EurJOC European Journal of Organic Chemistry

SHORT COMMUNICATION

DOI: 10.1002/ejoc.201402450

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

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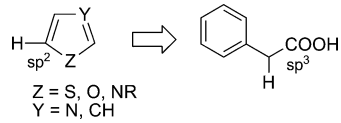
Keywords: Synthetic methods / Homogeneous catalysis / Palladium / C–H activation / Arylation / Grignard reagents / Carboxylic acids

The reaction of arylacetic acid with aryl halides in the presence of a palladium(0) catalyst proceeds with a Grignard reagent (2 equiv.) to afford diarylated acetic acids. Deprotonation was confirmed by treatment with allyl bromide, which revealed that the use of EtMgCl or *t*BuMgCl at room temperature to 60 °C resulted in complete deprotonation. After deprotonation of (4-methoxyphenyl)acetic acid under such conditions, the resulting mixture was treated with 4-methoxybromobenzene in the presence of $Pd(tBu_3P)_2$ (2 mol-%) as a catalyst to give bis(4-methoxyphenyl)acetic acid in 86 % yield. The reaction with several aryl halides under similar conditions gave the corresponding diarylacetic acids.

Introduction

Transition-metal-catalyzed arylation at the α-position of carbonyl compounds is an effective tool in organic synthesis for the introduction of a substituent through the formation of a $C(sp^3)$–$C(sp^2)$ bond. A number of α-arylation reactions of carbonyl compounds such as ketones, esters, and amides by their reaction 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 acids as the carbonyl derivatives has not been achieved so far[3,4] because of difficulties in α-deprotonation and nucleophilic attack of the corresponding carboxylate owing to the increased electronegativity of the carbonyl carbon atom. Although deprotonative alkylation of carboxylic acids with lithium amide (2 equiv.) followed by treatment with organic halides through nucleophilic substitution has been reported,[3] to the best of our knowledge no examples of transition-metal-catalyzed coupling reactions have been shown to take place with aryl halides.

We recently reported the deprotonative metalation of several heteroaromatic compounds by using a stoichiometric amount of magnesium amide. We also showed that such deprotonative metalation could be achieved with a catalytically generated magnesium amide by using a Grignard reagent and a catalytic amount of a secondary amine; the thus-formed heteroaromatic organometallic species underwent transition-metal-catalyzed carbon–carbon bond formation 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 a $C(sp^3)$ carbon atom at the α-position of carbonyl compounds also occurs by transition-metal catalysis. However, the reaction conditions with the use of the Grignard reagent would allow nucleophilic attack directly at the carbonyl group; thereby, the above-mentioned deprotonating system is considered to be difficult. We thus decided to study the transition-metal-catalyzed deprotonative coupling of carboxylic acids, which are much less susceptible to nucleophilic attack. We herein describe that treatment of arylacetic acids with a Grignard reagent effectively results in deprotonation and that the thus-formed metallic species undergo cross-coupling with aryl halides in the presence of a palladium catalyst (Scheme 1).



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

Results and Discussion

Among the α-arylation reactions of carbonyl compounds, several bases have been employed for the deprotonation reaction. It was found that bases such 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 °C 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 corresponding allylated carboxylic acid **2**. Deproton-

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201402450.

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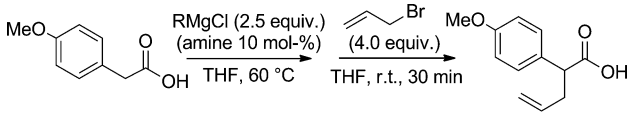
ation of **1** was examined under several conditions, as summarized in Table 1. If the reaction was performed with *t*BuMgCl at room temperature for 1 h with further stirring at room temperature for 30 min after the addition of allyl bromide, **2** was obtained in 61% yield. An improved yield was observed in the deprotonation at 60 °C for 3 h (85%). The use of *i*PrMgCl·LiCl resulted in an inferior yield (74%), and the substrate did not undergo deprotonation at all with the use of PhMgCl. The reaction with the use of EtMgCl under similar conditions afforded **2** in 78% yield. The yield of **2** with EtMgCl was slightly improved in the presence of *N*,*N*-dicyclohexylamine (10 mol-%, 88%). Several amines were found to be similarly effective in the deprotonation at 60 °C for 3 h (78–92%). In contrast, the reaction with EtMgCl at room temperature for 3 h was found to be effective. The addition of allyl bromide resulted in **2** in quantitative yield. Accordingly, deprotonation of arylacetic acid **1** with a bulky Grignard reagent was found to take place, although an elevated temperature was required. This result is in contrast to the deprotonation of heteroaromatic compounds,[5i] for which the addition of a catalytic amount of a secondary amine effectively enhanced the reaction. The addition of amine was found to slightly improve the deprotonation if a sterically less-hindered Grignard reagent (e.g., EtMgCl) was employed at 60 °C, probably to avoid nucleophilic attack of the ethyl group at the carbonyl group. However, the addition of an amine was not required if deprotonation was performed at room temperature.

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



1 **2**

RMgCl	Amine[b]	Time [h]	Temp. [°C]	Yield[c] [%]
*t*BuMgCl	–	1	r.t.	61
*t*BuMgCl	–	0.5	60	77
*t*BuMgCl	–	3	60	85
*i*PrMgCl·LiCl	–	3	60	74
PhMgCl	–	3	60	no product
EtMgCl	–	3	60	78
EtMgCl	Cy_2NH[c]	3	60	88
EtMgCl	TMPH[c]	3	60	84
EtMgCl	iPr_2NH	3	60	84
EtMgCl	Et_2NH	3	60	88
EtMgCl	CyMeNH[c]	3	60	92
EtMgCl	DMP[c]	3	60	78
EtMgCl	Ph_2NH	3	60	78
EtMgCl	–	3	r.t.	quant.

[a] The reaction was performed with **1** (0.5 mmol) and RMgCl (1.25 mmol) in THF (1.25 mL) in the presence/absence of amine (10 mol-%). [b] Cy = cyclohexyl, TMP = 2,2,6,6-tetramethylpiperidine-1-yl, DMP = *cis*-2,6-dimethylpiperidine-1-yl. [c] Yield of isolated product..

With the likely deprotonation conditions in hand, the coupling reaction with aryl halides was examined. Table 2 summarizes the results. After deprotonation with *t*BuMgCl at 60 °C for 3 h, the reaction of (4-methoxy)phenylacetic acid (**1**) with 4-methoxy-1-bromobenzene (**3a**) was performed in THF at 60 °C for 3 h in the presence of several palladium and nickel catalysts. The reaction with $Pd(tBu_3P)_2$ (2.0 mol-%) afforded corresponding diarylacetic acid **4a** in 86% yield, whereas other nickel and palladium catalysts such as $NiCl_2$dppe, $NiCl_2$dppf, $NiCl_2(PPh_3)$IPr, $PdCl_2$dppf, and PEPPSI-SIPr[7] resulted in much inferior yields. The use of $Pd_2(dba)_3$·$CHCl_3$ with several bulky phosphines JohnPhos, XPhos, RuPhos, DavePhos, and *t*BuXPhos (see ref.[8] for definitions of ligands) resulted in 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** by using 4-methoxy-1-bromobenzene (**3a**) and *t*BuMgCl with several transition metal catalysts.[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
$Pd_2(dba)_3$·$CHCl_3$	JohnPhos	80
$Pd_2(dba)_3$·$CHCl_3$	XPhos	95
$Pd_2(dba)_3$·$CHCl_3$	RuPhos	87
$Pd_2(dba)_3$·$CHCl_3$	DavePhos	68
$Pd_2(dba)_3$·$CHCl_3$	*t*BuXPhos	46

[a] The reaction was performed with **1** (0.5 mmol) and *t*BuMgCl (1.5 mmol) in THF (1.5 mL) at 60 °C for 3 h; then, the catalyst (2 mol-% with additive ligand) and **3a** (3.0 equiv.) were added. [b] dppe = diphenylphosphinoethane, dppf = diphenylphosphinoferrocene, IPr = 1,3-di(2,6-diisopropylphenyl)imidazolidene, dba = dibenzylideneacetone, PEPPSI: see ref.[7] [c] The ratio of additive ligand/catalyst = 2. For the definitions of the additives: see ref.[8] [d] Yield of isolated product.

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

In addition to (4-methoxy)phenylacetic acid (**1**), the reaction of several α-arylacetic acids was examined. Deprotonation of (naphthalen-1-yl)acetic acid (**5**) was performed with EtMgCl (2.5 equiv.) at room temperature. After stirring for 3 h, the addition of the aryl halide and $Pd(tBu_3P)_2$ (2 mol-%) followed. Further stirring at 60 °C led to the corresponding product. As shown in Table 4, the reaction of

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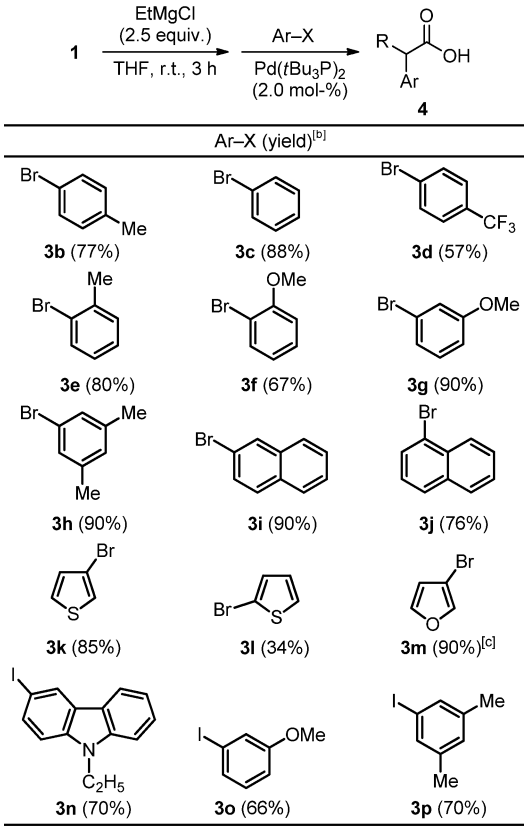
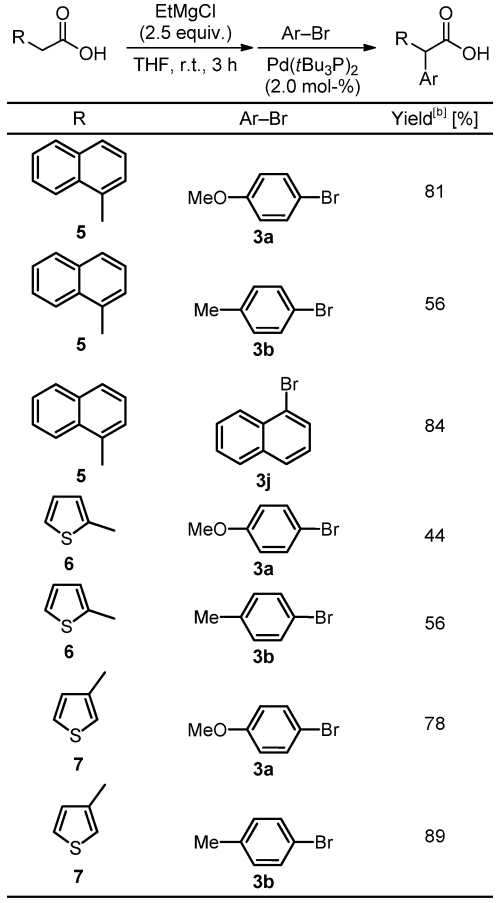
Table 3. Arylation of **1** with various aryl halides.[a]



[a] Unless otherwise specified, the reaction was performed with **1** (0.5 mmol) and EtMgCl (1.25 mmol) in THF (1.25 mL) in the presence/absence of amine (10 mol-%) for deprotonation, which was followed by reaction with the aryl halide (1.5 mmol) in the presence of $Pd(tBu_3P)_2$ (2 mol-%) for 2 h. [b] Yield of isolated product. [c] The reaction time was 17 h.

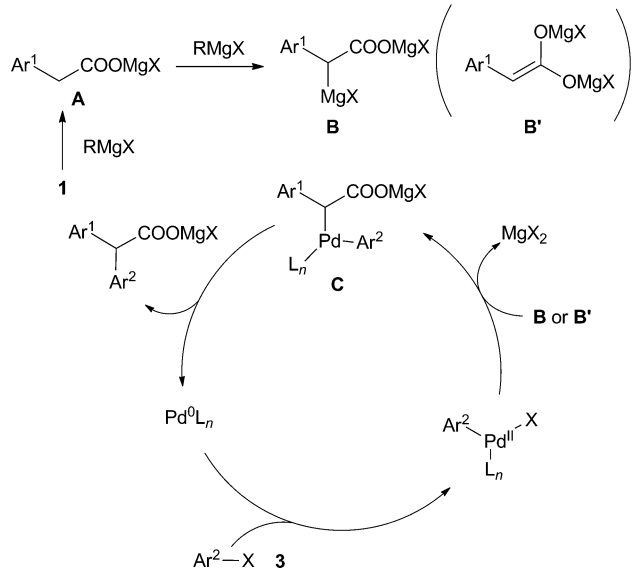
Table 4. Arylation of α-arylacetic acid with aryl bromide.



[a] The reaction was performed with **1** (0.5 mmol) and EtMgCl (1.25 mmol) in THF (3 mL) for deprotonation, which was followed by the coupling reaction at 60 °C with the aryl bromide (2.0 equiv.) in the presence of $Pd(tBu_3P)_2$ (2.0 mol-%). [b] Yield of isolated product.

4-bromotoluene (**3b**) afforded the corresponding diarylacetic acid in 56% yield. A similar reaction with **3j** also furnished the product in 84% yield. In addition, α-heteroarylated acetic acid derivatives (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.

Although further studies are necessary to understand the reaction mechanism completely, we consider that the following pathway is plausible (Scheme 2): The initial stage of the reaction is deprotonation at the α-position of formed carboxylate **A**, which leads to corresponding α-metallocarboxylate **B** or enolate **B′**. The aryl halide reacts with the palladium(0) catalyst to give an arylpalladium(II) halide. Reaction of the palladium(II) species with **B** or **B′** induces transmetalation to form **C**, and reductive elimination gives the coupling product accompanied by regeneration of Pd^0. Given that the acidity of the α-proton of the carboxylate derived from **1** is much lower than that of other carbonyl compounds, such as that in ketones, esters, and amides, the use of weaker bases is insufficient for deprotonation. The use of a Grignard reagent or a magnesium amide efficiently results in deprotonation. Moreover, the nucleophilicity of



Scheme 2. Plausible reaction mechanism for the palladium-catalyzed deprotonative arylation of carboxylic acids with Grignard reagents.

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the carboxylate would also be much lower, and thereby, the use of a Grignard reagent does not allow addition to the carbon atom of the carbonyl group. Indeed, attempted deprotonation of esters and ketones with *t*BuMgCl was found to be ineffective.

Conclusions

In conclusion, palladium-catalyzed arylation of α-arylacetic acids was found to successfully 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 a Grignard reagent or the combined use of a Grignard reagent with a catalytic amount of a secondary amine and it proceeded at room temperature to 60 °C within 3 h. It is remarkable that diarylacetic acids, which were prepared by arylation of related derivatives such as esters and amides following hydrolysis, can be obtained in the direct arylation reaction.

Experimental Section

Preparation of Bis(4-methoxyphenyl)acetic Acid (4a) as a Typical Procedure: A THF solution of EtMgCl (0.93 M, 1.34 mL, 1.25 mmol) was added to a solution of (4-methoxyphenyl)acetic acid (**1**; 0.083 g, 0.5 mmol) in THF (1.5 mL) at room temperature. The resulting mixture was stirred at room temperature for 3 h, and then $Pd(tBu_3P)_2$ (5.1 mg, 0.01 mmol) was added followed by 4-methoxy-1-bromobenzene (**3a**; 0.198 g, 1.0 mmol). After stirring the mixture at 60 °C for 3 h, the resulting mixture was passed through a pad of Celite, 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 (300 MHz, $CDCl_3$): δ = 3.78 (s, 6 H), 4.95 (s, 1 H), 6.86 (d, J = 8.7 Hz, 4 H), 7.23 ppm (d, J = 8.7 Hz, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.3, 55.5, 114.2, 129.8, 130.6, 159.0, 179.0 ppm. IR (ATR): $\tilde{\nu}$ = 2959 (br.), 2839, 1700, 1609, 1509, 1246, 1031, 809 cm^{-1}. HRMS (ESI+): calcd. for $C_{16}H_{15}O_4$ $[M]^+$ 271.0970; found 271.0971.

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

This work was partially supported by the Japan Society for the Promotion of Science (JSPS) through Kakenhi B (grant numbers 22350042 and 25288049) and the Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT) through Special Coordination Funds for Promoting Science and Technology, Creation of Innovation Centers for Advanced Interdisciplinary Research Areas (Innovative Bioproduction Kobe). S. T. thanks the JSPS for a Research Fellowship for Young Scientists.

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Received: April 19, 2014
Published Online: ■

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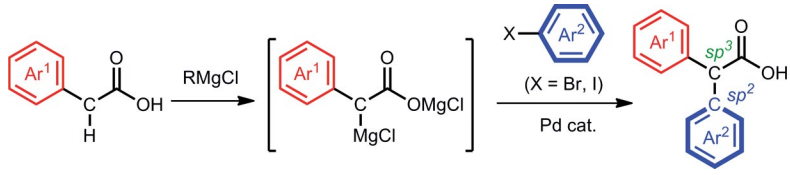

Functionalization at the C–H bond of α-arylcarboxylic acids with a Grignard reagent results in metalation. Treatment of the metalated intermediates with aryl halides in the presence of a Pd catalyst leads to diarylcarboxylic acids in good to excellent yields through the formation of a $C(sp^3)$–$C(sp^2)$ bond. The use of the Grignard reagent is the key to a successful coupling reaction.

Keywords: Synthetic methods / Homogeneous catalysis / Palladium / C–H activation / Arylation / Grignard reagents / Carboxylic acids

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