Conversion between Difluorocarbene and Difluoromethylene Ylide

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Dedicated to Professor Jean'ne M. Shreeve on the occasion of her 80th birthday

Abstract: The interconversion between difluoromethylene ylide and difluorocarbene is described. The difluoromethylene ylide precursor, $Ph_3P^+CF_2CO_2^-$, could be turned into an efficient difluorocarbene reagent, whereas the classical difluorocarbene reagents, HCF₂Cl and FSO₂CF₂CO₂TMS, could generate highly reactive difluoromethylene ylide. Thus the Wittig difluoro-olefination and difluorocyclopropanation could be selectively realized by using the same reagent. In addition, the ylides obtained from different carbene sources showed different reactivity in Wittig reactions.

Keywords: carbenes · difluorocyclopropanation · difluoro-olefination \cdot fluorine \cdot ylides

Introduction

Difluorocarbene and difluoromethylene phosphonium ylide are highly reactive intermediates in the construction of fluorine-containing organic molecules.^[1] As a singlet carbene,^[2] difluorocarbene (:CF₂) is stabilized by two fluorine atoms and reacts readily with electron-rich substrates.^[3] Triphenylphosphine can trap difluorocarbene to form phophonium ylide (Ph₃P⁺CF₂⁻) in situ.^[4] It seems that Ph₃P⁺CF₂⁻ might be more stable than difluorocarbene. However, computational examination of the binding and structure of difluoromethylene phosphonium ylide showed some discrepancy.^[5] Using ab initio molecular orbital energy at the SCF level, Dixon and Smart found that the bond length between carbon and phosphorus in H₃P⁺CF₂⁻ was 3.54 Å, which means that : CF₂ and PH₃ could be regarded as two separate species with little interaction.^[5a] However, a later calculation of $H_3P^+CF_2^-$ at the HF/3-21G* level by Francl et al. showed that the C-P bond length was 1.635 Å, which could be interpreted as a double bond between carbon and phosphrous.^[5b] Recently, Dolbier found that the calculated C-P bond length in $Ph_3P^+CF_2^-$ at the M06-2X/6-311+G (2df, 2p) level is 1.815 Å.^[4b] The dissociation of Ph₃P⁺CF₂⁻ to difluorocarbene and PPh₃ in this case would only have to cross a 9.27 kcalmol⁻¹ energy barrier, which suggested the possibility of interconversion between the ylide $(Ph_3P^+CF_2^-)$ and carbene (:CF₂).

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nylphosphine to form the difluoromethylene phosphonium ylide (Ph₃P+CF₂⁻) was first described by Franzen,^[6] but a later study claimed that the reaction could not be repeated.^[7] Other attempts to trap the difluorocarbene from CF_2Br_2 or $(CF_3)_2Cd$ with PPh₃ were not successful.^[7,8] The generation of the vlide from difluorocarbene was also proposed by Fugua et al. in the Wittig reaction of aldehvde with ClCF₂CO₂Na/PPh₃.^[9] However, Burton et al. proposed that Ph₃P⁺CF₂⁻ was generated from Ph₃P⁺CF₂CO₂⁻, not from the combination of difluorocarbene and PPh3.[10] Recently, we successfully synthesized the intermediate $Ph_3P^+CF_2CO_2^-$ and confirmed the conjecture made by Burton et al.^[11] The association of difluorocarbene with PPh₃ and the successful application in subsequent Wittig reaction was reported by Robins and Nowak, but a toxic reagent, (CF₃)₂Hg, was employed as the difluorocarbene precursor.^[4a] Dolbier et al. employed FSO₂CF₂CO₂CH₃ as the difluorocarbene source to generate the ylide ($Ph_3P^+CF_2^-$) and successfully realized the Wittig difluoro-olefination.[4b] However, starting from common and easily available difluorocarbene reagents such as HCF2Cl, attempts to form Ph₃P⁺CF₂⁻ were not successful.^[7] Therefore, to make this vlide formation procedure widely applicable for difluoroolefination, it would be worthwhile to investigate the conversion from difluorocarbene to difluoromethylene ylide.

The capture of difluorocarbene from HCF₂Cl by triphe-

As for the reverse process, Burton and co-workers observed the dissociation of the difluoromethylene ylide into difluorocarbene in the reaction of (bromodifluoromethyl)triphenylphosphonium bromide with tertiary phosphine and trialkyl phosphite.^[12] A similar process was proposed by Jaiswal et al. during the preparation of hydrofluorocarbons.^[13] However, this procedure was not applied in typical reactions involving difluorocarbene. Thus the conversion from the difluoromethylene vlide to difluorocarbene remains to be further investigated.

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Results and Discussion

We have previously demonstrated that the phosphobetaine intermediate ($Ph_3P^+CF_2CO_2^-$, 1) is an efficient and reliable precursor of difluoromethylene ylide.^[11] The simple decarboxylation of $Ph_3P^+CF_2CO_2^-$ at temperatures below 80 °C can give the difluoromethylene ylide, which would make it feasible and convenient to explore the conversion from difluoromethylene ylide to difluorocarbene. 4-Vinyl-1,1'-biphenyl (**2a**) was chosen as a model substrate to detect the generation of difluorocarbene. It was found that the desired reaction did not happen in polar solvents (Table 1, entries 1

Table 1. Conditions	for	the	difluorocyclopropanation	with
$Ph_3P^+CF_2CO_2^-$. ^[a]			F F	

F	$Ph_3P^+CF_2CO_2^- + Ph$) — 2a	Solvent	Ph	X
Entry	Solvent	<i>T</i> [°C]	$1:2a^{[b]}$	<i>t</i> [h]	Yield [%] ^[c]
1	DMF	80	2:1	8	ND ^[d]
2	DG	80	2:1	8	$ND^{[d]}$
3	methyl benzoate	90	2:1	2	24
4	1,4-dioxane	80	2:1	8	45
5	THF	80	2:1	8	30
6	<i>p</i> -xylene	80	2:1	8	77
7	cyclohexane	80	2:1	8	73
8	<i>p</i> -xylene	80	2:1	4	75
9	<i>p</i> -xylene	80	1.5:1	4	54
10	<i>p</i> -xylene	60	2:1	8	22
11	<i>p</i> -xylene	90	2:1	8	80
12 ^[e]	<i>p</i> -xylene	90	2:1	8	80

[a] 0.1 mmol of **2a** in 1 mL of solvent. [b] Molar ratio. [c] Determined by ¹⁹F NMR spectroscopy with the quantitative addition of trifluoromethylbenzene as the internal standard. [d] Not detected by ¹⁹F NMR spectroscopy. [e] 0.8 mmol of **2a** in 1.2 mL of *p*-xylene. DG = diglyme.

and 2). To our delight, the difluorocyclopropanation did occur in less-polar solvents (Table 1, entries 3-5). Better vields were obtained in cyclohexane or para-xylene (Table 1, entries 6 and 7). These results suggest that polar solvents could help to stabilize the charge-separation ylide $Ph_3P^+CF_2^-$, whereas less-polar or non-polar solvents would favor the dissociation of the ylide into difluorocarbene. Further screening of the reaction temperature and molar ratio showed that a 2:1 ratio of 1 to 2a at 90 °C for 8 h were the optimal reaction conditions (Table 1, entry 11). Due to the volatility of the product, less solvent (0.1 mmol of 2a in 1 mL of para-xylene) was used so that the reaction mixture could be directly subject to column chromatography after the completion of the reaction, thus reducing the inevitable loss of the product during work-up. The reaction proceeded equally well for a scaled-up reaction in a small amount of para-xylene (Table 1, entry 12), indicating the high efficiency of this reaction.

We then investigated the scope of the reaction under the optimal reaction conditions. In most cases, the reaction proceeded very well to give the difluorocyclopropanation prod-



Table 2. Reactions of difluorocarbene generated from the ylide $(Ph_3P^+CF_2^-)$.^[a]



[a] Reaction conditions: 1 (1.6 mmol) and 2 (0.8 mmol) in *p*-xylene (1.2 mL) for 8 h at 90 °C. [b] Yield of isolated product. [c] Performed for 1 h.

uct in moderate to good yields (Table 2, entries 1-6). An electron-rich alkene reacted better than an electron-poor alkene (Table 2, entry 3 vs. 4). Moderate yield could be obtained in the case of the disubstituted alkene (Table 2, entry 6), indicating that the steric hindrance did not significantly influence the reaction. Besides the difluorocyclopropanation reaction, heteroatom-hydrogen bond insertion (X-H, X=O, S, N) is another typical reaction of difluorocarbene.^[14] However, due to the poor electrophilicity of difluorocarbene, excess base was usually required to produce the heteroatom anion, thereby promoting its reaction with difluorocarbene.[14b-d, 15] It was found that the difluorocarbene derived from Ph₃P⁺CF₂CO₂⁻ inserted smoothly into the X-H bond without the addition of any base, giving good yields of the difluoromethylation product (Table 2, entries 7-9). The above difluorocyclopropanation and difluoromethylation reactions demonstrated the successful conversion from difluoromethylene ylide to difluorocarbene. The difluorocarbene can be generated at a relatively low reaction temperature without any external additive or catalyst, which might make the difluoromethylene ylide precursor



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 $(Ph_3P^+CF_2CO_2^-, 1)$ a simple and convenient difluorocarbene reagent.

The successful conversion from difluoromethylene ylide to difluorocarbene prompted us to investigate its reverse process, from difluorocarbene to difluoromethylene ylide. Although many difluorocarbene reagents have been developed, most are inefficient or difficult to obtain: difluorodiazirine, Me₃SnCF₃, and (CF₃)₂Hg, for instance, require several steps to prepare and involve expensive or toxic materials.^[16] The generation of difluorocarbene from hexafluoropropylene oxide (HFPO) must be carried out in an autoclave at high temperature.^[17] Chlorodifluoromethane (HCF₂Cl) is a classical difluorocarbene reagent from which difluorocarbene can be easily generated in the presence of base, such as potassium tert-butoxide or hydroxide.^[14a,18] Speziale and Ratts once tried to capture the difluorocarbene from HCF₂Cl by PPh₃ to form the difluoromethylene ylide Ph₃P⁺CF₂⁻; however, their attempts failed.^[7] It was suggested that difluorocarbene preferentially reacted with the strong base rather than PPh₃. We thought that reducing the concentration of base might help the capture of difluorocarbene with PPh₃. It was reported that the low concentration of alkoxy anion produced from the ring-opening reaction of ethylene epoxide could be used as the base for the generation of :CF₂ from HCF₂Cl.^[19] Therefore, this procedure was adopted for the trapping of difluorocarbene with PPh₃.

In the presence of propylene oxide and tetra-*n*-butylammonium chloride, the reaction of 4-bromobenzaldehyde with HCF₂Cl and PPh₃ gave the difluoro-olefination product, indicating the formation of difluoromethylene ylide Ph₃P⁺CF₂⁻ in the reaction (Table 3, entry 1). Among the solvents tested, DMF was shown to be the most suitable for the difluoro-olefination (Table 3, entries 1–4). This indicated

Table 3. Optimization of reaction conditions for difluoro-ole fination with $\mathrm{HCF_2CL}^{[a]}$

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Ph ₃ P + HCF ₂ Cl + Br		Br CHC	2	► MSBr´	Br		
		4a	<i>n</i> Bu₄l	NCI	5a		
Entry	Solvent	<i>n</i> Bu ₄ NCl [equiv]	Т [°С]	PO ^[b] [equiv]	<i>t</i> [h]	Yield ^[c] [%]	
1	DMF	0.4	80	1.0	4	15	
2	DG	0.4	80	1.0	4	<1	
3	$MB^{[d]}$	0.4	80	1.0	4	6	
4	<i>p</i> -xylene	0.4	80	1.0	4	3	
5	DMF	0.4	90	1.0	4	24	
6	DMF	0.4	110	1.0	4	42	
7	DMF	0.4	110	1.0	6	51	
8	DMF	0.4	110	2.0	6	56	
9 ^[e]	DMF	0.4	110	2.0	6	80	
10 ^[e]	DMF	0.2	110	2.0	6	83	
11 ^[e]	DMF	0.1	110	2.0	6	75	
12 ^[e]	DMF	_	110	2.0	6	42	
13 ^[e]	DMF	_	110	_	6	$ND^{[f]}$	

[a] Performed on a 0.1 mmol scale based on **4a**. [b] Propylene oxide. [c] Determined by ¹⁹F NMR spectroscopy with the quantitative addition of trifluoromethylbenzene as the internal standard. [d] Methylbenzoate. [e] 50 mg 4 Å MS was added. [f] Not detected by ¹⁹F NMR spectroscopy.

that polar solvents favored the ylide formation, which is consistent with the previous observation.[4b] Further optimization of the temperature, the amount of propylene epoxide and the reaction time revealed that a moderate yield of the desired product could be obtained after being heated at 110°C for 6 h in the presence of 2 equivalents of propylene oxide (Table 3, entry 8). Water was known to be detrimental to the reaction of $:CF_2$ or $Ph_3P+CF_2-:^{[4b,14d]}$ Therefore, 4 Å MS were employed to remove trace amounts of water in the reaction. It was found that the yield was significantly increased with the addition of 4 Å MS (Table 3, entry 9). Under these conditions, we tried to reduce the amount of nBu_4NCl . The reaction proceeded smoothly, even when only a catalytic amount of nBu₄NCl was used (Table 3, entries 10 and 11). To our surprise, the difluoro-olefination reaction took place even without the presence of nBu_4NCl (Table 3, entry 12), suggesting that 4 Å MS acted both as a drying agent and as a Lewis acid to promote the ring opening of propylene epoxide. In the absence of propylene oxide, no desired product was detected (Table 3, entry 13), which means that the alkoxy anion from propylene epoxide initiated the reaction of HCF₂Cl.

The difluoromethylene ylide derived from HCF₂Cl could be applied to the difluoro-olefination of a variety of aryl aldehydes, giving the corresponding *gem*-difluoroalkenes in good to excellent yields (Table 4, entries 1–5). The relatively lower yield of *meta*-trifluoromethyl benzaldehyde obtained is due to the high volatility of the product; the yield determined by ¹⁹F NMR analysis was 81 % (Table 4, entry 2). Heteroaryl aldehydes are also suitable substrates for this reaction (Table 4, entries 6 and 7). The reaction proceeded quite well for the α , β -unsaturated aldehyde or enolizable aldehyde (Table 4, entries 8 and 9). However, even in the case of an activated ketone, only a moderate yield of difluoroolefinated product could be obtained (Table 4, entry 10).

This reaction occurred through the following process (Scheme 1). The ring-opening reaction of propylene oxide



Scheme 1. Formation of difluorocarbene and difluoromethylene ylide from HCF₂Cl.

by chloride afforded the alkoxy anion. This then abstracted a proton from HCF₂Cl to form the chlorodifluoromethyl anion, which underwent decomposition to give difluorocarbene and a chloride anion. The chloride anion entered into the next reaction cycle. Therefore, only a catalytic amount of nBu_4NCl was needed for the reaction. If water was present in the reaction system, the alkoxy anion would be con-

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Table 4. Wittig difluoro-olefination with HCF2Cl.^[a]



[a] Reaction conditions: Ph₃P (1.6 mmol), HCF₂Cl (3.5 mmol), 4 Å MS (75 mg), nBu_4NCl (0.16 mmol), propylene epoxide (1.6 mmol), and 4 (0.8 mmol) in DMF (1.5 mL) for 6 h at 110 °C. [b] Yield of isolated product. [c] Determined by ¹⁹F NMR spectroscopy with trifluoroacetic acid as the internal standard.

sumed. Thus molecular sieves were used to remove it. Because the alkoxy anion was generated by ring-opening of the epoxide, it might always exist in very low concentrations and not impede the capture of difluorocarbene with PPh₃, which would help the formation of difluoromethylene ylide.

It should be noted that the difluoromethylene ylide derived from HCF₂Cl did not react well with electron-deficient aldehydes, such as 4-nitrobenzaldehyde. This was also reported by Fuqua and Dolbier and co-workers.^[4b,9c] As we know, the reactivity of difluorocarbene from different precursors varied greatly. This prompted us to consider that different difluorocarbene sources might make some difference in the reactivity of the corresponding difluoromethylene ylides. Recently, trimethylsilyl fluorosulfonyldifluoroacetate (FSO₂CF₂CO₂TMS; TFDA) has been found to be an efficient difluorocarbene reagent that can react smoothly with electron-deficient alkenes.^[20] To explore the applicability of this ylide formation method and the reactivity of the ylide from different carbene sources, we investigated the generation and reaction of difluoromethylene ylide from TFDA. It has been reported that $FSO_2CF_2CO_2TMS$ (TFDA) could smoothly generate difluorocarbene in methylbenzoate.^[20a,c] The first attempt at Wittig difluoro-olefination of 4bromobenzaldehyde with TFDA in the presence of PPh₃ was made in this solvent. Indeed, the reaction gave the desired product, indicating the successful conversion from difluorocarbene to difluoromethylene ylide Ph₃P⁺CF₂⁻, but only a low yield was obtained (Table 5, entry 1). Some other

Table 5. Optimization of reaction conditions for Wittig difluoro-olefination of $FSO_2CF_2CO_2TMS$.

Ph ₃ P + FSO ₂ CF ₂ COOTMS +					
6	7	ы	4a	Ы	
Entry	Solvent	Т [°С]	<i>t</i> [h]	Molar ratio 6:7:4a	Yield [%] ^[a]
1	$MB^{[b]}$	120	2	2:2:1	26
2	DMF	120	2	2:2:1	12
3	p-xylene	120	2	2:2:1	27
4	benzonitrile	120	2	2:2:1	19
5	CH ₃ CN	120	2	2:2:1	53
6	EA	120	2	2:2:1	76
7	EA	70	2	2:2:1	72
8	EA	80	2	2:2:1	83
9	EA	90	2	2:2:1	86
10	EA	100	2	2:2:1	85
11	EA	90	2	1:1:1	46
12	EA	90	2	1.5:1.5:1	80
13	EA	90	2	2.5:2.5:1	94
14	EA	90	2	3:3:1	91
15	EA	90	0.5	2.5:2.5:1	70
16	EA	90	1	2.5:2.5:1	95

[a] Determined by ¹⁹F NMR spectroscopy with the quantitative addition of trifluoromethylbenzene as the internal standard. [b] Methylbenzoate.

solvents were then investigated (Table 5, entries 2–6) and it was found that solvent had significant impact on the reaction. In ethyl acetate (EA), the result was much better than that in other solvents (Table 5, entry 6). After further screening of the reaction temperature, reaction time, and the molar ratio of $Ph_3P/FSO_2CF_2CO_2TMS/substrate$ (Table 5, entries 7–16), we decided that EA as solvent, a reaction temperature of 90°C, and a molar ratio of 2.5:2.5:1 were the optimal conditions (Table 5, entry 16).

The reaction could be applied to a variety of carbonyl compounds including aromatic, heteroaromatic, and aliphatic aldehydes and activated ketones (Table 6). More importantly, the reaction worked very well in the case of electron-deficient aldehydes (Table 6, entries 3 and 9), demonstrating a higher reactivity of the difluoromethylene ylide obtained from TFDA in comparison with other reported methods.^[4b,9c] In the case of 4-nitrobenzaldehyde (Table 6, entry 3), difluoro-olefination with difluoromethylene ylide usually gave very low yields of the expected difluoro-olefinated product; only 2.1% yield was obtained by Fuqua's method,^[9c] and only 15% yield by Dolbier's method.^[4b] This indicated that ylides obtained from different carbene sources have different reactivity.

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Table 6. Wittig difluoro-olefination of FSO₂CF₂CO₂TMS.^[a]



[a] Reaction conditions: Ph_3P (2.0 mmol), $FSO_2CF_2CO_2TMS$ (2.0 mmol), NaF (0.016 mmol), and **4** (0.8 mmol) in EA (1.5 mL) for 1 h at 90 °C. [b] Yield of isolated product.

Conclusion

The interconversion between difluoromethylene ylide and difluorocarbene has been successfully achieved. By changing the reaction conditions, the difluoromethylene ylide precursor, $Ph_3P^+CF_2CO_2^-$, was converted into an efficient difluorocarbene reagent, whereas the classical difluorocarbene reagents, HCF_2CI and $FSO_2CF_2CO_2TMS$, generated the highly reactive difluoromethylene ylide. The difluoromethylene ylides obtained from different difluorocarbene reagents showed different reactivity in Wittig reactions. Therefore, the difluoro-olefination and difluorocyclopropanation could be selectively conducted by using the same reagent. Further research on the conversion between other fluorinated ylide and carbene is currently underway.

Experimental Section

General methods: Solvents and reagents were purchased from commercial sources and used as received, unless otherwise noted. The solvents *para*-xylene, DMF, and EA were distilled over CaH₂. ¹H, ¹³C and ¹⁹F NMR spectra were detected on a 500, 400or 300 MHz NMR spectrometer. Data for ¹H, ¹³C and ¹⁹F NMR were recorded as follows: chemical shift (δ , ppm), multiplicity (s=singlet, d=doublet, t=triplet, m= multiplet, q=quartet), coupling constant/s in Hz. Mass spectra were obtained on a GC-MS. High-resolution mass data were recorded on a high resolution mass spectrometer in the EI or ESI mode.

Dissociation of difluoromethylene ylide to carbene: $Ph_3P^+CF_2CO_2^-$ (1, 570 mg, 1.6 mmol) and 4-vinyl-1,1'-biphenyl (2a, 144 mg, 0.8 mmol) were added to a 5 mL sealed tube. The mixture was degassed and then *para*-xylene (1.2 mL) was added under N₂. The reaction mixture was stirred at 90 °C for 8 h. After being cooled to room temperature, the solution was subjected to flash column chromatography to give the pure product 3a. Wittig difluoro-olefination of HCF₂Cl: Ph₃P (420 mg, 1.6 mmol), 4-bro-

mobenzaldehyde (4a, 148 mg, 0.8 mmol), and 4 Å MS (75 mg) were added to a 5 mL sealed tube. The mixture was degassed and then a solution of HCF₂Cl in DMF (2.3M, 1.5 mL) was added under N₂. The reaction mixture was stirred at 110 °C for 6 h. After being cooled to room temperature, the solution was subjected to flash column chromatography to give the pure product **5**a.

Wittig difluoro-olefination of $FSO_2CF_2CO_2TMS$: Ph₃P (525 mg, 2.0 mmol), 4-bromobenzaldehyde (4a, 148 mg, 0.8 mmol), and NaF (1.6 mg, 0.038 mmol) were added to a 25 mL Schlenk tube. The mixture was degassed and then EA (1.2 mL) was added under N₂. The reaction mixture was stirred at 90 °C for 1 min. $FSO_2CF_2CO_2TMS$ (501 mg, 2.0 mmol) was added dropwise over 10 min. The resulting mixture was stirred at the same temperature for another 1 h. After being cooled to room temperature, it was subjected to flash column chromatography directly to give the pure product **5a**.

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FULL PAPER



phosphonium ylide, generated from $Ph_3P^+CF_2CO_2^-$, was turned into an efficient difluorocarbene reagent, whereas the classical difluorocarbene reagents, HCF₂Cl and

FSO₂CF₂CO₂TMS, generated the highly reactive difluoromethylene ylide. Interestingly, it was found that the ylides obtained from different carbene sources showed different reactivity in Wittig reactions (see scheme).

Ylides -

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Conversion between Difluorocarbene and Difluoromethylene Ylide

These are not the final page numbers!