Palladium-Catalyzed Cross-Couplings of Unsaturated Halides Bearing Relatively Acidic Hydrogen Atoms with Organozinc Reagents

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Abstract: A wide range of polyfunctional aryl, heteroaryl, alkyl, and benzylic zinc reagents were coupled with unsaturated aryl halides bearing an acidic NH or OH proton, using palladium(II) acetate (1 mol%), and S-Phos (2 mol%) as catalyst without the need of protecting groups.

Key words: palladium catalysis, cross-coupling, functionalized zinc reagents, polyfunctional biaryls

Introduction

Palladium-catalyzed cross-coupling reactions between organometallic reagents and unsaturated halides are of central importance in modern synthetic organic chemistry. The resulting cross-coupling products are highly relevant as pharmaceuticals, agrochemicals, natural products, or new materials.1 The most popular palladium-catalyzed cross-coupling, the Suzuki reaction, uses organoboronic acids or derivatives as nucleophiles,2 due to the commercial availability, air stability, and functional group compatibility of the organoboron reagents. However, difficulties concerning their tendency to form boroxines and competitive deboronation remain.3 Also, due to the covalent nature of the C–B bond, these cross-couplings proceed under harsher conditions compared to the corresponding Negishi cross-coupling using organozinc reagents,4 which also display a high functional group compatibility.5 Recently, we have reported reaction conditions and a catalytic system allowing the cross-coupling of organozinc reagents with unsaturated aryl halides bearing relatively acidic hydrogens without the use of protecting groups.6 No excess of the zinc reagent and no additional base for deprotonation of the acidic proton prior to the cross-coupling were necessary. We found that the use of palladium(II) acetate (1 mol%) and S-Phos (2 mol%), introduced by Buchwald7 as a catalytic system, allowed an efficient cross-coupling between various organozinc re-
agents and unsaturated halides bearing relatively acidic NH groups. By adding the zinc reagent slowly (typically over 90 min via a syringe pump), also more acidic alcohol and phenol protons were tolerated. Herein, we wish to report a typical practical procedure illustrating this method.

**Scope and Limitations**

A variety of functionalized zinc reagents were coupled with unsaturated aryl halides bearing acidic hydrogen atoms under mild conditions (1–3 h, 25 °C). Thus, the ester-substituted arylzinc reagent $1a$ (1.2 equiv), prepared by direct zinc insertion into the corresponding aryl iodide, with 4-bromoaniline ($2a$) in the presence of palladium(II) acetate (1 mol%) and S-Phos (2 mol%) led within 1 hour at 25 °C to the biphenyl aniline $3a$ in 88% isolated yield (Table 1, entry 1). We also scaled up this cross-coupling reaction starting with 20 mmol of the aryl bromide with a slightly increased yield (Procedure 1). The relatively acidic NH$_2$ protons$^9$ do not disturb the cross-coupling reaction, which obviously occurs faster than the competitive deprotonation. Interestingly, the reaction can be extended to 2,5-dibromoanilines, although with moderate yields. Thus the aryloxy group $1a$ (2.4 equiv) reacts with the dibromoaniline $2b$, affording the 2,4,6-trisubstituted phenylamine $3b$, a useful intermediate for the synthesis of thioarylaminyls,$^{10}$ in 47% yield (entry 2). Unprotected 5-bromoindole ($2c$) was also suitable for the cross-coupling procedure and the arylated indole $3c$ was obtained in 85% yield (entry 3) after the reaction with 4-cyanophenylzinc.

| Entry | Zinc reagent | Unsaturated halide | Product | Yield (%)$^a$
<table>
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<tbody>
<tr>
<td>1</td>
<td>$1a$</td>
<td>$2a$</td>
<td>$3a$</td>
<td>88 (95)$^b$</td>
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<tr>
<td>2</td>
<td>$1a$</td>
<td>$2b$</td>
<td>$3b$</td>
<td>47$^d$</td>
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<tr>
<td>3</td>
<td>$1b$</td>
<td>$2c$</td>
<td>$3c$</td>
<td>85</td>
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<td>4</td>
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<td>$2d$</td>
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<td>81</td>
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<td>$1b$</td>
<td>$2e$</td>
<td>$3e$</td>
<td>78$^e$</td>
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<td>6</td>
<td>$1d$</td>
<td>$2f$</td>
<td>$3f$</td>
<td>65$^f$</td>
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<tr>
<td>7</td>
<td>$1c$</td>
<td>$2g$</td>
<td>$3g$</td>
<td>91$^g$</td>
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<td>8</td>
<td>$1e$</td>
<td>$2h$</td>
<td>$3h$</td>
<td>75$^g$</td>
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<tr>
<td>9</td>
<td>$1f$</td>
<td>$2i$</td>
<td>$3i$</td>
<td>88$^g$</td>
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$^a$ Yield of analytically pure product.
$^b$ Reaction was carried out on a 20 mmol scale.
$^c$ Ar = 4-EtO$_2$CC$_6$H$_4$.
$^d$ Amount of zinc reagent used: 2.4 equiv.
$^e$ The zinc reagent was added slowly over 90 min via a syringe pump.
iodide reagent 1b. Also, 2-chlorobenzylzinc chloride reagent 1c, prepared by direct zinc insertion into the benzyl chloride, reacted smoothly with 2-bromoaniline (2d; 27 mmol) within two hours at 25 °C, leading to the diarylmethane 3d in 81% yield (entry 4). For the coupling of unsaturated halides bearing more acidic OH functions, it was found that the slow addition of the zinc reagent was crucial for obtaining a high yield. Thus, adding the arylzinc 1b reagent (1.2 equiv) slowly over 90 minutes (via syringe pump) to a solution of the iodobenzyl alcohol 2e, palladium(II) acetate (1 mol%), and S-Phos (2 mol%) led to the functionalized biaryl 3e in 78% yield (entry 5).

Similarly, the reaction of benzylzinc chloride reagent 1d with the alkenyl bromide 2i, bearing a acidic OH group, furnished the desired coupling product 3f in 65% yield (entry 6). In the case of benzylzinc reagents, even more acidic phenolic protons were tolerated by our protocol.12 Adding the benzylzinc chloride reagent 1e (1.3 equiv) slowly (over 90 min) to a solution of 3-bromophenol (2g; 32 mmol), palladium(II) acetate (1 mol%), and S-Phos (2 mol%) provided the phenol 3g in 91% yield (entry 7). Also the benzylzinc reagent 1e (1.2 equiv), bearing a ketone function, reacts smoothly with 5-bromosalicylaldehyde (2h), leading to the polyfunctional diarylmethane 3h in 75% yield (entry 8). Finally the cyano-substituted alkylzinc bromide reagent 1f could be coupled with the secondary iodobenzyl alcohol 2i to give the benzylic alcohol 3i in 88% yield (entry 9).

In summary, an efficient cross-coupling of various functionalized zinc reagents with unsaturated halides bearing acidic protons was demonstrated. No use of protecting groups or deprotonation by an additional base prior to the cross-coupling of these acidic protons is required. We have extended our previous work to the scaled-up and optimized cross-coupling of aryl- and alkenyl halides, bearing acidic NH or OH functions. These reactions could be performed with standard laboratory glassware and did not require the use of expensive chemicals or catalysts. Further studies are underway in our laboratory to extend this method.

All reactions were carried out under argon in dried glassware. All starting materials were purchased from commercial suppliers and used without further purification, unless otherwise stated. THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under N2. S-Phos was purchased from Strem or prepared according to the literature. Yields refer to isolated compounds estimated to be &gt;95% pure as determined by 1H NMR spectroscopy and capillary GC analysis.

Zinc Reagent 1a
Anhyd LiCl (56 mmol, 2.38 g) was placed in an argon-flushed flask and dried for 30 min at 150 °C under high vacuum (1 mbar). Zn powder (76 mmol, 4.98 g) was added under argon and the heterogeneous mixture was stirred for 2 h. After cooling to 25 °C, the flask was evacuated and refilled with argon three times. THF (50 mL) was added and the Zn was activated with 1,2-dibromoethane (2.5 mmol, 0.22 mL) and TMSCl (2.5 mmol, 0.32 mL). Ethyl 4-iodobenzoate (50 mmol, 13.8 g) was added neat and the mixture stirred at 25 °C for 24 h. The solution of 1a was carefully separated from the remaining Zn powder by using a syringe and transferred to another dry and argon-flushed flask. Titrination of the Zn reagent (typically 1 mL) with I2 indicated a concentration of 0.94 M.

Zinc Reagent 1b
Anhyd LiCl (56 mmol, 2.38 g) was placed in an argon-flushed flask and dried for 30 min at 150 °C under high vacuum (1 mbar). Zn powder (76 mmol, 4.98 g) was added under argon and the heterogeneous mixture was dried again for 30 min at 150 °C under high vacuum (1 mbar). After cooling to 25 °C, the flask was evacuated and refilled with argon three times. THF (50 mL) was added and the Zn was activated with 1,2-dibromoethane (2.5 mmol, 0.22 mL) and TMSCl (2.5 mmol, 0.32 mL). 4-Iodobenzenonitrile (50 mmol, 11.5 g) was added neat and the mixture stirred at 25 °C for 24 h. The solution of 1b was carefully separated from the remaining Zn powder by using a syringe and transferred to another dry and argon-flushed flask. Titration of the Zn reagent (typically 1 mL) with I2 indicated a concentration of 0.95 M.

Zinc Reagent 1c
Anhyd LiCl (84 mmol, 3.57 g) was placed in an argon-flushed flask and dried for 30 min at 150 °C under high vacuum (1 mbar). Zn powder (114 mmol, 7.47 g) was added under argon and the heterogeneous mixture was dried again for 30 min at 150 °C under high vacuum (1 mbar). After cooling to 25 °C, the flask was evacuated and refilled with argon three times. THF (75 mL) was added and the Zn was activated with 1,2-dibromoethane (2.5 mmol, 0.22 mL) and TMSCl (2.5 mmol, 0.32 mL). The mixture was cooled in a water bath. 2-Chlorobenzyl chloride (75 mmol, 12.07 g) was added neat and the mixture and stirred for 2 h. The solution of 1c was carefully separated from the remaining Zn powder by using a syringe and transferred to another dry and argon-flushed flask. Titration of the Zn reagent (typically 1 mL) with I2 indicated a concentration of 0.92 M.

Zinc Reagent 1d
Anhyd LiCl (56 mmol, 2.38 g) was placed in an argon-flushed flask and dried for 30 min at 150 °C under high vacuum (1 mbar). Zn powder (76 mmol, 4.98 g) was added under argon and the heterogeneous mixture was dried again for 30 min at 150 °C under high vacuum (1 mbar). After cooling to 25 °C, the flask was evacuated and refilled with argon three times. THF (50 mL) was added and the Zn was activated with 1,2-dibromoethane (2.5 mmol, 0.22 mL) and TMSCl (2.5 mmol, 0.32 mL). The mixture was cooled in a water bath. Benzyl chloride (50 mmol, 6.33 g) was added neat and the mixture and stirred for 12 h. The solution of 1d was carefully separated from the remaining Zn powder by using a syringe and transferred to another dry and argon-flushed flask. Titration of the Zn reagent (typically 1 mL) with I2 indicated a concentration of 0.93 M.

Zinc Reagent 1e
Anhyd LiCl (56 mmol, 2.38 g) was placed in an argon-flushed flask and dried for 30 min at 150 °C under high vacuum (1 mbar). Zn powder (76 mmol, 4.98 g) was added under argon and the heterogeneous mixture was dried again for 30 min at 150 °C under high vacuum (1 mbar). After cooling to 25 °C, the flask was evacuated and refilled with argon three times. THF (50 mL) was added and the Zn was activated with 1,2-dibromoethane (2.5 mmol, 0.22 mL) and TMSCl (2.5 mmol, 0.32 mL). The mixture was cooled to 0 °C. 1-(3-Chloromethylphenyl)pentan-1-one (50 mmol, 10.54 g) was added neat and the mixture was warmed to 25 °C and stirred for 4 h. The solution of 1e was carefully separated from remaining Zn powder by using a syringe and transferred to another dry and argon-flushed flask. Titration of the Zn reagent (typically 1 mL) with I2 indicated a concentration of 0.87 M.
Zinc Reagent 1f

Anhyd LiCl (56 mmol, 2.38 g) was placed in an argon-flushed flask and dried for 30 min at 150 °C under high vacuum (1 mbar). Zn powder (76 mmol, 4.98 g) was added under argon and the heterogeneous mixture was dried again for 30 min at 150 °C under high vacuum (1 mbar). After cooling to 25 °C, the flask was evacuated and refilled with argon three times. THF (50 mL) was added and the Zn was activated with 1,2-dibromoethane (2.5 mmol, 0.22 mL) and TMSCI (2.5 mmol, 0.32 mL). 4-Bromobutyronitrile (50 mmol, 7.40 g) was added neat and the mixture stirred at 50 °C for 24 h. The solution of 4f was carefully separated from the remaining Zn powder by using a syringe and transferred to another dry and argon-flushed flask. Titration of the Zn reagent (typically 1 mL) with $I_2$ indicated a concentration of 1.0 M.

**Procedure 1**

4'-Aminobiphenyl-4-carboxylic Acid Ethyl Ester (3a)

A dry and argon-flushed 100 mL Schlenk-tube was charged with 4-bromobenzaldehyde (2a; 3.44 g, 20 mmol), Pd(OAc)$_2$ (45 mg, 0.2 mmol), S-Phos (164 mg, 0.4 mmol), and THF (20 mL). After stirring the mixture for 5 min, 4-(ethoxycarbonyl)phenylzinc iodide (1a; 25.5 mL, 0.94 M in THF, 24 mmol) was added (Caution! The reaction is exothermic. For conducting the reaction on a bigger scale we recommend the use of a reflux condenser and addition of the Zn reagent over 10–15 min). The mixture was stirred for 1 h at 25 °C. Then, the mixture was quenched with a sat. aq NH$_4$Cl (40 mL), extracted with Et$_2$O (3 × 50 mL), and the combined organic phases were washed with sat. aq Na$_2$SO$_4$. Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane–Et$_2$O, 7:3) yielded 3a as a white solid (4.88 g; 95%); mp 86.8–88.4 °C.

IR (KBr): 3421 (w), 3334 (w), 2985 (w), 1693 (vs), 1629 (w), 1595 (s), 1464 (s), 1414 (m), 1364 (s), 1197 (m), 1132 (m), 1103 (m), 1023 cm$^{-1}$ (m).

HRMS: $m/z$ calcd for C$_{15}$H$_{15}$NO$_2$: 241.1103; found: 241.1101.

1H NMR (CDCl$_3$, 300 MHz, 25 °C):

- $d = 7.2$ Hz, 3 H).
- $d = 7.90–7.83$ (m, 2 H), 7.39–7.13 (m, 4 H), 6.80–6.78 (m, 1 H), 6.69–6.64 (m, 2 H), 4.96 (s, 1 H), 4.06 (s, 2 H).
- $d = 166.6, 16.4, 14.7, 14.3, 13.1, 13.0, 129.2, 126.1, 120.1, 61.1, 60.6, 14.4, 14.4.

MS (EI, 70 eV): $m/z$ (%) = 461 (100, [M$^+$]), 416 (22), 388 (5), 287 (8), 241 (6).

HRMS: $m/z$ calcd for C$_{17}$H$_{19}$NO$_3$: 285.1365; found: 285.1359.

4-(1H-Indol-5-yl)benzotriazole (3e)

4-Cyanophenylzinc iodide (1b; 3.8 mL, 0.95 M in THF, 3.6 mmol) was added to a solution of 5-bromobenzaldehyde (2c; 588 mg, 3 mmol), Pd(OAc)$_2$ (6.7 mg, 0.06 mmol), and S-Phos (24.6 mg, 0.06 mmol) in THF (2 mL), according to Procedure 1. The mixture was stirred for 1 h at 25 °C. Then, the mixture was quenched with sat. aq NH$_4$Cl (15 mL) and extracted with Et$_2$O (3 × 15 mL). The combined organic phases were washed with sat. aq thiourea (15 mL) and dried (Na$_2$SO$_4$). Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane–Et$_2$O, 7:3) yielded 3e as a colorless solid (558 mg, 85%); mp 122.6–123.7 °C.

IR (KBr): 3371 (br w), 2981 (w), 2871 (w), 1704 (s), 1615 (s), 1507 (s), 1465 (s), 1367 (m), 1276 (vs), 1187 (s), 1105 (s), 1081 (s), 1018 cm$^{-1}$ (s).

HRMS: $m/z$ calcd for C$_{17}$H$_{19}$NO$_3$: 285.1365; found: 285.1359.

2-Chlorobenzylphenoxyamine (3d)

A dry and argon-flushed 100 mL Schlenk-tube was charged with 2-bromobenzaldehyde (2d; 4.46, 27 mmol), Pd(OAc)$_2$ (60 mg, 0.27 mmol), and S-Phos (221 mg, 0.54 mmol) in THF (25 mL), according to Procedure 1. The mixture was stirred for 2 h at 25 °C. Then, the mixture was quenched with sat. aq

1H NMR (CDCl$_3$, 300 MHz, 25 °C):

- $d = 7.90–7.83$ (m, 2 H), 7.39–7.13 (m, 4 H), 6.80–6.78 (m, 1 H), 6.69–6.64 (m, 2 H), 4.96 (s, 1 H), 4.06 (s, 2 H).
- $d = 166.7, 166.2, 144.7, 143.2, 131.7, 130.3, 129.2, 126.1, 120.1, 61.1, 60.6, 14.4, 14.4.

MS (EI, 70 eV): $m/z$ (%) = 241 (100, [M$^+$]), 220 (49), 184 (15), 183 (100), 182 (17), 181 (20), 165 (49), 153 (20), 152 (22).

HRMS: $m/z$ calcd for C$_{13}$H$_{11}$ClO: 218.0496; found: 218.0495

PRACTICAL SYNTHETIC PROCEDURES

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NHCl (50 mL) and extracted with Et2O (3 × 75 mL). The combined organic phases were washed with sat. aq thiourea (60 mL) and dried (Na2SO4). Purification of the crude residue obtained after evaporation of the solvents by flash chromatography (pentane–Et2O, 5:1) yielded 3d as a pale yellow oil (4.78 g, 81%).

IR (film): 3372 (w), 3022 (w), 2974 (w), 1619 (m), 1493 (m), 1455 (m), 1442 (m), 1276 (w), 1189 (w), 1120 (w), 1048 (m), 1036 (s), 743 (vs), 682 cm–1 (m).

1H NMR (600 MHz, CDCl3, 25 °C): δ = 7.43–7.41 (m, 1 H), 7.20–7.12 (m, 3 H), 7.04–6.99 (m, 2 H), 6.80–6.73 (m, 2 H), 3.99 (s, 2 H), 3.67 (s, 2 H).

13C NMR (150 MHz, CDCl3, 25 °C): δ = 144.4, 136.8, 134.3, 130.8, 130.0, 129.4, 127.8, 127.8, 127.0, 123.6, 118.6, 116.0, 34.9.

MS (70 eV, EI): m/z (%) = 217 (27, [M+]), 183 (16), 182 (100), 181 (4) (52), 91 (41).

MS (EI, 70 eV): m/z (%) = 217 (33, [M+]), 183 (100), 182 (20), 181 (9) (19), 179 (20), 166 (31), 119 (20), 108 (17), 106 (20), 95 (10), 75 (10), 65 (6).
References


(9) Typical $pK_a$ values (in DMSO) for anilines range between 20–30; for a comprehensive compilation of $pK_a$ data see http://www.chem.wisc.edu/areas/reich/pkatable/index.htm and references cited therein.


(12) Our experiments indicate a relative kinetic basicity of zinc reagents: arylyzinc halide > alkylzinc halide > benzylic zinc halide. For further experimental details, see ref. 7.