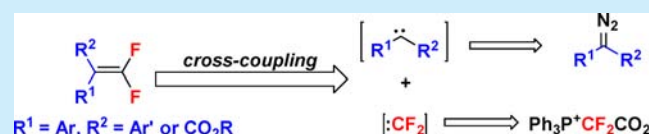


Cross-Coupling between Difluorocarbene and Carbene-Derived Intermediates Generated from Diazocompounds for the Synthesis of *gem*-Difluoroolefins

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S Supporting Information

ABSTRACT: Cross-coupling between difluorocarbene and carbene-derived intermediates generated from diazocompounds was developed to give *gem*-difluoroolefins, which constitutes a fast practical pathway to achieve hindered *gem*-difluoroolefins. The cross-coupling between difluorocarbene and aryl diazoacetates proceeded smoothly in the presence of a copper source, whereas its coupling with diaryl diazomethanes occurred well under metal-free conditions. A mechanism involving a copper–difluorocarbene complex was proposed.



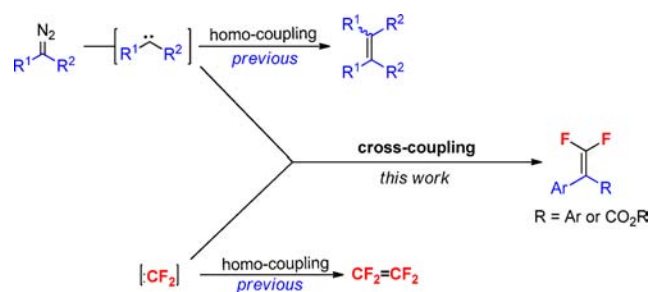
Recent decades have witnessed significant advances in the chemistry of difluorocarbene.¹ The singlet difluorocarbene is stabilized by π -donation from fluorine and is destabilized by the negative inductive effect of the highly electronegative fluorine. Because of these stabilizing and destabilizing effects of fluorine, difluorocarbene shows moderate electrophilicity.^{1c} As a valuable intermediate, it has been applied to a wide variety of organic transformations, including trifluoromethylation,² difluoromethylation of the X–H bond (X = N, O, S),^{1h,3} [2 + 1] cycloaddition with multibonds,^{1f,h,4} homocoupling to produce tetrafluoroethylene (TFE),⁵ and coordination with transition metals.⁶ The homocoupling reaction is one of the most important industrial applications of difluorocarbene. Although the homocoupling reaction has been well studied, cross-coupling of difluorocarbene with other carbenes, allowing access to *gem*-difluoroolefins, remains a significant challenge.

gem-Difluoroolefins have received a great deal of attention in organic synthesis and medicinal chemistry because of the unique chemical and biological properties of *gem*-difluorovinyl functionality.⁷ Consequently, determined efforts have been devoted to the exploration of efficient approaches for the preparation of *gem*-difluoroolefins. Traditional synthetic methods include *gem*-difluoroolefination of carbonyl compounds such as the Wittig reaction,^{1c,7g,8} the Julia–Kocienski reaction,^{7f} and the Horner–Wadsworth–Emmons reaction,⁹ and the incorporation of *gem*-difluorovinyl-containing building blocks into the target molecules.¹⁰ Recently, Hu and co-workers described a novel approach of *gem*-difluoroolefination¹¹ utilizing the Rupert–Prakash reagent (TMSCF₃)¹² via a β -fluoride elimination in 10 h. This transformation can be applied to $Ar^1Ar^2C=N_2$. However, its application for the conversion of diazoacetate (a very common diazo compound)¹³ has been less successful. On the basis of the structure

of *gem*-difluoroolefins, it is reasonable to speculate that the most straightforward synthetic protocol might be the cross-coupling between difluorocarbene and another carbene. However, this strategy has never been considered or successfully achieved. In this paper, we demonstrate a successfully fast cross-coupling reaction of difluorocarbene with other carbene precursors such as aryl diazoacetates and diaryl diazomethanes (Scheme 1), giving the corresponding *gem*-difluoroalkenes. Interestingly, homocoupling of diazocompounds or difluorocarbene was suppressed in this transformation.

We have shown that difluoromethylene phosphobetaine ($Ph_3P^+CF_2CO_2^-$, PDFA) is an efficient difluorocarbene reagent because decarboxylation of PDFA and subsequent dissociation of the P–CF₂ bond can readily take place.^{2d,4,7g,8c,14} Owing to its stability, facile accessibility, and ease of handling, PDFA was selected as the difluorocarbene source for the cross-coupling

Scheme 1. Synthesis of *gem*-Difluoroolefins



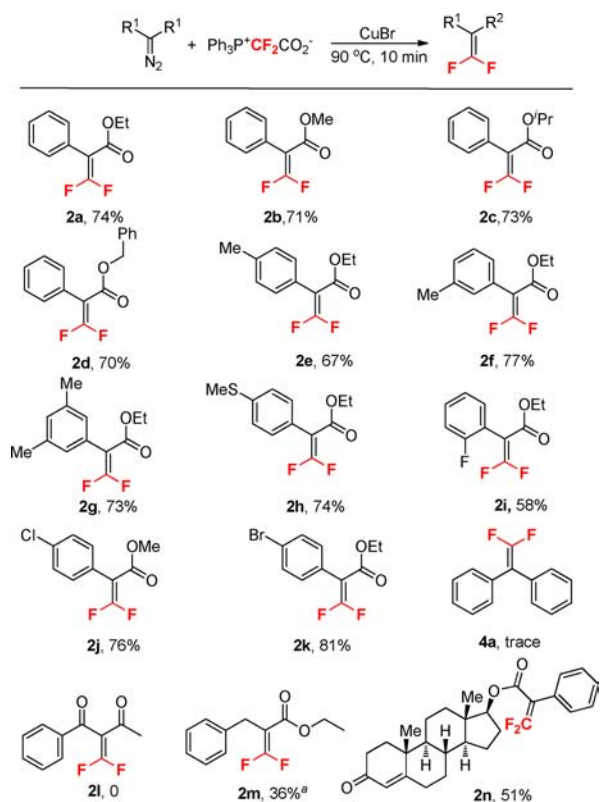
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with phenyldiazoacetate (**1a**). After screening various reaction conditions [Table 1 in the Supporting Information (SI)], we found that the cross-coupling employing CuBr proceeds fluently in a mixed solvent ($V_{p\text{-xylene}}: V_{\text{dioxane}} = 1 \text{ mL}: 0.5 \text{ mL}$) at 90 °C with **1a** and PDFA (molar ratio 1:1.4) for just 10 min.

To explore the scope of this Cu-mediated cross-coupling reaction, the optimized conditions were applied to the conversion of a variety of aryl diazoacetates. As shown in Scheme 2, the reactions occurred very fast to give the desired

Scheme 2. Cu-Mediated Cross-Coupling of Difluorocarbene, Showing Isolated Yields



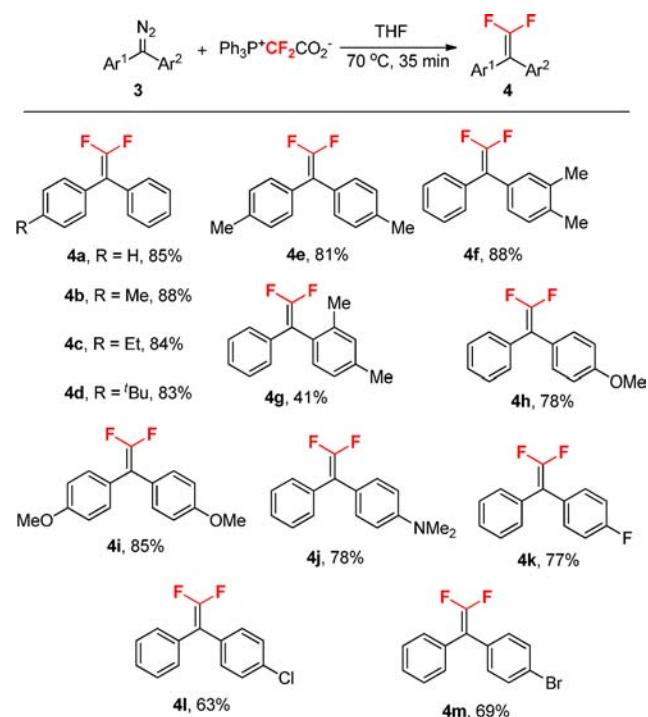
^aDetermined by ¹⁹F NMR.

products. The ester moiety showed no side steric effect on this reaction (**2a–d**), as evidenced by the good yield obtained for product **2c** featuring an isopropyl group. Various functional groups on the phenyl ring were compatible with this coupling process, and the corresponding products were obtained in moderate to good yields (**2e–k**). Notably, the Br (Cl) substituent remained intact under these conditions, providing possibilities for further transformations (**2j**, **2k**). The utility of this cross-coupling was demonstrated by the development of a short route to a derivative of testosterone phenylacetate (**2n**). Unexpectedly, the reaction was not applicable to diphenyl diazomethane (**3a**), which might be because **3a** is more reactive and is not compatible with the copper(I) complex even at room temperature. And it was found that both the aryl ring and the ester group are significant to this reaction (**2l**, **2m**).

The successful cross-coupling of difluorocarbene with aryl diazoacetates prompted us to screen more reaction conditions for the conversion of diphenyl diazomethane. The screening of reaction conditions showed that 1.3:1 of **3a** to PDFA at 70 °C for 35 min in THF were the optimal reaction conditions (see SI, Table 2).

With the reaction conditions optimized, we then investigated the substrate scope for the metal-free cross-coupling of difluorocarbene with diaryl diazomethanes (Scheme 3). The

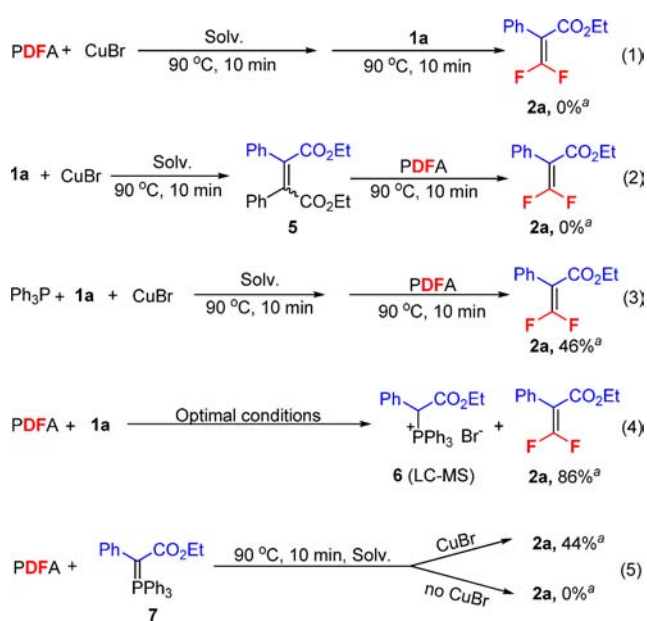
Scheme 3. Metal-Free Cross-Coupling of Difluorocarbene, Showing Isolated Yields



reaction conditions could tolerate various functional groups and afforded corresponding *gem*-difluoroolefins. The examination of electronic effects of the substituents indicated that electron-donating groups were more favorable for this conversion (**4a–j** vs **4k–m**). The dramatic difference between yields for **4g** (41%) and **4f** (88%) suggests that steric hindrance had a clear side effect. The compatibility of the Br (Cl, F) substituent with this protocol also provides possibilities for further transformations (**4k–m**).

More experimental evidence was collected to elucidate the mechanism for the coupling with aryl diazoacetates (Scheme 4). It was found that CuBr can significantly accelerate the dissociation of PDFA. After the mixture of PDFA and CuBr was stirred at 90 °C for 10 min, PDFA was completely consumed as determined by ¹⁹F NMR spectroscopy (eq 1). **1a** was added into this system, and the resulting mixture was further stirred at the same temperature for 10 min. Desired product **2a** was not detected, indicating that the intermediate obtained from the reaction of PDFA with CuBr is highly reactive or is not an intermediate for the coupling reaction (eq 1). As is well-known, Cu-mediated homocoupling of diazo compounds proceed well to give olefins.¹⁵ However, the reaction of olefin **5** with PDFA did not furnish product **2a**, suggesting that **2a** is not produced from olefin **5** (eq 2). Considering that the dissociation of PDFA would release Ph₃P, we envisioned that Ph₃P may play an important role in the reaction. This hypothesis was supported by the successful conversion of PDFA with the intermediate obtained from the reaction of Ph₃P, substrate **1a**, and CuBr (eq 3). For the reaction of substrate **1a** with PDFA under optimal reaction conditions, phosphonium salt **6** was detected by LC–MS (eq

Scheme 4. Experimental Evidence for the Coupling with Aryl Diazoacetate

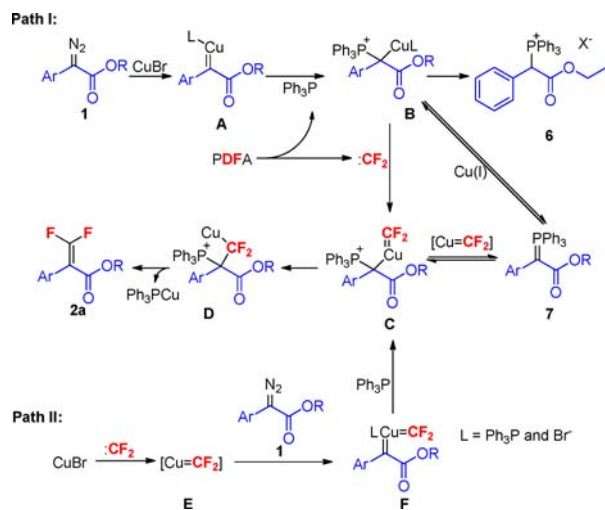


^aThe yields were determined by ¹⁹F NMR spectroscopy using trifluoromethylbenzene as the internal standard. In all reactions, the loadings of all reagents were as established for optimal conditions. Solv. = *p*-xylene (1 mL) + 1,4-dioxane (0.5 mL).

4). Salt **6** may be produced from its corresponding phosphonium ylide **7**. Ylide **7** can react with PDFFA to give product **2a** in the presence of CuBr, meaning that ylide **7** may be involved in the cross-coupling reaction (eq 5). Without CuBr, product **2a** was not observed, further suggesting that a copper source is necessary for this reaction (eq 5).

Because both PDFFA and substrate **1** can react rapidly with CuBr, we propose that the cross-coupling reaction may proceed via two pathways (Scheme 5). Copper carbene **A** may be readily formed and then be trapped by Ph₃P generated from PDFFA to give intermediate **B** (path I). Hydrolysis of intermediate **B** by trace water present in the reaction system affords phosphonium salt **6**. The coordination of difluor-

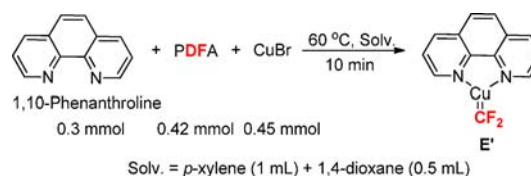
Scheme 5. Proposed Reaction Mechanism for the Cross-Coupling with Aryl Diazoacetate



ocarbene produced from PDFFA to intermediate **B** furnishes Cu–difluorocarbene **C**. An equilibrium between intermediates **B** (**C**) and ylide **7** may be established. Subsequently, migratory insertion of difluorocarbene to the Cu–C bond in species **C** leads to the formation of a new Cu species **D**, reductive elimination of which gives the final product **2**. Another possibility is that intermediate **C** might be formed from Cu–difluorocarbene species **E** (path II). Species **E** may be initially produced, and its reaction with diazo compound **1** gives intermediate **F**. Subsequent electrophilic attack at PPh₃ also generates intermediate **C**.

A Cu–difluorocarbene complex has been proposed,¹⁶ but it has never been observed. Much effort has been made to isolate or characterize intermediate **C**, but all attempts were frustrated. We then tried to stabilize species **E** by coordination with an appropriate ligand. With the use of 1,10-phenanthroline as the ligand, carbene species **E'** may be formed (Scheme 6).

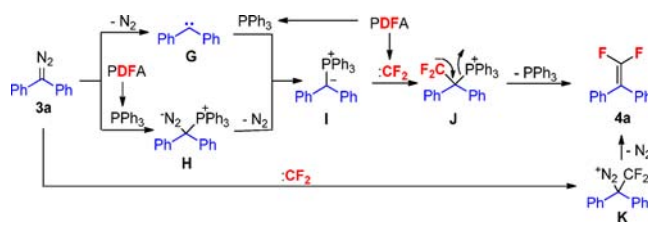
Scheme 6. Stabilization of Cu–Difluorocarbene Species



Although the isolation of **E'** by flash column chromatography was unsuccessful, difluoromethane (CH₂F₂) was detected by ¹⁹F NMR spectrometry in the eluents (ethyl acetate and petroleum ether). CH₂F₂ was not observed before the attempted isolation of intermediate **E'**. Its formation may be due to the hydrolysis of intermediate **E'** during isolation (a similar process has been previously reported).¹⁷

The proposed mechanism for the cross-coupling reaction with diaryl diazomethanes is shown in Scheme 7. The reactive

Scheme 7. Proposed Mechanism for the Cross-Coupling with Diaryl Diazomethanes

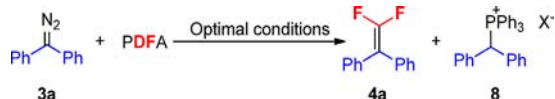


substrate **3a** may undergo denitrogenation to produce carbene **G**, which is trapped by PPh₃ produced from PDFFA to give ylide **I**. Another possibility is the reaction of PPh₃ with substrate **3a** to generate intermediate **H**, which undergoes denitrogenation to furnish ylide **I**. The nucleophilic attack of ylide **I** at difluorocarbene generated from PDFFA affords intermediate **J**. β -PPh₃ elimination of this intermediate gives the final product **4**.¹⁸ Of course, :CF₂ could also react directly with Ar₂C=N₂. As an electrophile, it could add at the C end of the polar C⁻—N₂⁺ bond. The intermediate thus formed would then lose N₂ with the formation of Ar₂C=CF₂.

The proposed mechanism shown in Scheme 7 was further supported by experimental evidence. The reaction of substrate **3a** with PPh₃ did occur albeit giving some unknown side products. For the coupling of **3a** with PDFFA, phosphonium salt

8 was detected in the reaction system by LC–MS (Scheme 8). Salt 8 is likely formed from ylide I via hydrolysis.

Scheme 8. Observation of Phosphonium Salt 8



In summary, we have described the fast cross-coupling of difluorocarbene with carbene generated from diazo compounds to give *gem*-difluoroolefins. Interestingly, the coupling with aryl diazoacetate proceeded smoothly in the presence of a copper source, whereas the coupling with diaryl diazomethanes proceeded under metal-free conditions. The copper–difluorocarbene complex may be involved in this coupling reaction. This work represents the first protocol for the synthesis of *gem*-difluoroolefins via cross-coupling of difluorocarbene.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03159.

Experimental procedures, analytical data for products, NMR spectra of products (PDF)

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Notes

The authors declare no competing financial interest.

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