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Palladium-Catalyzed Cross-Coupling of Ethyl Bromodifluoroacetate with Aryl Bromides or Triflates and Cross-Coupling of Ethyl Bromofluoroacetate with Aryl Iodides

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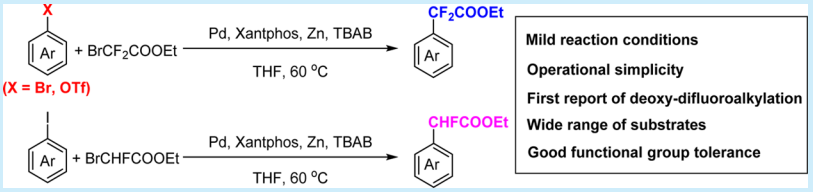
Supporting Information



ABSTRACT: A palladium-catalyzed Negishi cross-coupling reaction of ethyl bromodifluoroacetate with aryl bromides or aryl triflates to construct $C(sp^2)-CF_2$ bonds is described. The reaction was conducted under mild reaction conditions, and no preparation of organozinc reagents is required. This is the first report encompassing the conversion of aryl triflates into products containing $C-CF_2$ bonds. In addition, the construction of $C(sp^2)-CHF$ bonds was achieved under mild conditions via a cross-coupling of aryl iodides with ethyl bromofluoroacetate.

Fluorinated molecules are of increasing significance as materials, agrochemicals, and pharmaceuticals.[1] In the pharmaceutical sciences, fluorinated molecules are often enlisted to modulate the lipophilicity or the metabolic stability of biologically active scaffolds.[2] They also change the noncovalent interactions of aryl groups, providing a method to alter binding affinity and binding selectivity.[3] Difluoromethylene (CF_2) groups are considered to be especially desirable structures because they are bioisosteres of carbonyl groups or ethers.[4]

Aryldifluorocarboxylic acid derivatives are particularly valuable in pharmaceutical sciences because they contain two fluorine atoms at a metabolically labile benzylic position.[4c,5] Moreover, aryldifluorocarboxylic acid derivatives are valuable synthetic precursors because their carbonyl unit can be transformed into a wide range of functional groups. Although aryl difluoromethyl ketones[6] and aryl difluoroacetamides[7] have been prepared from aryl halides by catalytic methods, the synthesis of aryldifluoroacetates from aryl halides is limited.

The coupling of difluoroacetates with heteroarenes or alkenes has been achieved only in the presence of stoichiometric amounts of copper powder[8] or by radical additions.[9] Classic preparations of aryldifluoroacetates rely on deoxyfluorination of hydroxyl or carbonyl groups with deoxo-fluor, DAST, or their derivatives,[10] or difluorination of enolates.[11] Other methods for installation of ethyl aryldifluoroacetates required arylboronic acids,[12] aryl Grignard reagents,[13] arylzinc[13] reagents, or α-silyldifluoroacetates[14] as coupling partners, but these reagents are not as widely available as are aryl halides and bromodifluoroacetate.

The cross-couplings of aryl iodides with halodifluoroacetates were first described by Kobayashi et al. and later by Kumadaki et al.[15] under reaction conditions comprising superstoichiometric copper in DMSO solvent. This method has been used to prepare fluorinated arenes, and the yields are generally modest. Unfortunately, aryl bromides do not react with halodifluoroacetates under these conditions.[15d,e] Thus, we sought a method to couple the low-cost ethyl bromodifluoroacetate with common reagents, such as aryl bromides and aryl triflates. In addition, only one example of the cross-coupling of ethyl bromofluoroacetate with an aryl iodide was recently reported by analogous copper-mediated methods in a 23% yield.[16] Herein, we report a palladium catalyzed Negishi cross-coupling of ethyl bromodifluoroacetate with aryl bromides and, for the first time, aryl triflates. We also report the cross-coupling of ethyl bromofluoroacetate with aryl iodides under similarly mild conditions to form the α-aryl monofluoro esters in good yield. These results show that the coupling can be conducted with catalytic amounts of metal complexes.

Christman and co-workers showed that the organozinc reagent $BrZnCF_2COOEt$ can be prepared *in situ* via oxidative addition of activated Zn(0) to $BrCF_2COOEt$.[17] Aryl bromides are known to undergo oxidative addition to Pd(0).[18] We envisioned that, provided the transmetalation of $BrZnCF_2COOEt$ to palladium(II) complex [ArPdLnBr] occurs, the desired ethyl aryldifluor-

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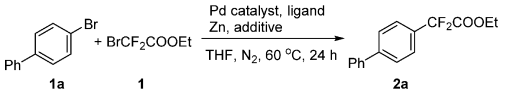
oacetates could be formed via the reductive elimination of the palladium(II) complex [ArPdLn(CF_2COOEt)]. Although the Reformatsky−Negishi type coupling of aryl halides with $BrZnCH_2COOR$ is well established by Hartwig in 2003[17c] and recently reported by Zhang,[17d] the related coupling of $BrZnCF_2COOEt$ was reported by Zhang to proceed to low conversion.[17d] In light of these studies, we initiated our investigation to identify a catalyst that would lead to the construction of $C(sp^2)-CF_2$ bonds via Negishi cross-coupling of the zinc enolates of difluoro esters.

The cross-coupling of 4-bromo-1,1′-biphenyl **1a** and $BrCF_2COOEt$ **1** in the presence of zinc powder and the combination of a Pd precursor and ligand was chosen as a model system to determine conditions that would lead to the coupled product. Initial experiments with a series of ligands occurred in modest yields. For example, those conducted with Q-phos as a ligand gave the desired product **2a** in a 17% yield (Table 1, entry 1), those with Amphos did not form **2a** (Table 1, entry 2),

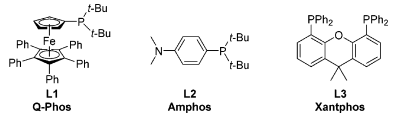
Table 1. Optimization of Reaction Conditions[a]



1a 1 2a

entry	catalyst	additive	ligand	solvent	yield (%)
1	$Pd(COD)Cl_2$	–	**L1**	THF	17
2	$Pd(COD)Cl_2$	–	**L2**	THF	0
3	$Pd(COD)Cl_2$	–	**L3**	THF	23
4	**Pd 1**	–	**L3**	dioxane	14
5	**Pd 1**	–	**L3**	DMF	0
6	**Pd 1**	–	**L3**	THF	68
7	**Pd 1**	*n*-Bu_4NI	**L3**	THF	65
8	**Pd 1**	*n*-Bu_4NCl	**L3**	THF	0
9	**Pd 1**	TBAB	**L3**	THF	94
10[b]	**Pd 1**	TBAB	**L3**	THF	77
11[c]	**Pd 1**	TBAB	**L3**	THF	10
12[d]	**Pd 1**	TBAB	**L3**	THF	67
13	$Pd(OAc)_2$	TBAB	**L3**	THF	63
14	$Pd(dba)_2$	TBAB	**L3**	THF	83
15	$Pd(COD)Cl_2$	TBAB	**L3**	THF	80
16	$Pd(CH_3CN)_2Cl_2$	TBAB	**L3**	THF	68

[a]Reactions performed on a 0.50 mmol scale. Yield is that of the isolated product. Pd **1**: [Pd(π-cinnamyl)Cl]$_2$. Reaction conditions: **1a** (1.0 equiv), $BrCF_2COOEt$ (3.0 equiv), palladium catalyst (10 mol %), ligand (30 mol % for **L1** or **L2**, or 15 mol % for **L3**), Zn (3.0 equiv), and additive (1.5 equiv) in solvent (5.0 mL) under N_2 at 60 °C for 24 h. [b]TBAB (2.0 equiv). [c]Zn (2.0 equiv). [d][Pd(π-cinnamyl)Cl]$_2$ (0.025 equiv, Pd catalyst 5 mol %), and Xantphos (7.5 mol %).

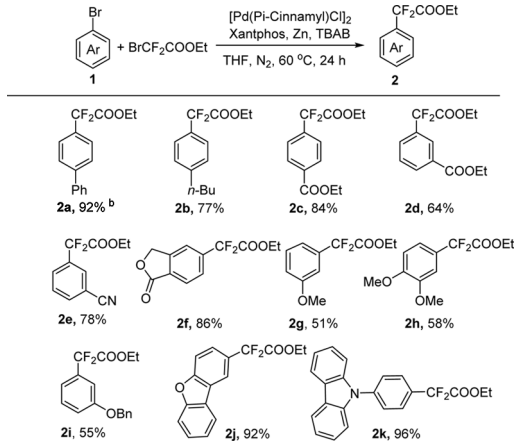


and those conducted with Xantphos gave **2a** in an only slightly higher 23% yield (Table 1, entry 3). The identity of the solvent also strongly influenced the yield. No desired product was obtained from reactions catalyzed by [Pd(π-cinnamyl)Cl]$_2$ and Xantphos, even at 80 °C, in DMF (Table 1, entry 5), acetonitrile, toluene, or dichloroethane, and the yield in dioxane was only 14% (Table 1, entry 4). However, the yield was much higher (68%) for analogous reactions in THF (Table 1, entry 6), which could result from the ability of THF to stabilize the organozinc reagent by forming a "Reformasky reagent" with the dimeric structure $(BrZnCF_2COOEt-THF)_2$.[19]

To improve the yields further, we focused on the transmetalation step, which we expected to be the rate-limiting step.[20] Alkylzinc species were shown recently to form a higher-order zincate species prior to transmetalation,[21] but the mechanism of transmetalation of fluoroalkylzinc species has not yet been reported. Organ et al. previously proposed that halide ions can assist transmetalation by forming "fluoroalkylzincate" species.[21b] Although addition of *n*-Bu_4NI had little influence on the reaction (Table 1, entry 7), and addition of *n*-Bu_4NCl completely suppressed the reaction (Table 1, entry 8), the addition of *n*-Bu_4NBr (TBAB) increased the yield of cross-coupling to 94% (Table 1, entry 9). The yield of **2a** was a lower 77% when the amount of TBAB was 2.0 equiv (Table 1, entry 10), instead of 1.5 equiv. Reducing the amount of activated zinc powder to 2.0 equiv resulted in a dramatic decrease in the yield of **2a** to 10% (Table 1, entry 11). A series of Pd sources were evaluated under conditions with THF as solvent and TBAB as additive. [Pd(π-cinnamyl)Cl]$_2$was the most active catalyst precursor of the ones tested (Table 1, entries 9, 13−16). In the presence of 5 mol % [Pd(π-cinnamyl)Cl]$_2$ and 15 mol % Xantphos the desired product was obtained in 94% yield. At a lower [Pd(π-cinnamyl)Cl]$_2$ loading of 2.5 mol %, the yield of **2a** was only 67% (Table 1, entry 12).

The conversion of a variety of aryl bromides to the corresponding $ArCF_2COOEt$ was investigated under the optimized reaction conditions (Scheme 1). Aryl bromides

Scheme 1. Cross-Coupling of Ethyl Bromodifluoroacetate with Aryl Bromides[a]



[a]Yield is that of the isolated product. Conditions: aryl bromides **1** (0.50 mmol), $BrCF_2COOEt$ (1.5 mmol), [Pd(π-Cinnamyl)Cl]$_2$ (5.0 mol %), Xantphos (15 mol %), Zn (1.5 mmol), and TBAB (0.75 mmol) in THF (5.0 mL) under N_2 at 60 °C for 24 h. [b]Conducted at 1.2 mmol scale.

containing either electron-donating or -withdrawing groups coupled with $BrCF_2COOEt$ in moderate to excellent yields within 24 h. Ether (**2g**, **2h**, **2i**), ester (**2c**, **2d**, **2f**), and nitrile (**2e**) functional groups were well tolerated under the reaction conditions. Aldehydes and ketones were found to be incompatible with the reaction, probably due to nucleophilic attack of the organozinc reagents on the carbonyl groups. Reactions with substrates containing dibenzofuryl (**2j**) or carbazolyl (**2k**) moieties proceeded smoothly under the standard reaction conditions, affording the desired products in high yields. In addition, aryl iodides coupled with $BrCF_2CO_2Et$ under the same

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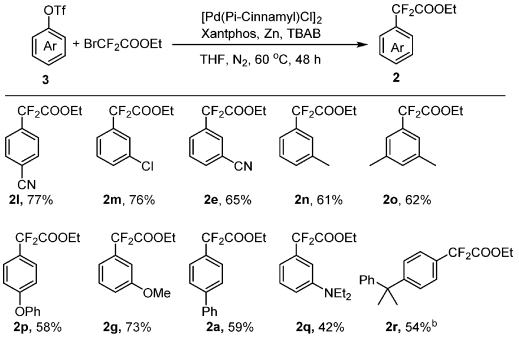
conditions within 12 h, affording the desired products in good to excellent yields (see details in Supporting Information Part V). Unfortunately, the reaction with aryl bromides bearing an ortho substituted group resulted in poor yields or no reaction. Aryl chlorides also did not react with $BrCF_2COOEt$ under these conditions.

Aryl triflates can be readily prepared from phenols and are used extensively as synthetic precursors in cross-coupling reactions. However, the transformation of C−O bonds to C−CF_2 bonds has not been reported. We found that aryl triflates **3** couple with $BrCF_2COOEt$ under our reaction conditions to afford the corresponding products **2** (Scheme 2). The yields were slightly lower and the reaction time longer (48 h) than those of reactions of aryl bromides, but synthetically useful amounts of product were formed. The reaction conditions were found to tolerate ether (**2p**, **2g**), tertiary amino (**2q**), chloro (**2m**), and cyano (**2l**, **2e**) groups.

Scheme 2. Cross-Coupling of Ethyl Bromodifluoroacetate with Aryl Triflates[a]

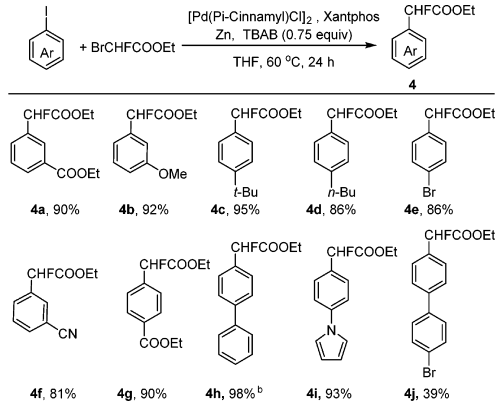


[a]Yield is that of the isolated product. Conditions: aryl triflates **3** (0.50 mmol), $BrCF_2COOEt$ (1.5 mmol), Zn (1.5 mmol), [Pd(π-Cinnamyl)-Cl]$_2$ (5 mol %), Xantphos(15 mol %), and TBAB (0.75 mmol) in THF (5.0 mL) under N_2 at 60 °C for 48 h. [b]Conducted at 2.0 mmol scale.

Indeed, the cross-coupling occurred smoothly when 0.75 equiv of TBAB was used, resulting in the desired products **4** in good to excellent yield in most cases. The scope of the coupling of $BrCHFCO_2Et$ is summarized in Scheme 3. The reaction conditions were found to tolerate ester (**4a**, **4g**), ether (**4b**), bromo (**4e**, **4j**), and nitrile (**4f**) groups. Neither aryl bromides nor aryl chlorides reacted with $BrCHFCO_2Et$ under these conditions.

Ethyl aryldifluoroacetates can serve as precursors to prepare a wide range of compounds containing a CF_2 unit. For example, ethyl aryldifluoroacetates can be hydrolyzed to aryl difluoroacetic acids[14] (Figure 1, **a**), decarboxylated to difluoroarenes[14] (Figure 1, **b**), transformed to trifluoromethylarenes by Selectfluor in the presence of silver salts (Figure 1, **c**),[23] or reduced to the corresponding alcohol (Figure 1, **d**).[24] Grignard reactions with ethyl aryldifluoroacetates afforded the corresponding secondary alcohols[24] (Figure 1, **e**), and the aryldifluoroamides underwent nucleophilic acyl substitution with amines to form aryldifluoroamides[24] (Figure 1, **f**).

Scheme 3. Cross-Coupling of Ethyl Bromofluoroacetate with Aryl Iodides[a]



[a]Yield is that of the isolated product. Conditions: aryl iodides (0.50 mmol), BrCFHCOOEt (1.5 mmol), [Pd(π-Cinnamyl)Cl]$_2$ (5 mol %), Xantphos (15 mol %), Zn (1.5 mmol), and TBAB (0.38 mmol) in THF (5.0 mL) under N_2 at 60 °C for 24 h. [b]Conducted at 1.2 mmol scale.

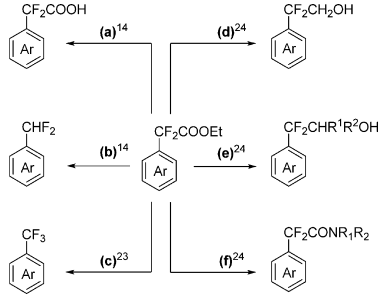


Figure 1. Transformation of ethyl aryldifluoroacetates.

In summary, we have developed a versatile, palladium-catalyzed system for constructing aryl C(sp^2)−CF_2 bonds from aryl iodides, bromides, or triflates and for constructing C(sp^2)−CHF bonds from aryl iodides. A broad range of aryl bromides, iodides, and triflates were coupled with ethyl bromodifluoroacetate in moderate to excellent yields. Under similarly mild reaction conditions, aryl iodides were coupled with ethyl bromofluoroacetate to afford α-aryl-α-fluoroacetates efficiently.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00938.

Detailed experimental procedure, characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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