmol scale in a pressure tube. [b]Conversion of $TMSCF_2X$ and yields of **2** were determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard. [c]Isolated yield of **2a**.

$TMSCF_2Br$ did not afford any difluoroolefin **2b** (Table 1, entry 4). As determined by ^{19}F NMR, besides the side product (difluoromethyl)triphenylphosponium bromide (δ −127.9, dd, $^3J_{P\text{-}F}$ = 80 Hz, $^2J_{F\text{-}H}$ = 47 Hz) as reported in the Wittig olefination with $FSO_2CF_2CO_2Me$ [25], a new product which was assigned as difluorinated phosphonium salt **4** (δ −88.8, ddd, $^2J_{F\text{-}F}$ = 298 Hz, $^3J_{P\text{-}F}$ = 97 Hz, $^3J_{F\text{-}H}$ = 3.3 Hz, 1F; δ −106.6, ddd, $^2J_{F\text{-}F}$ = 298 Hz, $^3J_{P\text{-}F}$ = 101 Hz, $^3J_{F\text{-}H}$ = 24 Hz, 1F) 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 $TMSCF_2Cl$ 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 $TMSCF_3$ as the difluoromethylene source was tested. The results showed that no desired reaction took place when PPh_3 and either substoichiometric or stoichiometric amounts of NaI were used



Scheme 4: Proposed different reaction pathways of the difluorinated ylide in the presence of TMSCl and TMSBr.

(Table 1, entries 5 and 6). Although it has been known that $TMSCF_3$ can be used in the difluoromethylenation 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 $TMSCF_2Cl$ was investigated. As shown in Figure 1, a variety of structurally diverse aromatic aldehydes were successfully converted into *gem*-difluoroalkenes **2a**–**g** in moderate to good yields. It should be mentioned that the aromatic aldehydes with substituents such as *t*-butylthio, methoxy, and bromo groups on the phenyl ring showed similar reactivity. Moreover, this approach is also amenable to enolizable aldehydes, for example, *gem*-difluoroolefin **2h** could be obtained in 47% yield. Although a non-activated ketone such as acetophenone is unreactive under similar conditions, activated ketones could undergo this Wittig olefination reaction. Representative results for the olefination at a

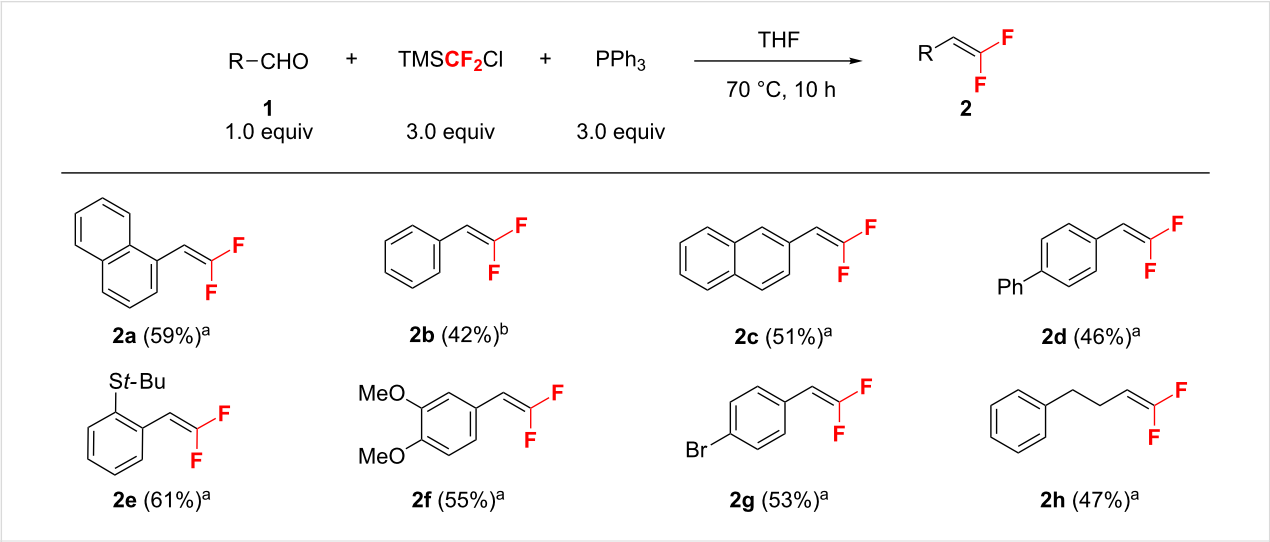


Figure 1: *gem*-Difluoroolefination of aldehydes. Reactions were performed on 0.5 mmol scale in a pressure tube. [a]Isolated yield. [b]Yield was determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard.

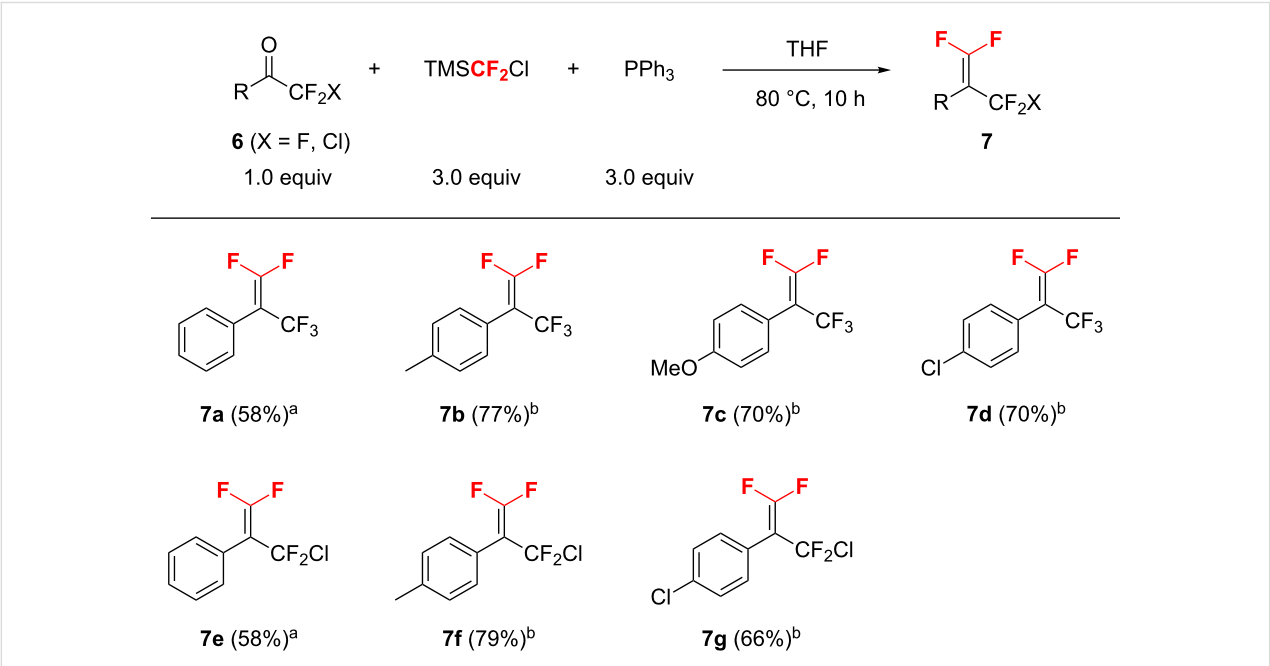


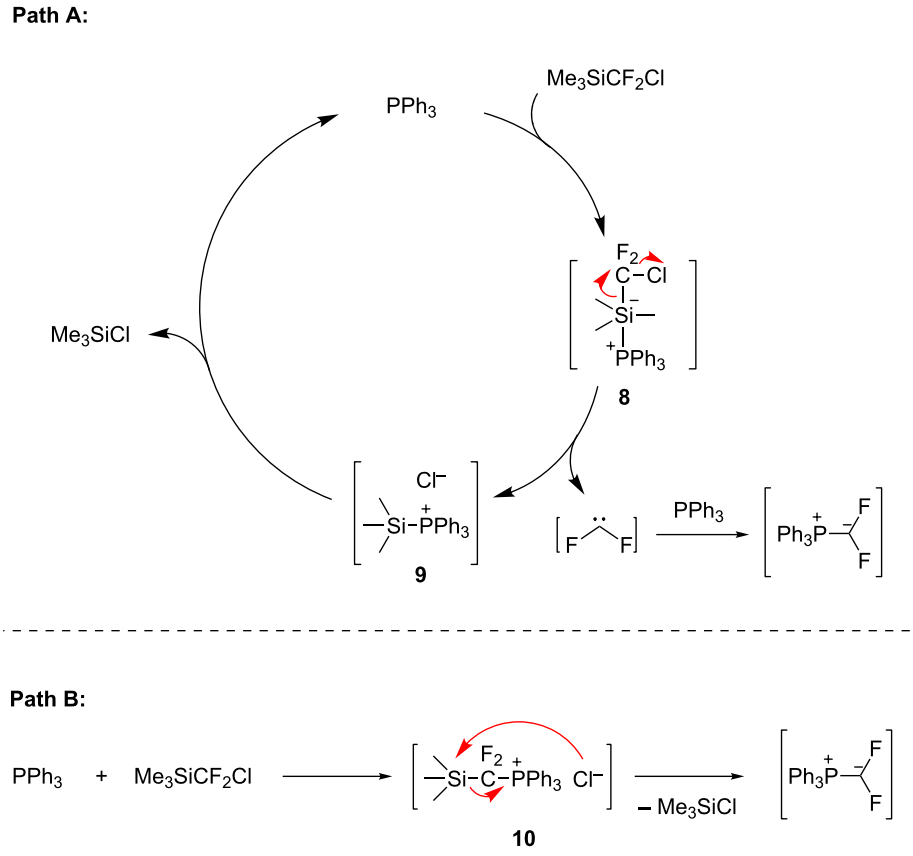
Figure 2: *gem*-Difluoroolefination of activated ketones. Reactions were performed on 0.5 mmol scale in a pressure tube. [a]Yield was determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard. [b]Isolated yield.

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 Ph_3PF_2 (δ −41.2, d, $^1J_{P\text{-}F}$ = 668 Hz) [25], HCF_2Cl, 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 $TMSCF_2Cl$ to release $:CF_2$ [31], which combined with PPh_3 to form the ylide. However, the experiment at room temperature showed that PPh_3 could significantly accelerate the decomposition of $TMSCF_2Cl$, which indicated that PPh_3 should have participated in the activation of $TMSCF_2Cl$. Consequently, two plausible mechanisms are proposed (Scheme 5): one is the initial activation of the C–Si bond by PPh_3 (Path A), the other is the initial activation of the C–Cl bond by PPh_3 (Path B). In Path A, PPh_3 firstly coordinates the silicon atom of $TMSCF_2Cl$ to form activated penta-coordinated silicon species **8** [41] and activates both the C–Si and the C–Cl bond. Next, the release of CF_2 leads to silylphosphonium salt **9**. Finally, the fragmentation of **9** occurs to give TMSCl with regeneration of PPh_3; meanwhile, the trapping of $:CF_2$ by PPh_3 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 $Ph_3P{=}CF_2$ [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 difluoromethylenation reagent (chlorodifluoromethyl)trimethylsilane ($TMSCF_2Cl$) 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 PPh_3, the reaction of $TMSCF_2Cl$ with aldehydes and activated ketones is effective. Comparative reactions with $TMSCF_2Br$ and $TMSCF_3$ 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 $TMSCF_2Cl$ and PPh_3.

substituent of $TMSCF_2X$ can influence the reactivity of these fluorinated silanes in difluoromethylene transfer reactions. Further research on the synthetic application of $TMSCF_2X$ (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 $TMSCF_2Cl$) 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]

Acknowledgements

Support of our work by the National Basic Research Program of China (2012CB821600 and 2012CB215500) the National Natural Science Foundation of China (20825209 and 21202189), and the Chinese Academy of Sciences is gratefully acknowledged.

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This article appeared online after our submission of this article. It is a paper describing the deoxygenative *gem*-difluoroolefination of carbonyl compounds with the difluorocarbene/phosphine procedures, i.e. HCF_2Cl/propylene epoxide/*n*-Bu_4NCl (cat.)/Ph_3P.; $FSO_2CF_2CO_2TMS$/NaF (cat.)/Ph_3P.
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