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Iron-catalyzed Chemoselective Cross-coupling of α-Bromocarboxylic Acid Derivatives with Aryl Grignard Reagents

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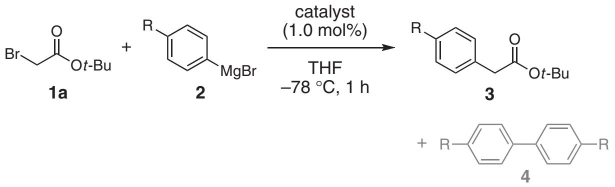
We have developed a simple and effective synthetic method of α-arylcarboxylic acid derivatives based on the iron-catalyzed cross-coupling reaction of α-bromocarboxylic acid derivatives with aryl Grignard reagents. The reaction proceeds smoothly at −78 °C in a chemoselective manner to produce the coupling product in good to excellent yields.

α-Arylcarboxylic acids and their derivatives are useful synthetic intermediates of pharmaceuticals, or important bioactive compounds themselves, such as loxoprofen or lumiracoxib.[1] Due to their significance, a number of synthetic methods for this class of compounds have been already developed,[2] however, further effort is needed to establish more practical methods to overcome several drawbacks associated with the classical methods: for example, the use of toxic reagents such as NaCN, the requirement of multistep transformations and/or harsh reaction conditions, just to name a few. Catalytic cross-coupling reactions have been recognized as a straightforward strategy to synthesize α-arylcarboxylic acid derivatives from aryl halides with preformed or in situ generated enolates by a single-step operation. The most popular metal catalysts utilized are palladium[3] and nickel.[3a,4] However, the disadvantages are the usage of toxic and expensive catalysts, the need for the preparation of the enolate substrate, undesired side reactions such as multiple arylation, and racemization at the α-carbon atom of the carbonyl group. We envisioned that iron catalysts can solve the above problems since iron makes low-toxic, economical, and environmentally friendly catalysts. In addition, we anticipated that the easily available α-bromocarboxylic acid derivatives[5] could be used as the electrophilic substrate due to the distinctive reactivity of the iron catalyst toward alkyl halide electrophiles.[5,6] Herein we report the cross-coupling reaction of α-bromocarboxylic acid derivatives with aryl Grignard reagents in the presence of a catalytic amount of $Fe(acac)_3$.

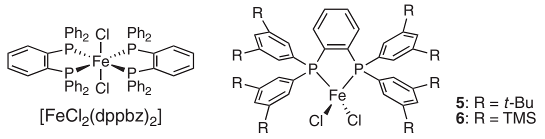
For the purpose of catalyst screening, *tert*-butyl bromoacetate (**1a**) was coupled with *p*-tolylmagnesium bromide in the presence of various metal catalysts (Table 1). To minimize the undesired nucleophilic attack of the Grignard reagent to the carbonyl group, we chose the bulky *tert*-butyl ester, and the reactions were carried out at −78 °C. In the absence of a transition-metal catalyst, the desired product **3** was formed in 15% yield along with 42% recovery of **1a** after 1 h; it is noteworthy that, after 24 h, the coupling product **3** was obtained in a decreased yield (5%) despite the further consumption of **1a** (Entries 1 and 2). Conceivably, side-reactions including nucleophilic attack to the ester group and halogen–metal exchange reaction competed with the coupling reaction, and several unidentified by-products were obtained under the reaction conditions. On the other hand, the desired cross-coupling reaction proceeded smoothly in the presence of 1 mol % iron catalyst regardless of the forms of the precatalyst used (Entries

Table 1. Cross-coupling of bromoacetate **1a** with aryl Grignard reagents



Entry	ArMgBr (equiv)	Catalyst[a]	Products (Yield/%)[b]		RSM /%
			3	**4**[c]	**1a**
1	*p*-tolMgBr (2.0)	none	15	<1	42
2[d]	*p*-tolMgBr (2.0)	none	5	<1	21
3	*p*-tolMgBr (2.0)	$FeCl_2(dppbz)_2$[e]	74	12	<1
4	*p*-tolMgBr (2.0)	Fe complex **5**[e]	77	8	<1
5	*p*-tolMgBr (2.0)	Fe complex **6**[e]	84	8	<1
6	*p*-tolMgBr (2.0)	$FeCl_3$	77	11	<1
7	*p*-tolMgBr (2.0)	$Fe(acac)_3$	85	8	<1
8	*p*-tolMgBr (1.5)	$Fe(acac)_3$	84	9	<1
9	*p*-tolMgBr (1.2)	$Fe(acac)_3$	62	9	10
10	*p*-tolMgBr (2.0)	$Co(acac)_2$	82	8	<1
11	*p*-tolMgBr (2.0)	$Ni(acac)_2$	84	5	<1
12	*p*-tolMgBr (2.0)	$Cu(acac)_2$	5	5	47
13	*p*-tolMgBr (2.0)	$Pd(acac)_2$	5	<1	49
14	*p*-anisylMgBr (1.5)	$Fe(acac)_3$ (0.1 mol %)	85	4	<1
15	*p*-anisylMgBr (1.5)	$Co(acac)_2$ (0.1 mol %)	32	1	36
16	*p*-anisylMgBr (1.5)	$Ni(acac)_2$ (0.1 mol %)	34	1	37

[a] 1.0 mol % catalyst was used unless otherwise noted. [b] Yields were determined by NMR using 1,1,2,2-tetrachloroethane as an internal standard. [c] Based on the amount of the ArMgBr **2** used. [d] The reaction was carried out for 24 h. [e] Structures of iron complexes are shown below.



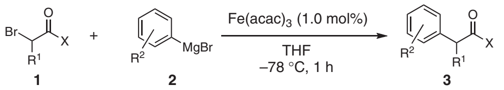
3–7): *p*-tolylacetate **3** was obtained in 74–85% yield, accompanied by the formation of the by-product 4,4′-dimethylbiphenyl (**4**) in 8–12% yield. $Fe(acac)_3$ gave the coupling product in the highest yield (85%) with the minimum amount of by-product **4** (Entry 7).[7] The coupling product was obtained in 84% even when the amount of the Grignard reagent was reduced to 1.5 equivalents (Entry 8). The reaction proceeded in a chemoselective manner, and none of the alcohol or ketone by-products, potentially formed by the Grignard addition reaction, was detected by GC or ^{1}H NMR. The yield of the cross-coupling product significantly depends on the experimental procedure,[8,9] and the best result was obtained by the representative procedure described in note 8.

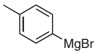
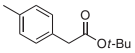
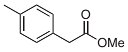
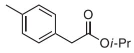
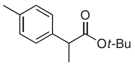
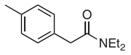
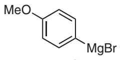
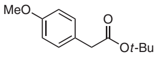
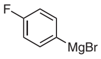
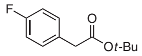
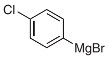
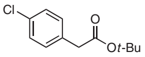
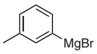
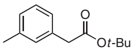
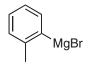
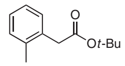
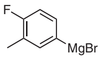
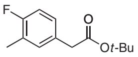
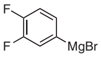
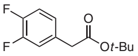
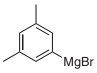
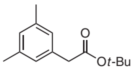
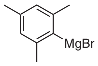
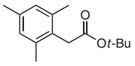
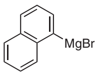
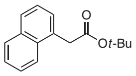
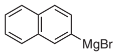
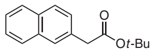
The catalytic activities of the other transition metals were also studied by using the corresponding acetylacetonato complexes as in Entries 10–13:[10] $Co(acac)_2$ and $Ni(acac)_2$ showed a comparable catalytic activity with $Fe(acac)_3$ to give the product in 82% and 84% yields, respectively (Entries 10 and 11). The yields were substantially lower with the $Cu(acac)_2$ or $Pd(acac)_2$ catalyst (Entries 12 and 13). The reaction of **1a** with *p*-tolylmagnesium bromide was equally catalyzed by the acetylacetonato complexes of iron, cobalt, and nickel. On the other hand, clear difference among these metals was observed in the cross-coupling of **1a** with *p*-anisylmagnesium bromide at a lower catalyst loading; only 0.1 mol % of $Fe(acac)_3$ gave the coupling product in 85% yield (Entry 14), while 0.1 mol % of $Co(acac)_2$ and $Ni(acac)_2$ gave the product in 32% and 34% yields, respectively (Entries 15 and 16). The results of the side-by-side experiments with various transition metals suggest that a trace metal contaminant, if any, is not likely to be acting as the true effective catalyst for the present iron-catalyzed coupling reaction.[10] Because of the high catalytic activity as well as the economical and operational advantages of the iron complex, we chose $Fe(acac)_3$ as the precatalyst for the following studies.

Table 2 summarizes the scope of the present arylation reaction of α-bromocarboxylic acid derivatives. The size of the ester alkoxy substituent is critical for maximizing the yield of the desired coupling products. The larger substituents gave the better yields: the reaction with methyl bromoacetate (**1b**) did not give the coupling product due to the competitive nucleophilic addition of the Grignard reagent to the ester group, only to afford a mixture of the alcohol and ketone by-products (Entry 2). When isopropyl bromoacetate (**1c**) was subjected to the same reaction conditions, the coupling product was obtained in 15% yield along with the formation of several by-products (Entry 3). *tert*-Butyl α-bromopropionate (**1d**), a secondary alkyl bromide, gave low yield even when the reaction was carried out according to Fürstner's conditions (Entry 4). It should be noted that Fürstner reported the reaction of ethyl α-bromobutyrate with phenylmagnesium bromide gave the coupling product in 87% yield in the presence of $[Li(tmeda)]_2[Fe(C_2H_4)_4]$.[5] Our result suggests the low-valent iron species proposed in Fürstner's report are not likely to be involved as the catalytically active species in the present coupling reaction. A moderate yield was obtained when *N*,*N*-diethylbromoacetamide (**1e**) was used as a substrate (Entry 5).

Reactions of **1a** with a variety of arylmagnesium bromides were studied next: *p*-substituted aryl Grignard reagents such as *p*-tolyl (**2a**), *p*-anisyl (**2b**), *p*-fluorophenyl (**2c**), and *p*-chlorophenyl (**2d**) Grignard reagents gave the desired products in high

Table 2. Cross-coupling of α-bromocarboxylic acid derivatives with aryl Grignard reagents



Entry	Electrophile	ArMgBr[a]	Coupling product	Yield[b]/%
1	**1a** (R^1 = H, X = O*t*-Bu)	 **2a**	 **3a**	78
2	**1b** (R^1 = H, X = OMe)	**2a**	 **3b**	$<1^{c}$
3	**1c** (R^1 = H, X = O*i*-Pr)	**2a**	 **3c**	15^{c}
4	**1d** (R^1 = Me, X = O*t*-Bu)	**2a**	 **3d**	16^{c}, $26^{c,d}$
5	**1e** (R^1 = H, X = NEt_2)	**2a**	 **3e**	44
$6^{e,f}$	**1a**	 **2b**	 **3f**	84
7	**1a**	 **2c**	 **3g**	90
8	**1a**	 **2d**	 **3h**	81
9	**1a**	 **2e**	 **3i**	70
10	**1a**	 **2f**	 **3j**	41
11	**1a**	 **2g**	 **3k**	90
12	**1a**	 **2h**	 **3l**	70
13	**1a**	 **2i**	 **3m**	53
14	**1a**	 **2j**	 **3n**	18^{c}
15	**1a**	 **2k**	 **3o**	37^{c}
16	**1a**	 **2l**	 **3p**	82

[a] 1.5 equivalents of Grignard reagents were used in Entries 1–8, and 3.0 equivalents of Grignard reagents were used in Entries 9–16. [b] Isolated yields unless otherwise noted. [c] NMR yields. [d] Reaction was carried out according to the Fürstner's conditions (see note 5): $Fe(acac)_3$ (5 mol %), ArMgBr (1.2 equiv), THF, −20 °C, 0.5 h. [e] 0.1 mol % of $Fe(acac)_3$ was used. [f] 20 mmol scale see note 8.

yields (Entries 1 and 6–8). *m*-Tolyl (**2e**) and *o*-tolyl (**2f**) Grignard reagent gave the corresponding arylation products in fair to modest yields (Entries 9 and 10). Disubstituted aryl Grignard reagents including 4-fluoro-3-methylphenyl (**2g**),[11] 3,4-difluorophenyl (**2h**),[12] and 3,5-xylyl (**2i**)[13] Grignard reagents afforded the coupling products in moderate to high yields (Entries 11–13). In contrast, a low yield (18%) was obtained when mesitylmagnesium bromide (**2j**), a trisubstituted aryl Grignard reagent, was used (Entry 14). This result suggested that the present reaction is sensitive to the steric hindrance of aryl Grignard reagents. The reactions of **1a** with 1-naphthylmagnesium bromide (**2k**) and 2-naphthylmagnesium bromide (**2l**) further support this conclusion: the more sterically demanding reagent **2k** gave the product in 37% yield, while the less demanding reagent **2l** gave the product in 82% yield (Entries 15 and 16). Although the reaction mechanism remains unclear at the current stage of the study, we suppose that bare ferrate species, which do not bear any auxiliary ligand, are responsible for the coupling reaction based on the observation that all the iron complexes examined in this study gave comparable results despite the ligands on the precatalyst, and also that extra additives did not affect the coupling reactions.[14] In order to expand the substrate scope of the present reaction and also to develop an asymmetric variant of the α-arylation reaction, detailed mechanistic studies will be needed to clarify the catalytically active species. Further investigation along this line is ongoing in our laboratory and will be reported in due course.

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7 Fe(acac)$_3$ was purchased from Aldrich Chemical Co. and readily applied to the coupling reaction without purification.

8 A representative procedure (Table 2, Entry 6): Under a positive pressure of argon, to a solution of *tert*-butyl bromoacetate (3.89 g, 19.9 mmol) in dry THF (40.0 mL) was dropwise added a *p*-anisylmagnesium bromide solution (1.0 M in THF, 30.0 mL, 1.5 equiv) at −78 °C. To the mixture was slowly added a solution of Fe(acac)$_3$ (7.1 mg, 0.1 mol %) in dry THF (4.0 mL) over 1 h, and the resulting mixture was stirred at −78 °C for 1 h. After quenching with 3 M aqueous solution of hydrochloric acid, the mixture was extracted with EtOAc, passed through a pad of Florisil®, and concentrated in vacuo. The residue was chromatographed on silica gel (*n*-hexane/toluene = 4/1, 2/1, 1/1) to give the desired product (3.74 g, 84%, colorless oil).

9 The yields of the desired coupling products decreased dramatically when the reaction was carried out under the procedure described as follows: to a pre-cooled mixture of a bromoacetate and an iron catalyst was slowly added a THF solution of a Grignard reagent, the corresponding α-arylated ester was obtained in less than 30% yield.

10 a) S. L. Buchwald, C. Bolm, *Angew. Chem., Int. Ed.* **2009**, *48*, 5586. b) R. B. Bedford, M. Nakamura, N. J. Gower, M. F. Haddow, M. A. Hall, M. Huwe, T. Hashimoto, R. A. Okopie, *Tetrahedron Lett.* **2009**, *50*, 6110.

11 Compound data of the corresponding product, *tert*-butyl (4-fluoro-3-methylphenyl)acetate (**3k**): IR (neat, cm^{-1}): ν 2978, 1728, 1607, 1367, 1295, 1254, 1136, 1038, 954, 851, 796, 753, 688; ^{1}H NMR (392 MHz, CDCl$_3$): δ 1.44 (s, 9H), 2.25 (d, $J = 1.8$ Hz, 3H), 3.45 (s, 2H), 6.89–6.99 (m, 1H), 7.00–7.11 (m, 2H); ^{13}C NMR (99 MHz, CDCl$_3$): δ 14.5 (d, $J = 3.8$ Hz), 28.0 (3C), 41.7, 80.9, 114.9 (d, $J = 22.5$ Hz), 124.7 (d, $J = 16.9$ Hz), 127.9 (d, $J = 7.5$ Hz), 130.0 (d, $J = 3.8$ Hz), 132.3 (d, $J = 4.7$ Hz), 160.4 (d, $J = 244$ Hz), 171.0; HRMS *m*/*z*: M$^+$ calcd for $C_{13}H_{17}FO_2$ 224.1213; found, 224.1213; Anal. Calcd for $C_{13}H_{17}FO_2$: C, 69.62; H, 7.64; F, 8.47%. Found: C, 69.66; H, 7.69; F, 8.38%.

12 Compound data of the corresponding product, *tert*-butyl (3,4-difluorophenyl)acetate (**3l**): IR (neat, cm^{-1}): ν 2978, 1731, 1501, 1367, 1252, 1209, 1136, 957, 884, 799, 753, 711; ^{1}H NMR (392 MHz, CDCl$_3$): δ 1.44 (s, 9H), 3.48 (s, 2H), 6.95–7.02 (m, 1H), 7.09–7.15 (m, 2H); ^{13}C NMR (99 MHz, CDCl$_3$): δ 28.0 (3C), 41.7, 81.3, 117.1 (d, $J = 16.9$ Hz), 118.2 (d, $J = 17.8$ Hz), 125.3 (dd, $J = 5.6$, 3.8 Hz), 131.5 (dd, $J = 5.6$, 3.8 Hz), 149.4 (dd, $J = 247$, 12.2 Hz), 150.2 (dd, $J = 248$, 12.2 Hz), 171.2; HRMS *m*/*z*: M$^+$ calcd for $C_{12}H_{14}F_2O_2$, 228.0962; found, 228.0957; Anal. Calcd for $C_{12}H_{14}F_2O_2$: C, 63.15; H, 6.18; F, 16.65%. Found: C, 63.12; H, 6.23; F, 16.68%.

13 Compound data of the corresponding product, *tert*-butyl (3,5-xylyl)acetate (**3m**): IR (neat, cm^{-1}): ν 2979, 1728, 1610, 1517, 1437, 1368, 1283, 1208, 1136, 968, 873, 791, 767, 753, 710; ^{1}H NMR (392 MHz, CDCl$_3$): δ 1.44 (s, 9H), 2.30 (s, 6H), 3.45 (s, 2H), 6.88 (s, 3H); ^{13}C NMR (99 MHz, CDCl$_3$): δ 21.5 (2C), 28.1 (3C), 42.4, 80.7, 127.0 (2C), 128.5, 134.4, 137.9 (2C), 171.2; HRMS *m*/*z*: M$^+$ calcd for $C_{14}H_{20}O_2$, 220.1463; found, 220.1468; Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15; O, 14.52%. Found: C, 76.25; H, 9.23; O, 14.78%.

14 The iron-catalyzed coupling reaction of *tert*-butyl bromoacetate with *o*-tolylmagnesium bromide was carried out in the presence of the following additives: the α-arylated ester was obtained in 42%, 6%, and 1% yield in the presence of 1,4-dioxane (10 equiv), *N*-methylpyrrolidone (NMP, 10 equiv), and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA, 3.0 equiv), respectively.