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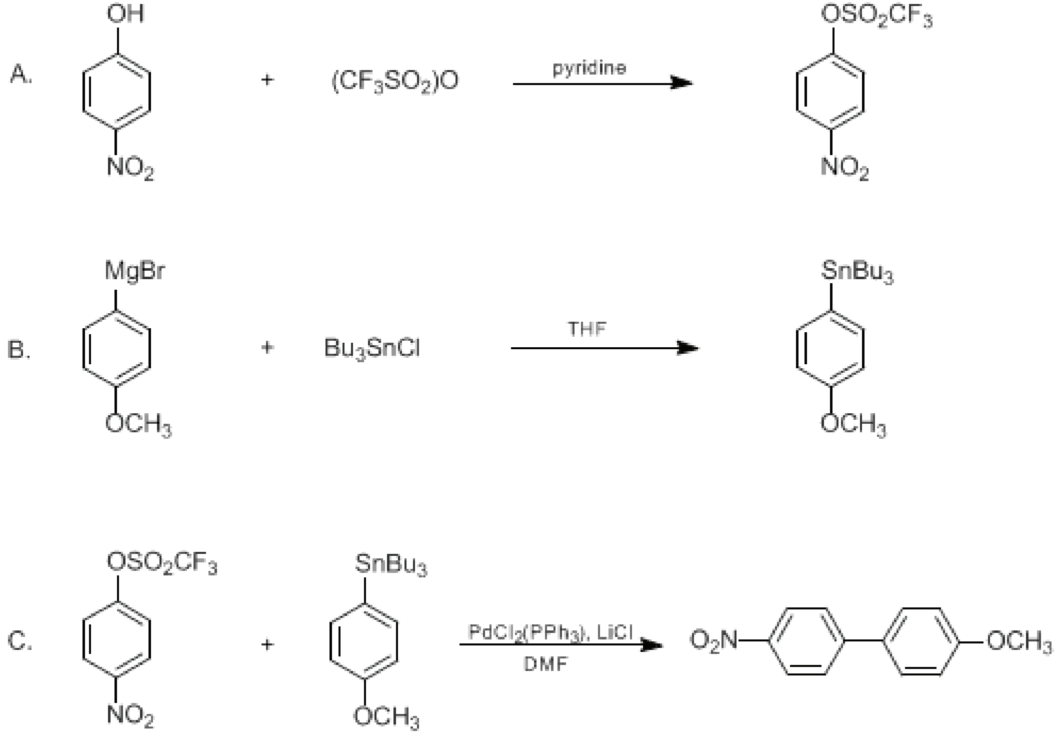
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

Organic Syntheses, Vol. 71, p. 97 (1993); Coll. Vol. 9, p.553 (1998).

4-METHOXY-4'-NITROBIPHENYL
[1,1'-Biphenyl, 4-methoxy-4'-nitro-]



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Discussion Addendum: *Org. Synth*. **2011**, *88*, 197.

1. Procedure

CAUTION! Many organotin compounds are toxic.[2] Their preparation and use should be carried out in a well-ventilated hood.

A. *4-Nitrophenyl trifluoromethanesulfonate* **(1)**. A dry, 100-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, nitrogen gas inlet, and rubber septum (Note 1) is charged sequentially with 10.0 g (71.9 mmol) of 4-nitrophenol and 38 mL of pyridine (Note 2). The stirred solution is cooled to 0°C and 13.5 mL (80 mmol) of trifluoromethanesulfonic anhydride (Note 3) is added through the septum via a syringe. The rate of addition is such that the internal temperature of the flask never exceeds 25°C (Note 4). The solution is allowed to warm slowly to room temperature and is maintained at room temperature for 25 hr. The reaction is quenched by pouring it into a 250-mL separatory funnel that contains 100 mL of water and 50 mL of diethyl ether. The two phases are separated and the aqueous phase is extracted with four additional 50-mL portions of diethyl ether. The combined organic fractions are dried over magnesium sulfate, filtered, and concentrated to provide 18.7 g of crude **1** as a yellow, crystalline, solid.

The crude product is dissolved in 50 mL of diethyl ether and adsorbed onto 20 g of Celite 521 by evaporation of the diethyl ether under reduced pressure. The dry Celite 521 is then added to the top of a column containing 200 g of silica gel (32–63 micron) and the column is eluted with a mobile phase of 9:1 hexanes-ethyl acetate. The fractions containing the product (R_f = 0.50, 9:1 hexanes-ethyl acetate) are collected and concentrated under reduced pressure to yield 17.7 g (91%) of **1** as a colorless, crystalline, solid (Note 5).

B. *Tributyl(4-methoxyphenyl)stannane* **(2)**. A dry, 250-mL, three-necked, round-bottomed flask, equipped with a reflux condenser, magnetic stirring bar, and nitrogen gas inlet, is charged with 2.91 g (120 mmol) of magnesium turnings (Note 1) and (Note 6). The flask is fitted with a rubber septum and charged sequentially via syringe with 85 mL of tetrahydrofuran (Note 7), 14.0 mL (112 mmol) of 4-bromoanisole (Note 8), and 0.05 mL of methyl iodide (Note 9). The rubber septum is immediately replaced with a Teflon stopper. Within 5 min, the reaction spontaneously warms to reflux temperature and continues to boil for approximately 10 min. The reaction is stirred an additional 2 hr without external heating or cooling. The flask is fitted with a rubber septum and 30.5 mL (112 mmol) of tributyltin chloride is added to the green solution via a syringe (Note 10). The septum is again replaced with a Teflon stopper and the reaction is heated at reflux for 12 hr.

Upon cooling to room temperature, a gray precipitate forms and the reaction is quenched with 220 mL of saturated, aqueous ammonium chloride. The resulting mixture is poured into a 1-L separatory funnel and extracted with 220 mL of diethyl ether. The organic fraction is washed two times with 100 mL of water, and once with 100 mL of brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 44.1 g of crude product as a pale yellow oil. Purification of this material by bulb-to-bulb distillation (140–145°C, 0.5 mm) (Note 11) into a chilled (−78°C) receiving flask yields 41.0 g (92%) of **2** as a clear, colorless oil (Note 12).

C. *4-Methoxy-4'-nitrobiphenyl* **(3)**. A dry, 500-mL, three-necked, round-bottomed flask equipped with a reflux condenser, magnetic stirring bar, nitrogen gas inlet, and rubber septum (Note 1) is charged sequentially with 300 mL of anhydrous N,N-dimethylformamide (Note 13), 15.0 g (55.4 mmol) of 4-nitrophenyl trifluoromethanesulfonate **(1)**, 27.8 g (70.0 mmol) of tributyl(4-methoxyphenyl)stannane **(2)** (Note 14), 7.5 g of dry lithium chloride (Note 15), and 1.6 g (4 mol percent) of bis(triphenylphosphine) palladium(II) chloride (Note 16). The rubber septum is replaced with a Teflon stopper and the yellow mixture is heated at 100–105°C for 2.5 hr. After approximately 20 min, the reaction turns dark brown.

The reaction mixture is cooled to room temperature and then vacuum-filtered through a 350-mL, medium frit, sintered-glass Büchner funnel that is filled to a height of 4 cm with ethyl acetate-impregnated Celite 521. Four 100-mL portions of ethyl acetate are used to wash the pad of Celite 521. The filtrate is partially concentrated by removal of ethyl acetate under reduced pressure. The resulting brown liquid is slowly poured into 1.5 L of water. After standing for 8 hr, the precipitate is collected by vacuum filtration and air dried. The solid is dissolved in 500 mL of acetonitrile, the resulting solution is poured into a 1-L separatory funnel, and is washed with three 300-mL portions of hexanes. The acetonitrile layer is concentrated to provide 24 g of crude product as a brown solid.

The crude product is dissolved in a minimum amount of dichloromethane and adsorbed onto 25 g of silica gel (32–63 micron) by subsequent evaporation of the dichloromethane under reduced pressure. The sample of dry, dark brown silica gel is added to the top of a column containing 500 g of silica gel (32–63 micron) with a mobile phase of hexanes. The polarity of the mobile phase is gradually increased from hexanes to 95:5 hexanes-ethyl acetate. The fractions containing the desired product (R_f = 0.26, 95:5 hexanes-ethyl acetate) are combined and concentrated under reduced pressure to yield 6.9 g of **3** as a yellow solid. Additional purification is required to remove traces of tin by-products. Compound **3** is dissolved in 70 mL of ethyl acetate and stirred over 70 mL of saturated, aqueous potassium fluoride for 24 hr. The two phases are separated and the organic phase is dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting yellow solid is recrystallized from ethyl alcohol to provide 6.1 g (48%, 2 crops) of **3** as yellow needles (Note 17), (Note 18), and (Note 19).

2. Notes

1. All glassware is oven-dried at 140°C overnight and assembled while hot under a nitrogen atmosphere.
2. 4-Nitrophenol (99%+) is purchased from the Aldrich Chemical Company, Inc., as a golden yellow solid and used as received. Pyridine is freshly distilled from calcium hydride.
3. Trifluoromethanesulfonic anhydride is purchased from the Aldrich Chemical Company, Inc., and used as received. It may also be prepared from trifluoromethanesulfonic acid.[3]
4. The reaction turns deep red upon addition of the anhydride.
5. 4-Nitrophenyl trifluoromethanesulfonate exhibits the following properties: mp 54–55°C (lit.[4] 53°C); IR (KBr) cm^{-1}: 3125, 3094, 1625, 1590, 1537, 1487, 1423, 1352, 1253, 1214, 1137, 1012, 900, 862,

759, 744, 692, 613; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.50 (d, 2 H, J = 9.2), 8.37 (d, 2 H, J = 9.2); high resolution mass spectrum (isobutane CI): 271.9848 (271.9840 calcd for $C_7H_5F_3NO_5S$).

6. Magnesium turnings (99.99%) are purchased from Johnson Matthey/Alfa Products and used as received.

7. Tetrahydrofuran is freshly distilled from sodium benzophenone ketyl.

8. 4-Bromoanisole is purchased from the Aldrich Chemical Company, Inc., and used as received.

9. Methyl iodide is purchased from the Aldrich Chemical Company, Inc., and used as received. Methyl iodide is used as a catalyst to initiate the Grignard reaction.

10. Tributlytin chloride is purchased from the Aldrich Chemical Company, Inc., and used as received. The reaction warms upon the introduction of tributyltin chloride, but it does not boil spontaneously .

11. Tributyl(4-methoxyphenyl)stannane is reported to boil at 158–160°C (0.5 mm).[5]

12. Tributyl(4-methoxyphenyl)stannane exhibits the following properties: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.88 (t, 9 H, J = 7.3), 1.02 (m, 6 H), 1.33 (m, 6 H), 1.53 (m, 6 H), 3.80 (s, 3 H), 6.90 (d, 2 H, J = 8.5), 7.37 (d, 2 H, J = 8.5). The peaks at 1.02 and 7.37 ppm show coupling with tin; mass spectrum (isobutane CI) 399, 397, 395, 291, 289, 287. The product is at least 97% pure by GC analysis (30 m, Supelco SPB-1 fused silica column).

13. Anhydrous N,N-dimethylformamide (water <0.005%) is purchased from the Aldrich Chemical Company, Inc., and transferred via cannula directly from the Sure/Seal bottle into the reaction flask. The solvent is deoxygenated by bubbling nitrogen through it for 45 min prior to the addition of compound **2**.

14. Tributyl(4-methoxyphenyl)stannane **(2)** is added to the reaction flask via a 30-mL syringe.

15. Lithium chloride is dried by heating at 130°C under reduced pressure (0.5 mm) for 24 hr.

16. Bis(triphenylphosphine)palladium(II) chloride (98%) is purchased from the Aldrich Chemical Company, Inc., and used as received.

17. 4-Methoxy-4'-nitrobiphenyl **(3)** has the following properties: mp 109–110°C (lit.[6] 111°C); IR (KBr) cm^{-1}: 3062, 2968, 2838, 1600, 1509, 1487, 1345, 1253, 1034, 1017, 857, 845, 830, 817, 757, 724, 696; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.88 (s, 3 H), 7.01 (d, 2 H, J = 8.7), 7.58 (d, 2 H, J = 8.7), 7.68 (d, 2 H, J = 8.7) 8.26 (d, 2 H, J = 8.7); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 55.4, 114.5, 124.1, 127.0, 128.5, 131.0, 146.4, 147.1, 160.4; mass spectrum (isobutane CI): 230 (MH). Anal. Calcd for $C_{13}H_{11}NO_3$: C, 68.10; H, 4.84; N, 6.11. Found: C, 67.99; H, 4.87; N, 6.13.

18. The checkers also recover 170 mg (2%) of 4,4'-dimethoxybiphenyl **(4)** (R_f = 0.38, 95:5 hexanes-ethyl acetate) and 310 mg (3%) of 4-amino-4'-methoxybiphenyl **(5)** (R_f = 0.28, 4:1 hexanes-ethyl acetate) as minor byproducts. Compound **5** is recovered from the column by increasing the eluent polarity to 4:1 hexanes-ethyl acetate.

4,4'-Dimethoxybiphenyl **(4)** has the following properties: mp 175–177°C (lit.[7] 176–178°C); IR (KBr) cm^{-1}: 2958, 2914, 2840, 1608, 1503, 1277, 1251, 1184, 1042, 1012, 825, 810; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.85 (s, 6 H), 6.96 (d, 4 H, J = 8.7), 7.48 (d, 4 H, J = 8.7); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 55.3, 114.1, 127.7, 133.5, 158.7; high resolution mass spectrum (70 eV, EI): 214.0993 (214.0994 calcd for $C_{14}H_{14}O_2$).

4-Amino-4'-methoxybiphenyl **(5)** has the following properties: mp 143–144°C (lit.[8] 144–145.5°C): IR (KBr) cm^{-1}: 3396, 3334, 3224, 3033, 2965, 2837, 1636, 1608, 1500, 1270, 1241, 1181, 1035, 1015, 817; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.69 (broad s, 2 H), 3.84 (s, 3 H), 6.75 (d, 2 H, J = 8.5), 6.95 (d, 2 H, J = 8.8), 7.37 (d, 2 H, J = 8.4); 7.46 (d, 2 H, J = 8.8); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 55.3, 114.1, 115.4, 127.4, 127.6, 131.3, 133.8, 145.2, 158.4; high resolution mass spectrum (70 eV, EI): 199.0990 (199.0997 calcd for $C_{13}H_{13}NO$).

19. The checkers found that using tetrakis(triphenylphosphine)palladium(0) as the catalyst and dioxane as the solvent resulted in significant reduction of the nitro-substituent in the coupled product.[9] Biphenyls **3** and **5** are obtained in ratios as high as one to one under these conditions.

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

The introduction of a bond between two aromatic rings is a familiar problem in organic synthesis. A wide variety of classical and non-classical methods are available for the preparation of unsymmetrical biaryl compounds.[10] However, many of these methods are non-selective and require harsh conditions in order to obtain reasonable yields. A relatively mild and versatile method for the formation of carbon-carbon bonds is the palladium-catalyzed coupling of functionalized organostannanes with organic electrophiles.[11] [12,13] [14] [15] Aryl halides[16] [17] [18] and aryl trifluoromethanesulfonates (triflates)[9,19] [20] couple with organostannanes to provide a selective method for the formation of aryl-aryl bonds. Aryl triflates are especially important starting materials because of their stability and ease of formation.[21,22]

The palladium-catalyzed cross-coupling reaction featured in this procedure occurs under neutral conditions in the presence of many synthetically useful functional groups (e.g. alcohol, ester, nitro, acetal, ketone, and aldehyde). The reaction works best in N,N-dimethylformamide with bis (triphenylphosphine)palladium(II) chloride, $PdCl_2(PPh_3)_2$, as the catalyst. Lithium chloride is added to prevent decomposition of the catalyst.[19,20] It is presumed that conversion of the intermediate aryl palladium triflate to an aryl palladium chloride is required for the transmetallation step to proceed.[9]

In a recent study examining ligand effects on the palladium-catalyzed cross-coupling reaction between aryl triflates and vinylstannanes, tri-2-furylphosphine and triphenylarsine were observed to provide significant rate enhancements (10^2-10^3 greater than with triphenylphosphine-based catalysts).[23] [24] Although not reported, these ligands may also be useful for aryl-aryl cross-coupling reactions.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 9, 258
- Org. Syn. Coll. Vol. 10, 102
- Org. Syn. Coll. Vol. 10, 423

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

nitro, acetal, ketone

hexanes

brine

sodium benzophenone ketyl

Tributlytin chloride

ethyl alcohol (64-17-5)

ethyl acetate (141-78-6)

diethyl ether (60-29-7)

ammonium chloride (12125-02-9)

acetonitrile (75-05-8)

magnesium turnings (7439-95-4)

nitrogen (7727-37-9)

pyridine (110-86-1)

Methyl iodide (74-88-4)

dichloromethane (75-09-2)

palladium chloride (7647-10-1)

magnesium sulfate (7487-88-9)

dioxane (5703-46-8)

Tetrahydrofuran (109-99-9)

potassium fluoride (7789-23-3)

N,N-dimethylformamide (68-12-2)

Lithium chloride (7447-41-8)

calcium hydride (7789-78-8)

Triphenylarsine (603-32-7)

trifluoromethanesulfonic acid (1493-13-6)

Trifluoromethanesulfonic anhydride (358-23-6)

4-bromoanisole (104-92-7)

tetrakis(triphenylphosphine)palladium(0) (14221-01-3)

tributyltin chloride (1461-22-9)

4-Methoxy-4'-nitrobiphenyl,
1,1'-Biphenyl, 4-methoxy-4'-nitro- (2143-90-0)

4-Nitrophenyl trifluoromethanesulfonate (17763-80-3)

4-nitrophenol (100-02-7)

Tributyl(4-methoxyphenyl)stannane (70744-47-7)

bis(triphenylphosphine)palladium(II) chloride

4,4'-dimethoxybiphenyl (2132-80-1)

4-amino-4'-methoxybiphenyl

palladium triflate

tri-2-furylphosphine (5518-52-5)

4-nitrophenyl fluorosulfonate