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Fluorinated Ylides/Carbenes and Related Intermediates from Phosphonium/Sulfonium Salts

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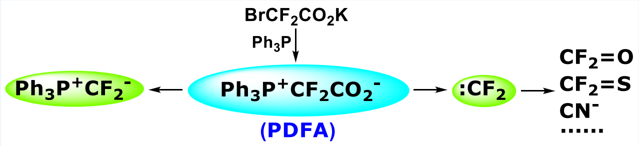
CONSPECTUS: Owing to the special effects of the fluorine element, including high electronegativity and small atomic radius, the incorporation of a fluorinated group into organic molecules may modify their physical, chemical, and biological properties. Fluorine-containing compounds have found widespread application in a variety of areas, and thus, the development of efficient reagents and methods for the incorporation of fluorinated groups has become a subject of significant interest.



Described in this Account are our recent discoveries in the chemistry of fluorinated ylides/carbenes and related intermediates generated from phosphonium/sulfonium salts. Initially, we obtained the (triphenylphosphonio) difluoroacetate, $Ph_3P^+CF_2CO_2^-$ (PDFA), which was proposed as a reactive intermediate but had never been successfully synthesized. PDFA, shelf-stable and easy to prepare, is not only a mild ylide ($Ph_3P^+CF_2^-$) reagent, but also an efficient difluorocarbene source. It can directly generate difluorocarbene, via the first generation of ylide $Ph_3P^+CF_2^-$, simply under warming conditions without the need for any additive. Interestingly, difluorocarbene chemistry was then discovered by using PDFA as a reagent. Difluorocarbene can be oxidized to $CF_2{=}O$, can react with elemental sulfur to afford $CF_2{=}S$, and can be trapped by $NaNH_2$ or NH_3 to give CN^-. The development of these processes into synthetic tools allowed us to achieve various reactions, including the challenging ^{18}F-trifluoromethylthiolation and cyanodifluoromethylation. It was found that a substituent on the cation of a phosphonium salt can be directly transferred as a nucleophile despite the cation's high electrophilicity. This transfer process is like an "umpolung" of the cation, which may provide more opportunities for the synthetic utilities of phosphonium salts. The investigation of this transfer process led us to find that iodophosphonium salts, active intermediates which can be easily generated, may efficiently promote deoxygenative functionalizations of aldehydes and alcohols. Dehydroxylative substitution of alcohols by this protocol permits the use of unprotected amines with higher pK_a values as nucleophiles, which is an attractive feature compared with the Mitsunobu reaction. On the basis of the ylide-to-carbene process ($Ph_3P^+CF_2^- \rightarrow :CF_2$), we further developed sulfonium salts as precursors of fluorinated ylides and fluorinated methyl carbenes. In particular, the studies on difluoromethylcarbene, remaining largely unexplored, may deserve more attention. The discoveries may find utility in the synthesis of biologically active fluorine-containing molecules.

■ KEY REFERENCES

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- Yu, J.; Lin, J.-H.; Xiao, J.-C. Reaction of Thiocarbonyl Fluoride Generated from Difluorocarbene with Amines. *Angew. Chem., Int. Ed.* **2017**, *56*, 16669−16673.[2] *The transformation of difluorocarbene into thiocarbonyl fluoride was developed into a synthetic tool to convert amines into various products, including HCF_2S-containing heterocycles.*
- Yu, J.; Lin, J.-H.; Yu, D.; Du, R.; Xiao, J.-C. Oxidation of difluorocarbene and subsequent trifluoromethoxylation. *Nat. Commun.* **2019**, *10*, 5362.[3] *The oxidation of highly reactive difluorocarbene was achieved, and this oxidation process was applied to the effective ^{18}O-trifluoromethoxylation.*
- Zhang, M.; Lin, J.-H.; Xiao, J.-C. Photocatalyzed Cyanodifluoromethylation of Alkenes. *Angew. Chem., Int. Ed.* **2019**, *58*, 6079−6083.[4] *Difluorocarbene can be trapped by $NaNH_2$ or NH_3 to provide cyanide anion, and cyanodifluoromethylation of alkenes was achieved on the basis of this process without using any toxic cyanation reagent.*

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1. INTRODUCTION

Fluorine sits at the top right of the periodic table of chemical elements. This position in the periodic table implies that fluorine exhibits many unique properties, such as high electronegativity and small atomic radius. Owing to these special effects, the incorporation of fluorine atom(s) into an organic molecule may profoundly modify its physical, chemical, and biological properties. Therefore, organofluorine chemistry has played a distinctive role in many significant areas, including pharmaceutical/agrochemical developments and material sciences.[5] Because of the wide applications of fluorine-containing compounds, the development of efficient reagents and methods for the incorporation of fluorinated motifs into organic molecules has become a field of great fundamental interest.

On the basis of our experience with ionic liquids[6] and our interest in organofluorine chemistry,[7] we decided to start the research on fluorine-containing organic salts. Organic salts are commonly identified as reactive intermediates in a wide variety of reactions, such as $AlCl_3$-promoted Friedel−Crafts alkylation and Vilsmeier−Haack reactions. Therefore, we wish to develop fluorine-containing reagents from those reactive salt intermediates, as indicated in the subtitle of the book edited by Bertrand,[8] "from fleeting intermediates to powerful reagents." During our investigation on the fluorine-containing organic salts, we obtained a shelf-stable salt, $Ph_3P^+CF_2CO_2^-$ (triphenylphosphonio)difluoroacetate (PDFA),[9] which was proposed as a reactive intermediate for Wittig *gem*-difluoroolefination in the 1960s[10] but had never been successfully synthesized. It had been revealed that the nonfluorinated counterpart, $Ph_3P^+CH_2CO_2^-$, is unstable because of decarboxylation.[11] For the unknown monofluorine substituted salt, $Ph_3P^+CFHCO_2^-$, our attempts at its synthesis failed, probably also because of its low stability. Apparently, the two fluorine substituents are essential for its stability. Surprisingly, we found that PDFA was not only an effective phosphonium ylide ($Ph_3P^+CF_2^-$) reagent, but also an efficient difluorocarbene ($:CF_2$) precursor. Difluorocarbene can be readily generated from ylide $Ph_3P^+CF_2^-$ via a direct P-CF_2 bond cleavage. Based on this process, we speculated that fluorinated carbenes might also be produced from sulfonium ylides. This curiosity also drove us to investigate the utility of fluorinated sulfonium salts.

This Account summarizes our recent discoveries in the chemistry of fluorinated ylides/carbenes and other intermediates generated from phosphonium/sulfonium salts. Related work will be briefly discussed when necessary.

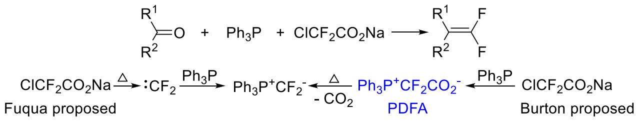
2. PHOSPHONIUM SALTS

Our research into phosphonium salts started with the phosphobetaine, PDFA, from which new difluorocarbene chemistry was discovered. This reagent was also used by others in their studies.[12] The investigation of a Wittig reaction with phosphonium ylide $Ph_3P^+CF_2^-$ allowed us to obtain some unexpected findings, which demonstrate new utilities of phosphonium salts.

2.1. $Ph_3P^+CF_2CO_2^-$ (PDFA)

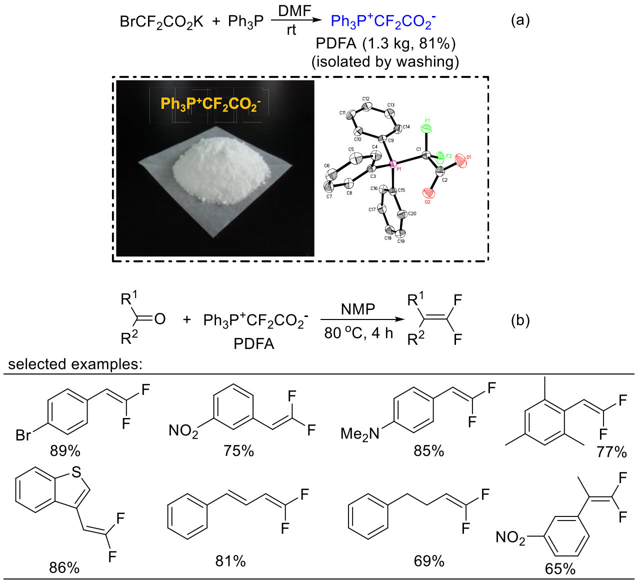
2.1.1. PDFA as a Phosphonium Ylide Reagent. Faqua et al.[10a] and Burton and Herkes[10b] independently reported a Wittig *gem*-difluoroolefination of carbonyls with $Ph_3P/ClCF_2CO_2Na$ in the 1960s (Scheme 1). Phosphonium ylide $Ph_3P^+CF_2^-$ is apparently a key intermediate for this process. However, they had different opinions on how this ylide is generated. Since $ClCF_2CO_2Na$ had been used as a difluorocarbene precursor,[13] Faqua et al. tended to think that the difluorocarbene produced from $ClCF_2CO_2Na$ is trapped by Ph_3P to provide the ylide.[10a] Based on the observation that Ph_3P could accelerate the decomposition of $ClCF_2CO_2Na$, Burton and Herkes proposed that Ph_3P first reacts with $ClCF_2CO_2Na$ to form PDFA and decarboxylation of this salt gives the ylide.[10b] As Burton and Herkes's attempts at the synthesis of PDFA failed, the mechanism remained unclear until recently, when we came across a route to PDFA.[9]

Scheme 1. Wittig Reaction with $Ph_3P/ClCF_2CO_2Na$



PDFA cannot be obtained by the reaction of Ph_3P with $ClCF_2CO_2Na$. Due to the low reactivity of $ClCF_2CO_2Na$, almost no reaction between Ph_3P and $ClCF_2CO_2Na$ would be observed at room temperature. At a higher temperature, even though PDFA may be produced, it is hard to detect because of its rapid decarboxylation. We found that the use of $BrCF_2CO_2K$ instead of $ClCF_2CO_2Na$ can smoothly afford this salt at room temperature (Scheme 2a).[14] PDFA could be isolated simply by washing with water and organic solvents, and it is a shelf-stable (T_d = 105 °C) and easy-to-handle solid. As Burton and Herkes predicted, carbonyls were able to undergo Wittig *gem*-difluoroolefination with PDFA under mild conditions (Scheme 2b). Ylide $Ph_3P^+CF_2^-$ would be easily generated from PDFA by decarboxylation under warming conditions. Therefore, the successful synthesis of PDFA not only allowed us to elucidate the reaction mechanism for the transformation described in Scheme 1, but also provided an efficient phosphonium ylide reagent.

Scheme 2. Synthesis and Utility of PDFA



2.1.2. PDFA as a Difluorocarbene Reagent. Although the dissociation of phosphonium ylide $Ph_3P^+CF_2^-$ into difluorocarbene has been proposed[15] and the activation barrier was calculated to be quite low,[16] no difluorocarbene reagent was developed on the basis of this process. We found that PDFA could generate difluorocarbene via a direct cleavage of the P$-$CF$_2$ bond in ylide Ph$_3$P$^+$CF$_2^-$ (Ph$_3$P$^+$CF$_2^-$ → Ph$_3$P + :CF$_2$).[17] The facile bond cleavage could be explained by electronic effects. Usually, the P$-$C bond in phosphonium ylide (R$_3$P$^+$-C$^-$) has a double-bond character,[18] and thus, this bond would not easily undergo a direct dissociation to generate a carbene species. Recent studies have shown that the double-bond character is not ascribed to a $d_\pi-p_\pi$ interaction, which was invoked in traditional ylide chemistry,[18a] but due to a $\sigma^*_\pi-p_\pi$ interaction between the LUMO (σ^*_π) on the phosphine moiety (R$_3$P) and the p orbital on the carbon (Figure 1a).[18b] The anionic carbon in common ylides adopts sp^2 hybridization to maximize the $\sigma^*_\pi-p_\pi$ interaction.[18b] However, in the case of fluorinated ylide Ph$_3$P$^+$CF$_2^-$, the sp^2 hybridization would result in severe electronic repulsion between carbon lone pair and fluorine lone pairs (Figure 1b). The electronic repulsion drives the carbon center to adopt sp^3 hybridization, which reduces the $\sigma^*_\pi-p_\pi$ interaction and therefore weakens the P$-$CF$_2$ bond. Furthermore, due to its high electronegativity, the F atom prefers to bond with a carbon orbital that has more p character, because it is easier to withdraw electrons from a p orbital than an s orbital,[19] meaning that sp^3 hybridization would be favored over sp^2 hybridization for the CF$_2$ carbon. Our explanation is also supported by Dolbier et al.'s Ph$_3$P$^+$$-CF_2^-$ structural calculations, which showed an sp^3 character of the CF$_2$ carbon and a weaker P$-$C bond strength compared with non-fluorinated ylide Ph$_3$P$^+$$-CH_2^-$.[16]

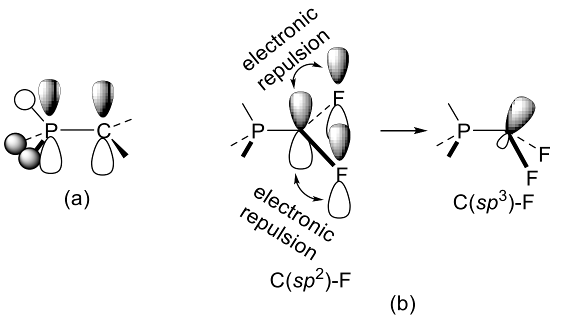
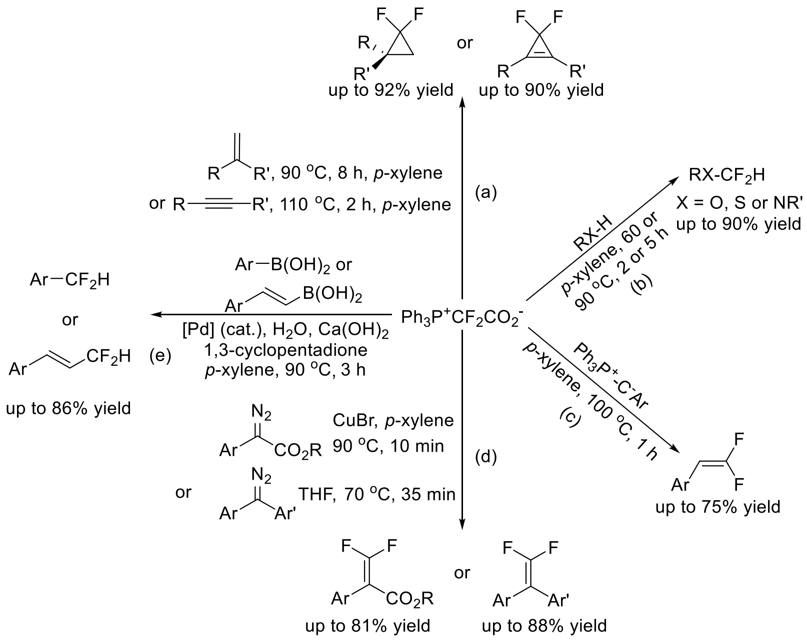


Figure 1. Factors influencing the facile cleavage of the P$-$CF$_2$bond in ylide Ph$_3$P$^+$CF$_2^-$. (a) $\sigma^*_\pi-p_\pi$ interaction in common ylides. (b) Driving force for sp^3 hybridization of the CF$_2$ carbon.

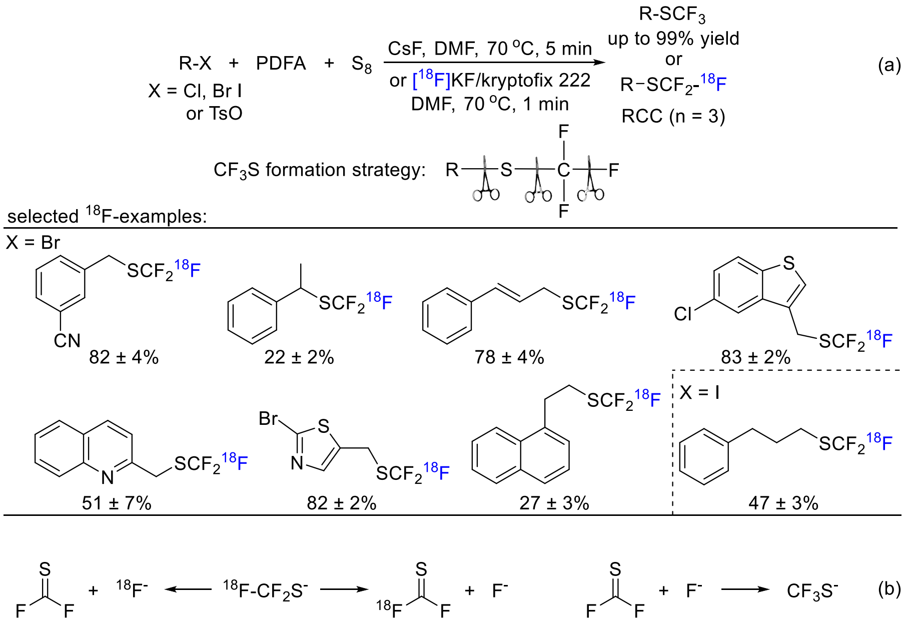
Compared with other difluorocarbene reagents,[20] PDFA is quite attractive due to its facile accessibility and ease of handling, and its ability to generate difluorocarbene simply under warming conditions without the need of any additive. It exhibits good reactivity in common difluorocarbene reactions, including [2 + 1] *gem*-difluorocyclization of unsaturated bonds (Scheme 3a),[17,21] difluorocarbene insertion into X$-$H bond (X = N, O, S) (Scheme 3b),[17,21,22] coupling of difluorocarbene with phosphonium ylide (Scheme 3c),[23] and cross-coupling of difluorocarbene with other carbenes generated from diazo compounds (Scheme 3d).[24] Although the chemistry of metal-difluorocarbene complexes has been a subject of extensive studies, the difluorocarbene transfer through transition-metal catalysis remains challenging.[25] Recently, we developed a Pd-catalyzed :CF$_2$ transfer process to achieve the difluoromethylation of boronic acids (Scheme 3e).[26]

On the basis of previous findings that difluorocarbene can be trapped by the F$^-$ anion to provide the CF$_3^-$ anion,[27] and of the recent studies which revealed that the CF$_3^-$ anion could react with S$_8$ (elemental sulfur) to produce the CF$_3$S$^-$ anion,[28] we originally postulated that PDFA/S$_8$/F$^-$ may serve as a CF$_3$S$^-$ source for trifluoromethylthiolation via the sequential formation of CF$_3^-$ and CF$_3$S$^-$ anions (:CF$_2$ → CF$_3^-$ → CF$_3$S$^-$). Indeed, nucleophilic substitution of various benzyl and alkyl halides with this reagent system occurred smoothly. Three chemical bonds were effectively formed within 5 min in this process.[29] The high efficiency and the involvement of an external F$^-$ anion for C$-$F bond formation prompted us to apply this method to ^{18}F-labeling in collaboration with Liang et

Scheme 3. PDFA as a Difluorocarbene Reagent



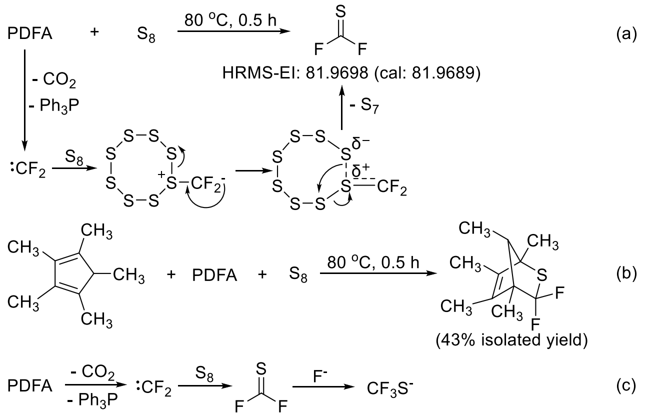
Scheme 4. ^{18}F-Trifluoromethylthiolation



al. (Scheme 4a).[29] Analogous to nonradioactive reactions, ^{18}F-trifluoromethylthiolation was also suitable for the transformation of benzylic, allylic and aliphatic halides. Some radiolabeled products were isolated, and the radiochemical yields ranged from 37% to 53%. Low specific activity (21 mCi/μmol) was obtained because of the instability of the ^{18}F$-$CF$_2$S$^-$ anion (Scheme 4b). ^{18}F$-$CF$_2$S$^-$ may be decomposed by different paths to generate CF$_2$=S and the F$^-$ anion, and the combination of CF$_2$=S and the F$^-$ anion provides the CF$_3$S$^-$ anion, resulting in low specific activity. Although many trifluoromethylthiolation methods have been developed,[30] no previous method can be easily applied to direct ^{18}F-trifluoromethylthiolation.[31]

Surprisingly, further mechanistic investigations of this trifluoromethylthiolation revealed that difluorocarbene is not first trapped by F$^-$ anion, but by elemental sulfur to give thiocarbonyl fluoride (CF$_2$=S), which can be detected by HRMS(EI) spectroscopy (Scheme 5a) and could also be trapped by a conjugated diene to generate a Diels–Alder cyclization product (Scheme 5b).[1,2] Computational calculations indicate that the conversion from :CF$_2$ into CF$_2$=S is kinetically and thermodynamically favorable (Scheme 5a).[1] Both difluorocarbene[20] and elemental sulfur[32] are electrophilic species, but in this reaction elemental sulfur may act as a nucleophile and difluorocarbene may be an electrophile. Apparently, CF$_3$S$^-$ is generated from PDFA/S$_8$/F$^-$ via the formation of CF$_2$=S without involving CF$_3^-$ (Scheme 5c).

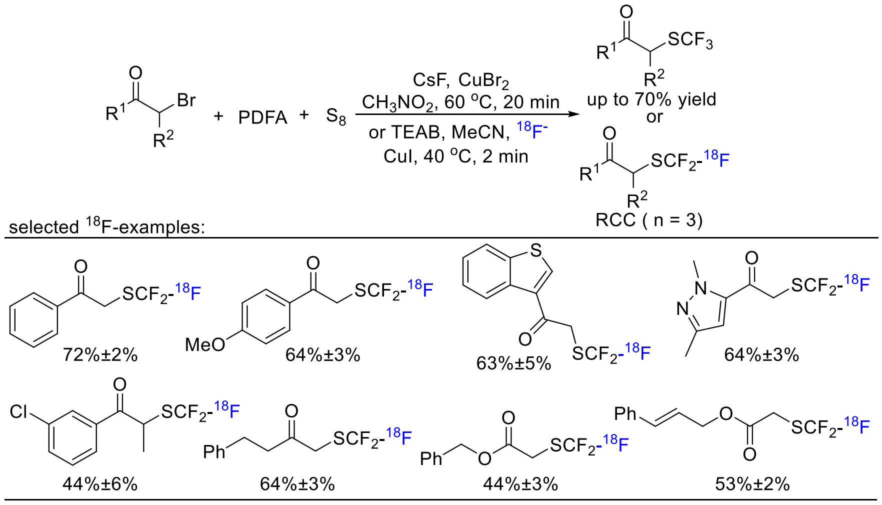
Scheme 5. Mechanistic Investigations and ^{18}F-Trifluoromethylthiolation



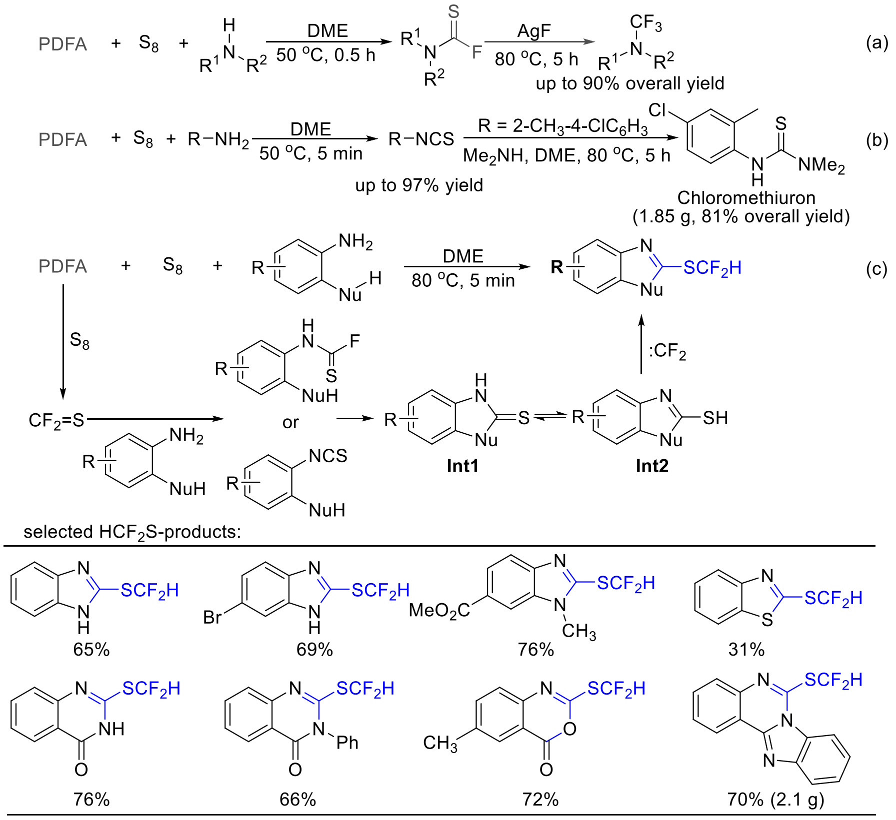
After elucidating the reaction mechanism, we further investigated the trifluoromethylthiolation of α-bromocarbonyl compounds[1] since the α-CF$_3$S-carbonyl group has been identified as an important motif in a pharmaceutical, Cefazaflur.[30] Under the above trifluoromethylthiolation conditions,[29] almost no desired product was observed for the conversion of α-bromocarbonyl compounds. A detailed survey of the reaction conditions showed that the presence of a copper source gave a good yield under mild conditions. The high efficiency also allowed us to apply this CF$_3$S-installation protocol to ^{18}F-trifluoromethylthiolation in collaboration with Liang et al. (Scheme 6).[1] Both α-bromo ketones and esters could undergo ^{18}F-trifluoromethylthiolation, and moderate radiochemical conversions were obtained. Some radiolabeled products were isolated by semipreparative HPLC, and 30–42% radiochemical yields were obtained. The specific activity was also quite low (2.02 mCi/μmol), which may be a main limitation of this radiolabeling protocol.

The mechanistic investigations of the above difluorocarbene-based trifluoromethylthiolation led us to develop a convenient route to thiocarbonyl fluoride via a rapid reaction of difluorocarbene with elemental sulfur. Although thiocarbonyl fluoride is an important fluorinated gas, its use in academic research remains largely unexplored because special safety precautions are required during storage and transportation of this compound due to its high toxicity and low boiling point (−54 °C).[33] Furthermore, its preparation usually requires the use of hazardous reagents (such as thiophosgene) and/or harsh reaction conditions (e.g., pyrolysis at 500 °C).[33] In our protocol, thiocarbonyl fluoride could be mildly generated and immediately transformed without any need of its isolation, transportation, or storage. The convenient operations

Scheme 6. ^{18}F-Trifluoromethylthiolation of α-Bromocarbonyl Compounds



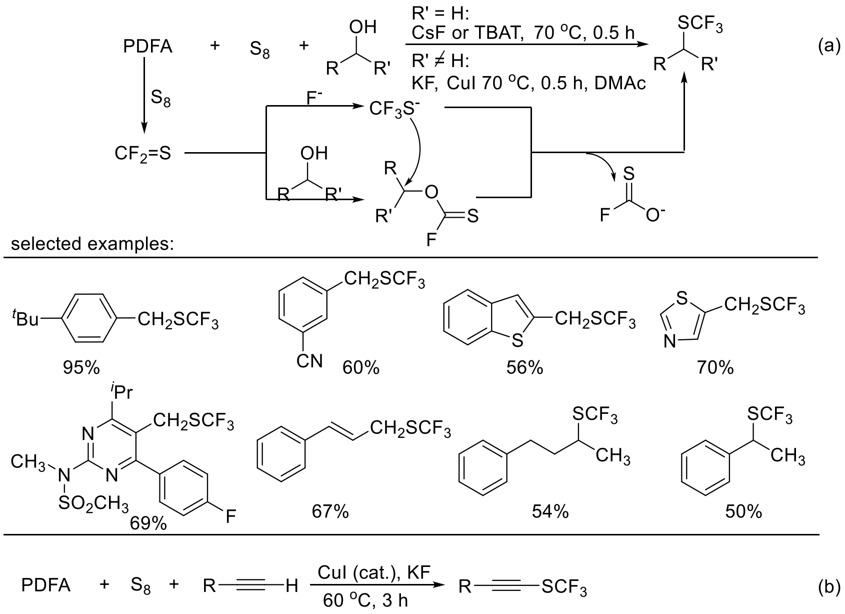
Scheme 7. Reactions of Thiocarbonyl Fluoride with Amines



prompted us to make efforts to develop the CF$_2$=S formation process into a useful synthetic tool.

Since thiocarbonyl fluoride is an electrophilic species, we then investigated its reaction with nucleophilic amines (Scheme 7).[2] PDFA appears to be not compatible with amines due to the electrophilicity of difluorocarbene. However, the side reaction of difluorocarbene with amines was suppressed and thiocarbonyl fluoride was generated smoothly to react with amines, reflecting a rapid reaction between difluorocarbene and elemental sulfur. Interestingly, quite different products were observed depending on the structures of amines. Secondary amines were converted to thiocarbamoyl fluorides, which could be further transformed into CF$_3$-amines in one pot by using a reported method[34] (Scheme 7a). In the case of primary amines, isothiocyanates would be provided rapidly (5 min) (Scheme 7b). A short route to the insecticide Chloromethiuron was developed through the isothiocyanation process, and a high overall yield (81%) was obtained on a gram scale (Scheme 7b). For aryl amines containing an *ortho*-nucleophilic group, HCF$_2$S-substituted heterocycles were constructed efficiently, and a reaction time of 5 min gave good yields (Scheme 7c). Aromatization (Int1 → Int2) is the driving force for the HCF$_2$S installation via a difluorocarbene insertion. A wide substrate scope and good functional group

Scheme 8. Trifluoromethylthiolation with PDFA/S_8

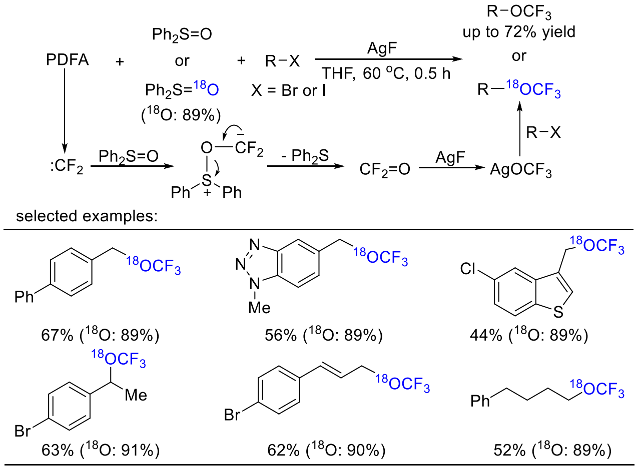


tolerance were observed. A gram scale did not lead to a decrease in the yield (see the last example in Scheme 7c). The rapid tandem reaction is a quite interesting process since a heterocycle is constructed and a $CSCF_2H$ moiety is incorporated.

For the reaction of thiocarbonyl fluoride with alcohol nucleophiles in the presence of fluoride anion, a dehydroxylative trifluoromethylthiolation of alcohols was observed (Scheme 8a).[35] Since the :CF_2 → $CF_2{=}S$ process occurs very fast, the side reaction of difluorocarbene with the nucleophilic alcohols is suppressed. $CF_2{=}S$ generated in situ can not only be trapped by F^- anion to deliver CF_3S^- anion, but also efficiently activate the hydroxyl group. The $CF_2{=}S$ formation process was also used as a tool to achieve trifluoromethylthiolation of terminal alkynes (Scheme 8b).[36]

Since difluorocarbene can be trapped by elemental sulfur to provide thiocarbonyl fluoride, we speculated that difluorocarbene might undergo a direct oxidation to give carbonyl fluoride. It can be imagined that the oxidation of a highly active electron-deficient species is quite challenging. Much effort was devoted to this oxidation process, but it seemed that the reaction could not occur at all based on the experimental results that no carbonyl fluoride was observed by ^{19}F NMR spectroscopy. When we almost gave up this challenging project, one day we suddenly realized that carbonyl fluoride may be too reactive to detect. Even if produced, it would react rapidly with Ph_3P generated from PDFA. It occurred to us that the oxidation reaction might be confirmed by a trifluoromethoxylation reaction with a PDFA/[O]/F^- reagent system, just like the above trifluoromethylthiolation.[1,29] The examination of a large number of oxidants revealed that the difluorocarbene-based trifluoromethoxylation of alkyl halides proceeded smoothly by using PDFA/$Ph_2S{=}O$/AgF as the CF_3O^- source (Scheme 9).[3] DFT calculations revealed that the oxidation of difluorocarbene with $Ph_2S{=}O$ is a kinetically and thermodynamically favorable process. The electrophilicity of difluorocarbene is the key to the successful oxidation. AgF is able to readily trap $CF_2{=}O$ to afford CF_3OAg, which is an important intermediate for the subsequent trifluoromethoxylation. The use of $Ph_2S{=}^{18}O$ as the oxygen source could enable highly efficient ^{18}O-trifluoromethoxylation. Although many trifluoromethoxylation approaches have emerged,[37] this is the most effective protocol for $CF_3{}^{18}O$ incorporation.

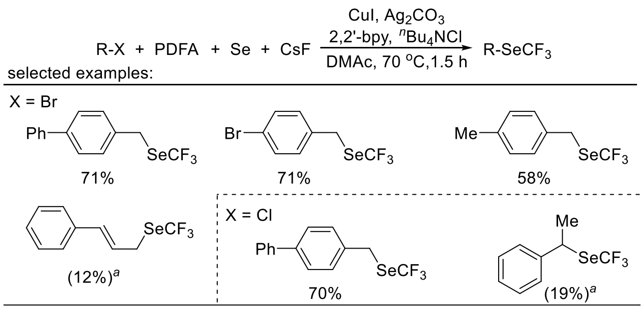
Scheme 9. Oxidation of Difluorocarbene and Subsequent Trifluoromethoxylation



As O, S, and Se elements are in the same column of the periodic table, selenylation of difluorocarbene for trifluoromethylselenolation would also deserve investigations. Trifluoromethylselenolation did occur, but two transition metal sources (CuI and Ag_2CO_3) were needed, probably because CF_3Se^- exhibits much lower reactivity than CF_3O^- or CF_3S^- (Scheme 10).[38] Even though selenocarbonyl fluoride ($CF_2{=}Se$) could not be detected from the reaction system, we speculate that its formation is essential for this trifluoromethylselenolation process.

Although difluorocarbene insertion into N−H bonds may be observed for the reaction of difluorocarbene with organic amines,[20] we still wondered if a suitable nitrogen source could convert difluorocarbene into a $CF_2{=}NH$ species, like the above $CF_2{=}X$ (X = O, S, Se) formation process. $CF_2{=}NH$

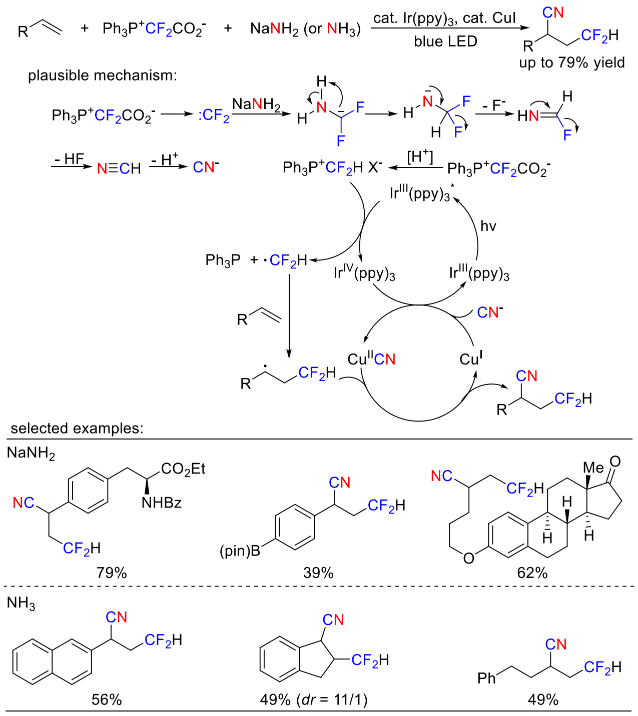
Scheme 10. Selenylation of difluorocarbene and Subsequent Trifluoromethylselenolation



[a] Yields determined by ^{19}F NMR spectroscopy.

was not obtained, but we found that cyanide anion would be generated by using $NaNH_2$ or NH_3 as a nitrogen source. This transformation was adopted to realize the photocatalyzed cyanodifluoromethylation of alkenes (Scheme 11).[4] The use of

Scheme 11. Difluorocarbene-Based Cyanodifluoromethylation of Alkenes



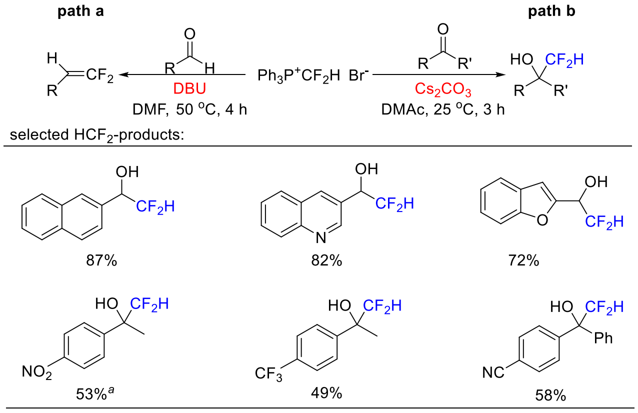
sodium picrate as a CN^- indicator clearly shows that PDFA and $NaNH_2$ are the carbon and the nitrogen sources of the CN^- anion, respectively. The side cyclopropanation of alkenes with difluorocarbene was suppressed,[17] mainly because of the high reactivity of $NaNH_2$ (or NH_3) toward difluorocarbene. This protocol is quite attractive since both CN and CF_2H groups are incorporated under mild conditions without using any toxic cyanation reagent.

As shown above, new difluorocarbene chemistry was discovered. Difluorocarbene can be oxidized and can also be transformed into other reactive intermediates, such as thiocarbonyl fluoride. The conversions of difluorocarbene were developed into synthetic tools to enable various reactions. Difluorocarbene often exhibits high reactivity toward both substrates and other reagents, which might potentially lead to complex side reactions. However, highly selective transformations were observed in the case of PDFA. These surprising discoveries may provide more opportunities for the difluorocarbene chemistry.

2.2. Electrophilic Phosphonium Salts as Nucleophiles

Obviously, phosphonium ylide $Ph_3P^+CF_2^-$ can be produced either from PDFA by decarboxylation[9] or from $[Ph_3P^+CF_2H]$ X^- by deprotonation. Indeed, we found that $[Ph_3P^+CF_2H]$ X^- can really act as an ylide precursor to achieve Wittig reaction by using DBU as the base (Scheme 12, path a).[39] However, when Cs_2CO_3 was used as the base, a completely different reaction, difluoromethylation of aldehydes, was observed unexpectedly (path b).[40] The unexpected reaction path is ascribed to a high affinity of oxygen toward the cationic phosphonium and a lower basicity of Cs_2CO_3, which will be discussed below. Cations of phosphonium salts are apparently electrophilic, but the HCF_2 group is transferred as a nucleophile, a process which looks like an “umpolung” of the cation. The nucleophilic difluoromethylation process could be extended to various aldehydes and ketones, and moderate to high yields were obtained under mild conditions.

Scheme 12. Unexpected Difluoromethylation

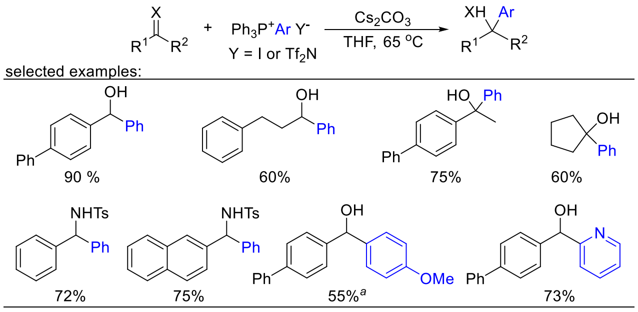


[a] The reaction was performed at −10 °C.

We wondered if this strategy can be extended to other phosphonium salts and thus investigated the nucleophilic arylation with tetraarylphosphonium salts.[41] It was found that various aldehydes, ketones, and imines could all be transformed into the phenylation products, demonstrating a wide substrate scope (Scheme 13). Besides phenylation, other arylation such as pyridination can also be achieved when a pyridyl phosphonium salt is used. In the case of phosphonium salts containing different aryl substituents, the aryl group substituted with electron-withdrawing groups would be preferred for this transfer. Enolizable aldehydes and ketones show good reactivity toward this arylation, reflecting that the in situ generated aryl-anion equivalent exhibits high nucleophilicity and low basicity. The transformation is not particularly sensitive to water and is compatible with a variety of functional groups including cyano and ester groups. Compared with the aryl metal reagents that are usually moisture sensitive, phosphonium salts are quite attractive due to their easy availability, high stability, and ease of handling.

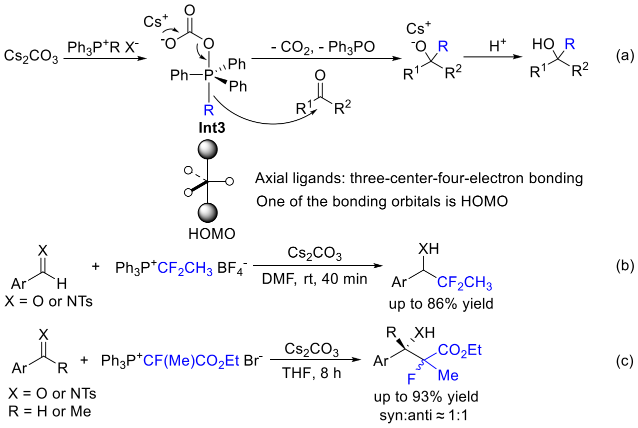
Scheme 14a describes the plausible nucleophilic reaction mechanism, which is supported by a series of experimental

Scheme 13. Nucleophilic Arylation with Phosphonium Salts



[a] $(p\text{-MeOC}_6H_4)_4P^+\ I^-$ was used as the reagent.

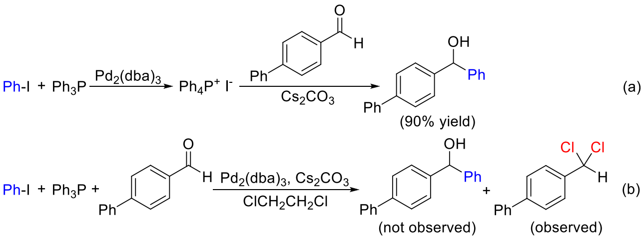
Scheme 14. Electrophilic Phosphonium Salts as Nucleophiles



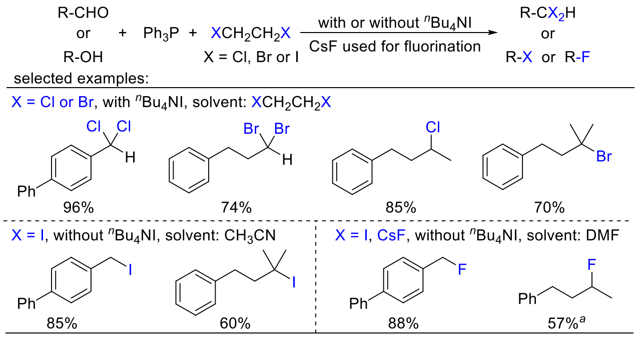
evidence, including the confirmation of the reaction between Cs_2CO_3 and phosphonium salts alone, the identification of byproducts such as CO_2 and Ph_3PO, and the exclusion of other reaction paths.[40,41] Due to the high affinity of oxygen toward the positive phosphonium, Cs_2CO_3 would readily attack at the phosphonium salt to produce a trigonal bipyramidal intermediate (Int3), which is unstable and would readily undergo decarboxylation to release the axial R group to directly attack electrophiles. Although Int3 can be considered as a R^- equivalent, the naked R^- anion may not be formed; otherwise, cyano and ester groups would not be tolerated and enolizable aldehydes and ketones would prefer to undergo deprotonation by the basic R^-. When considering the formation and the subsequent reaction of Int3, questions arise as to what group would sit in the axial position and why the axial group rather than the equatorial group is transferred. For a pentacoordinated phosphorus species, the trigonal bipyramidal structure is energetically preferred. In the bipyramidal structure, axial ligands are attached to the central P atom by three-center-four-electron bonds.[42] One of these bonding orbitals is nonbonding and is the HOMO (highest occupied molecular orbital) of the coordinated phosphorus species. If the axial ligands are more electronegative, the HOMO would be lower in energy and thus the phosphorus species would be more stable. Therefore, the occupancy of the axial position by electron-withdrawing groups is thermodynamically favorable. Since there is a nonbonding orbital for the axial ligand bonding, axial bonds are thus longer than equatorial ones.[42] As a result, the axial group would be easier to cleave. We have also used this strategy to achieve nucleophilic difluoroethylation (Scheme 14b)[43] and monofluoroalkylation (Scheme 14c).[44]

2.3. Iodophosphonium-Salts-Promoted Deoxygenative Functionalizations

Scheme 15. Unexpected Deoxygenative Dichlorination of Aldehydes



Scheme 16. Deoxygenative Halogenation of Aldehydes and Alcohols

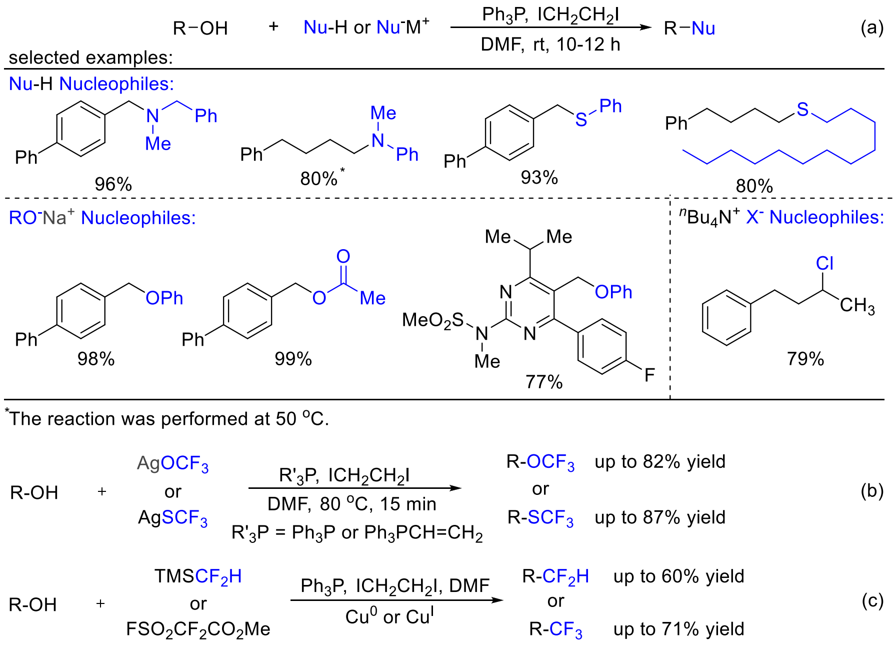


[a] AgF was used instead of CsF.

In the above nucleophilic arylation, phosphonium salt $Ph_4P^+I^-$ has to be prepared in advance through a Pd-catalyzed quaternization of Ph_3P with Ph−I (Scheme 15a). We originally thought that it would be more convenient to combine the two-step process into a one-pot tandem reaction, i.e., to perform the phenylation of aldehydes directly with Ph_3P/PhI in the presence of a Pd catalyst. Various reaction conditions were screened, but no desired phenylation was observed. However, when $ClCH_2CH_2Cl$ was used as the solvent, a deoxygenative dichlorination product was detected (Scheme 15b).

The investigations into the unexpected dichlorination revealed that a mixture of $Ph_3P/ClCH_2CH_2Cl/I^-$, in which I^- was produced from PhI, would generate an iodophosphonium species ($Ph_3P^+I\ X^-$) that could effectively activate the carbonyl group for dichlorination. $Ph_3P/XCH_2CH_2X/I^-$ (X = Cl or Br) and Ph_3P/ICH_2CH_2I were then developed into efficient reagent systems to promote convenient deoxygenative fluorination, chlorination, bromination, and iodination of aldehydes and alcohols (Scheme 16). The mechanism will be discussed later. The easily available XCH_2CH_2X (X = Cl or Br) is not only the halide source but also the reaction solvent. ICH_2CH_2I is a solid and thus the use of a reaction solvent such as DMF or CH_3CN is necessary. The deoxygenative halogenation could be extended to a wide range of aldehydes and alcohols. The reaction also occurred smoothly by replacing Ph_3P with $(EtO)_3P$, and the byproduct $(EtO)_3P{=}O$ could be removed by aqueous washing, which may be convenient for purification. Mild reaction conditions and a wide substrate

Scheme 17. Dehydroxylative Functionalization of Alcohols

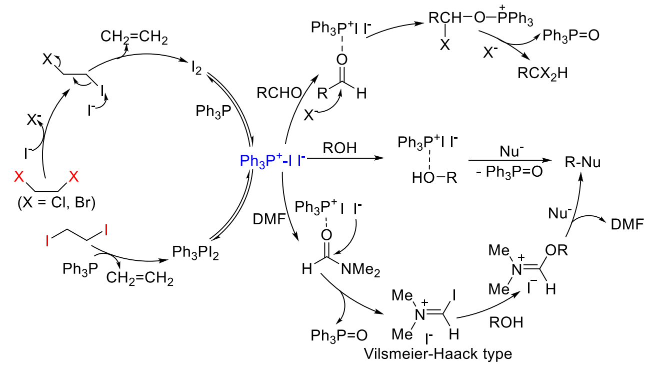


scope make this deoxygenative halogenation protocol attractive compared with Appel reaction.[45]

Although iodination of alcohols with Ph_3P/ICH_2CH_2I proceeds rapidly, the reaction may be suppressed if another nucleophile is present, as evidenced by the above fluorination. Therefore, Ph_3P/ICH_2CH_2I was used to enable nucleophilic substitution of alcohols by a wide range of nucleophiles, including unprotected amines (Scheme 17a).[46] The widely used method for nucleophilic substitution of alcohols is the Mitsunobu reaction, which suffers from the use of an explosive azodicarboxylate reagent.[47] Furthermore, the nucleophiles are required to be relatively acidic in the Mitsunobu reaction, meaning that unprotected amines with higher pK_a values are not suitable nucleophiles.[47] The R_3P/ICH_2CH_2I-promoted process was further extended to other dehydroxylative reactions, such as trifluoromethoxylation (Scheme 17b),[48] trifluoromethylthiolation (Scheme 17b),[49] and fluoroalkylation (Scheme 17c).[49] Different phosphines R_3P may be used in different reactions. For fluoroalkylation, a copper source was necessary to effectively complete the conversion.

The proposed mechanism is shown in Scheme 18. Unlike common alkyl iodides, which would lead to quaternization of trivalent phosphines, ICH_2CH_2I forms a strong P−I halogen bond with Ph_3P. The halogen bonding drives the formation of five-coordinate intermediate, Ph_3PI_2, by releasing ethylene gas. Ph_3PI_2 is in equilibrium with iodophosphonium salt, $Ph_3P^+I\ I^-$. The process from Ph_3P/ICH_2CH_2I to $Ph_3P^+I\ I^-$ occurs very fast in DMF. For the $Ph_3P/XCH_2CH_2X/I^-$ (X = Cl or Br) system, iodophosphonium salt is generated via the formation of molecular iodine. Iodophosphonium salt can directly activate aldehydes and alcohols by coordination and may first react with the solvent DMF, if DMF is used as the solvent, to generate a Vilsmeier−Haack-type intermediate,[50] which could also activate alcohols for the subsequent nucleophilic substitution. Whether the substitution proceeded through an S_N1 or S_N2 process depends on the substrates used. Substitution of secondary alkyl alcohols led to the inversion of configuration with partial racemization.[46,51] In the case of secondary benzyl alcohols, complete racemization was observed.[48]

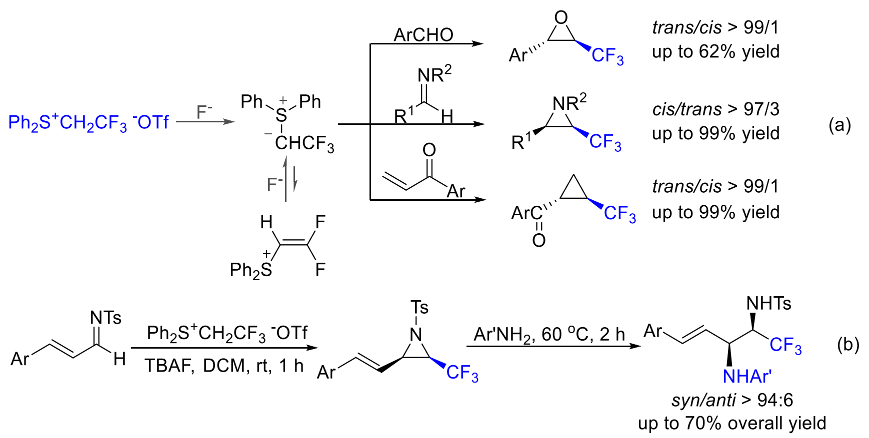
Scheme 18. Plausible Mechanism of Dehydroxylative Functionalizations



3. SULFONIUM SALTS

In addition to phosphonium ylide and difluorocarbene, we are also interested in the chemistry of sulfonium ylides and other fluorinated carbenes. The discoveries in the phosphonium-ylide-to-carbene process led us to think whether fluorinated carbenes can be produced from sulfonium ylides. Our previous studies in CF_3−sulfonium salts[52] drove us to first investigate the use of CF_3CH_2−sulfonium salt as an ylide precursor. Although $Ph_2S^+CH_2CF_3$ TfO^- (Tf = CF_3SO_2) had been reported,[53] a tedious synthetic procedure is required and its synthetic utility remained unknown. We found that a reaction of Ph_2S with CF_3CH_2OTf can efficiently give this sulfonium salt, which could be purified simply by washing with diethyl ether. While β-fluorine elimination from ylide $Ph_2S^+CH^-CF_3$ may readily occur, the Johnson−Corey−Chaykovsky reaction of aldehydes, imines, and α,β-unsaturated ketones with this ylide proceeded smoothly to afford the cyclization products with high diastereoselectivity when CsF was used as the base to suppress the β-fluorine elimination (Scheme 19a).[54] The

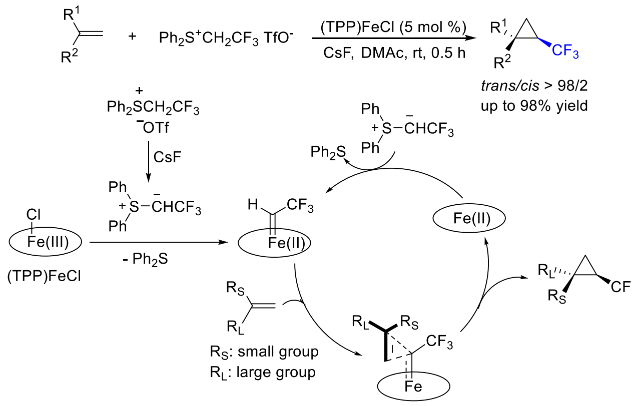
Scheme 19. $Ph_2S^+CH_2CF_3$ TfO^- as an Ylide Reagent



cyclization of imines was applied to a one-pot synthesis of CF_3-containing vicinal diamines (Scheme 19b).[55]

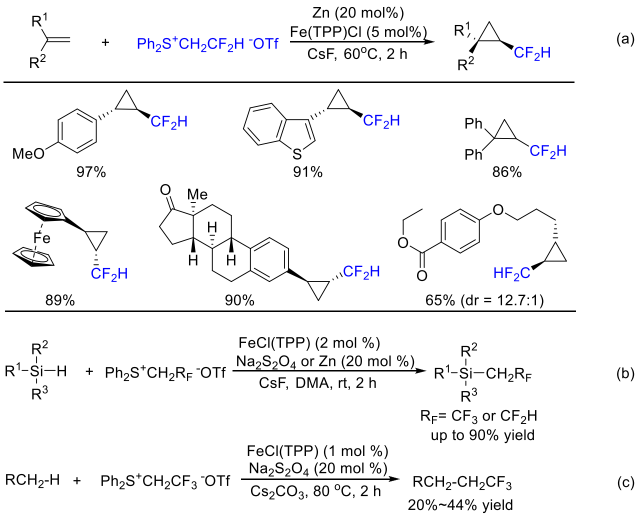
The successful development of the fluorinated sulfonium ylide reagent ($Ph_2S^+CH_2CF_3$ TfO^-) prompted us to further examine whether trifluoromethylcarbene (:$CHCF_3$) can be produced from ylide $Ph_2S^+CH^-CF_3$. It was found that the direct thermal S−CH bond cleavage to form :$CHCF_3$ cannot occur. The ylide may prefer to undergo decomposition by β-fluorine elimination rather than S−CH bond cleavage. Unlike the case in phosphonium ylide $Ph_3P^+CF_2^-$ (see Figure 1 and the fluorine effect explanations), fluorine atoms are not attached to the anionic carbon in sulfonium ylide $Ph_2S^+CH^-CF_3$, meaning that there is no special fluorine effect to weaken the S-CH bond. Fortunately, we found that a Fe complex, (TPP)FeCl (TPP = 5,10,15,20-tetraphenyl-21H,23H-porphine), was able to efficiently catalyze the cyclopropanation of aryl alkenes with $Ph_2S^+CH_2CF_3$ TfO^- (Scheme 20).[56] The mechanistic investigations indicate that the Fe complex leads to the cleavage of the ylide S-CH bond to form a Fe-trifluoromethylcarbene species, Fe = $CHCF_3$. The experimental evidence to support the Fe-carbene process includes the isolation of Ph_2S in a high yield, the observation of $CF_3CH{=}CHCF_3$, which should be formed via carbene homocoupling, and the conversion of sulfonium ylide $Ph_2S^+CH^-CF_3$ into phosphonium ylide $Ph_3P^+CH^-CF_3$. Although the Fe source used is a trivalent Fe(III) complex, the real catalyst should be a divalent Fe(II) complex since Fe(III) may be easily reduced in the reaction system. High diastereoselectivity and a wide substrate scope were observed for this cyclopropanation reaction. Compared with another commonly used trifluoromethylcarbene source, CF_3CHN_2, which is a toxic and explosive gas,[57] $Ph_2S^+CH_2CF_3$ TfO^- is attractive due to its easy availability and the convenient operations.

Scheme 20. Trifluoromethylcarbene Source



We then considered whether $Ph_2S^+CH_2CF_2H$ TfO^- could act as a difluoromethylcarbene precursor to achieve the cyclopropanation of alkenes catalyzed by (TPP)FeCl.[58] However, no desired product was observed under the same conditions as that with $Ph_2S^+CH_2CF_3$ TfO^-, demonstrating quite different reactivities between these two sulfonium reagents. A detailed screening of reaction conditions showed that the use of catalytic amount of zinc powder gave the expected product in a high yield. Zinc powder serves as a reductant to reduce Fe(III) to Fe(II). The cyclopropanation process was extended to a wide range of alkenes (Scheme 21a). Excellent diastereoselectivity was obtained for the conversions of aryl alkenes (*trans*/*cis* > 20/1). In the case of alkyl alkenes, the reactions gave products with lower diastereoselectivity. The chemistry of difluoromethylcarbene remains largely unex-

Scheme 21. Cyclopropanation of Alkenes with Difluoromethylcarbene and the Insertion of Carbenes into the X−H Bond



plored. HCF_2CHN_2 is another difluoromethylcarbene precursor, but it is also a toxic and explosive gas. Furthermore, almost no diastereoselectivity was observed when it was used in cyclopropanation.[59] Both trifluoromethylcarbene and difluoromethylcarbene generated from the sulfonium salts can be inserted into the Si−H bond (Scheme 21b).[60] Although the challenging insertion of trifluoromethylcarbene into the Csp^3−H bond was achieved, the products were obtained only in low yields (Scheme 21c).[60] For the reactions of $Ph_2S^+CH_2CF_3$ TfO^-, no reductant is necessary in the cyclopropanation of alkenes (Scheme 20), but the insertion of trifluoromethylcarbene into the X−H bond (X = Si or C) requires a reductant, $Na_2S_2O_4$, to increase the yields. The reason for the necessity of a reductant is presently unclear.

4. CONCLUSIONS

A story is presented about how we developed reagents and designed reactions, what we obtained unexpectedly, and how we proceeded further. The chemistry of fluorinated ylides and carbenes is the story line as the carbenes are generated from the ylides. Related discoveries in phosphonium salts are also discussed because those results were obtained during the investigation of ylide reactions. PDFA, which is shelf-stable and could be easily prepared on a kilogram scale, can readily undergo decarboxylation to generate phosphonium ylide and difluorocarbene under warming conditions without any additive. The facile generation of difluorocarbene from ylide is explained from the perspective of electronic effects. The development of PDFA allowed us to discover new difluorocarbene chemistry. A preliminary design of difluorocarbene-based trifluoromethylthiolation and the deeper mechanistic investigations led us to develop the formation of thiocarbonyl fluoride into a synthetic tool and to achieve the oxidation of difluorocarbene and cyanodifluoromethylation of alkenes. Based on the process from phosphonium ylide to difluorocarbene, we also developed fluorinated sulfonium salts as sulfonium ylide reagents and tri- or difluoromethylcarbene precursors. The studies on difluoromethylcarbene remain largely unexplored and merit close attention. We hope that we can develop more reagents by the idea of "from fleeting intermediates to powerful reagents" and that new chemistry of fluorinated ylides/carbenes can be further discovered.

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Notes

The authors declare no competing financial interest.

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Jin-Hong Lin received his Ph.D. in 2011 at Shanghai Institute of Organic Chemistry (SIOC), Chinese Academy of Sciences, under the supervision of Prof. Ji-Chang Xiao. He then joined Prof. John Welch's group at the State University of New York at Albany for postdoctoral studies. Since 2013, he has worked at SIOC as an associate professor. His current research interests focus on the development of fluorinated organic salts as reagents.

Ji-Chang Xiao received his Ph.D. in 2003 from Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, under the supervision of Prof. Qing-Yun Chen. Then he conducted his postdoctoral research with Prof. Jean'ne M. Shreeve at the University of Idaho. In 2005, he began his independent career as a professor at SIOC. His current research interests include fluorine-containing compounds, molten salts, and extraction materials.

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