



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.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

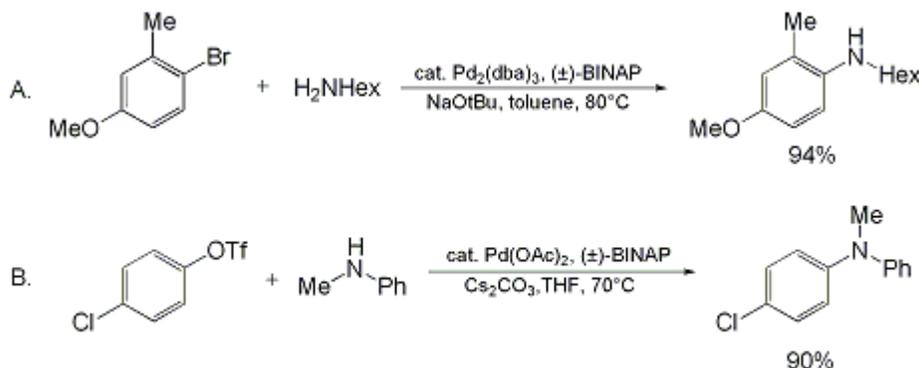
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions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

Organic Syntheses, Coll. Vol. 10, p.423 (2004); Vol. 78, p.23 (2002).

PALLADIUM-CATALYZED AMINATION OF ARYL HALIDES AND ARYL TRIFLATES: N-HEXYL-2-METHYL-4- METHOXYANILINE AND N-METHYL-N-(4-CHLOROPHENYL) ANILINE

[Benzenamine, 4-chloro-N-methyl-N-phenyl-]



Submitted by John P. Wolfe and Stephen L. Buchwald¹.

Checked by Holly Norling and Louis S. Hegedus.

1. Procedure

A. N-Hexyl-2-methyl-4-methoxyaniline. A 250-mL, round-bottomed flask equipped with a magnetic stirbar and a rubber septum is flame-dried and allowed to cool to room temperature under an argon purge. The septum is removed and the flask is charged with tris(dibenzylideneacetone)dipalladium(0) (114 mg, 0.125 mmol, 0.5 mol% Pd) (Note 1), (±)-BINAP (233 mg, 0.375 mmol, 0.75 mol%) (Note 1), and sodium tert-butoxide (NaOtBu) (6.73 g, 70.0 mmol, 1.4 equiv) (Note 2). The septum is again placed on the flask, and the flask is purged with argon for 5 min. Toluene (50 mL) (Note 3) is added and stirring is started. The flask is charged with 4-bromo-3-methylanisole (10.0 g, 50.0 mmol, 1.0 equiv) (Note 4), n-hexylamine (7.9 mL, 60.0 mmol, 1.2 equiv) (Note 5), and additional toluene (50 mL). The resulting dark red mixture is placed in an oil bath that is heated to 80°C with stirring until the aryl bromide has been completely consumed as judged by GC analysis (18-23 hr) (Note 6). The mixture is removed from the oil bath, allowed to cool to room temperature, then poured into a separatory funnel. The reaction flask is rinsed with ether (2 × 50 mL), brine (100 mL), deionized water (20 mL), and again with ether (50 mL). All rinses are added to the separatory funnel, the funnel is shaken, and the layers are separated. The aqueous layer is extracted with ether (50 mL), and the combined organic extracts are dried over anhydrous magnesium sulfate. The mixture is filtered; the magnesium sulfate is washed with ether (50 mL), filtered, and the organic solution is concentrated under reduced pressure to give the crude product as a brown oil. This oil is then distilled (bulb-to-bulb, bp 92°C at 0.001 mm) to afford 10.35 g (94%) of the desired product as a pale yellow oil (Note 7). A small amount of viscous material remains in the distillation flask following the distillation.

B. N-Methyl-N-(4-chlorophenyl)aniline. A 250-mL, three-necked, round-bottomed flask equipped with a reflux condenser, magnetic stirbar, one glass stopper, and rubber septa, covering the condenser and the remaining neck of the flask, is flame-dried and allowed to cool to room temperature under an argon purge. The septum is removed and the flask is charged with palladium acetate (337 mg, 1.5 mmol, 3.0 mol% Pd) (Note 1) and (±)-BINAP (1.4 g, 2.25 mmol, 4.5 mol%). The septum is again placed on the flask, and the flask is purged with argon for 5 min. Tetrahydrofuran (THF) (50 mL) (Note 8) is added and the mixture stirred at room temperature for 10 min until a peach-colored suspension forms. The flask is charged with 4-chlorophenyl trifluoromethanesulfonate (13.0 g, 50.0 mmol, 1.0 equiv) (Note 9), and N-methylaniline (6.5 mL, 60.0 mmol, 1.2 equiv) (Note 5). The septum is removed from

the flask, and cesium carbonate (Cs_2CO_3) (22.8 g, 70.0 mmol, 1.4 equiv) (Note 10) is added under a flow of argon. The septum is again placed over the flask, and the flask is purged with argon for 30 seconds. Additional THF (50 mL) is added, the reaction mixture is immersed in a 70°C oil bath so that the level of the oil is even with the level of solvent in the flask and stirring is begun. The internal temperature of the reaction is monitored using a thermocouple and is found to be 60°C ($\pm 1^\circ\text{C}$) (Note 11). The mixture is stirred at this temperature until all the starting triflate has been consumed as judged by GC analysis (23–45 hr) (Notes 6, 12). The mixture is removed from the oil bath and allowed to cool to room temperature. Ether (100 mL) and hexanes (50 mL) are added to the flask and the solution formed is filtered through Celite. The flask is rinsed with ether (3×50 mL) and the rinses are filtered through Celite. The organic extracts are combined and concentrated under reduced pressure, and 1/1 (v/v) hexanes/ether (200 mL) is added. A yellow precipitate forms, and the mixture is filtered through a 1.5-inch deep plug of silica gel on a 3"-diameter type D fritted funnel. The flask is rinsed with 1/1 (v/v) hexanes/ether (2×100 mL), and the rinses are filtered through the plug of silica gel. The organic solution is concentrated under reduced pressure to give a light brown oil. The material is distilled (bulb to bulb, 0.002 mm). A low boiling fraction (bp 58–70°C) is collected; the distillation is stopped and the low boiling material is rinsed out of the receiver bulb. The distillation is resumed (bulb-to-bulb, bp 84°C at 0.002 mm) to give a yellow solid that melts at room temperature to give 9.72 g (90%) of the desired product as a pale yellow oil (Note 13).

2. Notes

1. $\text{Pd}_2(\text{dba})_3$, palladium acetate, and (\pm)-BINAP were purchased from Strem Chemical Company and used without further purification. (The checkers recrystallized $\text{Pd}(\text{OAc})_2$ from benzene prior to use. When it was used as obtained from the supplier, the reaction did not go to completion.)
2. Sodium *tert*-butoxide is purchased from Aldrich Chemical Company, Inc., and used without further purification. The bulk of this material is stored under nitrogen in a Vacuum Atmospheres Glovebox. Small portions (10–15 g) were removed from the glovebox in glass vials and weighed in the air. The checkers stored sodium *tert*-butoxide, purchased in 5-g bottles, in a desiccator and weighed it out in air.
3. Toluene is distilled under nitrogen from molten sodium.
4. 4-Bromo-3-methylanisole is purchased from Aldrich Chemical Company, Inc., and used without further purification.
5. All amines were purchased from Aldrich Chemical Company, Inc., and distilled under argon from calcium hydride (CaH_2).
6. Reaction times were considerably longer when run on a large scale than the previously published reaction times. This may be due to the lower internal temperature of the large scale reactions (for example, a reaction run on a 50-mmol scale in a 70°C oil bath was found to have an internal temperature of only 60°C). Longer reaction times in reactions that used cesium carbonate as a base may also be due in part to differences in stirring rate.
7. Analytical data for this compound are as follows: ^1H NMR (300 MHz, CDCl_3) δ : 0.90 (t, 3 H, $J = 6.6$), 1.30–1.67 (m, 8 H), 2.13 (s, 3 H), 3.09 (t, 2 H, $J = 7.2$), 3.12 (s, br, 1 H), 3.74 (s, 3 H), 6.53–6.57 (m, 1 H), 6.69–6.71 (m, 2 H); ^{13}C NMR (75 MHz, CDCl_3) δ : 14.0, 17.6, 22.6, 26.9, 29.6, 31.6, 44.7, 55.6, 110.7, 111.5, 116.8, 123.5, 140.7, 151.4; IR (neat) cm^{-1} : 3414, 2928, 1514, 1225, 1051. Anal. Calcd for $\text{C}_{14}\text{H}_{23}\text{NO}$: C, 75.97; H, 10.47. Found: C, 75.93; H, 10.45.
8. THF was distilled under argon from sodium benzophenone ketyl.
9. 4-Chlorophenyl trifluoromethanesulfonate ^{2a} is prepared according to the procedure of stille^{2b,c} as follows: A 500-mL, oven-dried, round-bottomed flask equipped with a Teflon stirbar and a rubber septum is allowed to cool to room temperature under an argon purge. The septum is removed and the flask was charged with 4-chlorophenol (16.1 g, 125 mmol) (Note 14). The septum is again placed on the flask, the flask is purged with argon, and pyridine (125 mL) (Note 14) is added via syringe. The mixture is cooled to 0°C with stirring in an ice-water bath and trifluoromethanesulfonic anhydride (163 mmol) (Note 14) is added dropwise via syringe. After the addition is complete, the mixture is stirred at 0°C for 15 min, then allowed to warm to room temperature and stirred for 22 hr. The mixture is diluted with hexanes/ether (300 mL, 1/1 v/v) and transferred to a separatory funnel. The mixture is washed with aqueous hydrochloric acid (HCl) (1 M, 2×200 mL), and brine (200 mL), and the layers are separated. The organic layer is dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure. The crude material is Kugelrohr-distilled under vacuum (bp 90°C at water aspirator vacuum) to afford 31 g (95%) of the title compound as a colorless oil. This material is passed through a short

plug of silica gel prior to use in palladium-catalyzed amination reactions.

10. Cesium carbonate was obtained from Chemetal and used without further purification. The bulk of this material was stored under nitrogen in a Vacuum Atmospheres Glovebox. Small portions (~50 g) were removed from the glovebox in glass bottles and weighed in the air. (The checkers stored the cesium carbonate in a desiccator under argon, and weighed it in air.)

11. The formation of a side product, N,N'-dimethyl-N,N'-diphenyl-1,4-phenylenediamine, was observed if the internal reaction temperature exceeded 65°C.

12. This reaction was run three times on a 50-mmol scale. Two of the three reactions were complete in <30 hr. The third reaction was run with a batch of triflate that had not been passed through silica as described above (Note 9); this reaction took 45 hr to proceed to completion. A second sample of the triflate was passed through a plug of silica; the reaction was repeated (on a 40-mmol scale) and proceeded to completion in 26 hr.

13. Analytical data for this compound are as follows: ¹H NMR (300 MHz, CDCl₃) δ: 3.28 (s, 3 H), 6.88-7.32 (m, 9 H) ; ¹³C NMR (75 MHz, CDCl₃) δ: 40.3, 120.5, 121.4, 122.2, 125.5, 129.0, 129.3, 147.6, 148.6 ; IR (neat) cm⁻¹: 3061, 2943, 1601, 1452, 1156, 817 ; GC/MS (m/z) 219. Anal. Calcd for C₁₃H₁₂ClN: C, 71.87; H, 5.57. Found: C, 71.95; H, 5.81.

14. 4-Chlorophenol, trifluoromethanesulfonic anhydride, and anhydrous pyridine were purchased from Aldrich Chemical Company, Inc., and used without further purification.

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

Aniline derivatives are frequently used in many areas of chemistry, including pharmaceuticals,^{3a} agrochemicals,^{3b} photography,^{3c} pigments,^{3d} xerography,^{3e} and materials.^{3f} Classic methods for the construction of aryl carbon-nitrogen bonds usually require harsh reaction conditions and/or activated substrates, and are often inefficient or unreliable.^{4 5a}

The palladium-catalyzed amination of aryl halides has recently emerged as a powerful alternative to other methods for the synthesis of aryl amines.⁵ This method allows for the cross-coupling of aryl halides and triflates with amines in the presence of a stoichiometric amount of a base and catalytic amounts of palladium complexes bearing tertiary phosphine ligands. As shown in Tables I and II, the Pd/BINAP catalyst is highly effective for reactions of aryl bromides and triflates with primary and cyclic secondary amines. Use of the strong base NaOtBu allows for rapid reactions with low levels of the palladium catalyst (usually 0.05-0.5 mol % Pd) while a high degree of functional group tolerance is observed if Cs₂CO₃ is used as base.^{5a,d,e,i} Catalytic aminations of aryl triflates are most effective with Cs₂CO₃;^{5a,e} cleavage of the triflate moiety is observed in the presence of NaOtBu.^{5a,e}

Catalysts based on bulky, electron-rich phosphine ligands have recently been developed that are effective for aminations of aryl chlorides, as well as aryl bromides and triflates.^{5f,g,j} These catalysts also promote room temperature coupling reaction.^{5f,j}

The examples described here demonstrate that a variety of aryl halides or triflates with differing substitution patterns, electronic properties, and functional groups can be coupled with primary and secondary amines in high yield. The reactions are only modestly air sensitive, require no special equipment or techniques, and are amenable to large scale synthesis.

TABLE I
BINAP/Pd-CATALYZED AMINATION OF ARYL BROMIDES USING NaOBu^a

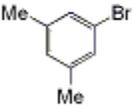
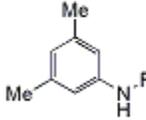
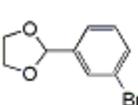
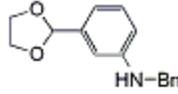
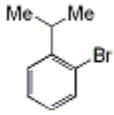
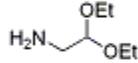
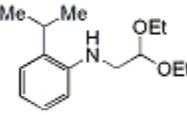
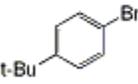
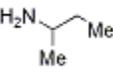
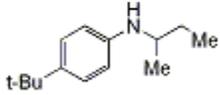
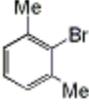
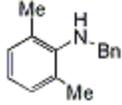
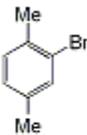
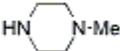
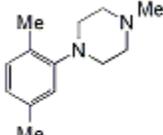
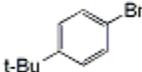
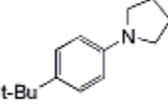
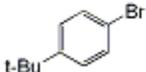
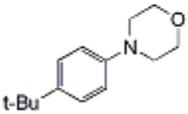
Entry	Halide	Amine	Product	Catalyst Loading (mol % Pd)	Reaction Time(hr)	Isolated Yield(%)	
1		RNH ₂		R=Hexyl	0.5	2	88
2				R=Bn	0.5	4	79
3				R=Cyclic	0.05	7	79
4				R=t-Bu	0.5	18	83
				4.0	25	76 ^b	
5		HexNH ₂		0.5 0.05	<1 1.5	96 ^c 97	
6		H ₂ NBn		0.5	2	81	
7				0.5	17	90	
8				2.0	18	79 ^b	
9		H ₂ NBn		0.5	18	87 ^b	

TABLE I (contd.)

BINAP/Pd-CATALYZED AMINATION OF ARYL BROMIDES USING NaOtBu^a

Entry	Halide	Amine	Product	Catalyst Loading (mol % Pd)	Reaction Time(hr)	Isolated Yield(%)
10				0.5	4	98 ^d
				0.05	6	94 ^d
11				0.5	20	83
12				0.5	22	93 ^d

(a) Reaction conditions: 1.0 equiv ArBr, 1.1-1.2 equiv amine, 1.4 equiv NaOtBu, cat. Pd₂(dba)₃, cat. BINAP, toluene (2 mL/mmol halide), 80°C. (b) The reaction was conducted at 100°C. (c) Control experiments showed no formation of the desired product after 17 hr at 100°C in the absence of palladium. (d) No solvent was used in the reaction.

TABLE II
 CATALYTIC AMINATION OF ARYL BROMIDES AND TRIFLATES USING Cs₂CO₃^a

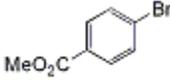
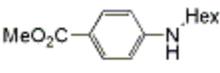
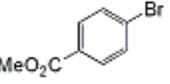
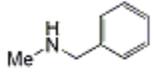
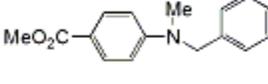
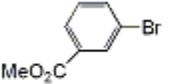
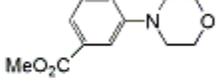
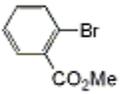
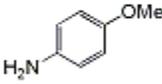
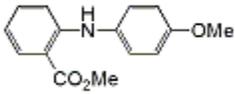
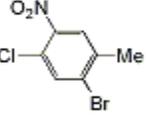
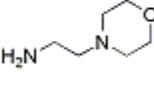
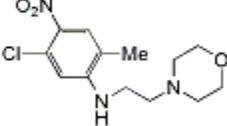
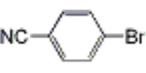
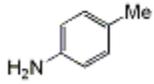
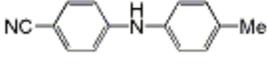
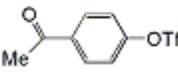
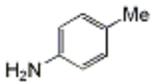
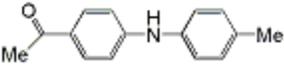
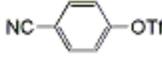
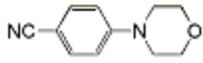
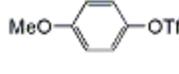
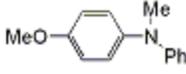
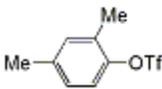
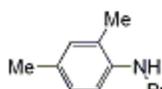
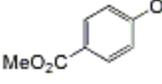
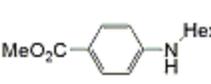
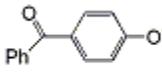
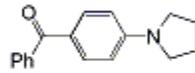
Entry	Halide	Amine	Product	Catalyst ^b	Mol% Pd	Reaction Time(hr)	Yield %
1		H ₂ NHex		A	2	21	72
2				B	3	16	75
				C	3	22	87 ^c
3				B	1	20	86
4				B	3	20	92
5				A	2	16.5	75
6				A	1	26	80
7				B	3	4	90 ^d
8				B	3	16	84 ^e
9				B	3	16	88 ^e

TABLE II (contd.)

CATALYTIC AMINATION OF ARYL BROMIDES AND TRIFLATES USING Cs₂CO₃^a

Entry	Halide	Amine	Product	Catalyst ^b	Mol% Pd	Reaction Time(hr)	Yield %
10		BnNH ₂		B	5	5	90 ^f
11		H ₂ NHex		B	3	5	87 ^{f,g}
12		HN(C ₄ H ₉)		B	3	6	92

(a) Reaction Conditions: 1.0 equiv halide, 1.2 equiv amine, 1.4 equiv Cs₂CO₃, cat. Pd₂(dba)₃ or Pd(OAc)₂, cat. BINAP (1.5 L/Pd), toluene (0.25 M), 100°C. (b) A=Pd₂(dba)₃/(S)-BINAP; B=Pd(OAc)₂/(S)-BINAP; C=Pd(OAc)₂/(±)-BINAP. (c) Base added last to the reaction mixture. (d) Reaction run in THF at 65°C. (e) Reaction run at 80°C. (f) 2.0 equiv of amine used in reaction. (g) Reaction run in 1,4-dioxane at 80°C.

References and Notes

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Appendix

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

N-Methyl-N-(4-chlorophenyl)aniline:
Benzenamine, 4-chloro-N-methyl-N-phenyl- (13); (174307-94-9)

Tris(dibenzylideneacetone)dipalladium (0):
Palladium, tris(1,5-diphenyl-1,4-pentadien-3-one)di- (9); (52409-22-0)

rac-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl:
rac-BINAP:
Phosphine, [1,1'-binaphthalene]-2,2'-diylbis {diphenyl- (11); (98327-87-8)

4-Bromo-3-methylanisole:
Anisole, 4-bromo-3-methyl- (8);
Benzene, 1-bromo-4-methoxy-2-methyl- (9); (27060-75-9)

Hexylamine (8);
1-Hexanamine (9); (111-26-2)

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

4-Chlorophenyl trifluoromethanesulfonate:
Methanesulfonic acid, trifluoro-, p-chlorophenyl ester (8);
Methanesulfonic acid, trifluoro-, 4-chlorophenyl ester (9); (29540-84-9)

N-Methylaniline:
Aniline, N-methyl- (8);
Benzenamine, N-methyl- (9); (100-61-8)

Cesium carbonate:
Carbonic acid, dicesium salt (9); (534-17-8)

4-Chlorophenol: TOXIC:
Phenol, p-chloro- (8);
Phenol, 4-chloro- (9); (106-48-9)

Pyridine (8,9); (110-86-1)

Trifluoromethanesulfonic anhydride:
Methanesulfonic acid, trifluoro-, anhydride (8,9); (358-23-6)