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Palladium-Catalyzed C−H Ethoxycarbonyldifluoromethylation of Electron-Rich Heteroarenes

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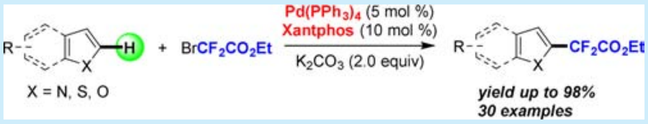
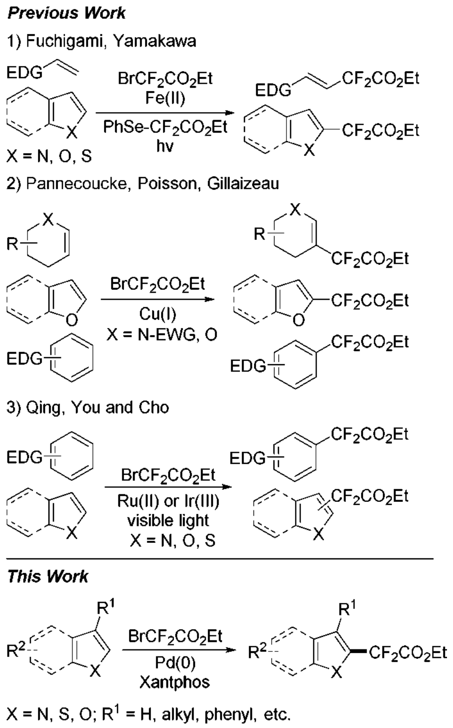
Supporting Information

ABSTRACT: The first Pd-catalyzed C−H ethoxycarbonyldifluoromethylation with $BrCF_2CO_2Et$ has been developed. The use of a bidentate phosphine ligand (Xantphos) is critical for the reaction to occur. A variety of electron-rich heteroarenes, including indoles, furans, thiophenes, and pyrroles, can be ethoxycarbonyldifluoromethylated in moderate to excellent yields. The reactions take place at the C−H bonds adjacent to the heteroatoms with high regioselectivity. This method provides a new protocol for the introduction of difuoroalkyl groups into electron-rich heteroarenes.



As fluoroalkyl groups can endow organic molecules with novel and useful physical and biological properties; they are widely present in functional materials, pharmaceuticals, agrochemicals, and fine chemicals.[1] In particular, the difluoromethylene group, a bio-isostere for an ethereal oxygen atom, is an appealing functionality due to their unique properties.[2] While a number of trifluoromethylation reactions have been developed,[3] efficient and general difluoroalkylation methods are comparatively rare.[4] Traditionally, difluoroalkylated molecules are synthesized via the deoxyfluorination of aldehydes or ketones with DAST, PPHF, SF_4, $ClFO_3$, or XeF_2.[5] However, these methodologies generally suffer from harsh conditions, poor functional group tolerance, and the use of highly toxic regents. Recently, the direct installation of difluoroalkyl groups by using reagents containing difluoromethylene groups has gained great interest.[6] In particular, a variety of transition metal-catalyzed reactions have been developed.[7]

Scheme 1. Direct C−H Ethoxycarbonyldifluoromethylation Reactions



The CF_2CO_2Et moiety is extremely appealing because it can be transformed into a variety of other difluoromethylene-containing functional groups.[8] It is of great importance to develop efficient methods for incorporating this significant structural motif into organic molecules. Notably, several significant methods for the introduction of CF_2CO_2Et employing aryl iodides or arylboronic acids have been developed.[9] While these methods rely on the use of prefunctionalized substrates, a new strategy via direct C−H functionalization has attracted considerable attention recently, and some interesting reactions have been reported (Scheme 1). The current C−H ethoxycarbonyldifluoromethylation reactions can be classified into three categories according to the methods of generation of CF_2CO_2Et species and the mechanism of the difluoromethylation: (1) radical addition followed by the dehydrogenation of electron-rich (hetero)arenes with electrophilic CF_2 radicals, which are generated from halogenated or selenium-based CF_2CO_2Et reagent;[10] (2) copper-catalyzed direct C−H functionalization of electron-rich olefins involving Cu(I)/Cu(III) redox cycle process;[11] and (3) visible light-induced C−H difluoromethylation of electron-rich (hetero)arenes catalyzed by Ru(II) or Ir(III).[12] However, to the best of

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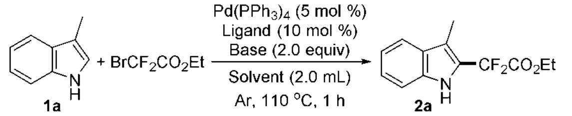
our knowledge, palladium has not been developed as the catalyst in this type of reactions. Herein, we present the first example of Pd-catalyzed introduction of the CF_2CO_2Et moiety onto heteroarenes with ethyl 2-bromo-2,2-difluoroacetate ($BrCF_2CO_2Et$) by means of C−H functionalization.

Our initial investigation focused on the reaction of 3-methylindole **1a** with ($BrCF_2CO_2Et$) to access the difluoroalkylated product **2a** (Table 1). When the reaction mixture in 1,4-dioxane was stirred at 110 °C under an argon atmosphere for 1 h by using $Pd(PPh_3)_4$ as the catalyst and K_2CO_3 as the base, no desired product was observed (entry 1). Fortunately, the addition of ligand $PCy_3·HBF_4$ gave rise to product **2a** in 12% yield (entry 2). Ligand screening revealed that bidentate phosphine ligand Xantphos was the optimal one and the yield was improved to 67%. The other bidentate ligand DPEphos and sterically hindered monodentate phosphine ligand Sphos (entries 3 and 4) were far less efficient. While bases such as KOAc, Cs_2CO_3, and K_2CO_3 gave similar yields, the reaction was low yielding in the presence of strong base KOH (entries 6−8). 1,4-Dioxane proved to be the optimal solvent as the other solvents were less productive (entries 10−13). Gratifyingly, the yield was improved significantly just by decreasing the concentration of the reaction mixture, and it further increased to 91% in 2 h (entries 14 and 15). Control experiments demonstrated that no desired product was generated in the absence of a base or Pd catalyst (entries 9 and 16).

Table 1. Optimization of Reaction Conditions.[a]



entry	base	solvent	ligand	yield (%)[b]
1	K_2CO_3	1,4-dioxane	-	-
2	K_2CO_3	1,4-dioxane	$PCy_3·HBF_4$	12
3	K_2CO_3	1,4-dioxane	Sphos	17
4	K_2CO_3	1,4-dioxane	DPEphos	23
5	K_2CO_3	1,4-dioxane	Xantphos	67
6	KOAc	1,4-dioxane	Xantphos	64
7	Cs_2CO_3	1,4-dioxane	Xantphos	65
8	KOH	1,4-dioxane	Xantphos	11
9	-	1,4-dioxane	Xantphos	-
10	K_2CO_3	THF	Xantphos	56
11	K_2CO_3	CH_3CN	Xantphos	48
12	K_2CO_3	DMSO	Xantphos	25
13	K_2CO_3	DMA	Xantphos	24
14[c]	K_2CO_3	1,4-dioxane	Xantphos	87
15[c,d]	K_2CO_3	1,4-dioxane	Xantphos	91(88)[e]
16[c,d,f]	K_2CO_3	1,4-dioxane	Xantphos	-

[a] Reaction conditions: 3-Methylindole (0.2 mmol, 1.0 equiv), $BrCF_2CO_2Et$ (0.4 mmol, 2.0 equiv), $Pd(PPh_3)_4$ (0.01 mmol, 5 mol %), ligand (0.02 mmol, 10 mol %), base (0.4 mmol, 2.0 equiv), solvent (2.0 mL), Ar, 110 °C, 1 h. [b] Yields were determined by ^1H NMR analysis of crude product using CH_2Br_2 as the internal standard. [c] 1,4-Dioxane 4.0 mL. [d] 2 h. [e] Isolated yield. [f] No $Pd(PPh_3)_4$. Sphos = 2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl; DPEphos = Bis[(2-diphenylphosphino)phenyl] ether; Xantphos = 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene.

With the optimized reaction conditions in hand, we next investigated the substrate scope of this new difluoromethylation protocol. Gratifyingly, various substituted indoles underwent the difluoromethylation reaction efficiently, giving the desired products in moderate to excellent yields (Figure 1). Notably, the reaction took place at C2-position with high selectivity for the substrates without 3-substituents. A range of functional groups, such as ester, nitrile, and amide, were well-tolerated. It is noted that reactive chloro and bromo group survived the reaction conditions. In general, the reactions of the substrates bearing a 3-alkyl group were a little higher yielding.

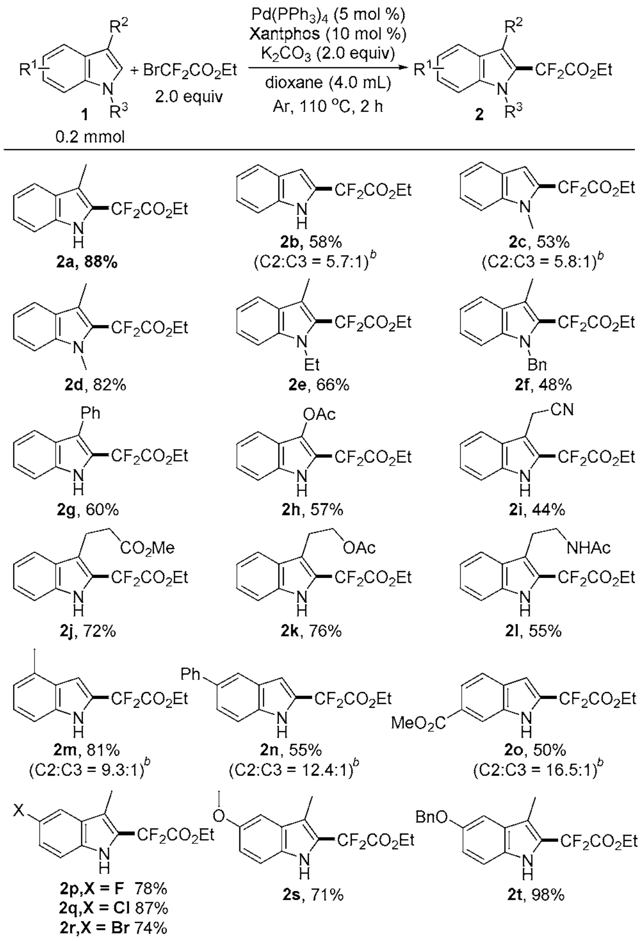


Figure 1. Palladium-catalyzed C−H ethoxycarbonyldifluoromethylation of indoles. (a) Isolated yields of major products. (b) The ratios of isomers were determined by GC−MS.

The reactivity of other electron-rich heteroarenes such as furans, thiophenes, and pyrroles were also examined. Unsurprisingly, the desired difluoromethylation products were obtained under the same reaction conditions with moderate to good yields (Figure 2). The C−H bonds adjacent to the heteroatoms were functionalized with excellent selectivity for all of the heteroarenes examined. Both electron-withdrawing and donating substituents were compatible with the protocol. Interestingly, difunctionalized product (**4d′**) was obtained in 26% yield for 3,4-ethylenedioxythiophene (**3d**) .

In summary, an efficient and convenient method for the synthesis of ethoxycarbonyldifluoromethylated electron-rich heteroarenes with $BrCF_2CO_2Et$ has been developed by means of C−H functionalization. Palladium is used to catalyze this type of reaction for the first time, and ligand Xantphos plays a crucial role in the reaction. Compared to the current C−H ethoxycarbonyldifluoromethylation reactions, this new trans-

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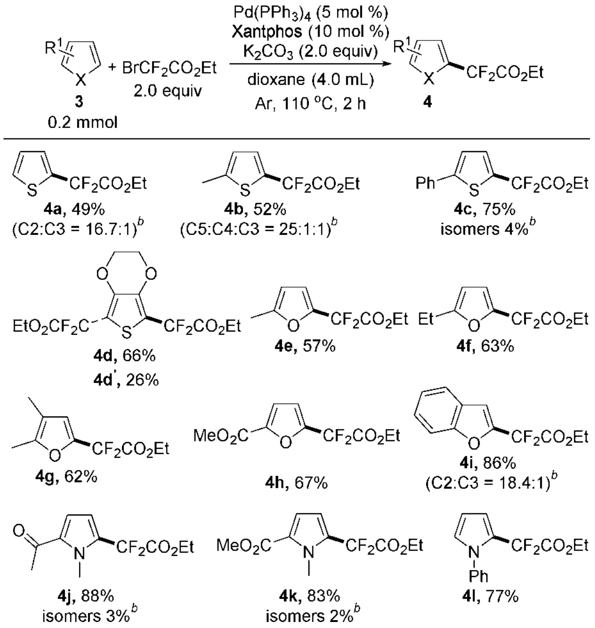

Figure 2. Palladium-catalyzed C−H ethoxycarbonyldifluoromethylation of electron-rich heteroarenes. (a) Isolated yields of major products. (b) The ratios of isomers were determined by GC−MS.

formation has broader substrate scopes or is operationally more convenient. A range of electron-rich heteroarenes can be transformed into the corresponding products bearing CF_2CO_2Et. Since CF_2CO_2Et can be transformed into other difluoromethylene-containing functional groups, this reaction provides a new protocol for the introduction of difluoroalkyl groups into heteroarenes. Further studies aimed at elucidating the reaction mechanism and expanding this protocol to other molecules are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures, spectroscopic data of authentic compounds, and characterization of products. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01024.

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Notes

The authors declare no competing financial interest.

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