Palladium-Catalyzed α-Arylation of Carboxylic Acid Derivatives with Grignard Reagent

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SHORT COMMUNICATION

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Palladium-catalyzed α-Arylation of Carboxylic Acid Derivatives with Grignard Reagent

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Keywords: Palladium catalyst / Carboxylate / Arylation / Grignard reagent / Diarylcarboxylic acid

The reaction of arylacetic acid and aryl halides in the presence of palladium(0) catalyst proceeds with 2 equivalents of Grignard reagent affording diarylated acetic acid. Deprotonation is confirmed by treatment with allyl bromide to reveal that the use of EtMgCl or *t*BuMgCl at room temperature to 60 °C results in complete deprotonation. After deprotonation of (4-methoxyphenyl)acetic acid under such conditions the resulting mixture is treated with 4-methoxybromobenzene in the presence of 2 mol % Pd(*t*Bu$_3$P)$_2$ as a catalyst leads to the bis(4-methoxyphenyl)acetic acid in 86% yield. The reaction with several aryl halides under similar conditions also gives the corresponding diarylacetic acids.

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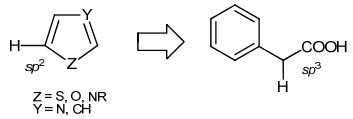
Introduction

Transition-metal-catalyzed arylation reaction at the α-position of carbonyl compounds is an effective tool in organic synthesis for the introduction of a substituent in forming a C*sp*^{3}–C*sp*^{2} bond. A number of α-arylation of carbonyl compounds such as ketones, esters, amides, etc. by the reaction of such carbonyl compounds with aryl halides in the presence of a transition-metal catalyst has been shown to take place.[1,2] Nevertheless, the related reaction of carboxylic acid as a carbonyl derivative has not been achieved so far[3,4] because of difficulties for the α-deprotonation as well as nucleophilic attack of the corresponding carboxylate due to the increased electron negativity of the carbonyl carbon atom. Although deprotonative alkylation of carboxylic acids with two equivalents of lithium amide and following treatment of organic halides via nuclephilic substitution,[3] no example of transition-metal-catalyzed coupling reaction has been shown to take place with aryl halides to the best of our knowledge.

On the other hand, we have recently shown deprotonative metalation of several heteroaromatic compounds using a stoichiometric amount of magnesium amide. We have also shown such deprotonative metalation is achieved with a catalytically-generated magnesium amide with Grignard reagent and a catalytic amount of secondary amines and the thus formed heteroaromatic organometallic species underwent transition-metal-catalyzed carbon–carbon bond formationn leading to give cross-coupling products[5] and π-conjugated polymers.[6] In addition to such C*sp*^{2}–C*sp*^{2} coupling, it is intriguing that the related reaction at the C*sp*^{3} carbon atom of the α-position of carbonyl compounds also occurs by transition metal catalysis. However, the reaction condition using Grignard reagent would allow nucleophilic attack directly to the carbonyl group, thereby, the above-mentioned deprotonating system is considered to be difficult. We thus envisaged to study transition-metal-catalyzed deprotonative coupling of carboxylic acid, which is much less reactive toward nucleophilic attack. We herein describe that treatment of arylacetic acid with Grignard reagent effectively deprotonates and the thus formed metallic species underwent cross coupling with aryl halides in the presence of palladium catalyst. (Scheme 1)



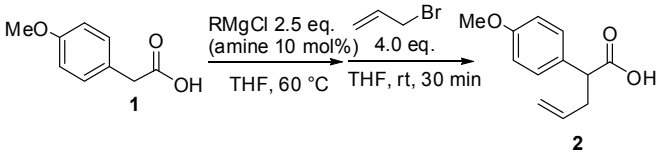
Scheme 1. Deprotonative metalation at C(*sp*^{2})–H or C(*sp*^{3})–H bond.

Results and Discussion

Among α-arylation reactions of carbonyl compounds several bases have been employed for the deprotonation reaction. It was found that such bases as metal carbonates, phosphates, and alkoxides[2] showed insufficient basicity for the deprotonation of carboxylic acids. Indeed, no deprotonation of (4-methoxyphenyl)acetic acid (**1**) took place at 60 ºC for 24 h with the above bases. By contrast, the reaction of **1** with a Grignard reagent was found to take place to result in deprotonation, which was confirmed by treatment of the reaction mixture with allyl bromide to afford the corresponding allylated carboxylic acid **2**. Deprotonation of **1** was examined under several conditions as summarized in Table 1. When the reaction was carried out with *t*BuMgCl at room temperature for 1 h and further stirring at room temperature for 30 min after the addition of allyl bromide, **2** was obtained in 61% yield. An improved yield was observed in the deprotonation at 60 °C for 3 h (85%). The use of *i*PrMgCl·LiCl resulted in inferior yield (74%) and that of PhMgCl did not undergo deprotonation at all. The reaction with EtMgCl under similar conditions afforded **2** in 78% yield. The yield of **2** with EtMgCl was slightly improved in the presence of 10 mol% *N*,*N*-dicyclohexylamine (88%). Several amines were found to be similarly effective in the deprotonation at 60 ºC for 3 h (78-92%). On the other hand, the reaction with EtMgCl at room temperature for 3 h was found to be effective. Following addition of allyl bromide resulted in giving **2** in a quantitative yield. Accordingly, deprotonation of arylacetic acid **1** with a bulky Grignard reagent was found to take place although the elevated temperature was required. The result contrasts to the deprotonation of

heteroaromatic compounds,[5i] in which addition of a catalytic amount of secondary amine effectively enhanced the reaction. The addition of amine was found to slightly improve the deprotonation when a sterically less hindered Grignard reagent (EtMgCl) is employed at 60 °C, probably, to avoid nucleophilic attack of the ethyl group to the carbonyl group. However, addition of amine was not required when deprotonation is carried out at room temperarture.

Table 1. Deprotonation of (4-methoxy)phenylacetic acid (**1**) with a Grignard reagent in the presence/absence of secondary amine[a]



RMgX[a]	Amine[b]	Time, Temp (h, °C)[c]	Yield, %
*t*BuMgCl	none	1, rt	61
	none	0.5, 60	77
	none	3, 60	85
*i*PrMgCl·LiCl	none	3, 60	74
PhMgCl	none	3, 60	no product
EtMgCl	none	3, 60	78
	Cy_2NH[c]	3, 60	88
	TMPH[c]	3, 60	84
	iPr_2NH	3, 60	84
	Et_2NH	3, 60	88
	CyMeNH[c]	3, 60	92
	DMP[c]	3, 60	78
	Ph_2NH	3, 60	78
EtMgCl	none	3, rt	quant.

[a] The reaction was carried out with 0.5 mmol of **1** and 1.25 mmol of RMgX in 1.25 mL of THF in the presence/absence of 10 mol% of amine [b] Isolated yield. [c] Cy: cyclohexyl; TMP: 2,2,6,6-tetramehtylpiperidine-1-yl; DMP: *cis*-2,6-dimethylpiperidine-1-yl.

With the likely deprotonation conditions in hand, the coupling reaction with aryl halide was examined. Table 2, summarizes the results. After deprotonation with *t*BuMgCl at 60 ºC for 3 h, the reaction of (4-methoxy)phenylacetic acid **1** with 4-methoxy-1-bromobenzene (**3a**) was carried out in THF at 60 ºC for 3 h in the presence of several palladium or nickel catalysts. The reaction with $Pd(tBu_3P)_2$ (2.0 mol%) afforded the corresponding diarylacetic acid **4a** in 86% yield, whereas other nickel or palladium catalysts such as $NiCl_2$dppe, $NiCl_2$dppf, $NiCl_2(PPh_3)$IPr, $PdCl_2$dppf, PEPPSI-SIPr[7] resulted in much inferior yields. The use of $Pd_2(dba)_3{\cdot}CHCl_3$ with several bulky phosphines John Phos, X Phos, Ru Phos, Dave Phos, and *t*Bu XPhos[8] underwent the arylation to afford **4a** in reasonable yields. It was found that several palladium(0) complexes served as an effective catalyst to undergo the arylation reaction, in which bulky and electron-donating ligands efficiently promoted the catalytic reaction.

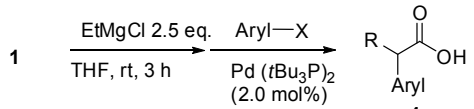
Table 2. Arylation of **1** with 4-methoxy-1-bromobenzene (**3a**) with *t*BuMgCl and several transition metal catalyst.[a]

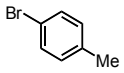
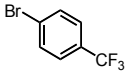
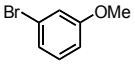
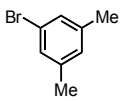
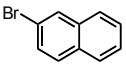
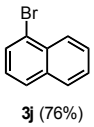
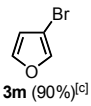
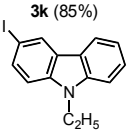
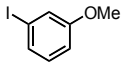
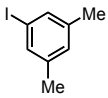
Catalyst[b]	Additive, ligand[c]	Yield, %[d]
$NiCl_2$dppe		17
$NiCl_2$dppf		55
$NiCl_2(PPh_3)$IPr		55
PEPPSI-IPr		14
$PdCl_2$dppf		40
$Pd(tBu_3P)_2$		86
$Pd_2(dba)_3{\cdot}CHCl_3$	+ JohnPhos	80
$Pd_2(dba)_3{\cdot}CHCl_3$	+ XPhos	95
$Pd_2(dba)_3{\cdot}CHCl_3$	+ RuPhos	87
$Pd_2(dba)_3{\cdot}CHCl_3$	+ DavePhos	68
$Pd_2(dba)_3{\cdot}CHCl_3$	+ *t*Bu XPhos	46

[a] The reaction was carried out with 0.5 mmol of **1** and 1.5 mmol of *t*BuMgCl in 1.5 mL of THF at 60 ºC for 3 h, then, 2 mol% of catalyst (additive ligand) and 3.0 equiv. of **3a** were added. [b] DPPE: diphenylphosphinoethane; DPPF: diphenylphosphinoferrocene; IPr: 1,3-di(2,6-diisopropylphenly)imidazolidene; PEPPSI: see ref 7. [c] The ratio of additive ligand/catalyst = 2. Abbreviation of additives: see ref 8. [d] Isolated yield.

The reaction of **1** was performed with a variety of aryl halide as represented in Table 3 under similar conditions. Aryl bromides bearing electron-donating substituents similarly underwent the coupling reaction whereas the reaction of electron-deficient bromide bearing CF_3 group **3d** resulted in slightly lower yield. Several *o*-substituted aryl bromides **3e** and **3f** also reacted to afford the arylated products. Both 1- and 2-bromonaphthalene (**3i** and **3j**) similarly effected the reaction. Heteroaromatic halides such as 2-bromothiophene (**3l**), 3-bromothiophene (**3k**), 3-bromofuran (**3m**), and 9-iodo-*N*-ethylcarbazole (**3n**) also afforded the corresponding coupling product in moderate to excellent yields. Although several aryl iodides, **3o** and **3p,** similarly underwent the coupling reaction efficiently, the reaction of the corresponding chlorides resulted in no reaction under similar conditions.

Table 3. Arylation of **1** with various aryl halides[a]

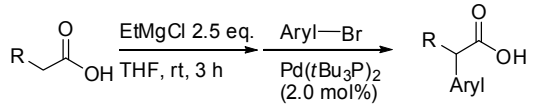


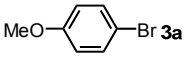
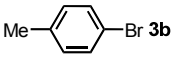
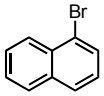
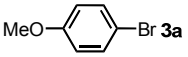
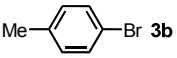
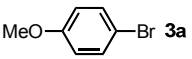
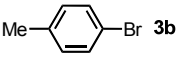
Aryl halide (yield)[b]	Aryl halide (yield)[b]	Aryl halide (yield)[b]
 **3b** (77%)	 **3c** (88%)	 **3d** (57%)
 **3e** (80%)	 **3f** (67%)	 **3g** (90%)
 **3h** (90%)	 **3i** (90%)	 **3j** (76%)
 **3k** (85%)	 **3l** (34%)	 **3m** (90%)[c]
 **3n** (70%)	 **3o** (66%)	 **3p** (70%)

[a] Unless otherwise specified, the reaction was carried out with 0.5 mmol **1** and 1.25 mmol EtMgCl in 1.25 mL THF in the presence/absence of 10 mol% amine for deprotonation and then the reaction with aryl halide (1.5 mmol) in the presence of $Pd(tBu_3P)_2$ (2 mol%) for 2 h. [b] Isolated yield. [c] The reaction period: 17 h.

In addition to (4-methoxy)phenylacetic acid **1**, the reaction of several α-arylacetic acids was examined. Deprotonation of (naphthelen-1-yl)acetic acid (**5**) was carried out with 2.5 equiv. of EtMgCl at room temperature. After stirring there for 3 h, addition of aryl halides and 2 mol% Pd(tBu$_3$P)$_2$ followed. Further stirring at 60 ºC lead to the corresponding product. As shown in Table 4, the reaction of 4-bromotoluene (**3b**) afforded the corresponding diarylacetic acid in 56% yield. The similar reaction with **3j** also furnished the product in 84% yield. In addition, α-heteroarylated acetic acid derivative (thiophen-2-yl)acetic acid (**6**) and (thiophen-3-yl)acetic acid (**7**) also underwent the reaction to afford the corresponding arylated products in good to excellent yields.

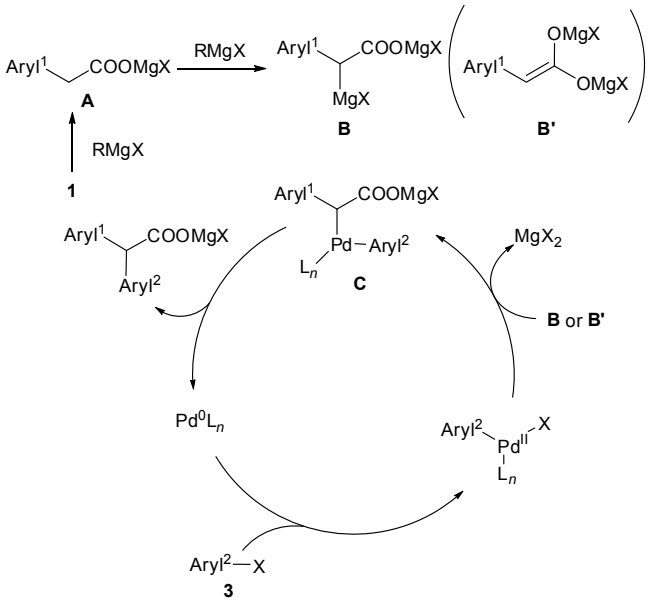
Table 4. Arylation of α-arylacetic acid with aryl bromide.



R−	Aryl-Br	Yield, %[b]
 **5**	 **3a**	81
	 **3b**	56
	 **3j**	84
 **6**	 **3a**	44
	 **3b**	56
 **7**	 **3a**	78
	 **3b**	89

[a] The reaction was carried out with 0.5 mmol **1** and 1.25 mmol EtMgCl in 3 mL THF for deprotonation and the coupling reaction at 60 °C with 2.0 equiv. of aryl bromide in the presence of 2.0 mol% Pd(tBu$_3$P)$_2$. [b] Isolated yield.

Although further studies are necessary for the complete understanding of the reaction mechanism, we consider that the following pathway is plausible: The initial stage of the reaction is deprotonation at the α-position of the formed carboxylate **A** leading to the corresponding α-metallo carboxylate **B** or the enolate **B'**. On the other hand, aryl halide reacts with palladium(0) catalyst to give arylpalladium(II) halide. Reaction of the palladium(II) species with **B** or **B'** induce transmetalation to form **C** and reductive elimination gives the coupling product accompanied by regeneration of Pd^0. Since acidity of the α-proton of carboxylate derived from **1** is much lower than that of other carbonyl compounds ketones, esters, and amides, use of weaker bases were insufficient for deprotonation. Use of Grignard reagent or magnesium amide efficiently underwent deprotonation. Moreover, nucleophilicity of the carboxylate would also be much lower, thereby, use of a Grignard reagent did not allow addition to the carbon atom of the carbonyl group. Indeed, attempted deprotonation of esters and ketones with tBuMgCl was found to be ineffective at all.



Scheme 2. Plausible reaction mechanism of palladium-catalyzed deprotonative arylation of caroboxylic acid with Grignard reagent

Conclusions

In conclusion, palladium-catalyzed arylation of α-arylacetic acid was found successfully to occur with several aryl halides in a deprotonative manner to afford the diarylacetic acids in good to excellent yields. The deprotonation reaction took place with Grignard reagent or the combined use of Grignard reagent with a catalytic amount of secondary amine to proceed at room temperature to 60 °C within 3 h. It is remarkable that diarylacetic acids, which have been prepared by arylation of the related derivatives such as esters and amides and following hydrolysis, can be obtained in the direct arylation reaction.

Experimental Section

Bis(4-methoxyphenyl)acetic acid (4a): To a solution of (4-methoxyphenyl)acetic acid (**1**, 0.083 g, 0.5 mmol) in 1.5 mL THF was added a THF solution of EtMgCl (0.93 M, 1.34 mL, 1.25 mmol) at room temperature. The resulting mixture was stirred at room temperature for 3 h, then, Pd(tBu$_3$P)$_2$ (5.1 mg, 0.01 mmol) and 4-methoxy-1-bromobenzene (**3a**, 0. 198 g, 1.0 mmol) were added successively. After stirring the mixture at 60 °C for 3 h, the resulting mixture was passed through a Celite pad and the filtrate was concentrated under reduced pressure to leave a crude oil, which was subjected to column chromatography on silica gel to afford **4a** in 86% yield. ^{1}H NMR ($CDCl_3$) δ 3.78 (s, 6H), 4.95 (s, 1H), 6.86 (d, J = 8.7 Hz, 4H), 7.23 (d, J = 8.7 Hz, 4H). ^{13}C NMR ($CDCl_3$) δ 55.3, 55.5, 114.2, 129.8, 130.6, 159.0, 179.0. IR (ATR) 2959(br), 2839, 1700, 1609, 1509, 1246, 1031, 809 cm^{-1}. HRMS (ESI+) found: 271.0971. Calcd for $C_{16}H_{15}O_4$ [M]$^+$: 271.0970.

Supporting Information (see footnote on the first page of this article): Further experimental details and copies of the ^{1}H NMR and ^{13}C NMR spectra.

Acknowledgments

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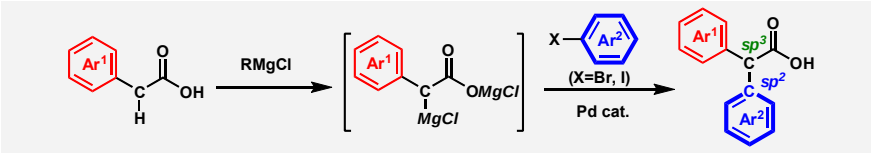
Layout 2:

Coupling reaction



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Palladium-catalyzed α-Arylation of Carboxylic Acid Derivatives with Grignard Reagent

Functionalization at the C-H bond of α-arylcarboxylic acid with 2 equivalents of Grignard reagent undergoes metalation. Treatment of aryl halide in the presence of palladium catalyst leads to diarylcarboxylic acid in good to excellent yields through the formation of C(sp^3)-C(sp^2) bond. Compared with examples of related reactions of carbonyl compounds such as ketone, ester, amide, etc., use of Grignard reagent toward carboxylic acid is the key for the successful coupling reaction.

Keywords: Palladium catalyst / Carboxylate / Arylation / Grignard reagent / Diaryl carboxylic acid