**Concise Report**

Palladium, Catalysis, Difluorocarbene, Fluorine, Cross-Coupling

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# Pd-Catalyzed Transfer of Difluorocarbene for Three Component Cross-Coupling†

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**Summary of main observation and conclusion** Outstanding accomplishments have been achieved in the chemistry of difluorocarbene, but transition-metal-catalyzed transfer of difluorocarbene for coupling remains a challenging task. Herein, we describe a Pd-catalyzed coupling of difluorocarbene with two aryl carbon centers to give difluoromethylenation products, which cannot be obtained by any previous difluorocarbene-transformation method.

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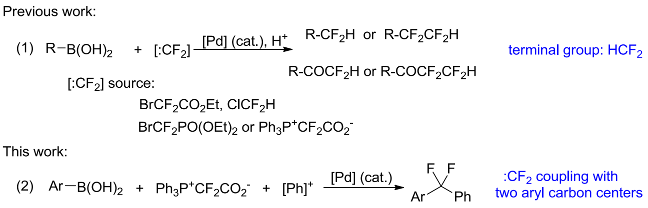
## Background and Originality Content

As the incorporation of fluorine atoms into organic molecules may lead to profound changes of their physicochemical properties, fluorine element has been recognized as a magic atom in various research areas, such as pharmaceutical/agrochemical developments and material sciences.[1] Difluorocarbene has proved to be a valuable intermediate for fluorine incorporation.[2] Typical difluorocarbene reactions include [2+1] cyclization of alkenes/alkynes[3] and difluoromethylation of X—H bonds (X = heteroatom).[4] Hu disclosed an efficient C—H difluoromethylation by using $TMSCF_2Br$, a reagent developed by them recently,[5] as a difluorocarbene source.[6] Difluorocarbene can also act as a dipolar $CF_2$ unit for consecutive bond-forming reactions,[7] which were described by Dilman.[8] Outstanding accomplishments have been achieved in the chemistry of difluorocarbene. However, the transition-metal-catalyzed transfer of difluorocarbene remains a challenging research area, despite the fact that metal carbenes have found widespread applications in organic synthesis.[9]

Traditional methods for the formation of metal-difluorocarbene complexes require a two-step procedure, the synthesis of $M\text{-}CF_3$ complexes and the subsequent defluorination.[10] In the previous studies of metal difluorocarbene species, a stoichiometric amount of metal sources was usually used and metal complexes were obtained as desired products.[10-11] Transition-metal-catalyzed coupling of difluorocarbene with other partners is quite challenging due to the high reactivity of difluorocarbene and side reactions of $M{=}CF_2$ intermediates.[12] Recently, Zhang reported highly effective catalytic methods to obtain various $HCF_2$-containing products (Scheme 1, eq 1).[13] On the basis of their work on Pd-catalyzed difluoromethylation of aryl boronic acids with $BrCF_2CO_2Et$,[13a] they further developed a more efficient method by using inexpensive and abundant industrial raw material $ClCF_2H$, which is also an ozone-depletion chemical, as a difluorocarbene source.[13b] Interestingly, they found that the nucleophilicity and electrophilicity of $Pd{=}CF_2$ species is controllable by switching the oxidation state of Pd: $Pd^0{=}CF_2$ is a nucleophile and $Pd^{II}{=}CF_2$ is an electrophile. The successive coordination of $:CF_2/:CF_2$ or $:CF_2/CO$ to Pd complexes was achieved to enable access to various products containing a $CF_2CF_2$, $COCF_2$ or $COCF_2CF_2$ unit.[13c] We have also developed a difluoromethylation of boronic acids with $Ph_3P^+CF_2CO_2^-$ via a difluorocarbene coupling (eq 1).[14] The above catalytic methods involve the coupling of difluorocarbene with a carbon center and a proton to afford products with $HCF_2$ as a terminal group. In continuation of our interest in the chemistry of difluorocarbene,[15] we have now investigated a Pd-catalyzed three-component coupling between difluorocarbene and two different aryl carbon centers to provide difluoromethylenation products (eq 2).

**Scheme 1** Pd-catalyzed coupling of difluorocarbene with other partners



## Results and Discussion

Since a proton source is needed in Pd-catalyzed difluoromethylation with difluorocarbene,[13-14] an electrophilic carbon source would be necessary for the three-component coupling. We have previously shown that a trimer of $Pd{=}CF_2$ can be easily obtained from the reaction of $Pd(PPh_3)_4$ with $Ph_3P^+CF_2CO_2^-$.[14] It was found that the coupling between boronic ester **1a**, the $Pd{=}CF_2$ trimer and a phenyl cation equivalent, $Ph_2IOTf$, could give the desired difluoromethylenation product in a 40% yield (Scheme 2, eq 1). Apparently, the stoichiometric use of Pd source would limit the practicability of this protocol. However, the use of $Pd(PPh_3)_4$ as a catalyst did not afford the desired product at all when $Ph_3P^+CF_2CO_2^-$ was used as a difluorocarbene source. To our delight, a 14% yield was obtained by using boronic acid **2a** instead of boronic ester **1a** in the presence of another ligand and a silver salt (eq 2).

Although a low yield was obtained in the catalytic version, the successful coupling by using the trimer prompted us to further screen catalytic reaction conditions. Significant effort was made in

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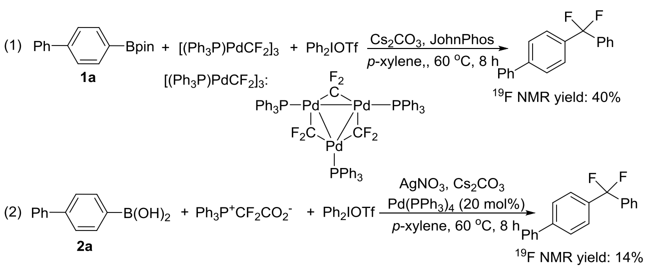
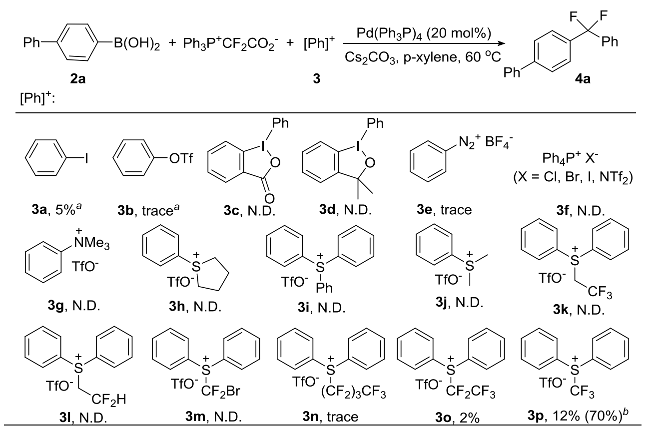
**Scheme 2** Preliminary investigation of the three-component coupling



order to increase the yield for the coupling between boronic acid **2a**, $Ph_3P^+CF_2CO_2^-$ and $Ph_2IOTf$, but all attempts failed. We believed that the phenyl cation equivalent played an important role, and thus a variety of equivalents were examined (Scheme 3). No desired product was detected in most cases. Fortunately, using trifluoromethyl sulfonium salt (**3p**) as a phenyl cation equivalent delivered **4a** in 12% yield. The sulfonium salt has served as an effective trifluoromethylation reagent,[16] and Zhang found that it can also act as an efficient phenylation reagent for coupling reactions.[17] The 12% yield indicated the possibility of the catalytic reactions, and thus a large number of reaction conditions were further screened (Please see supporting information). After a detailed survey, the yield was increased to 70% by using bathocuproine as a ligand.

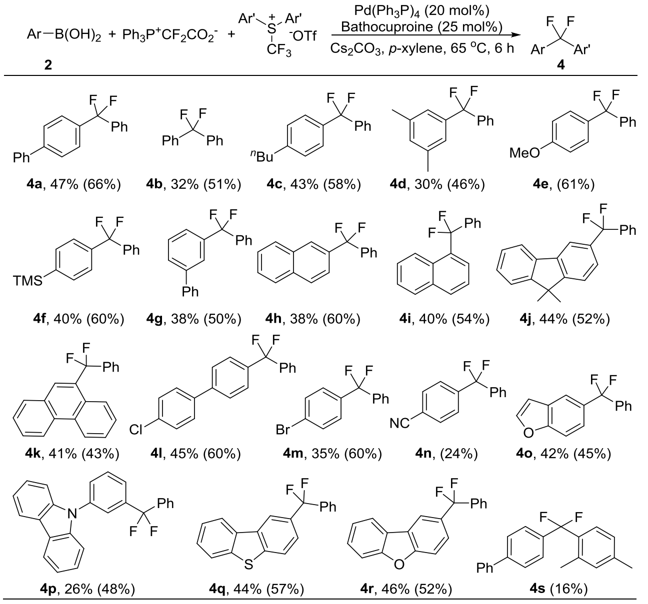
**Scheme 3** Screening coupling reaction conditions



Reaction conditions: **2a** (0.1 mmol), $Ph_3P^+CF_2CO_2^-$ (3 equiv), $[Ph]^+$ (1.5 equiv), $Pd(PPh_3)_4$ (20 mol%), $Cs_2CO_3$ (2 equiv) and *p*-xylene (1.5 mL) at 60 °C under a $N_2$ atmosphere for 8—12 h. N.D. = Not detected. The yields were determined by $^{19}F$ NMR spectroscopy. [a] 1 equiv of $[Ph]^+$ was used and the reaction time was 4 h. [b] The molar ratio of **2a** : $Ph_3P^+CF_2CO_2^-$ : $[Ph]^+$ = 1 : 3 : 3, bathocuproine (25 mol%) was used as a ligand, 1 mL of *p*-xylene was used, and the reaction time was 6 h.

With the optimal reaction conditions in hand, we then investigated the substrate scope of the Pd-catalyzed coupling between aryl boronic acids, difluorocarbene and the sulfonium salt. As shown in Scheme 4, the coupling process was extended to a wide range of boronic acids. Electron-rich, -neutral and -deficient aryl boronic acids could all undergo coupling reactions to afford the desired products in moderate to good yields. But a strong electron donating group would destabilize the product and thus it is hard to isolate the product by flash column chromatography (**4e**). The compatibility of TMS (**4f**) and halide groups (**4l—4m**) under these conditions may allow for further transformations of these products. The direct coupling between substrate **2** and sulfonium salt **3p** cannot be completely suppressed and thus Ar-Ph was produced as a side product in each coupling reaction. The removal of the side products led to lower isolated yields compared with the $^{19}F$ NMR yields because of the similar polarity between the expected products and side products. The yield was dramatically decreased by using other sulfonium salt (**4s**).

**Scheme 4** Substrate scope of the coupling reaction

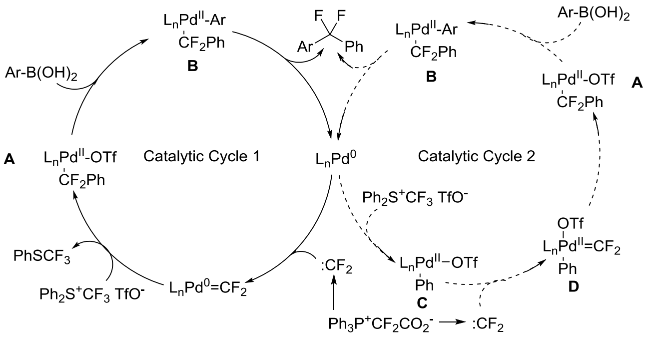


Isolate yields are shown. The numbers in parentheses are yields determined by $^{19}F$ NMR spectroscopy. Reaction conditions: **1** (0.2 mmol), $Ph_3P^+CF_2CO_2^-$ (0.6 mmol), $[Ar'_2SCF_3]^+[OTf]^-$ (0.6 mmol), $Pd(Ph_3P)_4$ (0.04 mmol), bathocuproine (0.05 mmol), $Cs_2CO_3$ (0.4 mmol) and *p*-xylene (1 mL) at 65 °C for 6 h under a $N_2$ atmosphere.

The incorporation of a $CF_2$ unit into organic molecules has received increasing attention.[18] Since some pharmaceuticals such as Ledipasvir contain a Ar-$CF_2$-Ar motif, it would be desirable to develop efficient methods for the installation of this moiety. Traditional deoxyfluorination of carbonyls suffers from the use of hazardous reagents, DAST or deoxofluor.[19] Recently, Szymczak found that $ArCF_2^-$ anion can be captured by a Lewis acid to give an isolable $ArCF_2^-$ anion equivalent, which can be used to synthesize $ArCF_2Ar$ molecules by using a stoichiometric amount of a transition metal.[20] Our straightforward approach is also quite attractive due to the safe operations and the use of a substoichiometric amount of a Pd source.

The coupling process may proceed via the coordination of difluorocarbene to $Pd^0$ to produce $Pd^0$=$CF_2$ complex, which further reacts with the sulfonium salt to generate $Pd^{II}$ species (intermediate **A**) (Scheme 5, catalytic cycle 1). The subsequent transmetallation and a reductive elimination gives the final product **4**. Three possibilities exist for the formation of intermediate **A**. It may be formed via an oxidative addition of sulfonium salt to $Pd^0$=$CF_2$ to give $PhPd^{II}$=$CF_2$ complex followed by a migratory insertion. Owing to the electron donation from a d orbital on Pd to the vacant p orbital on $CF_2$ carbon, the $CF_2$ carbon in $Pd^0$=$CF_2$ species may exhibit nucleophilicity.[13c] Therefore, the carbon may also attack the phenyl ring in the sulfonium salt via a nucleophilic aromatic substitution process ($S_NAr$) to directly deliver intermediate **A**. The third possibility is a radical process. A single-electron-transfer process may occur between $Pd^0$=$CF_2$ and the sulfonium salt to generate $Ph^\bullet$ radical and $Pd^{+\bullet}$=$CF_2$ species.[21] The combination of these two intermediates could also deliver intermediate **A**. Catalytic cycle 2 involves the first oxidative addition and the subsequent coordination of difluorocarbene. If the first step is the oxidation of $Pd^0$ to provide $PhPd^{II}$ (intermediate **C**), many other phenyl cation equivalents may be reactive for this coupling reaction. However, as shown in Scheme 3, most $[Ph]^+$ reagents failed. Therefore, catalytic cycle 2 is excluded. The coupling reaction can work only when an active $[Ph]^+$ reagent, $Ph_2S^+CF_3$ $TfO^-$, is used, probably because the $Pd^0{=}CF_2$ complex is a quite inert intermediate.

**Scheme 5** The plausible mechanism



## Conclusions

In summary, we have described the Pd-catalyzed transfer of difluorocarbene for three-component coupling reactions between aryl boronic acids, $Ph_3P^+CF_2CO_2^-$ and $Ph_2S^+CF_3$ $TfO^-$. This work represents the first example of coupling of difluorocarbene with two other aryl centers, and may provide more possibilities for the difluorocarbene chemistry.

## Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.202000297.

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