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Copper Catalyzed Cross-Coupling of Iodobenzoates with Bromozinc-difluorophosphonate

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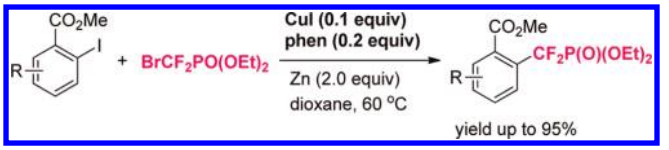
ABSTRACT



A copper-catalyzed cross-coupling of iodobenzoates with bromozinc-difluorophosphonate, generated from diethyl bromodifluoromethylphosphonate and zinc in dioxane, is reported. The notable features of this reaction are its high reaction efficiency, excellent functional group compatibility, and operational simplicity. This protocol provides a useful and facile access to aryldifluorophosphonates of interest in life science.

Owing to the unique properties of the fluorinated functional groups that often lead to pronounced activity enhancement of pharmaceuticals and agrochemicals,[1] fluorined compounds have gained extensive attention. Among them, aryldifluorophosphonates constitute a distinct class of fluorinated compounds. Because the difluoromethylene group (CF_2) can act as an isopolar-isosteric substitute for oxygen, and replacement of the phosphoryl ester oxygen with CF_2 leads to a nonhydrolyzable phosphate mimetic,[2] such difluorinated structures exhibit significant bioactivities as protein tyrosine phosphatase (PTP) inhibitors and have been used as valuable tools for drug discovery and development.[3] However, compared to the fluorination[4] and trifluoromethylation[5] of organic substrates, strategies for incorporation of the CF_2 group into organic molecules has been less explored.[6] Generally, aryldifluorophosphonates can be prepared by difluorination of unstable benzilic α-oxophosphonates with DAST,[7]electrophilic fluorination of phosphonates,[3a,8] and copper-mediated cross-coupling between aryl halides and metalated difluoromethylphosphonates.[9] Despite the utility of these methods, the requirement of multiple steps, functional group incompatibility, and use of expensive fluorinated

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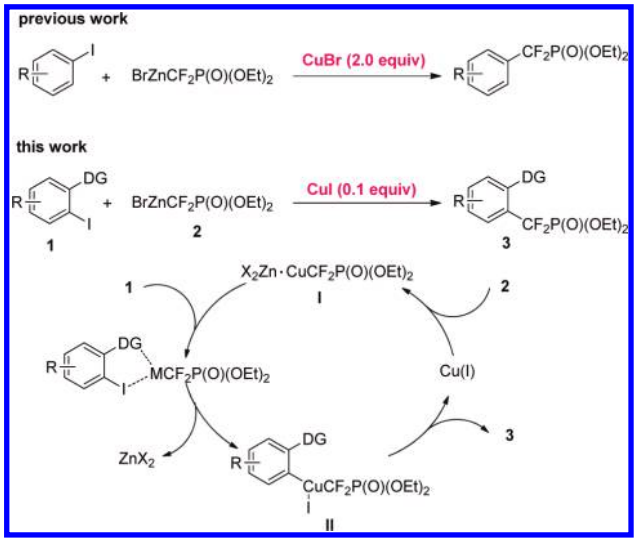
reagents or a large excess of copper restrict their widespread synthetic applications. From the point of view of new practical and environmentally benign processes, a transition-metal-catalyzed reaction would be an attractive alternative.

Several years ago, Shibuya and co-workers developed a copper-mediated cross-coupling of aryl iodides with bromozinc-difluorophosphonate for the synthesis of aryldifluorophosphonates.[9b] This reaction is significant and useful but requires a stoichiometric amount of CuBr. An attempt to reduce the loading of CuBr proved that copper could not catalyze the reaction, and a single electron transfer (SET) mechanism via a difluorophosphonate radical was proposed for this copper mediated cross-coupling.[9b] In our continuing efforts to develop transition-metal-catalyzed reactions for introduction of fluorinated functional groups into organic molecules,[10] we hypothesized that if installing a directing group ortho to the iodide to chelate and direct delivery of organocopper complex **I**,[11] the oxidative addition of copper to the aryl iodides would be facilitated, and thus the copper-catalyzed cross-coupling of aryl iodides with metalated difluoromethylphosphonate would be possible (Scheme 1). Herein, we present the first example of copper-catalyzed cross-coupling of iodobenzoates with bromozinc-difluorophosphonate. This reaction provides a convenient protocol for the preparation of aryldifluorophosphonates with high efficiency and excellent functional group compatibility.

Scheme 1. Cross-Coupling of Aryl Iodides with Bromozinc-difluorophosphonate



Given that a carboxylate ester is important and synthetically useful as well as can function as a directing group, we began this study by choosing methyl 2-iodobenzoate **1a** as a model substrate to test our hypothesis. Initially, according to Shibuya's conditions,[9b] a room temperature reaction of **1a** with bromozinc-difluorophosphonate **2**, generated from diethyl bromodifluoromethylphosphonate and zinc in DMF, in the presence of catalytic amount of CuBr (10 mol %) was investigated (Table 1, entry 1). However, only a trace amount of desired product **3a** was observed. Considering that ethereal solvents benefit the formation of **2**,[12] and diamine ligands can stabilize the soluble copper complexes by chelation and increase electron density at the copper center, we assumed that the use of dioxane as a solvent and 1,10-phenanthroline (phen) as a ligand may prevent decomposition of **I** to a difluorophosphonate radical[13] and improve the reaction efficiency. As expected, a 72% yield (determined by ^{19}F NMR) of **3** was afforded, when the reaction was carried out in dioxane with CuBr (10 mol %) and phen (20 mol %) at 50 °C (Table 1, entry 2). With a further increase in reaction temperature to 60 °C, a higher yield (94%, determined by ^{19}F NMR) was provided (Table 1, entry 3). The absence of copper failed to give any desired product (Table 1, entry 4), thus implying that a copper catalyst was involved in the catalytic cycle. Encouraged by these results, a variety of copper catalysts and solvents were examined. Among the copper catalysts tested, CuI was found to be the optimum catalyst, providing **3a** in 95% isolated yield (Table 1, entry 9), although other copper catalysts, such as $CuBr_2$, CuCl, $CuCl_2$, and $Cu(OAc)_2$, underwent the reaction smoothly (Table 1, entries 5−8). These findings clearly demonstrated that the present reaction is not sensitive to the nature of copper catalysts. However, the choice of solvent is crucial for the reaction efficiency. DMF and DMA led to a trace amount of **3a**, even in the presence of phen (Table 1, entries 10−11), which is in sharp contrast to previous results.[9b] Other solvents, such as DMPU, DMSO, and diglyme, were less effective than dioxane (Table 1, entries 12−14). The absence of phen led to a diminished yield (Table 1, entry 16), indicating that a diamine ligand also plays an important role in the copper catalytic cycle.

On the basis of the above observations, methyl 4-iodobenzoate **5** was also tested (Scheme 2). However, no more than a 20% yield of desired product **6** was observed, when

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(11) The organocopper complex **I** has been characterized; see: (a) Sprague, L. G.; Burton, D. J.; Guneratne, R. D.; Bennett, W. E. *J. Fluorine Chem.* **1990**, *49*, 75. (b) Yokomatsu, T.; Suemune, K.; Murano, T.; Shibuya, S. *J. Org. Chem.* **1996**, *61*, 7207.

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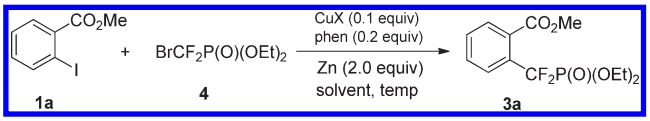
(13) The organocopper complex **I** decomposes slowly in DMF to give many products via a difluorophosphonate radical and carbene process at room temperature. See ref 11b.

(14) General procedure for copper-catalyzed cross-coupling of iodobenzoates with bromozinc-difluorophosphonate: To a stirred suspension of Zn dust (1.0 mmol) in dioxane (2 mL) was added bromodifluoromethanephosphonate (1.0 mmol) under N_2. After stirring for 3 h at 60 °C, the resulting mixture was cooled to room temperature, and CuI (0.1 equiv) and phen (0.2 equiv) were added. The reaction mixture was then stirred at the same temperature for 30 min, and iodobenzoate **1** (0.5 mmol) was added. The reaction was warmed to 60 °C and stirred for 24−48 h.

Table 1. Optimization of Copper-Catalyzed Cross-Coupling of Methyl 2-Iodobenzoate **1a** with Bromozinc-difluorophosphonate **2**[a]



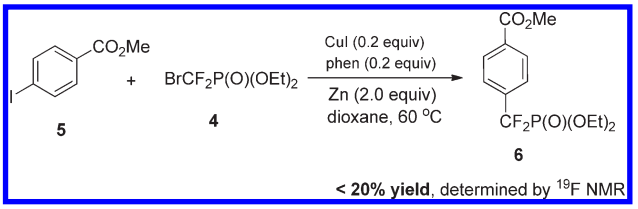
1a 4 3a

entry	CuX	solvent	temp (°C)	yield (%)[b]
1[c]	CuBr	DMF	25	trace
2	CuBr	dioxane	50	72
3	CuBr	dioxane	60	94
4	none	dioxane	60	NR
5	$CuBr_2$	dioxane	60	94
6	CuCl	dioxane	60	88
7	$CuCl_2$	dioxane	60	89
8	$Cu(OAc)_2$	dioxane	60	80
9	CuI	dioxane	60	98 (95)
10	CuI	DMF	60	trace
11	CuI	DMA	60	trace
12	CuI	DMPU	60	39
13	CuI	DMSO	60	20
14	CuI	diglyme	60	48
15[d]	CuI	dioxane	60	90
16[e]	CuI	dioxane	60	79
17[e]	CuI	dioxane	60	85

[a] Reaction conditions (unless otherwise specified): **1a** (0.5 mmol), **4** (2.0 equiv), Zn (2.0 equiv), solvent (2 mL), 24 h. [b] NMR yield determined by ^{19}F NMR using fluorobenzene as an internal standard (isolated yield in parentheses). [c] Reaction run in the absence of phen. [d] Using 0.1 equiv of phen. [e] Using 1.5 equiv of **4** and 1.5 equiv of Zn.

0.2 equiv of CuI and 0.2 equiv of phen were used. Further screening of different 1,10-phenanthroline derivatives and bipyridyl ligands led to similar results (see Table S1 in the Supporting Information), thus suggesting that the ortho-effect of the carboxylate ester in the substrates is essential to the reaction efficiency.

Scheme 2. Cross-Coupling of Methyl 4-Iodobenzoate **5** with Bromozinc-difluorophosphonate **2**

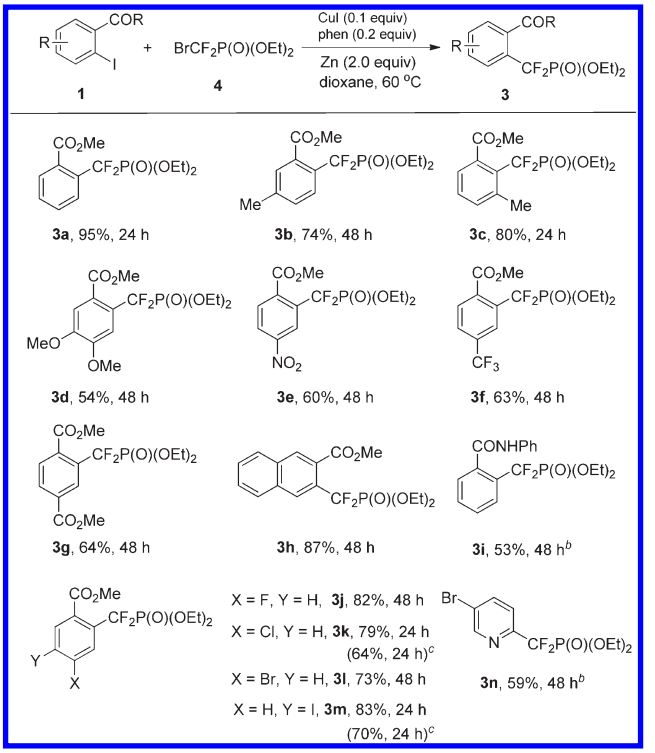


5 4 6

Under the optimum reaction conditions (Table 1, entry 9),[14] the substrate scope of the cross-coupling of iodobenzoates **1** with bromozinc-difluorophosphonate **2**, generated from diethyl bromodifluoromethylphosphonate and zinc in dioxane, was examined, and the representative results are illustrated in Scheme 3.

The present method allowed the preparation of aryldifluorophosphonates containing a range of functional

Scheme 3. Copper-Catalyzed Cross-Coupling of Iodobenzoates **1** with Bromozinc-difluorophosphonate[a]



1 4 3

3a, 95%, 24 h; **3b**, 74%, 48 h; **3c**, 80%, 24 h; **3d**, 54%, 48 h; **3e**, 60%, 48 h; **3f**, 63%, 48 h; **3g**, 64%, 48 h; **3h**, 87%, 48 h; **3i**, 53%, 48 h[b]; **3n**, 59%, 48 h[b]

[a] Reaction conditions (unless otherwise specified): **1** (0.5 mmol), **4** (2.0 equiv), Zn (2.0 equiv), CuI (0.1 equiv), phen (0.2 equiv), in dioxane (2 mL) at 60 °C. [b] Using 0.4 equiv of CuI and 0.4 equiv of phen. [c] Reaction run in 2-g scale.

groups, including ester, nitro, amide, bromide, and iodide, thus providing opportunities for further transformations. 2-g-scale reactions of **3k** and **3m** were also performed in good yields (**3k**, 64% yield; **3m**, 70% yield), indicating the good reliability of the process. Importantly, the heterocycle, pyridine, was also a suitable substrate, although 0.4 equiv of CuI was required (Scheme 3, **3n**), which is in sharp contrast to previous results that nitrogen-containing heterocycles could not furnish the corresponding products.[15]

To further demonstrate the utility of this protocol, transformations of **3k** and **3m** were conducted. As shown in Scheme 4, the phenylation of **3k** and alkynylation of **3m** provide rapid access to diversified aryldifluorophosphonates. Furthermore, the triple C−C bond in compound **3m** offers a unique and highly valuable opportunity for further synthetic transformations of interest in drug discovery and development.

To gain some mechanistic insights into the present reaction, the following experiments were performed (Table 2). The reaction carried out in the absence of ambient light had little influence on the reaction efficiency (Table 2, entry 2). The addition of nitrobenzene (1.0 equiv)

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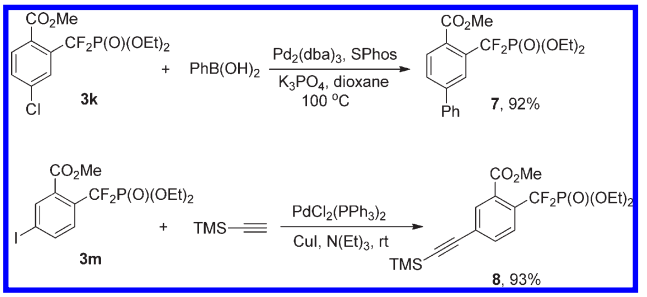
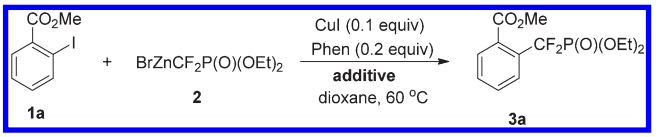
Scheme 4. Transformations of **3k** and **3m**



previously demonstrated to be an inhibitor of SET steps[16] had a negligible impact on the yield of this reaction (Table 2, entry 3). While the addition of a radical scavenger TEMPO (1.0 equiv) or a radical initiator AIBN (0.2 equiv) led to diminished yields (Table 2, entries 4–5), this is probably because organocopper complex **I** is prone to decompose to difluorophosphonate radical.[13] The addition of a radical initiatior or a scavenger could accelerate the decomposition of the key intermediate **I** and affect the copper catalytic cycle illustrated in Scheme 1; as a result, lower yields of **3a** were observed. Thus, on the basis of these preliminary results, a pure SET mechanism via a difluorophosphonate radical is not involved in the present copper catalytic cycle, and the proposed mechanism shown in Scheme 1 is possible. Further studies of the detailed mechanism are in progress.

In conclusion, the first example of copper-catalyzed cross-coupling of iodobenzoates with bromozinc-difluorophosphonates has been demonstrated. The directing group benzoate ester and solvent effect play important roles in the reaction efficiency. Application of the method leads to diversified aryldifluorophosphonates. Because of the high reaction efficiency, excellent functional group compatibility, and the ease of conducting such reactions, this protocol provides a useful and facile access to aryldifluorophosphonates of interest in life science.

Table 2. Effects of Additives on Copper-Catalyzed Cross-Coupling of Iodobenzoate with Bromozinc-difluorophosphonate



entry	additive (equiv)	yield (%)[a]
1	ambient light	98
2	dark	94
3	$PhNO_2$ (1.0)	95
4	TEMPO (1.0)	55
5	AIBN (0.2)	55

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

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Supporting Information Available. Detailed experimental procedures, and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org

The authors declare no competing financial interest.