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Palladium-Catalyzed Difluoroalkylation of Isocyanides: Access to Difluoroalkylated Phenanthridine Derivatives

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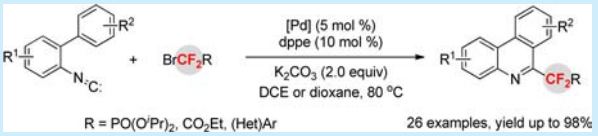
Supporting Information

ABSTRACT: An efficient and general method for the synthesis of difluoroalkylated phenanthridine derivatives through palladium-catalyzed reaction of difluoroalkyl bromides with isocyanides is described. The reaction can also be extended to perfluoroalkyl iodides. Mechanistic studies reveal that a difluoroalkyl radical via a single-electron-transfer pathway is involved in the reaction.

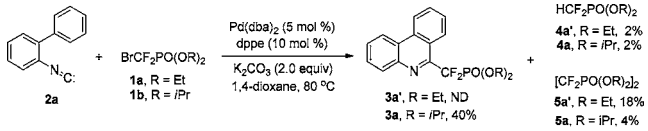


Owing to the unique properties of the difluoromethylene group (CF_2) that can dramatically improve the metabolic stability of bioactive molecules once the CF_2 group was incorporated at benzylitic position,[1] the development of new and efficient methods to prepare difluoroalkylated (hetero)-aromatics has become an intensive topic of organosynthetic chemistry. Over the past few years, significant progress has been made in this area.[2,3] However, efficient synthetic methods for the difluoroalkylated heteroarenes remains limited despite their importance in medicinal chemistry.[4] Phenanthridines are an important class of structural motif found in many bioactive natural alkaloids and biologically relevant compounds,[5] showing antibacterial, antitumoral, and antileukemic activities, etc.[6] Conceptually, introduction of the CF_2 group into such a structural motif would open a good possibility to discover some interesting new bioactive molecules.

Recently, the fluoroalkyl radical addition of 2-isocyanobiphenyls has become an efficient strategy to access 6-fluoroalkylated phenanthridines.[7] However, most of the efforts have been focused on the synthesis of perfluoroalkylated phenathridines through photocatalyzed reactions.[8] Inspired by our very recent work on the palladium-catalyzed difluoroalkylation of arylboronic acids, in which difluoroalkyl radicals via a single-electron transfer (SET) pathway are involved in the reaction,[3b,c] from an academic standpoint, we envisioned the feasibility of palladium-catalyzed difluoroalkylation of 2-isocyanobiphenyls from difluoroalkyl halides to construct 6-difluoroalkylated phenanthridines. To the best of our knowledge, such a transition-metal-catalyzed difluoroalkylation reaction has not been reported thus far. Herein, we describe an efficient method for the synthesis of 6-difluoroalkylated phenanthridines through the palladium-catalyzed reaction between 2-isocyanobiphenyls and difluoroalkyl halides.

Our initial studies focused on the palladium-catalyzed reaction of readily available diethyl bromodifluoromethylphosphonate ($BrCF_2PO(OEt)_2$) **1a** with isocyanide **2a** (Scheme 1). The use of **1a** is of interest because the $CF_2PO(OR)_2$ group-containing organic molecules have important applications in medicinal chemistry.[9] For instance, aryldifluoromethylphosphonates can

Scheme 1. Pd-Catalyzed Phosphonyldifluoromethylation of Isocyanide 2a with Bromodifluoromethylphosphonates



be used as protein tyrosine phosphatase inhibitors and exhibit significant bioactivities.[10] Hence, it is of great interest to introduce $CF_2PO(OR)_2$ group into organic molecules.[11]

However, after our extensive efforts, we found that it is difficult to obtain the desired product **3a′** due to the formation of the protonated $HCF_2PO(OEt)_2$ **4a′**, homocoupled product $[CF_2PO(OEt)_2]_2$ **5a′**, and other uncertain byproducts (Scheme 1). We ascribed these negative results to the supposition that the resulting difluoromethylene phosphonate radical **1a′** generated by Pd(0) via a SET pathway from **1a** was too reactive, and the formation of above the byproducts was faster than the reaction of **1a′** with isocyanide **2a**. We envisioned that if we replaced the ethyl group of **1a** with a bulky group, such as an isopropyl group, the difluoroalkyl radical generated in situ may be stabilized by steric effects,[12] thus benefiting the formation of 6-phosphonyldifluoromethylated phenanthridine **3a**. Accordingly, the sterically hindered diisopropyl bromodifluoromethyl phosphonate $BrCF_2PO(O\text{-}i\text{-}Pr)_2$ was used as a substrate. In the event, a 40% yield (determined by ^{19}F NMR) of **3a** was afforded, although some byproducts were observed when the reaction was carried out with **2a** (1.5 equiv), **1b** (1.0 equiv), $Pd(dba)_2$ (5 mol %), dppe (10 mol %), and K_2CO_3 (2.0 equiv) in dioxane at 80 °C (Scheme 1). No product **3a′** was detected under the same reaction conditions from **1a** because of the formation of many uncertain byproducts (Scheme 1).

Encouraged by these results, a survey of the reaction factors, such as solvents, palladium sources, ligands, and bases, was

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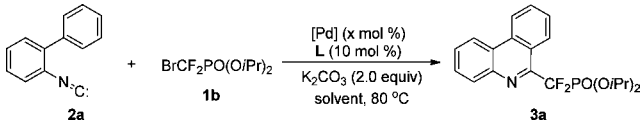
conducted (entries 2−14). It was found that a dramatically improved yield (60%) of **3a** was obtained when the halogenated solvent 1,2-dichloroethane (DCE) was used (entry 2). Among the tested palladium salts (entries 3−10), $PdCl_2$(dppe) showed higher activity, providing **3a** in 64% yield (entry 7). Switching $PdCl_2$(dppe) with $PdCl_2(PPh_3)_2$ afforded **3a** in an optimal yield (73% upon isolation, entry 10). Other palladium catalysts, such as $PdCl_2$(dppp) and $PdCl_2$(dppf), showed less activity (entries 8 and 9). The reaction is also sensitive to the ligands and bases (for details, see the Supporting Information). The combination of dppe and K_2CO_3 was still the best choice. However, only 1% yield of **3a** was produced when Xantphos, previously demonstrated to be a good ligand for difluoroalkylation reactions,[3b] was used (entry 12). No product was observed in the absence of either palladium catalyst or phosphine ligand (entries 13 and 14), thus demonstrating that both palladium and phosphine ligand did play essential roles for promotion of the reaction.

Table 1. Representative Results for Optimization of Pd-Catalyzed Reaction of 2a and 1b[a]



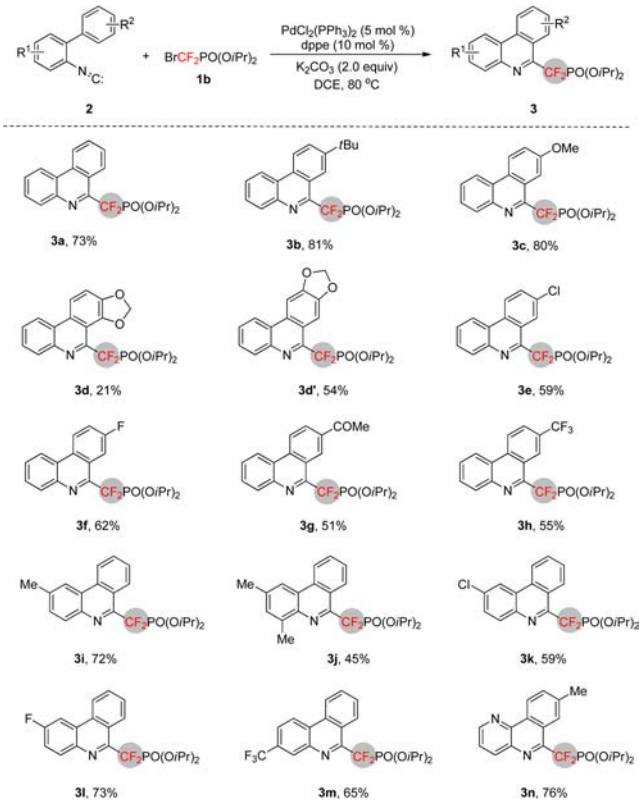
entry	[Pd] (x)	L	solvent	yield[b] (%)
1	$Pd(dba)_2$ (5)	dppe	dioxane	40
2	$Pd(dba)_2$ (5)	dppe	DCE	60
3	$Pd(OAc)_2$ (5)	dppe	DCE	26
4	$Pd(TFA)_2$ (5)	dppe	DCE	28
5	$Pd(PPh_3)_4$ (5)	dppe	DCE	47
6	$Pd_2(dba)_3$ (2.5)	dppe	DCE	38
7	$PdCl_2$(dppe) (5)	dppe	DCE	64
8	$PdCl_2$(dppp) (5)	dppe	DCE	56
9	$PdCl_2$(dppf) (5)	dppe	DCE	51
10	$PdCl_2(PPh_3)_2$ (5)	dppe	DCE	76 (73)
11[c]	$PdCl_2(PPh_3)_2$ (5)	dppe	DCE	58
12	$PdCl_2(PPh_3)_2$ (5)	Xantphos	DCE	1
13	none	dppe	DCE	nd
14	$PdCl_2(PPh_3)_2$ (5)	none	DCE	nd

[a]Reaction conditions (unless otherwise specified): **2a** (0.3 mmol, 1.5 equiv), **1b** (0.2 mmol, 1.0 equiv), K_2CO_3 (0.4 mmol, 2.0 equiv), Pd catalyst (5 mol %), ligand (10 mol %), anhydrous DCE (2 mL), 80 °C for 20 h. [b]Determined by ^{19}F NMR spectroscopy using fluorobenzene as an internal standard and the number within parentheses represents the yield of isolated product. [c]5 mol % of dppe was used.

Since the combination of $PdCl_2(PPh_3)_2$ (5 mol %) and dppe (10 mol %) provided an optimal yield of **3a**, we envisioned that a Pd^0/dppe complex $Pd(dppe)_2$ may initiate the reaction and produce difluoroalkyl radical. Accordingly, palladium complex $Pd(dppe)_2$[13] was prepared to promote the reaction. As expected, a comparable yield (78%) of **3a** was observed when **2a** was treated with **1b** under standard reaction conditions in the presence of $Pd(dppe)_2$ (for details, see the Supporting Information), thus indicating that $Pd(dppe)_2$ may be the promoter for the reaction.

To demonstrate the substrate scope of this method, a variety of biphenyl isocyanides were examined (Scheme 2). High yields of 6-phosphonyldifluoromethyl phenanthridines **3** were obtained when arylisonitriles **2** bearing electron-donating groups were employed (**3b−d,d′,3i**). The electron-deficient substrates

Scheme 2. Pd-Catalyzed Reaction of Biphenyl Isocyanides 2 with 1b[a]



[a]Reaction conditions: **2** (0.3 mmol, 1.5 equiv), **1b** (0.2 mmol, 1.0 equiv), K_2CO_3 (0.4 mmol, 2.0 equiv), $PdCl_2(PPh_3)_2$ (0.01 mmol, 5 mol %) and dppe (0.02 mmol, 10 mol %) in anhydrous DCE (2 mL), at 80 °C for 20 h. All reported yields are those of isolated products.

slightly diminished the yields, but moderate to good yields of **3** still can be provided (**3e−h,k−m**). The substituents at the different positions of the biphenyl isocyanides did not interfere with the reaction efficiency. In the case of disubstituted arylisocyanide **2d**, a mixture of regioisomers was provided with a ratio of 1:2.5 (**3d** and **3d′**). However, the sterically hindered substrate led to a low yield (**3j**). Importantly, the isocyanide bearing a pyridine instead of a benzene ring underwent the reaction smoothly, providing **3n** in good yield, thus providing a good opportunity for potential applications in medicinal chemistry.

Considering that *N*-containing heteroaromatics are important structural motifs found in numerous pharmaceuticals and agrochemicals, the reaction of **2** with heteroaryldifluoromethyl bromides was tested (Scheme 3). (Bromodifluoromethyl)benzo[*d*]oxazole **1c** furnished the corresponding product **6a** in excellent yield by employing $Pd(dba)_2$ as a catalyst and dioxane as a solvent. Extension of this method to bromodifluoromethylated benzothiazole, thiazole, and benzoimidazole also led to **6b−e** with high efficiency. Although a moderate yield of **6f** was produced, it is still synthetically useful for medicinal chemistry. Aryldifluoromethylated bromides and bromodifluoroacetate were also applicable to the reaction, producing the corresponding products in excellent yields (**6g−i**). The reaction was not restricted to difluoroalkyl bromides, as perfluoroalkyl iodides were also suitable substrates (**6j** and **6k**), thus demonstrating the generality of the current method.

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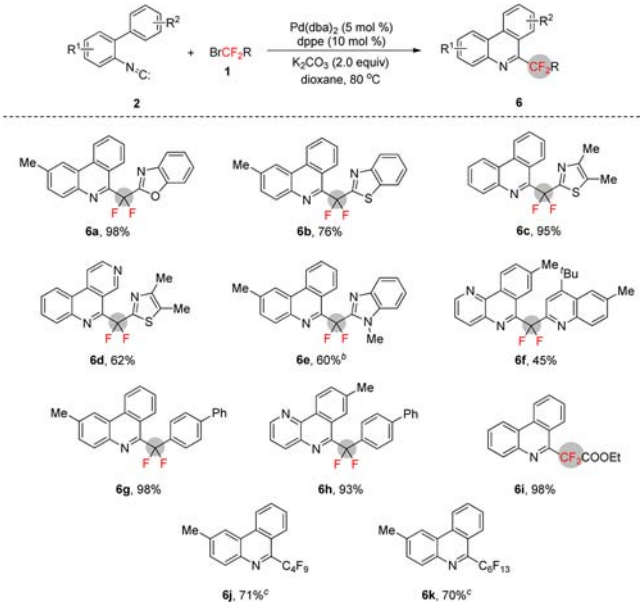
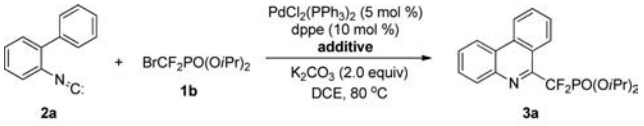
Scheme 3. Pd-Catalyzed Reaction of 2 with Difluoroalkyl Bromides and Perfluoroalkyl Iodides[a]



[a]Reaction conditions (unless otherwise specified): **2** (0.3 mmol, 1.5 equiv), **1** (0.2 mmol, 1.0 equiv), K_2CO_3 (0.4 mmol, 2.0 equiv), Pd $(dba)_2$ (0.01 mmol, 5 mol %), and dppe (0.02 mmol, 10 mol %) in anhydrous 1,4-dioxane (2 mL), 80 °C for 20 h. All reported yields are those of isolated products. [b]The reaction was conducted at 120 °C for 12 h. [c]Perfluoroalkyl iodides was used as fluoroalkylated reagents: **2** (0.3 mmol, 1.5 equiv), R_fI (0.2 mmol, 1.0 equiv), K_2CO_3 (0.4 mmol, 2.0 equiv), Pd $(TFA)_2$ (0.01 mmol, 5 mol %), Xantphos (0.012 mmol, 6 mol %) in anhydrous DCE (2 mL), 80 °C for 20 h.

To identify whether a difluoroalkyl radical existed in the reaction, radical inhibition experiments were conducted (Scheme 4). A significant decrease of the yields was observed

Scheme 4. Radical Inhibition Experiments[a]

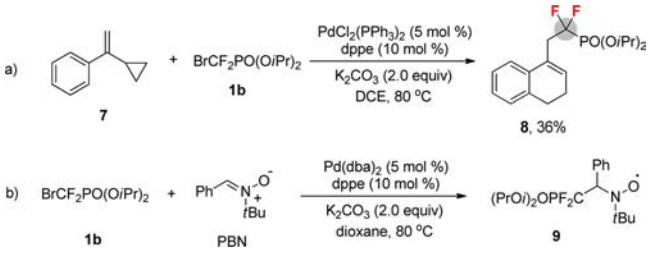


additive	3a, yield (%)[a]
none	72
1,4-dinitrobenzene (0.2 equiv)	20
1,4-dinitrobenzene (1.0 equiv)	0
hydroquinone (0.2 equiv)	9
hydroquinone (1.0 equiv)	8

[a]NMR yield determined by ^{19}F NMR using fluorobenzene as an internal standard.

when an ET scavenger, 1,4-dinitrobenzene,[14] or a radical inhibitor, hydroquinone, was added to the mixture of **2a** and **1b** in the presence of $PdCl_2(PPh_3)_2$ (5 mol %), dppe (10 mol %), and K_2CO_3 in DCE. Thus, these preliminary studies demonstrate that a SET pathway via a difluoroalkyl radical is involved in the reaction. To confirm that a free difluoroalkyl radical was generated during the reaction, a radical clock experiment was performed (Scheme 5a). A ring-expanded product **8** (36%

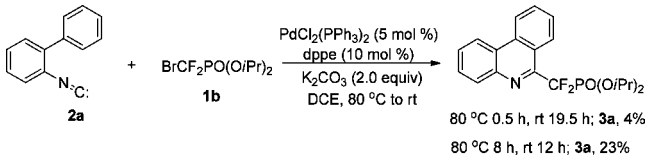
Scheme 5. Radical Clock and ESR Studies



determined by ^{19}F NMR) was provided when compound **7**[15] was treated with **1b** under standard reaction conditions. In addition, the ESR study of reaction of **1b** with spin-trapping agent phenyl *tert*-butyl nitrone (PBN) showed a spin adduct of the trapped $(i\text{-}Pr_2O)P(O)CF_2^{\cdot}$ radical $(i\text{-}Pr_2O)P(O)CF_2CHPhN(O)\text{-}t\text{-}Bu$ **9** was generated (Scheme 5b, for details, see Figure S2 in the Supporting Information). Thus, these results clearly demonstrate that a free difluoroalkyl radical is indeed generated during the reaction.

To gain further insight into the mechanism, several control experiments were performed. Considering that the difluoromethylene phosphonate radical is very reactive and a radical-chain propagation might proceed at room temperature as long as the reaction was initiated, the reaction of **2a** with **1b** was conducted under standard reaction conditions at the beginning (Scheme 6). After being heated for 30 min, the reaction mixture

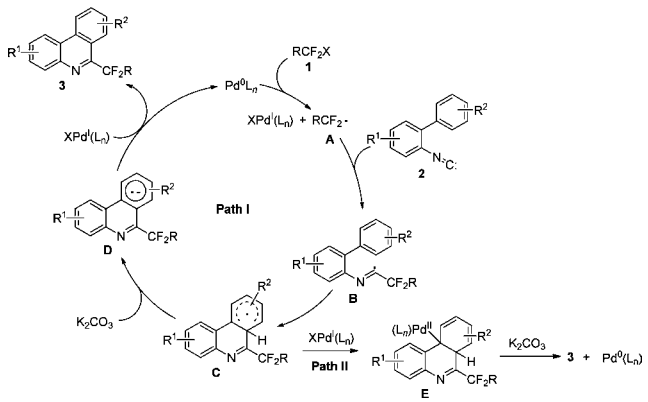
Scheme 6. Mechanistic Studies



was cooled to room temperature and stirred for 19.5 h. However, only 4% yield of **3a** was provided. Even when the heating time was prolonged to 8 h, the yield (23%) of **3a** was still very low (for details, see Table S2 in the Supporting Information). Thus, these results suggest that the generation of difluoromethylene phosphonate radical requires heating, even after reaction has been initiated.

On the basis of these results and previous reports,[7b,f] a plausible reaction mechanism was proposed (Scheme 7). The reaction is initiated by a $[Pd^0(L_n)]$-promoted SET pathway to

Scheme 7. Proposed Reaction Mechanism



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generate the difluoroalkyl radical **A** and $Pd^{I}(L_n)X$. **A** subsequently reacts with isocyanide to produce cyclohexadienyl radical **C**. After the generation of radical anion **D** by the abstraction of a proton from **C** with base,[7f] **D** then reacts with $Pd^{I}(L_n)X$ via a SET pathway to deliver product **3** and regenerate $Pd^{0}L_n$ (path I).[16] However, an alternative pathway through the reaction of **D** with difluoroalkyl bromide **1** via a SET process to deliver product **3** and the difluoroalkyl radical still cannot be ruled out (for details, see the Supporting Information). In addition, the recombination of $Pd^{I}(L_n)X$ with **C** to generate palladium complex **E**, which then undergoes β-hydride elimination to produce product **3** and regenerate $Pd^{0}(L_n)$ simultaneously, is also a possible pathway (path II).[3c,17]

In conclusion, we have disclosed an efficient and general method for the synthesis of difluoroalkylated phenanthridine derivatives through palladium-catalyzed reaction of difluoroalkyl bromides with isocyanides. The reaction can also be extended to perfluoroalkyl iodides. Mechanistic studies reveal that a difluoroalkyl radical via a SET pathway is involved in the catalytic cycle. Further studies to uncover the detailed mechanism as well as other derivative reactions are now in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02739.

Detailed experimental procedures and characterization data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(17) The use of Ni, Fe, Co, and Cu as catalysts to promote the current reaction has also been investigated (for details, see Table S3 in the Supporting Information). However, no product of **3a** was obtained, thus indicating that the Pd may be involved in the whole catalytic cycle and path II cannot be ruled out.

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