Organic LETTERS

Letter

pubs.acs.org/OrgLett

Direct Nucleophilic Difluoromethylation of Carbonyl Compounds

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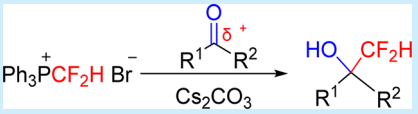
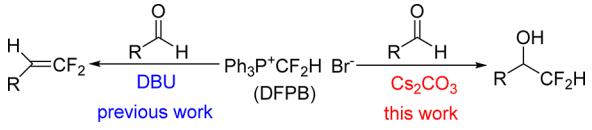
Supporting Information

ABSTRACT: Phosphonium salt ($[Ph_3P^+CF_2H]$ Br^-, DFPB) was found to be an efficient nucleophilic difluoromethylation reagent. Although DFPB is known as a phosphonium ylide precursor, its reaction with carbonyl compounds under traditional "Wittig reaction conditions" did not give the expected Wittig difluoroolefinated products, but afforded the nucleophilic difluoromethylation products, α-CF_2H alcohols. Mechanistic investigation reveals that the unexpected transformation proceeded via the direct transfer of the CF_2H group, which resulted from the high P−O affinity.



Difluoromethylene phosphobetaine ($Ph_3P^+CF_2CO_2^-$, PDFA), originally proposed as a Wittig difluoroolefination reaction intermediate by Burton et al., had not been previously detected or isolated.[1] Recently, we described the first synthesis of this intermediate and found that its simple decarboxylation provides facile access to the phosphonium ylide ($Ph_3P^+CF_2^-$) for Wittig difluoroolefination.[2] This ylide, $Ph_3P^+CF_2^-$, can undoubtedly be generated by the conventional deprotonation of the corresponding difluoromethyl triphenylphosphonium salt (DFPB) ($[Ph_3P^+CF_2H]$ Br) in the presence of a base such as DBU, leading to the subsequent Wittig difluoroolefination of aldehyde (Scheme 1).[3] However, further

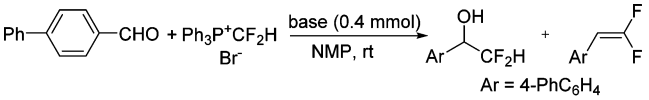
Scheme 1. Reaction of Carbonyl Compounds with DFPB



investigation revealed that the choice of base had a significant influence on the reaction path. The use of cesium carbonate as the base failed to give the expected *gem*-difluoroolefins. Instead, difluoromethylation of aldehydes occurred to give the corresponding alcohols (Scheme 1). The preliminary results of the unexpected direct difluoromethylation are reported herein.

Initially, it was believed that the Wittig difluoroolefination of aldehydes with DFPB should proceed smoothly in the presence of a base. It is true that olefin **3a′** was obtained as the major product when DBU was used as the base in the reaction of 4-phenyl benzaldehyde with DFPB in NMP (Scheme 2).[3] However, when Cs_2CO_3 was used instead of DBU, this reaction turned into a difluoromethylation process. The olefin **3a′** was almost completely suppressed whereas α-CF_2H alcohol **3a** was afforded in 76% yield. We isolated the olefin **3a′** and investigated the possible conversion of **3a′** in DFPB/DBU system in order to find out whether alcohol **3a** was generated

Scheme 2. Difluoromethylation vs Difluoroolefination



1a (0.2 mmol)	**2a** (0.4 mmol)	**3a**	**3a'**
base		yield[a]	
DBU		trace	48%
Cs_2CO_3		76%	trace

[a]Determined by ^{19}F NMR.

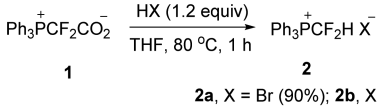
from olefin **3a′**. However, alcohol **3a** was not detected at all by ^{19}F NMR spectrometry, indicating that the alcohol **3a** was not formed from the Wittig difluoroolefination product **3a′**. Further optimization of the difluoromethylation reaction conditions [see Table 1 in Supporting Information (SI)] showed that a high yield (95%) could be obtained by performing the reaction in DMAc at room temperature with the use of 3 equiv of DFPB and 3 equiv of Cs_2CO_3.

We speculated that the reactivity of the phosphonium salt could be modified by varying the anion because of the differences in the solubility of the different salts. Our previous method for the synthesis of DFPB suffered from a tedious procedure,[3] which prompted us to explore the possibility of a more convenient and scalable approach. Fortunately, we found that DFPB could be readily obtained by the decarboxylative hydrogenation of PDFA in the presence of hydrobromic acid. Several other phosphonium salts were successfully prepared in this way with the corresponding acids (Scheme 3). All products were purified simply by extraction. Compared with the previous synthesis of difluoromethylphosphonium salts,[4] the present approach is attractive due to the short synthetic route and convenient purification procedure.

Received: May 17, 2016
Published: June 9, 2016

DOI: 10.1021/acs.orglett.6b01425
Org. Lett. 2016, 18, 3206−3209

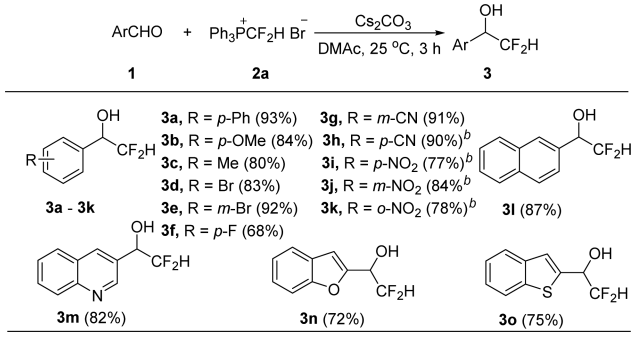
Scheme 3. Preparation of Difluoromethyl Phosphonium Salts



Although most salts were quite effective for difluoromethylation (see Table 2 in SI), none of them gave a higher yield than DFPB. It is noteworthy that the Wittig difluoroolefination was almost completely suppressed in all of these reactions.

With the optimal reaction conditions in hand (see entry 12 of Table 1 in SI), then we explored the scope of this unexpected nucleophilic difluoromethylation. As shown in Scheme 4, irrespective of whether the phenyl group was

Scheme 4. Difluoromethylation of Aldehydes

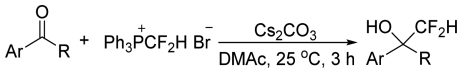


[a]Isolated yields. [b]The reaction was performed at −10 °C.

substituted by an electron-withdrawing or -donating group, all of the reactions proceeded smoothly to afford the desired products in moderate to excellent yields. Substrates containing a strong electron-withdrawing group required the use of a lower reaction temperature to achieve a high yield because the aldehyde groups in these substrates were prone to undergo a benzoin condensation in the presence of a base (**3h**−**k**). The reaction of *p*-cyano benzaldehyde should be conducted at a low temperature (**3h**), whereas *m*-cyano benzaldehyde (**3g**) reacted efficiently at room temperature. This difference in the reactivity might be attributed to the cyano group at the *p*-position, thus making the aldehyde group more electrophilic (σ_m = 0.56, σ_p = 0.66).[5] Heteroaryl aldehydes were also well tolerated under these conditions and gave the desired difluoromethylation products in good yields (**3m**−**o**). This reaction was found to be incompatible with alkyl aldehydes such as 4-phenylbutanal, probably because of the lower reactivity of these aldehydes toward nucleophiles.

Encouraged by these results, we further examined the difluoromethylation of ketones with DFPB (Table 1). In contrast to alkyl aldehydes, alkyl aryl ketones reacted efficiently under the optimal reaction conditions, most likely because of the activation of the carbonyl group by the aryl moiety (Table 1, entries 1−7). Electron-deficient substrates were smoothly converted to the desired products in moderate yields (Table 1, entries 1−6). In contrast, the presence of an electron-donating group (−OMe) on the phenyl ring led to a lower yield of the desired product, which might be attributed to the deactivation of the carbonyl group through a resonance effect (Table 1,

Table 1. Difluoromethylation of Ketones[a]



entry	Ar	R	**5**, yield (%)[a]
1[b]	*m*-NO_2-C_6H_4	Me	**5a**, 60
2[b]	*p*-NO_2-C_6H_4	Me	**5b**, 53
3[b]	*p*-CN-C_6H_4	Me	**5c**, 48
4	*m*-CF_3-C_6H_4	Me	**5d**, 50
5	*p*-CF_3-C_6H_4	Me	**5e**, 49
6	*p*-CF_3-C_6H_4	Et	**5f**, 49
7	*p*-MeO-C_6H_4	Me	**5g**, 21[c]
8	*p*-CF_3-C_6H_4	C_6H_5	**5h**, 62
9	*p*-CN-C_6H_4	C_6H_5	**5i**, 58

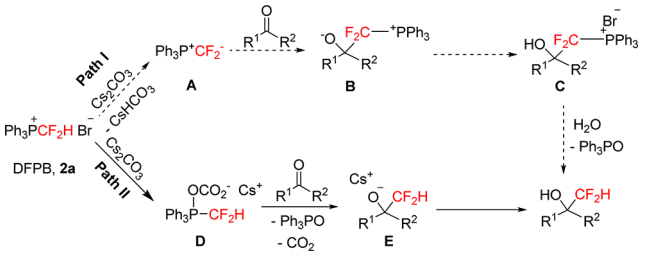
[a]Isolated yields. [b]The reaction was performed at −10 °C. [c]The yield was determined by ^{19}F NMR using trifluoromethylbenzene as an internal standard.

entry 7). This transformation was also found to be applicable to diaryl ketones, implying a moderate sensitivity to steric effects (Table 1, entries 8−9).

Although significant efforts have been devoted toward the development of efficient difluoromethylation methods,[6] direct difluoromethylation of carbonyl compounds remains a significant challenge. $PhMe_2SiCF_2H$[7] and $TMSCF_2H$[8] have been reported to be nucleophilic difluoromethylation reagents in the presence of a suitable Lewis base. However, the scope of these reagents has been limited by the use of harsh reaction conditions or the high volatility of $TMSCF_2H$. Furthermore, $PhMe_2SiCF_2H$ is a poor nucleophile for the conversion of ketones, and strongly basic conditions and low reaction temperatures are usually required for the nucleophilic addition of $TMSCF_2H$ to ketones. This protocol described herein provides a promising alternative and is quite attractive since solid DFPB can be easily accessed and handled.

The above difluoromethylation may not proceed via a SET mechanism because the addition of radical scavenger TEMPO [(2,2,6,6-tetramethylpiperidin-1-yl)oxyl] or single-electron-transfer (SET) inhibitor *p*-DNB (*p*-dinitrobenzene) did not dramatically suppress the difluoromethylation of aldehyde **1a** with DFPB (93% yield of **3a** for TEMPO, 75% yield of **3a** for *p*-DNB). The ylide path (Scheme 5, path I) that the

Scheme 5. Proposed Pathways for the Difluoromethylation



nucleophilic attack of ylide **A** at the carbonyl group to give betaine **B** followed by protonation and hydrolysis to afford the final product should be not plausible, even though recent studies have shown that ylide **A** could be used for stepwise difluoromethylation of aldehydes by protecting betaine **B**.[6g,9] If betaine **B** is formed, Wittig reaction product *gem*-difluoroolefin **3a′** should be produced. But *gem*-difluoroolefin almost cannot

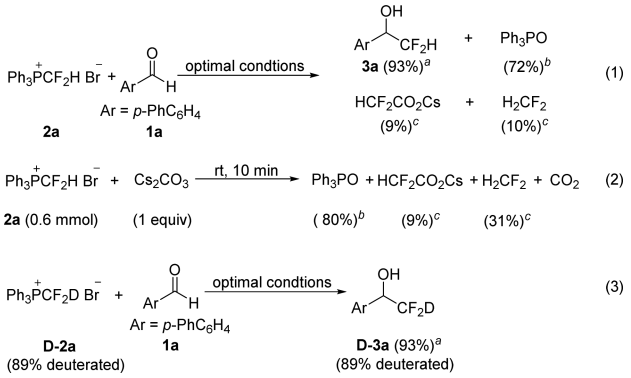
DOI: 10.1021/acs.orglett.6b01425
Org. Lett. 2016, 18, 3206−3209

be detected in any one of the above difluoromethylation reactions.

We propose that the reaction may proceed via direct transfer of the "CF_2H" group (Scheme 5, path II). On the basis of the strong affinity between phosphorus and oxygen[10] and of our previous observation that Cs_2CO_3 can attack at the positive phosphorus in tetraarylphosphonium salts to produce nucleophilic aryl species,[11] we believe that the direct attack of the carbonate anion at the positive phosphonium to give the five-coordinate phosphorus species **D** may be possible.[10a,d,g] The subsequent decarboxylation of intermediate **D** would result in the formation of Ph_3PO and the cleavage of the nucleophilic CF_2H group. Its nucleophilic attack at the carbonyl carbon would afford intermediate **E**, protonation of which furnishes the final product. Apparently, Cs_2CO_3 acts as a nucleophile instead of a base in this transformation.

More experimental evidence was collected to support the proposed mechanism (Scheme 6). In this plausible path,

Scheme 6. Experimental Evidence

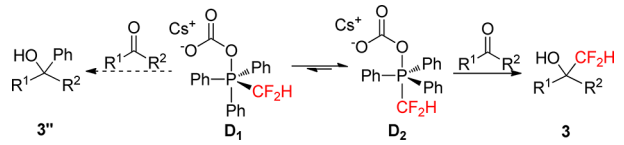


[a]Isolated yield based on **1a**. [b]Isolated yield based on DFPB **2a**. [c]Yields were determined by ^{19}F NMR based on DFPB **2a**.

Ph_3PO and CO_2 are generated as byproducts. Indeed, Ph_3PO was isolated in 72% yield from the difluoromethylation of **1a** (Scheme 6, eq 1). Besides Ph_3PO, HCF_2CO_2Cs and H_2CF_2 were also detected in the reaction mixture by ^{19}F NMR spectrometry (Scheme 6, eq 1). HCF_2CO_2Cs and H_2CF_2 may be produced by the nucleophilic attack of the CF_2H group in intermediate **D** at CO_2 and the proton, respectively. As shown in the proposed mechanism, Cs_2CO_3 should be able to convert DFPB into Ph_3PO even without the presence of a substrate. A mixture of DFPB and Cs_2CO_3 did lead to the full conversion of DFPB rapidly, giving Ph_3PO, HCF_2CO_2Cs, H_2CF_2, and CO_2 (Scheme 6, eq 2, for details; see SI). CO_2 was determined by GC-MS spectrometry in the gas phase of the reaction system, and further by the observation that the generated gas can turn the pure limewater into a milky solution (see SI). The difluoromethylation process should occur via the direct transfer of the CF_2H group without the cleavage of the CF_2–H bond, because the difluoromethylation of **1a** with deuterated salt **D-2a** gave the deuterated product **D-3a** almost exclusively (Scheme 6, eq 3).

It is noteworthy that intermediate **D** (Scheme 5) contains two potential leaving groups (CF_2H and Ph), but no phenylation product **3″** was detected (Scheme 7). This phenomenon could be explained by the reactivity of intermediate **D**. The five-coordinate phosphorus species **D** is a trigonal bipyramidal structure.[12] It is well-known that the axial

Scheme 7. Difluoromethylation vs Phenylation



bonds in trigonal bipyramidal phosphorus molecules are longer and weaker than the equatorial bonds,[12,13] which would make it easier for the carbonate anion to attack at the phosphonium from the axial direction to produce intermediate **D**. Furthermore, two significant configurations of intermediate **D** can be identified, configurations $\mathbf{D_1}$ and $\mathbf{D_2}$. Previous studies have shown that electronegative substituents preferentially reside at the axial positions of these structures,[10a,12,14] indicating that configuration $\mathbf{D_2}$ would be preferred over configuration $\mathbf{D_1}$ because the CF_2H group (σ_m = 0.29, σ_p = 0.32) is much more electronegative than the Ph group (σ_m = 0.06, σ_p = −0.01).[5] Given that the axial bonds of these systems are weaker, the corresponding axial group would be cleaved more easily than the equatorial groups.[10a,12] Therefore, the difluoromethylation proceeded smoothly and the phenylation was not observed.

In summary, we have developed an efficient nucleophilic difluoromethylation of aldehydes and ketones with DFPB in the presence of Cs_2CO_3 to afford α-CF_2H alcohols in moderate to high yields. The expected Wittig olefination was suppressed even though the reaction was performed under the conventional "Wittig reaction conditions". This protocol represents the first example of a direct nucleophilic transfer of a "CF_2H" group from phosphonium salt under basic conditions, in which the high P–O affinity plays an important role. DFPB may become a convenient and efficient difluoromethylation reagent because of its stability, facile accessibility, and ease of handling.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01425.

The optimization of reaction conditions, experimental procedures, and characterization for products (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Basic Research Program of China (2015CB931900, 2012CBA01200), the National Natural Science Foundation (21421002, 21472222, 21502214), the Chinese Academy of Sciences (XDA02020105, XDA02020106), and the Science and Technology Commission of Shanghai Municipality (15DZ1200102) for financial support.

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DOI: 10.1021/acs.orglett.6b01425
Org. Lett. 2016, 18, 3206−3209