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<td>Tanaka, Daiki / Tanaka, Shota / Mori, Atsunori</td>
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Palladium-catalyzed α-Arylation of Carboxylic Acid Derivatives with Grignard Reagent

Daiki Tanaka,[a] Shota Tanaka,[a] and Atsunori Mori*[a]

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 tBuMgCl at room temperature to 60 °C results in complete deprotonation.

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 alkoxydes showed insufficient basicity for the deprotonation of carboxylic acids. Indeed, no deprotonation of (4-methoxyphenyl)acetic acid under such conditions the resulting mixture is treated with 4-methoxybromobenzene in the presence of 2 mol % Pd(tBuP)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.

Scheme 1. Deprotonative metalation at C(sp²)–H or C(sp³)–H bond.

Introducation

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 Csp²–Csp² 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. Nevertheless, the related reaction of carboxylic acid as a carbonyl derivative has not been achieved so far 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 nucleophilic substitution, 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 formation leading to give cross-coupling products and π-conjugated polymers. In addition to such Csp²–Csp² coupling, it is intriguing that the related reaction at the Csp³ 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)
heteroaromatic compounds, 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 temperature.

With the likely deprotonation conditions in hand, the coupling reaction with aryl halide was examined. Table 2, summarizes the results. After deprotonation with tBuMgCl at 60 °C for 3 h, the reaction of (4-methoxy)phenylacetic acid 1 with 4-methoxy-1-bromobenzene (3a) was carried out in THF at 60 °C for 3 h in the presence of several palladium or nickel catalysts. The reaction with Pd(tBu3P)2 (2.0 mol%) afforded the corresponding diarylacetic acid 4a in 86% yield, whereas other nickel or palladium catalysts such as NiCl2dppe, NiCl2dpf, NiCl2(PPh3)IPr, PdCl2dpf, PEPPSI-SIPr resulted in much inferior yields. The use of Pd2(dba)3·CHCl3 with several bulky phosphines John Phos, X Phos, Ru Phos, Dave Phos, and tBu XPhos 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 1. Deprotonation of (4-methoxy)phenylacetic acid (1) with a Grignard reagent in the presence/absence of secondary amine[a]**

<table>
<thead>
<tr>
<th>RMgX[b]</th>
<th>Amine[b]</th>
<th>Time, Temp (h, °C)[c]</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>tBuMgCl</td>
<td>none</td>
<td>1, rt</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>none</td>
<td>0.5, 60</td>
<td>77</td>
</tr>
<tr>
<td></td>
<td>none</td>
<td>3, 60</td>
<td>85</td>
</tr>
<tr>
<td>jPrMgCl·LiCl</td>
<td>none</td>
<td>3, 60</td>
<td>74</td>
</tr>
<tr>
<td>PhMgCl</td>
<td>none</td>
<td>3, 60</td>
<td>no product</td>
</tr>
<tr>
<td>EtMgCl</td>
<td>none</td>
<td>3, 60</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>Cy2:NH[1]</td>
<td>3, 60</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>TMP[2]</td>
<td>3, 60</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>iPr2NH</td>
<td>3, 60</td>
<td>84</td>
</tr>
<tr>
<td></td>
<td>Et3NH</td>
<td>3, 60</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>CyMeNH[3]</td>
<td>3, 60</td>
<td>92</td>
</tr>
<tr>
<td></td>
<td>DMP[4]</td>
<td>3, 60</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>Ph2NH</td>
<td>3, 60</td>
<td>78</td>
</tr>
<tr>
<td>EtMgCl</td>
<td>none</td>
<td>3, rt quant.</td>
<td></td>
</tr>
</tbody>
</table>

[a] The reaction was carried out with 0.5 mmol of 1 and 1.25 mmol of RMgX in 1.5 mL of THF in the presence/absence of 10 mol% of amine [b] Isolated yield. [c] Cy: cyclohexyl; TMP: 2,2,6,6-tetramethylpiperidine-1-yl; DMP: cis-2,6-dimethylpiperidine-1-yl.

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 CF3 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 (3k), 3-bromothiophene (3k), 3-bromofuran (3m), and 9-iodo-N-ethycarbazole (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]**

<table>
<thead>
<tr>
<th>Aryl halide (yield)[b]</th>
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<th>Aryl halide (yield)[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>3b (77%)</td>
<td>3c (88%)</td>
<td>3d (57%)</td>
</tr>
<tr>
<td>3e (80%)</td>
<td>3f (87%)</td>
<td>3h (90%)</td>
</tr>
<tr>
<td>3j (90%)</td>
<td>3k (90%)</td>
<td>3m (70%)</td>
</tr>
<tr>
<td>3l (85%)</td>
<td>3n (66%)</td>
<td>3o (70%)</td>
</tr>
</tbody>
</table>

[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(tBu3P)2 (2.0 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 (naphth-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 ary1 halides and 2 mol% Pd(η5-Bu3P)2 followed. Further stirring at 60 °C 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 arylation products in good to excellent yields.

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

<table>
<thead>
<tr>
<th>Aryl-Br</th>
<th>Yield, %</th>
<th>R-</th>
<th>Aryl-Br</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeO-B-Br</td>
<td>81</td>
<td>5</td>
<td>MeO-B-Br</td>
<td>56</td>
</tr>
<tr>
<td>MeO-B-Br</td>
<td>84</td>
<td>3j</td>
<td>MeO-B-Br</td>
<td>56</td>
</tr>
<tr>
<td>MeO-B-Br</td>
<td>78</td>
<td>6</td>
<td>MeO-B-Br</td>
<td>89</td>
</tr>
</tbody>
</table>

[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(η5-Bu3P)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 carbonylate A leading to the corresponding α-metallo carbonylate B or the enolate B'. On the other hand, aryl halide reacts with palladium(0) catalyst to give ary1palladium(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 Pd0. Since acidity of the α-proton of carboxylate derived from I 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 carboxylic 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 diarylacteic 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 diarylactic 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(η5-Bu3P)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. 1H NMR (CDCl3) 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). 13C NMR (CDCl3) δ 55.3, 55.5, 114.2, 129.8, 136.8, 159.0, 179.0. IR (ATR) 2959(br), 2839, 1700, 1609, 1509, 1246, 1031, 809 cm-1. HRMS (ESI+) found: 271.0971. Calcd for C16H15O4 [M]+: 271.0970.

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

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Layout 2:

Coupling reaction

Functionalization at the C-H bond of $\alpha$-arylcarboxylic acid with 2 equivalents of Grignard reagent undergoes metatalation. 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