



# Cobalt-catalyzed cross-coupling reaction of arylzinc reagents with ethyl bromodifluoroacetate



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## ABSTRACT

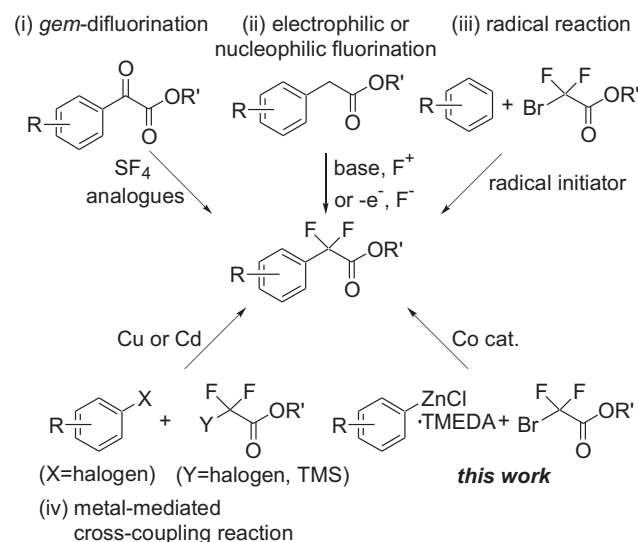
Transition metal-catalyzed cross-coupling reactions of arylmetal reagents with ethyl bromodifluoroacetate have been explored. After intensive investigations, we have successfully found that a cobalt-catalyzed cross-coupling reaction (catalytic alkoxycarbonyldifluoromethylation) of arylzinc reagents with ethyl bromodifluoroacetate smoothly proceeded to afford the corresponding ethyl aryldifluoroacetates in moderate to good yields.

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## 1. Introduction

Organofluorine compounds have attracted considerable attention from the fields of medicinal chemistry, agricultural chemistry, and material science because they show unique chemical, physical, and biological properties.<sup>1</sup> Therefore, the selective introduction of a fluorine-containing functional group at the desired position of organic substrates to synthesize various kinds of organofluorine compounds is one of the most important topics in current organic chemistry. Among them, aryldifluoroacetic acid derivatives have been known as important biological active and functionalized compounds<sup>2</sup> and, to date, several synthetic methods to prepare aryldifluoroacetic acid derivatives have been disclosed as follows (Scheme 1): (i) *gem*-difluorination of arylglyoxylic acid derivatives with sulfur tetrafluoride (SF<sub>4</sub>) analogues, such as diethylaminosulfur trifluoride (DAST),<sup>3a,b</sup> bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor),<sup>3c</sup> diethylaminodifluorosulfonium tetrafluoroborate (XtalFluor-E),<sup>3d</sup> and 4-*tert*-butyl-2,6-dimethylphenylsulfur trifluoride (Fluolead),<sup>3e</sup> (ii)  $\alpha$ -fluorination of arylacetates with electrophilic or nucleophilic fluorinating reagents,<sup>4</sup> (iii) radical-mediated alkoxycarbonyldifluoromethylation using difluoroacetates,<sup>5</sup> and (iv) metal-mediated cross-coupling reaction using difluoroacetates or  $\alpha$ -silyldifluoroacetates.<sup>6,7</sup> While transition-metal catalyzed cross-

coupling reactions play an important role in the formation of carbon–carbon bonds in organic synthesis, most of the metal-mediated cross-coupling reactions of difluoroacetates with arylmetal species or halogenated aromatics proceeded in the presence of stoichiometric amounts of Cu or Cd metals.<sup>6</sup> Recently,



Scheme 1. Methods for the preparation of aryldifluoroacetic acid derivatives.

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Amii et al. disclosed copper-catalyzed cross-coupling reactions of aryl iodides with  $\alpha$ -silyldifluoroacetates and they demonstrated the conversion of the resulting arylidifluoroacetates to the corresponding  $\alpha,\alpha$ -difluorotoluene derivatives.<sup>7</sup> While several methods are available to synthesize arylidifluoroacetic acid derivatives, it is still required to develop a facile method to access to those compounds. During the course of our development of the transition-metal catalyzed introduction of a fluorine-containing functional group to aromatic rings,<sup>8</sup> we initiated a project to develop a novel catalytic alkoxy-carbonyldifluoromethylation reaction.<sup>9</sup> Herein, we would like to report a cobalt-catalyzed cross-coupling reaction of arylzinc reagents **3** with ethyl bromodifluoroacetate (**4**).

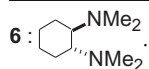
## 2. Results and discussion

At the beginning, we investigated the cross-coupling reactions between various phenylmetal species **1a–3a** and ethyl bromodifluoroacetate (**4**) as shown in Table 1. The initial attempts of alkoxy-carbonyldifluoromethylation reactions catalyzed by Pd,<sup>10</sup> Fe,<sup>11</sup> or Ni<sup>12</sup> complexes gave disappointing results, leading to the formation of trace amounts (<5%) of the expected coupling product (entries 1–3) even though the corresponding cross-coupling reactions with ethyl bromoacetate under the same reaction conditions were reported to proceed in good yield.<sup>10–12</sup> Fortunately, taking advantage of Yorimitsu and Oshima's procedure,<sup>13</sup> the cobalt-catalyzed cross-coupling reaction<sup>14,15</sup> of phenylmagnesium bromide (**2a**) with **4** in the presence of cobalt (II) chloride and *trans*-1,2-bis(dimethylamino)cyclohexane (**6**) gave promising results (entry 4), furnishing the desired ethyl 2,2-difluoro-2-phenylacetate (**5a**) in 22% yield (based on <sup>19</sup>F NMR).

**Table 1**  
Metal-catalyzed cross-coupling reaction of ethyl bromodifluoroacetate with phenylmetal species

1a: M=B(OH)<sub>2</sub>  
2a: M=MgBr  
3a: M=ZnCl

Entry	Ph–M	Catalyst, ligand	Conditions	Yield <sup>a</sup>
1	<b>1a</b> (1.2 equiv)	Pd(OAc) <sub>2</sub> (0.03 equiv) P( <i>o</i> -Tol) <sub>3</sub> (0.09 equiv) K <sub>2</sub> CO <sub>3</sub> (5.0 equiv)	rt, 20 h	<5%
2	<b>2a</b> (1.2 equiv)	FeCl <sub>3</sub> (0.05 equiv) TMEDA (1.2 equiv)	0 °C, 1 h	<5%
3	<b>3a</b> (2.0 equiv)	Ni(acac) <sub>2</sub> (0.01 equiv) PPh <sub>3</sub> (0.01 equiv)	0 °C, dropwise for 30 min; 10 min	<5%
4	<b>2a</b> (1.2 equiv)	CoCl <sub>2</sub> (0.05 equiv) <b>6</b> (0.06 equiv)	0 °C, 5 min; rt, 20 min	22%



<sup>a</sup> <sup>19</sup>F NMR yield (benzotrifluoride was used as an internal standard).

Thus, we decided to focus on the cobalt-catalyzed cross-coupling reaction and a further investigation was carried out as depicted in Table 2. While increasing the amount of the Grignard reagent to 2.4 equiv raised the yield slightly (entry 1), the yield was dramatically improved by slow addition of the Grignard reagent to a mixture of ethyl bromodifluoroacetate (**4**) and the cobalt catalyst in THF, leading to produce a 70% yield of **5a** (entry 2). Next, we employed other Grignard reagents under the slow addition condition. The reaction using 4-fluorophenylmagnesium bromide (**2b**)

**Table 2**  
Co-catalyzed cross-coupling reaction of ethyl bromodifluoroacetate with Grignard reagents

2a: X=H  
2b: X=F  
2c: X=OMe

5a: X=H  
5b: X=F  
5c: X=OMe

Entry	Ar–MgBr	Conditions	Yield <sup>a</sup>
1	<b>2a</b> (2.4 equiv)	0 °C, 5 min; rt, 20 min	34%
2	<b>2a</b> (1.3 equiv)	0 °C, dropwise for 30 min; 0 °C, 10 min	70%
3	<b>2b</b> (1.3 equiv)	rt, dropwise for 2 h; rt, 10 min	71%
4	<b>2c</b> (1.3 equiv)	rt, dropwise for 2 h; rt, 10 min	42%

<sup>a</sup> <sup>19</sup>F NMR yield (benzotrifluoride was used as an internal standard).

possessing an electron-withdrawing group produced ethyl 2,2-difluoro-2-(4-fluorophenyl)acetate (**5b**) in 71% yield (entry 3), however, the use of 4-methoxyphenylmagnesium bromide (**2c**) having an electron-donating group diminished the yield of ethyl 2,2-difluoro-2-(4-methoxyphenyl)acetate (**5c**) (42%, entry 4). We reasoned that the relative high reactivity of **2c** may cause side reactions such as an addition of the Grignard reagent to the carbonyl group of ethyl bromodifluoroacetate and the bromine–magnesium exchange reaction,<sup>16</sup> lowering the yield of the desired product.

To avoid these unwanted side reactions, instead of using Grignard reagents we then explored the Co-catalyzed reaction of arylzinc reagents<sup>14d</sup> having low nucleophilicity toward the carbonyl group and the bromine atom of **4** (Table 3). The first attempt using 4-methoxyphenylzinc chloride (**3c**), prepared from **2c** and zinc chloride, unfortunately did not proceed (entry 1), but any undesired side reaction was not observed. To enhance the reactivity of the zinc reagent, *N*-methyl-2-pyrrolidone (NMP) was employed as an additive,<sup>17</sup> however, the yield was not improved (entry 2). To our delight, we found that the coupling reaction took place to produce the desired product **5c** in moderate yield when **3c–N,N,N',N'**-tetramethylethylenediamine (TMEDA) complex, prepared by transmetalation of **2c** with ZnCl<sub>2</sub>–TMEDA complex, was used as an arylzinc reagent (entry 3).<sup>18</sup> After further optimization (entries 4 and 5), the reaction performed in the presence of 2 equiv of the arylzinc reagent **3c**–TMEDA complex at room temperature afforded the best result, yielding a 79% of **5c**.<sup>19</sup> Furthermore several amine ligands were explored under the reaction

**Table 3**  
Co-catalyzed cross-coupling reaction of ethyl bromodifluoroacetate with *p*-methoxyphenylzinc halides

3c (X=Cl)  
3c' (X=Br)

5c

Entry	Ar–ZnX	Additive	Conditions	Yield <sup>a</sup>
1	<b>3c</b> (1.2 equiv)	—	0 °C, dropwise for 30 min; rt, 30 min	5%
2	<b>3c'</b> (1.2 equiv)	NMP	0 °C, dropwise for 30 min; rt, 4 h	0%
3	<b>3c</b> (1.2 equiv)	TMEDA	0 °C, dropwise for 30 min; rt, 4 h	33%
4	<b>3c</b> (1.2 equiv)	TMEDA	rt, 4 h	43% (isolated 50%)
5	<b>3c</b> (2.0 equiv)	TMEDA	rt, 4 h	64% (isolated 79%)

<sup>a</sup> <sup>19</sup>F NMR yield (benzotrifluoride was used as an internal standard).

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