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Reactions of Carbonyl Compounds with Phosphorus Ylide Generated from Tribromofluoromethane and Tris(dimethylamino)phosphine

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The reactions of fluorinated ylide, generated from tris(dimethylamino)phosphine and tribromofluoromethane, with simple aldehydes and reactive ketones gave the expected Wittig reaction products. However, a ketone having a galactose skeleton afforded an acid fluoride, probably through an unprecedented Corey–Chaykovski-type epoxide formation reaction, followed by spontaneous Meinwald rearrangement.

Fluorinated ylides are widely used for fluoro-, difluoro-, chlorofluoro-, and bromofluoromethylenations of carbonyl compounds in the fields of synthetic organic chemistry and medicinal chemistry.[1] However, relatively few methods are available for bromofluoromethylenation reactions, and the triphenylphosphonium ylide **1** has been mainly utilized. It is usually prepared in situ, without isolation, from tribromofluoromethane ($CFBr_3$) and triphenylphosphine (PPh_3) under heating[2] or with the use of zinc metal,[1,3,4] diethylzinc,[5] or phosphite[6] as an additive (Figure 1A).[1,7]

On the other hand, tris(dimethylamino)phosphine (HMPT) has been used for difluoromethylenation[1,8] and chlorofluoromethylenation[9] reactions of carbonyl compounds (Figure 1B). Mixing of HMPT (2 mol) with CF_2Br_2 or $CFCl_3$ (1 mol) would afford the corresponding ylides **2a** or **2b**, which should react with reactive carbonyl compounds to give the corresponding fluoro-olefins. Indeed, we employed the HMPT-CF_2Br_2 system with the relatively reactive ketone **3** to obtain difluoro-olefin **4** (Figure 1B).[10] These methods are convenient owing to their simple procedures, but, as far as we know, no example of bromofluoromethylenation reaction using HMPT has yet been reported.[11] Herein we report unique reactivity of the putative ylide **2c** (Figure 1C).

We first investigated the reaction of carbonyl compounds with **2c**. Most of the aldehydes examined were converted to the corresponding bromofluoro-olefin, and the scope of this reaction is summarized in Table 1. The reaction was conducted with $CFBr_3$ (Xequiv) and HMPT (2Xequiv) at room temperature in THF (0.1 M concentration of the substrate), unless otherwise noted.[12] The optimum amounts of reagents were different for each substrate. For example, use of four equivalents of $CFBr_3$ ($X = 4$) gave the best result for **6a** (yield of **7a**: 92%), whereas in the case of **6e**, a smaller amount of reagents ($X = 3$) gave a better result (yield of **7e**: 72%). In all cases, the product **7** was a mixture of *E*- and *Z*-isomers, in accordance with previous reports on the reactions using PPh_3.[5] Several electron-donating substituents on the aromatic ring were tolerated, but electron-withdrawing nitro or fluoro substituents decreased the chemical yield of **7**. The reaction of benzaldehydes with –NHAc or –NHBoc groups gave messy mixtures and no bromofluoro-olefin was isolated. Aliphatic aldehydes **6p** and **6q** were converted to **7p** and **7q** in moderate yields.

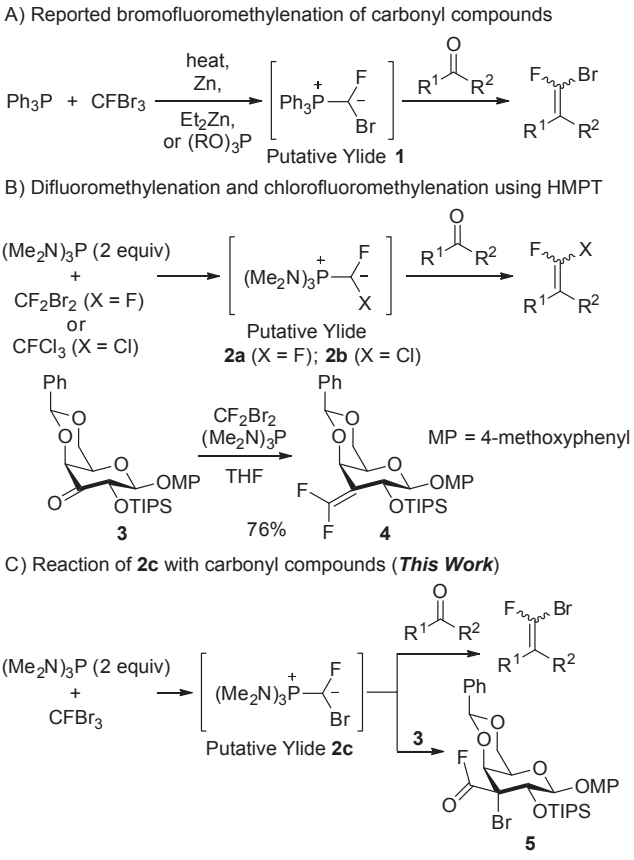
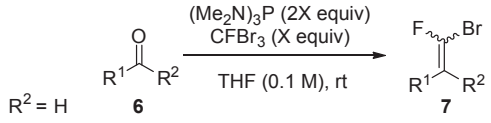


Figure 1. A) Bromofluoromethylenation of carbonyl compounds with putative ylide **1**; B) Fluoromethylenation of carbonyl compounds with putative ylide **2a** or **2b** and its application to ketone **3** (ref 10); C) Two different reactions of putative ylide **2c** generated from HMPT and $CFBr_3$ with carbonyl compounds.

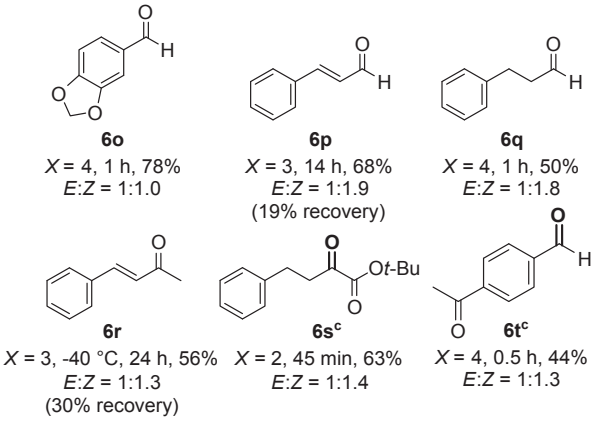
Although ketones such as acetophenones or cyclohexanones showed poor reactivity with **2c** (Table S1),[12] a few ketones such as **6r** or the α-ketoester **6s** were converted to the corresponding bromofluoro-olefin in acceptable yield. Thus, **2c** appeared to be a moderate nucleophile.[13] However, ketones that were not

Table 1. Bromofluoromethylenation of various aldehydes and ketones **6**



R^1	X	Time	Yield/%	E:Z ratio[b]
p-$MeOC_6H_4$ (**6a**)	4	22 h	92[a]	1.2:1
m-$MeOC_6H_4$ (**6b**)	4	2 h	81	1:1.2
o-$MeOC_6H_4$ (**6c**)	4	1 h	84	1:1.3
p-MeC_6H_4 (**6d**)	4	1 h	66	1:1.0
o-MeC_6H_4 (**6e**)	3	24 h	72	1:1.0
p-BrC_6H_4 (**6f**)	4	40 min	58	1:1.3
o-BrC_6H_4 (**6g**)	3	2 h	75	1:1.1
p-FC_6H_4 (**6h**)	3	30 min	44	1:1.2
o-FC_6H_4 (**6i**)	3	1.5 h	44	1:1.3
p-$O_2NC_6H_4$ (**6j**)	2	30 min	46	1:1.7
o-$O_2NC_6H_4$ (**6k**)	2	15 min	81	1:1.0
p-$HC{\equiv}CC_6H_4$ (**6l**)	2	4 h	62	1:1.0
o-$HC{\equiv}CC_6H_4$ (**6m**)	4	1.5 h	71	1:1.2
p-$MeO_2CC_6H_4$ (**6n**)	3	20 min	63	1:1.4

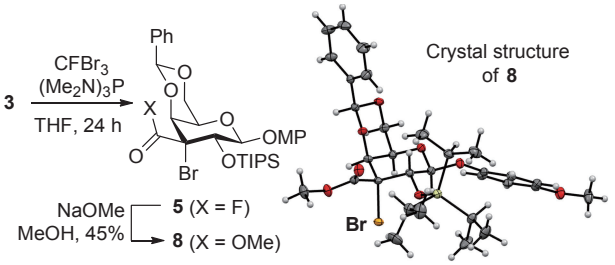
[a]6% of **6a** was recovered. [b]The E/Z ratio was determined by ^{1}H NMR of crude material. [c]The carbonyl group indicated by bold face in **6s** and **6t** was converted to the corresponding bromofluoro-olefin.



converted to **7**, were not completely inert, and were partially degraded (Table S1).[12] In fact, chemoselective olefination of aldehyde in **6t** in the presence of a ketone functionality was realized, though in only moderate yield without recovery of **6t**. These results suggested that **2c** might react with ketones, but the formation of bromofluoro-olefin was unfavored. We anticipated that other reaction pathways might exist after addition of **2c** to a carbonyl group. During the course of these investigations, we found a very interesting reaction process.

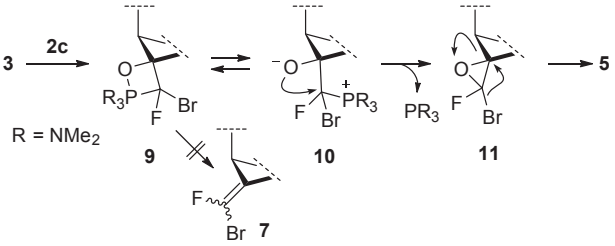
We examined bromofluoromethylenation of ketone **3**, which is quite electrophilic due to the ring-strain of the sugar skeleton (Figure 1C). We assumed that bromofluoromethylenation would proceed, because a similar difluoromethylenation reaction was successful.[10] However, treatment of ketone **3** with $CFBr_3$ (1.5 equiv) and HMPT (3 equiv) gave a complex mixture. Careful TLC analysis revealed a new spot on TLC upon partial addition of HMPT, but this later disappeared. Hence, the amount of HMPT was reduced to 2 equiv ($CFBr_3$: 1.5 equiv, Table 2, Entry 1). As a result, the new product could be isolated, but it was not the corresponding bromofluoro-olefin. Structural

Table 2. Formation of acid fluoride **5**



Entry	$CFBr_3$ /equiv	$(Me_2N)_3P$ /equiv	Temp. /°C	Yield of **5**[a]/%	Recoverd **3**/%
1[b]	1.5	2.0	rt	27	51
2	3.0	6.0	rt	0	ND[c]
3	3.0	5.0	rt	0	33
4	3.0	4.0	rt	31	32
5	3.0	3.1	rt	24	45
6	3.0	3.1	0	32	21
7[d]	3.0	3.1	−40	69	ND[c]

[a]Trace amounts of impurities were detected. [b]Reaction time: 1.5 h. [c]ND: Not detected. [d]Reaction time: 13 h.



Scheme 1. Plausible mechanism for the formation of acid fluoride **5**.

analysis revealed that, surprisingly, it was an α-bromoacid fluoride derivative **5**. The acid fluoride functionality was confirmed by ^{13}C NMR (δ 156.5 ppm, $J = 365$ Hz) and ^{19}F NMR (δ 24.8 ppm), while mass spectrometry showed the presence of a bromine atom. Treatment of **5** with sodium methoxide gave ester **8**, whose structure was confirmed by X-ray crystallographic analysis (Table 2).[14]

Formation of the α-bromoacid fluoride **5** was investigated with an increased amount of $CFBr_3$ (3 equiv, Table 2). It was found that one of the key factors determining the chemical yield of **5** was the amount of HMPT. When 6 equiv of HMPT (2 equiv with respect to $CFBr_3$) was used, a messy mixture was obtained again, probably due to decomposition of **5** (Entry 2). In contrast, when the amount of HMPT was decreased from 6 to 3.1 equiv, the yield of **5** increased (Entries 2–5). **5** was obtained when less than 5 equiv of HMPT was used (Entry 4), and 3.1 equiv of HMPT was enough to produce **5** (Entry 5). Another key factor was the reaction temperature. Lowering the reaction temperature improved the conversion of **3** and the chemical yield of **5**, and eventually **5** was obtained in 69% yield at −40 °C (Entry 7).

A possible reaction mechanism leading to **5** is shown in Scheme 1. We speculated that α-bromoacid fluoride functionality could be formed from α-bromo-α-fluoroepoxide **11** via tautomerization, corresponding to a spontaneous Meinwald-type rearrangement. A similar transformation was reported by Saloutin and co-workers.[15] Although α-bromo-α-fluoroepoxide

with the perfluoroalkyl group has been isolated,[16] **11** lacking the perfluoroalkyl group would be destabilized and spontaneously converted into the α-bromoacid fluoride. Electron-donating alkyl groups and the negative hyperconjugation effect of a fluorine atom might enhance the rearrangement. If this is the case, Corey–Chaykovsky-type epoxidation (CC-type reaction) should be implicated in the formation of **11** from **3** with **2c**. The observed experimental fact that a slight excess of HMPT with respect to $CFBr_3$ was sufficient for the formation of **5** supports the proposed mechanism.[17] In the mechanism shown in Scheme 1, HMPT would be regenerated after CC-type reaction, while two HMPT molecules are required to generate **2c**. CC-type reaction is well-known in sulfur ylide-mediated epoxidation.[18] Based on the proposed mechanism of the sulfur ylide-mediated CC-type reaction, an intramolecular S_N2 reaction of betaine **10**, which might be in equilibrium with the usual oxaphosphetane intermediate **9** in Wittig reaction, would give the labile **11**. Although selenium,[19] tellurium,[20] arsine,[21] and bismuth[22] ylide-mediated CC-type reactions have been already reported, as far as we know, this is the first example of CC-type reaction of a phosphorus ylide.[23]

On the other hand, application to simple aldehydes, ketones, or the corresponding glucose and mannose derivative of **3** did not result in the isolation of α-bromoacid fluorides or their hydrolyzed products (Scheme S2).[12] It is possible that this new process occurred with simple substrates because the α-bromoacid fluorides or epoxide intermediates would be readily decomposed under the reaction conditions. In contrast, compound **5** is sufficiently stable to be isolated, and may be kinetically stabilized due to the neighboring bulky TIPS group.

In conclusion, we found two different reactions of putative ylide **2c**, although the structural requirements for each process remain unclear. At least for more reactive carbonyl compounds, such as aldehydes or α-ketoesters, the reaction with **2c** provided the corresponding bromofluoro-olefin derivatives, which should be precursors of fluoro-olefin derivatives. For the specific substrate **3**, another reaction process from carbonyl compound into α-bromoacid fluoride derivative via a novel phosphorus ylide-mediate CC-type reaction, followed by spontaneous Meinwald rearrangement reaction, proceeded in a similar reaction system. Isolation of **5** suggested that this unique multi-sequence reaction might be more generally available as a highly functionalized one-carbon elongation reaction. Further investigations are in progress to examine this possibility.

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Supporting Information is available electronically on J-STAGE.

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