Organic LETTERS
Letter
pubs.acs.org/OrgLett

1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU)-Promoted Decomposition of Difluorocarbene and the Subsequent Trifluoromethylation

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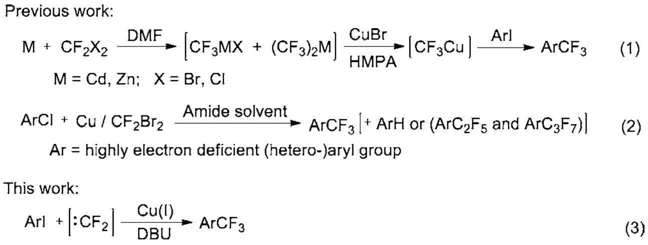
S *Supporting Information*

ABSTRACT: Difluorocarbene derived from various carbene precursors could be effectively decomposed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). This decomposition process was successfully applied in the subsequent trifluoromethylation of a variety of (hetero)aryl iodides without the addition of an external fluoride ion. Mechanistic investigation revealed the detailed difluorocarbene conversion process in which the decomposed difluorocarbene is finally transformed into a fluoride ion and carbon monoxide.

The chemistry of difluorocarbene has received a great deal of attention for the past decades.[1] Difluorocarbene is destabilized by the negative inductive effect of highly electronegative fluorine while it is stabilized by the back-donating effect of the lone pair electrons on fluorine. As a result, difluorocarbene is the most stable dihalocarbene and a moderately electrophilic species.[1d] The understanding of the chemical properties of difluorocarbene has led to its widespread applications in the synthesis of numerous fluorinated compounds. Typical organic transformations include its homocoupling to give tetrafluoroethylene (TFE),[2] electrophilic reaction with C-, O-, N-, S-, and P-nucleophiles,[3,1d] [2 + 1] cycloaddition with alkynes or alkenes,[1d] [^{18}F]-trifluoromethylation,[4] and coordination with transition metals.[5] It is well-known that the difluorocarbene generated in situ is often easy to decompose in the presence of nucleophiles, giving some unexpected byproducts. This kind of decomposition was usually regarded as an unavoidable side reaction in difluorocarbene transformation. And it has rarely been developed into valuable synthetic tools for organic chemists. In continuation of our research interest in the chemistry of difluorocarbene[6] and trifluoromethylation,[7] we have now investigated the utilization of the decomposition of difluorocarbene in copper-mediated trifluoromethylation.

Copper-mediated trifluoromethylation via the decomposition of difluorocarbene was first reported by Burton and co-workers.[8] They found that DMF could initiate the decomposition to produce a fluoride ion, which is readily trapped by difluorocarbene to give the trifluoromethide and further realize the trifluoromethylation (eq 1, Scheme 1).[8] Similar processes were also found in other polar amide solvents, accompanied by some side reactions (eq 2, Scheme 1).[9] However, this process was not deeply investigated. The issue of what the difluorocarbene turns into after decomposition was not fully addressed. Furthermore, these approaches for trifluoromethylation often suffer from tedious procedures or competitive side reactions. We have developed an efficient protocol for the trifluoromethylation of (hetero)aromatic iodides via the decomposition of difluorocarbene promoted by DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) (eq 3, Scheme 1). The preliminary results are described herein.

Scheme 1. Trifluoromethylation via the Decomposition of Difluorocarbene



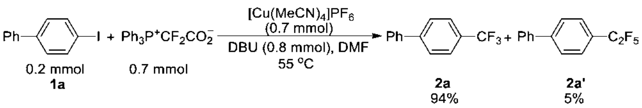
We have previously found that the difluorocarbene could be conveniently generated from the decarboxylation of difluoromethylene phosphobetaine ($Ph_3P^+CF_2CO_2^-$, PDFA),[6b] also an efficient difluoromethylene phosphonium ylide reagent.[10] Therefore, the PDFA was adopted as the difluorocarbene precursor to explore the possible conversion from difluorocarbene to trifluoromethide. We speculated that an amine might be a suitable choice for this transformation because of its high nucleophilicity toward difluorocarbene and good solubility in organic solvents.[11] The examination of different amines showed that DBU was highly efficient for the conversion (see Supporting Information (SI)). Control experiments were performed to investigate the necessity of using DBU. The desired trifluoromethylation did not occur in the absence of DBU. Without the presence of aryl iodide and a copper source, heating the solution of DBU and PDFA in DMF afforded a large amount of trifluoromethane (HCF_3) (see SI, Figure 1a). But almost no HCF_3 could be detected by just heating PDFA in DMF in the absence of DBU (see SI, Figure 1b), indicating that DBU promoted the conversion from $:CF_2$ to CF_3^- and DMF was not essential to transform the $:CF_2$ from PDFA to CF_3^-.

Received: December 8, 2014
Published: January 14, 2015

DOI: 10.1021/ol503548s
Org. Lett. 2015, 17, 532−535

The reaction of PDFA with 4-phenyl iodobenzene in the presence of DBU and $[Cu(CH_3CN)_4PF_6]$ in DMF proceeded very smoothly to afford the desired trifluoromethylation product in 94% yield determined by ^{19}F NMR with trifluoromethylbenzene as an internal standard (Scheme 2).

Scheme 2. Trifluoromethylation of 1a with PDFA

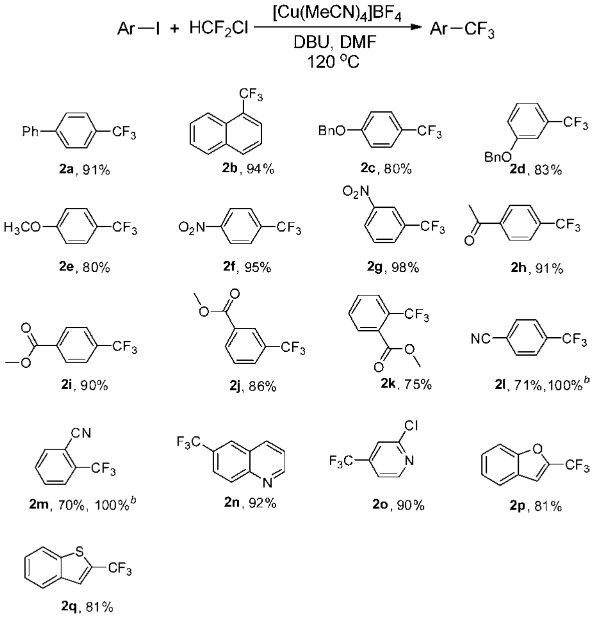


However, a low yield of pentafluoroethylated product was always formed,[12] making the purification very difficult due to the similar polarity between the trifluoromethylated and pentafluoroethylated products. The same situation was also found for other substrates such as 1-iodonaphthalene and 4-nitroiodobenzene. It is known that the reactivity of the difluorocarbene from a different carbene source varied greatly. Therefore, other difluorocarbene precursors were investigated.

Chlorodifluoromethane (HCF_2Cl) is a classical difluorocarbene reagent from which difluorocarbene can be easily generated in the presence of a base.[13] When HCF_2Cl was used instead of PDFA, it was found that the desired trifluoromethylation did occur. Further screening of copper complexes, temperatures, molar ratios of DBU/Cu(I), and reaction times revealed that 2:1 DBU/Cu(I) at 120 °C for 5 h in the presence of $[Cu(CH_3CN)_4BF_4]$ were the optimal reaction conditions (see SI). To our delight, no pentafluoroethylated product was observed during the course of the reaction. Different from Burton's method,[8] DMF is not indispensable for the reaction since less polar solvents such as *p*-xylene and 1,4-dioxane also worked, although lower yields were obtained. Therefore, DBU acted both as the base for the generation of $:CF_2$ from HCF_2Cl and as the promoter for the conversion of $:CF_2$ to trifluoromethide. However, its homologue, DBN (1,5-diazabicyclo[4.3.0]non-5-ene), was not efficient for this reaction. Other bases such as propoxide can generate $:CF_2$ from HCF_2Cl,[6b] but not effectively for the conversion.

Under this optimal reaction conditions, it was found that this procedure could be applied to a variety of aryl (Scheme 3, **2a**−**2m**) and heteroaryl (**2n**−**2q**) iodides, giving the corresponding trifluoromethylation products in moderate to excellent yields. The electron-donating (**2a**−**2e**) or -withdrawing (**2f**−**2m**) groups on the aryl ring did not significantly influence the reaction. But the substitution position (**2i**−**2k**) showed a slight effect on the reaction, which may have resulted from the steric hindrance. Although quantitative NMR yields could be obtained in the case of cyanophenyl iodides (**2l**−**2m**), their lower isolated yields might be caused by the workup due to the relatively high volatility of the trifluoromethylation products. In all cases, no pentafluoroethylation byproducts were detected. It should be noted that in some cases the substrates (aryl iodides) cannot always be completely consumed (**2a**−**2e**, **2j**−**2k**), resulting in the difficulty of purification due to almost the same separation value between the iodide substrates and the trifluoromethylated products. Fortunately, the problem was successfully solved by oxidizing the remaining aryl iodide with *m*-CPBA (*meta*-chloroperoxybenzoic acid) after removing the copper source by filtration (see SI). Subsequent flash column chromatography gave the pure products.

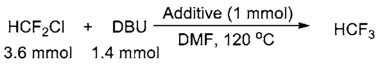
Scheme 3. Scope of the Trifluoromethylation[a]



[a]Isolated yields. [b] Determined by ^{19}F NMR with trifluoromethylbenzene as the internal standard.

^{19}F NMR measurement of the above reaction course showed the presence of $[CuCF_3]$ and HCF_3, demonstrating a successful conversion from difluorocarbene ($:CF_2$) to trifluoromethyl anion (CF_3^-). The formation of CF_3^- should be accomplished by the combination of $:CF_2$ with the fluoride anion (F^-) which might only derive from the decomposition of $:CF_2$, since no external F^- was added. When the reaction was performed without the presence of a substrate and copper source, but with the solution of HCF_2Cl and DBU in DMF heated, it was found that HCF_3 was still formed (Scheme 4, see SI, Figure 2b), which means that the substrate and copper source might not be involved in the conversion from $:CF_2$ to CF_3^-. Moreover, HCF_3 was also formed when the reaction of HCF_2Cl and DBU was heated in *p*-xylene rather than in DMF (see SI, Figure 2c). As is the case for PDFA, the trifluoromethylation from HCF_2Cl could not be realized using DMF without the presence of DBU. Therefore, it was not DMF but DBU that initiated the decomposition of $:CF_2$ from PDFA or HCF_2Cl. It seemed that DMF might be only applicable to Burton's and Clark's reaction systems, CF_2X_2/M (X = Br, Cl; M = Cd, Zn, Cu).[8,9] In the above trifluoromethylation, DMF might mostly contribute to the stabilization of $[CuCF_3]$, which is similar to other copper-mediated trifluoromethylation reactions.[14] Furthermore, this DBU-promoted decomposition of $:CF_2$ might not proceed via a

Scheme 4. Measurement of the Reaction of HCF_2Cl with DBU



$$\underset{3.6\ \text{mmol}}{HCF_2Cl} + \underset{1.4\ \text{mmol}}{DBU} \xrightarrow[\text{DMF, 120 °C}]{\text{Additive (1 mmol)}} HCF_3$$

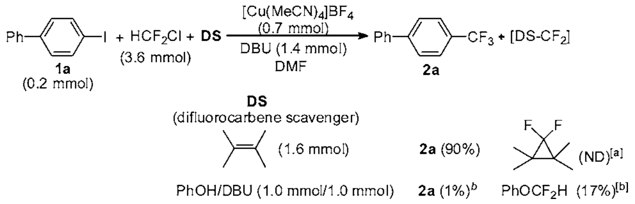
Additive	HCF_3:HCF_2Cl[a]
None	1.2:10
diallyl ether	0.9:10
1,4-dinitrobenzene	0.9:10
TEMPO	1.6:10

[a]The observed molar ratio determined by ^{19}F NMR analysis of the reaction mixture.

radical process. The addition of diallyl ether did not capture any radical intermediate and showed no influence on the formation of HCF_3 (Scheme4). And the yield of HCF_3 was almost the same in the presence of the radical scavengers such as TEMPO and 1,4-dinitrobenzene.

Undoubtedly, $:CF_2$ is generated from HCF_2Cl promoted by DBU. Interestingly, tetramethylethylene ($Me_2C{=}CMe_2$), a conventional $:CF_2$ scavenger, did not trap any difluorocarbene (Scheme 5). But the addition of phenol did give the difluoromethylation product, indicating the existence of difluorocarbene in the reaction. However, the presence of phenol simultaneously suppressed the trifluoromethylation greatly, with the formation of a large amount of HCF_3. Phenol also acted as the proton source and thus helped the formation of HCF_3. All this evidence suggests the reactivity order toward difluorocarbene might be DBU ≈ F^- > PhO^- ≫ $Me_2C{=}CMe_2$. The facile capture of difluorocarbene by DBU might explain why an organic base such as an amine has rarely been used for the generation of difluorocarbene.

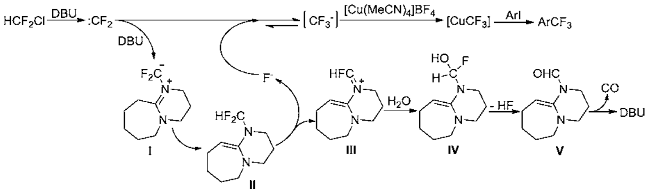
Scheme 5. Mechanistic Experiments Involving Difluorocarbene Scavenger



[a]ND = not detected. [b] Yield based on **1a** and large amount of HCF_3 was formed.

A plausible mechanism for the above trifluoromethylation was proposed as follows (Scheme 6). DBU first served as the base for the deprotonation of HCF_2Cl to generate the difluorocarbene. Then it acted as the nucleophile to react with $:CF_2$, giving the nitrogen ylide **I** which rearranged readily to difluoromethyl amine **II**. However, **II** is not very stable due to the negative hyperconjugation between lone pair electrons on the nitrogen atom and the C−F bond, resulting in the formation of **III** and the elimination of fluoride ion (F^-). The combination of F^- and:CF_2 afforded the trifluoromethyl anion (CF_3^-) and an equilibrium between them might be established herewith. The equilibrium would shift toward CF_3^- in the presence of $[Cu(MeCN)_4]BF_4$ and thus to form $[CF_3Cu]$.[15] Subsequent reaction with aryl iodides gave the trifluoromethylation products. Finally, it should be mentioned that the intermediate **III** with this kind of structure might be highly unstable. A trace amount of water, whether present in the reaction system or from the workup process, would lead to its decomposition, first to **IV** and then to **V** after the elimination of HF. Further decarbonylation of **V** produced CO and regenerated DBU.

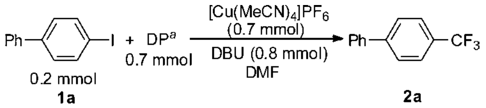
Scheme 6. Proposed Reaction Mechanism



The course of this trifluoromethylation was monitored by NMR in an attempt to obtain more information on how this reaction occurred. A very weak signal at −98.54 ppm (d, J = 58.6 Hz) could be observed in the ^{19}F NMR spectrum (see SI, Figure 2a), which might be assigned to $-NCF_2H$ of the intermediate **II**. For simplicity, the reaction of HCF_2Cl and DBU in DMF was then conducted without the addition of aryl iodide and $[Cu(MeCN)_4]BF_4$. It was found that the same ^{19}F NMR signal at −98.54 ppm (d, J = 58.6 Hz) increased significantly (see SI, Figure 2b). However, pure product still could not be obtained after flash column chromatography, which might result from its instability. This impure compound gave the same ^{19}F NMR spectrum as that before the column chromatography (see SI, Figure 3). The chemical shifts at 8.01 ppm (t, J = 58.6 Hz) on its ^1H NMR spectrum might be the proton of $-NCF_2H$ (see SI, Figure 3). And the same coupling constants (58.6 Hz) on its ^1H and ^{19}F NMR also indicated the presence of $-NCF_2H$. To our delight, HRMS (SI) of this impure compound further proved the existence of the intermediate **II** [HRMS-ESI $(M+H)^+$ Calcd: 203.1354, Found: 203.1358] (see SI, Figure 4). Moreover, the LRMS (ESI) analysis of the reaction mixture of HCF_2Cl and DBU in DMF revealed the presence of the intermediate **V** [$(M+H)^+$ Calcd: 181.13; found 181.25] (see SI, Figure 5), although its HRMS was not obtained due to its instability. In addition, the carbon monoxide (CO) formed from the decarbonylation of **V** was also detected by a test paper dipped with saturated aqueous solution of $PdCl_2$. Under the optimal reaction conditions, the color of the test paper gradually turned from yellow to black after keeping it above the reaction mixture for 3 min (see SI, Figure 6), indicating the release of CO from the reaction.[16] All this evidence suggested the possibility of the above trifluoromethylation process.

The applicability of this trifluoromethylation procedure via the DBU-promoted decomposition of difluorocarbene was also investigated. Without the addition of any external F^-,[17] it was found that the desired trifluoromethylation occurred smoothly in the case of $ClCF_2CO_2Na$[18] (entry 3, Table 1) and $BrCF_2CO_2K$[19] (entry 4), demonstrating the high efficiency of the DBU promoted conversion from $:CF_2$ to CF_3^-. However, the difluorocarbene precursor containing a silyl substituent such as $TMSCF_2Cl$[20] (entry 5) or $TMSCF_2Br$[21] (entry 6) failed to

Table 1. DBU Promoted Trifluoromethylation from Different Difluorocarbene Precursors



entry	DP	temp (°C)	time (h)	yield (%)[b]
1[c]	HCF_2Cl	120	5	93
2	PDFA	55	36	94
3	$ClCF_2CO_2Na$	70	9	73
4	$BrCF_2CO_2K$	70	9	74
5	$TMSCF_2Cl$[d]	120	3	trace
6	$TMSCF_2Br$[d]	120	3	trace

[a]DP: Difluorocarbene Precursor. [b]Determined by ^{19}F NMR. [c]3.6 mmol of HCF_2Cl and 1.4 mmol of DBU were used. [d]$^nBu_4NBr$ (3 mmol %) was used as the initiator.

DOI: 10.1021/ol503548s
Org. Lett. 2015, 17, 532−535

give the trifluoromethylation product, probably due to the interception of F^- by TMS, which would then impede the combination of F^- and $:CF_2$.

In summary, we have found that difluorocarbene derived from various carbene precursors could be decomposed by DBU and further converted to a trifluoromethyl anion without the addition of an external fluoride ion. Mechanistic investigation revealed the detailed difluorocarbene conversion process in which the decomposed difluorocarbene was finally transformed into a fluoride ion and carbon monoxide. This process was successfully applied in the trifluoromethylation of a variety of (hetero)aromatic iodides, which might convert many difluorocarbene precursors into efficient trifluoromethylation reagents.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, analytical data for products, NMR spectra of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by the National Natural Science Foundation (21032006, 21172240, 21421002, 21472222), National Basic Research Program of China (2015CB931900), and the Chinese Academy of Sciences. We thank Dr. Xiao-Wen Huang (Shandong University of Science and Technology) for helpful discussions.

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