



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

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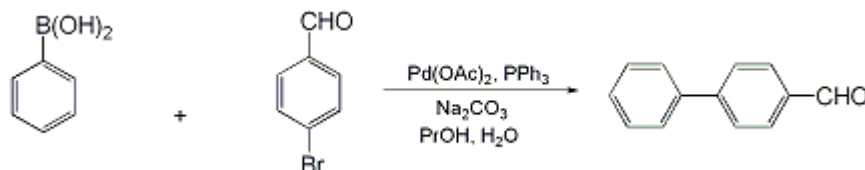
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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SYNTHESIS OF UNSYMMETRICAL BIARYLS USING A MODIFIED SUZUKI CROSS-COUPLING: 4- BIPHENYLCARBOXALDEHYDE

[[1,1'-Biphenyl]-4-carboxaldehyde]



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Checked by Steven Wenglowsky and Louis S. Hegedus.

1. Procedure

A 2-L, three-necked, round-bottomed flask equipped with a magnetic stirring bar, condenser, and a nitrogen gas inlet is charged with 50.0 g (0.270 mol) of 4-bromobenzaldehyde, 34.6 g (0.284 mol, 1.05 equiv) of benzeneboronic acid, and 485 mL of 1-propanol under a nitrogen purge. The mixture is stirred at room temperature for 30 min, allowing the solids to dissolve. The resulting solution is treated with 0.182 g (0.811 mmol, 0.003 equiv) of palladium acetate, 0.638 g (2.43 mmol, 0.009 equiv) of triphenylphosphine, 162 mL of 2 M sodium carbonate (Na_2CO_3) (0.324 mol, 1.20 equiv), 95.0 mL of deionized water and heated to reflux under a nitrogen atmosphere (Note 1).

After 45 min at reflux, a reaction aliquot checked by ^1H NMR indicates that the reaction is complete (Note 2), (Note 3) and (Note 4). The heat source is removed and 350 mL of water is added while the mixture is still hot. The nitrogen gas source is removed and the reaction is allowed to stir open to the atmosphere for 2.5 hr while cooling to room temperature (Note 5). The darkened mixture is diluted with 500 mL of ethyl acetate and transferred to a 2-L separatory funnel (Note 6). The two phases are separated and the aqueous layer is back-extracted with two additional 250-mL portions of ethyl acetate. The combined organic layers are washed with 250 mL of aqueous 5% sodium bicarbonate (NaHCO_3) followed by saturated brine, 2×250 mL (Note 7). The organic solution is placed in a 2-L Erlenmeyer flask with a magnetic stirring bar, treated with 25.0 g of Darco G-60 (Note 8) and stirred at room temperature for 30 min. To the mixture is added 50.0 g of sodium sulfate (Na_2SO_4) (Note 9) and stirring is continued for an additional 30 min.

A 2-L filter flask is equipped with an 11-cm Büchner funnel with filter paper. The funnel is charged with Celite to a depth of 1 cm (Note 10) and 50.0 g of Florisil is spread evenly on top of the Celite. The above mixture is filtered through this pad of filter aid (Note 11). The filter cake is rinsed with ethyl acetate, 2×100 mL. The resulting pale yellow filtrate is concentrated under reduced pressure to yield 47.3 g (96.2%) of pale yellow crystals (Note 12).

The crude solids are treated with 189 mL of hexanes (4 mL/g) and slurried at room temperature for 10 min before heating to reflux (Note 13). The resulting hazy solution is treated with 47.3 mL of methanol (1 mL/g), which clarifies the mixture (Note 14). Crystallization is induced by removing the heat source and allowing the mixture to cool slowly to room temperature over 2 hr. The flask is placed in a freezer to chill overnight. The thick slurry of crystals is filtered, rinsed with cold hexanes, 2×40 mL, and vacuum dried at room temperature to afford 42.5 g of pale yellow crystals (86.3% overall yield) (Note 15) and (Note 16).

2. Notes

1. 4-Bromobenzaldehyde and triphenylphosphine were purchased from Aldrich Chemical Company,

Inc. [Benzeneboronic acid](#) and [palladium acetate](#) were obtained from Lancaster Synthesis. [Sodium carbonate](#) was purchased from EM Science and deionized water was used to prepare the 2 M solution. Reagent grade [1-propanol](#) is available from Mallinkrodt Inc. All reagents and solvents are used without purification or degassing. There was no need to dry the glassware rigorously.

2. Upon dissolution of all the solids, the reaction mixture is pale yellow. The solution undergoes a sequence of color changes from yellow to orange ($t_{\text{r}} \sim 10$ min) to red ($t_{\text{r}} \sim 20$ min) to dark red/black ($t_{\text{r}} \sim 30$ min). This color change is generally indicative of reaction completeness in all of the coupling reactions performed here. These color changes were not observed by the checker in any of the runs. Instead, the organic portion was brown to dark brown for the duration of the reaction.

3. The reaction is monitored by ^1H NMR with sample preparation as follows: A 0.3-mL aliquot of the reaction mixture is removed and concentrated under reduced pressure for 10 min. The resulting residue is dissolved in 0.5 mL of [methyl sulfoxide-d](#) (DMSO-d_6) (Cambridge Isotope Labs) and filtered through a pipette with a glass wool plug directly into an NMR tube. The sample is checked on a Bruker ARX-500 MHz instrument. The checker used a Bruker 300 MHz instrument, which sufficed.

4. Reaction completeness is determined by observing the ^1H NMR signals of the aldehyde protons at 300-500 MHz. The starting material has an aldehydic proton signal at δ 10.00 while the product aldehyde signal is cleanly separated at δ 10.06. The 30-min sample showed no starting material remaining. This was confirmed by spiking the NMR tube with 3 mg of [4-bromobenzaldehyde](#) and reanalyzing the sample.

5. During the 2.5-hr stir time, the reaction mixture darkens considerably and a thin, black emulsion forms. Open air stirring is required to force formation of the emulsion layer early in the workup and thus prevent its formation during the recrystallization stage.

6. HPLC grade [ethyl acetate](#) is available from Mallinkrodt Inc.

7. During the washes, the thin, black emulsion that forms is taken with the organic layer on each separation until the final brine wash. The material is then discarded with the brine layer, aiding the subsequent purification steps.

8. Darco G-60, a 100-mesh activated [carbon](#), is available from Aldrich Chemical Company, Inc.

9. [Sodium sulfate](#) is available from EM Science.

10. Celite is available from Aldrich Chemical Company, Inc.

11. 200 Mesh Florisil is available from Aldrich Chemical Company, Inc.

12. ^1H NMR (DMSO-d_6) is consistent with the desired structure, but does indicate the presence of low levels of [benzeneboronic acid](#) and other aromatic impurities.

13. Reagent grade hexanes are available from Mallinkrodt Inc.

14. Reagent grade anhydrous [methanol](#) is available from Mallinkrodt Inc.

15. The recrystallized [4-biphenylcarboxaldehyde](#) exhibits the following physical properties: mp 58-59°C; ^1H NMR (500 MHz, DMSO-d_6) δ : 7.45 (t, 1 H, $J = 7.4$), 7.52 (t, 2 H, $J = 7.4$), 7.77 (d, 2 H, $J = 7.4$), 7.91 (d, 2 H, $J = 8.1$), 8.01 (d, 2 H, $J = 8.1$), 10.06 (s, 1 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ : 127.9, 128.2, 129.4, 129.9, 131.0, 135.9, 139.6, 146.7, 193.5; FD MS m/z : 182.2; IR (neat) cm^{-1} : 1700, 1680, 1606, 1170, 839; Anal. Calcd for $\text{C}_{13}\text{H}_{10}\text{O}$: C, 85.69; H, 5.53. Found: C, 85.60; H, 5.62.

16. On a smaller scale, crude [4-biphenylcarboxaldehyde](#) can be purified by flash chromatography using 93/7 hexanes/[ethyl acetate](#) ($R_f = 0.3$). Recoveries are typically 90-95%.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

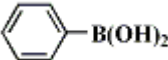
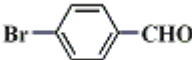
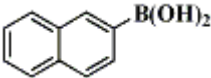
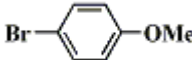
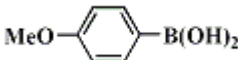
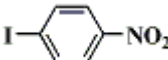
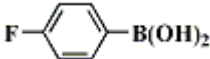
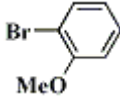
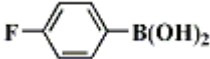
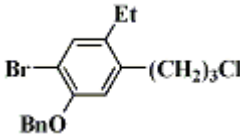
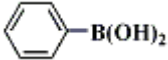
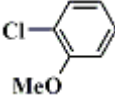
Although a variety of methods are available for preparing unsymmetrical biaryls, many of them suffer from the use of harsh conditions, the need for special apparatus and handling operations, or the employment of stoichiometric levels of [zinc](#) or [tin](#) reagents.^{2 3} The classic Suzuki cross-coupling between boronic acids and aryl halides uses [palladium](#) catalysis under mildly basic conditions to obviate a number of these problems.^{4 5} The increased availability of boronic acid derivatives along with the development of alternatives to the use of [tetrakis\(triphenylphosphine\)palladium\(0\)](#) has resulted in one of the most useful methods for forming carbon-carbon bonds between aromatic rings.^{6 7}

The procedure described here incorporates a number of modifications to the Suzuki coupling that result in a sound, efficient and scaleable means of synthesizing biaryls. First, the catalytic use of palladium acetate and triphenylphosphine to generate palladium(0) eliminates the need for the expensive air and light sensitive tetrakis(triphenylphosphine)palladium(0). No purification of reagents is necessary, no special apparatus is required, and rigorous exclusion of air from the reaction mixture is not necessary. Furthermore, homo-coupled products are not present in significant levels (as determined by 500 MHz ¹H NMR).

Further improvements to the cross-coupling process are observed by employing 1-propanol as solvent. The water miscibility of 1-propanol allows reaction mixtures to remain homogeneous in the presence of aqueous base. The 1-propanol/water ratio can be varied for each derivative to adjust for the solubility characteristics of starting materials, coupled products, and salt by-products. The reasonably high boiling point of 1-propanol (97°C; 88°C azeotrope with water) affords rate advantages over reactions normally run in tetrahydrofuran or ethanol.^{8,9} Reactions run in 1-propanol are typically complete within 30 min at reflux. Furthermore, additives (LiCl) or stronger bases [Ba(OH)₂, TlOH] are not necessary to obtain high yields.¹⁰

The Table lists the results of applying these modified conditions to a number of biaryl derivatives, including recent examples from the literature. With the exception of entry 6, that employs a non-reactive aromatic chloride, all the cross-couplings result in excellent yields and are indicative of the generality of this procedure.

TABLE
Preparation of Biaryls via Pd(0) Catalyzed Cross-Coupling of Boronic Acids with Aryl Halides^a

Entry	Boronic Acid	Aryl Halide	Purified Yield (%)	Ref.
1			86.3	11
2			82.7	12
3			83.4	13,14
4			96.8	
5			91.1	15
6			<10	

^aWith the exception of entry 1 (270-mmol scale), all reactions were performed on a 25-mmol scale and the products were purified by flash chromatography using varying ratios of hexanes/ethyl acetate to effect an R_f value of 0.3 for the desired compound.

References and Notes

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

4-Biphenylcarboxaldehyde (8);
[1,1'-Biphenyl]-4-carboxaldehyde (9); (3218-36-8)

4-Bromobenzaldehyde:
Benzaldehyde, 4-bromo- (9); (1122-91-4)

Benzeneboronic acid (8);
Boronic acid, phenyl- (9); (98-80-6)

1-Propanol:
Propyl alcohol (8);
1-Propanol (9); (71-23-8)

Palladium acetate:
Acetic acid, palladium(2+) salt (8,9); (3375-31-3)

Triphenylphosphine:
Phosphine, triphenyl- (8,9); (603-35-0)