Copper-Catalyzed Halogen Exchange in Aryl Halides

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Supporting Information

General Considerations

Reagents: Copper(I) iodide (fine powder) was purchased from Strem (98% pure). If granulated CuI, available from other sources, is used instead, it may be necessary to grind it. CuI is air-stable and does not require any special precautions other than storage in an amber vial. Racemic *trans*-1,2-cyclohexanediamine, *N,N'*-dimethylethylenediamine, and 1,3-propanediamine were purchased from Aldrich. Racemic *trans-N,N'*-dimethyl-1,2-cyclohexanediamine and racemic *trans-N,N'*-diethyl-1,2-cyclohexanediamine were prepared as reported previously.[1] These and other diamines form carbonate salts if exposed to air although we did not encounter any reproducibility problems even when using old samples of the liquid diamines that had turned light brown and contained some precipitate. Sodium iodide (99.9%, powder) was purchased from Alfa Aesar and stored in a dessicator. Although NaI was weighed out in the air, care was taken to minimize exposure to air due to the hygroscopicity of the salt, particularly during very humid periods of the year. Anhydrous dioxane, dimethylformamide, *n*-butanol, *m*-xylene, and 2-methoxyethyl ether were purchased from Aldrich in Sure/Seal™ bottles and used without further purification. All other reagents were commercially available and used without further purification. Flash column chromatography was performed with EM Science silica gel 60 (230-400 mesh).

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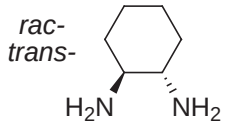
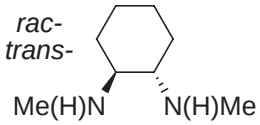
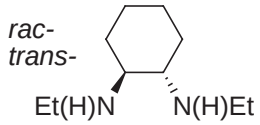
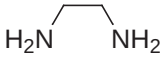
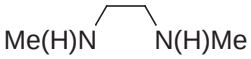
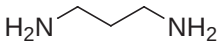
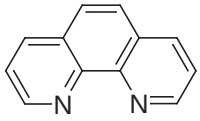
[1] Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421.

Techniques: The copper-catalyzed halogen exchange reactions are moderately sensitive to oxygen. Nevertheless, small amounts of oxygen are tolerated and neither glovebox techniques nor purification of the commercially available reagents are required. The following technique was used for the reactions that were performed in Schlenk tubes: After a 15 mL Schlenk tube with a screw thread (Kontes) was dried in an oven at 100 °C overnight, it was equipped with a 10×3 mm Teflon-coated stirring bar and a Teflon valve, evacuated, and backfilled with argon. The solid reagents were weighed out in the air by adding them directly to the Schlenk tube with the Teflon valve removed. The Schlenk tube was again fitted with the Teflon valve, evacuated and backfilled with argon. Under positive pressure of argon, the Teflon valve was replaced with a rubber septum, and the liquid reagents were added to the Schlenk tube using Hamilton mycrosyringes (if <500 μL) or all polypropylene/ polyethylene disposable syringes (if >500 μL). The rubber septum was replaced with a Teflon valve under positive pressure of argon. The Schlenk tube was sealed and heated in an oil bath for the specified time while stirring at the maximum rate achievable on a magnetic stirrer (sometimes the stirring rate had to be slightly reduced to minimize excessive depositing of the solids on the walls of the Schlenk tube).

Analytical methods: IR spectra were recorded on a Perkin-Elmer FT-IR 2000 instrument for all previously unknown compounds. Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz instrument with chemical shifts reported relative to residual deuterated solvent peaks or tetramethylsilane internal standard. Gas chromatographic analysis was performed on an Agilent 6890 instrument with an FID detector and an Agilent 10 m × 0.10 μm i.d. HP-1 capillary column. Mass spectra (GC/MS) were recorded on a Hewlett Packard model GCD. All yields reported in Table 1 refer to isolated yields (average of two runs) of compounds estimated to be >95% pure as determined by ^{1}H NMR and GC. In most cases, the aryl iodide product also contained traces (0.5-1.0%) of the aryl bromide starting material due to the separation difficulties. The procedures described in this section are representative, and thus the yields for the individual reactions may differ slightly from the average yields reported in Table 1. Compounds described in the literature were characterized by comparing their melting points, ^{1}H, and/or ^{13}C NMR spectra to the previously reported data. All new compounds were further characterized by elemental analysis (except for **4l** — a copy of the ^{1}H NMR spectrum is included).

Ligand Screening for the Halogen Exchange Reaction

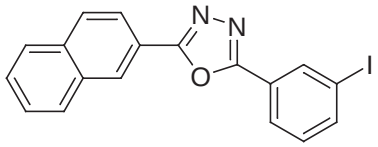
Ligand	Amount of ligand	Conversion of aryl bromide, %	GC yield of aryl iodide, %
No ligand	None	0.1	<0.1
	12 μL (0.10 mmol)	77	73
	16 μL (0.10 mmol)	99.3	98
	19.5 μL (0.101 mmol)	23	22
	6.8 μL (0.10 mmol)	73	69
	11 μL (0.10 mmol)	98	96
	8.5 μL (0.10 mmol)	72	69
	18.5 mg (0.103 mmol)	6	4
Ph_3P	26.5 mg (0.101 mmol)	<0.1	<0.1

Procedure: Nine Schlenk tubes were charged with CuI (9.6 mg, 0.050 mmol, 5.0 mol%), ligand (if solid at room temperature; 0.10 mmol, 10 mol%), sodium iodide (300 mg, 2.00 mmol), evacuated and backfilled with argon. Ligand (if liquid at room temperature, 0.10 mmol, 10 mol%), 5-bromo-*m*-xylene (136 μL, 1.00 mmol) and dioxane (1.0 mL) were added to each Schlenk tube. The reaction mixtures were stirred at 110 °C for 22 h. The resulting suspensions were

allowed to reach room temperature. Ethyl acetate (2 mL), water (2 mL), and dodecane (230 μL, internal GC standard) were added to each reaction mixture. A 50 μL sample of the supernatant solution was diluted with ethyl acetate (1 mL) and analyzed by GC. The results are compiled in the table above, and represent averaged data from two runs.

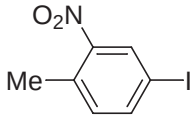
Copper-Catalyzed Conversion of Aryl Bromides into Aryl Iodides

General Procedure. A Schlenk tube was charged with CuI (9.6 mg, 0.050 mmol, 5.0 mol%), aryl bromide (if it is a solid at room temperature; 1.00 mmol), NaI (300 mg, 2.00 mmol), briefly evacuated and backfilled with argon. Racemic *trans-N,N'*-dimethyl-1,2-cyclohexanediamine (16 μL, 0.10 mmol, 10 mol%), aryl bromide (if it is a liquid at room temperature; 1.00 mmol), and dioxane (1.0 mL) were added under argon. The Schlenk tube was sealed with a Teflon valve and the reaction mixture was stirred at 110 °C for 22-24 h. The resulting suspension was allowed to reach room temperature, diluted with 30% aq ammonia (5 mL), poured into water (20 mL), and extracted with dichloromethane (3×15 mL). The combined organic phases were dried ($MgSO_4$ or Na_2SO_4), concentrated, and the residue was purified by flash chromatography on silica gel to provide the desired product.

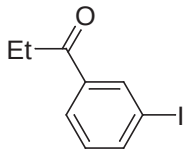


2-(3-Iodophenyl)-5-(2-naphthyl)-1,3,4-oxadiazole (4a). A Schlenk tube was charged with CuI (9.6 mg, 0.050 mmol, 5.0 mol%), 2-(3-bromophenyl)-5-(2-naphthyl)-1,3,4-oxadiazole (352 mg, 1.00 mmol), NaI (300 mg, 2.00 mmol), briefly evacuated and backfilled with argon. Racemic *trans-N,N'*-dimethyl-1,2-cyclohexanediamine (16 μL, 0.10 mmol, 10 mol%) and dioxane (1.0 mL) were added under argon. The Schlenk tube was sealed with a Teflon valve and the reaction mixture was stirred at 110 °C for 24 h. The resulting light green-gray suspension was allowed to reach room temperature, diluted with 30% aq ammonia (5 mL), poured into water (20 mL), and extracted with dichloromethane (3×15 mL). The combined organic phases were dried (Na_2SO_4), concentrated to ca. 2 mL volume. The product was allowed to crystallize at room temperature. After 15 min, hexane (20 mL) was added, the mixture was kept at room temperature for 15 h, and

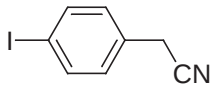
finally filtered to provide 382 mg (96% yield) of 2-(3-iodophenyl)-5-(2-naphthyl)-1,3,4-oxadiazole as white, fine needles. Mp: 156-158 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (s, 1H), 8.53 (t, *J* = 1.8 Hz, 1H), 8.22 (dd, *J* = 8.6, 1.8 Hz, 1H), 8.18 (dt, *J* = 7.9, 1.2 Hz, 1H), 8.03-7.93 (m, 2H), 7.95-7.88 (m, 2H), 7.65-7.53 (m, 2H), 7.30 (t, *J* = 7.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 163.2, 140.6, 135.5, 134.8, 132.8, 130.7, 129.1, 128.9, 128.1, 128.0, 127.5, 127.2, 126.1, 125.8, 123.2, 120.8, 94.4. IR (neat, cm^{-1}): 1558, 1540, 753, 731. Anal. Calcd. for $C_{18}H_{11}IN_2O$: C, 54.29; H, 2.78. Found: C, 54.29; H, 2.74.



4-Iodo-3-nitrotoluene (4b). Following the general procedure, 4-bromo-3-nitrotoluene (216 mg, 1.00 mmol) was converted into 4-iodo-3-nitrotoluene. Purification of the crude product by column chromatography on silica gel (hexane-ethyl acetate 10:1) provided the desired product as pale yellow fine needles (249 mg, 95% yield). Mp: 57-58 °C (lit. 59 °C).[2] The ^{1}H spectrum matched the one reported by Arotsky, et al.[2] ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.2, 134.7, 133.6, 90.2, 20.6.



3-Iodopropiophenone (4c). Following the general procedure, 3-bromopropiophenone (214 mg, 1.00 mmol) was converted into 3-iodopropiophenone. Purification of the crude product by column chromatography on silica gel (hexane-ethyl acetate 10:1) provided the desired product as a colorless oil (256 mg, 98% yield). The ^{1}H spectrum matched the one reported by Fukuyama, et al.[3] ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.3, 141.6, 138.6, 136.9, 130.2, 127.0, 94.4, 31.8, 8.0.



4-Iodophenylacetonitrile (4d). Following the general procedure, 4-bromophenylacetonitrile (197 mg, 1.00 mmol) was converted into 4-iodophenylacetonitrile. Purification of the crude product by column chromatography on silica gel (hexane-ethyl acetate 5:1) provided the desired

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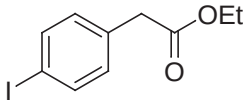
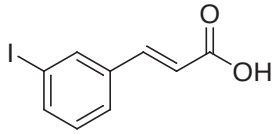
[2] Arotsky, J.; Darby, A. C.; Hamilton, J. B. A. *J. Chem. Soc., Perkin Trans. 2* **1973**, 595.
[3] Fukuyama, N.; Nishino, H.; Kurosawa, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 4363.

product as a tan solid (236 mg, 97% yield). Mp: 53-54 °C (lit. 56-57 °C).[4] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73-7.68 (m, 2H), 7.10-7.05 (m, 2H), 3.70 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.2, 129.7, 129.5, 117.2, 93.5, 23.2.



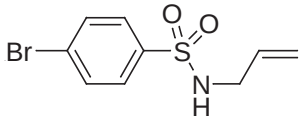
Ethyl 4-iodophenylacetate (4e). Following the general procedure, ethyl 4-bromophenylacetate (244 mg, 1.00 mmol) was converted into ethyl 4-iodophenylacetate. The reaction mixture was allowed to reach room temperature and filtered through a silica gel plug (1×1 cm) eluting with ethyl acetate (50 mL). The filtrate was concentrated and the residue was purified by column chromatography on silica gel (hexane-ethyl acetate 10:1) to provide the desired product as a pale tan, low melting solid (283 mg, 98% yield). Mp: 26-27 °C (lit. 28 °C).[5] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67-7.60 (m, 2H), 7.06-7.00 (m, 2H), 4.14 (q, J = 7.1 Hz, 2H), 3.54 (s, 2H), 1.24 (t, J = 7.1 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 137.5, 133.7, 131.2, 92.5, 61.0, 40.8, 14.1.



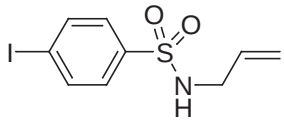
Preparation of 3-iodocinnamic acid (4f) through an *in situ* generated trimethylsilyl ester. A Schlenk tube was charged with CuI (9.6 mg, 0.050 mmol, 5.0 mol%), 3-bromocinnamic acid (228 mg, 1.00 mmol), NaI (300 mg, 2.00 mmol), evacuated and backfilled with argon. Racemic *trans-N,N'*-dimethyl-1,2-cyclohexanediamine (16 μL, 0.10 mmol, 10 mol%), 1,1,1,3,3,3-hexamethyldisilazane (211 μL, 1.00 mmol), and dioxane (1.0 mL) were added under argon. The Schlenk tube was sealed with a Teflon valve and the reaction mixture was stirred at 110 °C for 22 h. The resulting suspension was allowed to reach room temperature, poured into ether (20 mL), and washed with a solution of $Na_2S_2O_5$ (100 mg) in 10% aq HCl (3×20 mL). The organic phase was dried (Na_2SO_4) and concentrated. The residue was dissolved in hot ethanol (5 mL), and hot water (5 mL) was added to the solution. The product was allowed to crystallize at 0 ¡C for 15 h to provide 256 mg (93% yield) of 3-iodocinnamic as pale yellow needles. Mp: 186-188 °C (lit. 180-182 °C).[6] ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.47 (s, 1H), 8.08 (s, 1H), 7.77 (d, J = 7.8

[4] Maggioni & C. S. p. A. Fr. Patent M1687, March 11, 1963; *Chem. Abstr.* **1963**, *59*, 8764h.
[5] Watkinson, J. G.; Watson, W.; Yates, B. L. *J. Chem. Soc.* **1963**, 5437.
[6] Yuzikhin, O. S.; Vasil'ev, A. V.; Rudenko, A. P. *Russ. J. Org. Chem.* **2000**, *36*, 1743.

Hz, 1H), 7.72 (d, *J* = 7.8 Hz, 1H), 7.52 (d, *J* = 16.0 Hz, 1H), 7.22 (t, *J* = 7.8 Hz, 1H), 6.58 (d, *J* = 16.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.3, 142.3, 138.6, 136.6, 136.5, 130.9, 127.4, 120.6, 95.4.

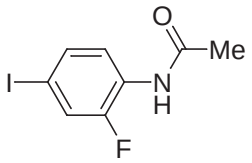


***N*-Allyl-4-bromobenzenesulfonamide.** To a solution of 4-bromobenzenesulfonamide (6.80 g, 26.6 mmol) in dichloromethane (50 mL) was added allylamine (5.0 mL, 66.5 mmol) at 0 °C. The clear, colorless solution was stirred at room temperature for 1 h. The reaction mixture was poured into ether (100 mL) and washed with 10% aq HCl (50 mL), water (2×50 mL), and saturated aq $NaHCO_3$ (50 mL). The organic phase was dried ($MgSO_4$) and concentrated. The residue crystallized upon treatment with hexane to provide 7.03 g (96% yield) of the desired product as fine, white crystals. Mp: 63-65 °C (lit. 64-65 °C).[7] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77-7.72 (m, 2H), 7.69-7.64 (m, 2H), 5.71 (ddt, *J* = 17.1, 10.2, 6.0 Hz, 1H), 5.18 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.12 (dq, *J* = 10.2, 1.5 Hz, 1H), 4.67 (t, *J* = 6.0 Hz, 1H), 3.61 (tt, *J* = 6.0, 1.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.0, 132.6, 132.4, 128.6, 127.6, 118.0, 45.7.

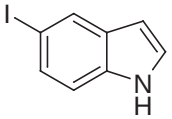


***N*-Allyl-4-iodobenzenesulfonamide (4g).** Following the general procedure, *N*-allyl-4-bromobenzenesulfonamide (277 mg, 1.00 mmol) was converted into *N*-allyl-4-iodobenzenesulfonamide. Purification of the crude product by column chromatography on silica gel (hexane-ethyl acetate 4:1) provided the desired product as white crystals (309 mg, 96% yield). Mp: 76-77 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91-7.85 (m, 2H), 7.61-7.56 (m, 2H), 5.71 (ddt, *J* = 17.1, 10.2, 6.0 Hz, 1H), 5.18 (dq, *J* = 17.1, 1.5 Hz, 1H), 5.12 (dq, *J* = 10.2, 1.5 Hz, 1H), 4.67 (t, *J* = 6.0 Hz, 1H), 3.61 (tt, *J* = 6.0, 1.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.6, 138.3, 132.6, 128.5, 118.0, 100.1, 45.7. IR (neat, cm^{-1}): 3264, 1571, 1329, 1162, 738. Anal. Calcd. for $C_9H_{10}INO_2S$: C, 33.45; H, 3.12. Found: C, 33.70; H, 3.08.

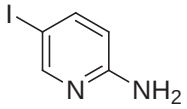
[7] Keasling, H. H.; Schumann, E. L.; Veldkamp, W. *J. Med. Chem.* **1965**, *8*, 548.



2-Fluoro-4-iodoacetanilide (4h). Following the general procedure, 2-fluoro-4-bromoacetanilide (233 mg, 1.00 mmol) was converted into 2-fluoro-4-iodoacetanilide. The reaction mixture was allowed to reach room temperature and filtered through a silica gel plug (1×0.5 cm) eluting with ethyl acetate (50 mL). The filtrate was concentrated and the residue was purified by column chromatography on silica gel (hexane-ethyl acetate 3:2) to provide the desired product as a white solid (265 mg, 95% yield). Mp: 153-154 ¡C (lit. 152-154 °C).[8] ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.81 (s, 1H), 7.74 (t, *J* = 8.4 Hz, 1H), 7.65 (dd, *J* = 10.4, 1.9 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 2.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.8 (s), 153.0 (d, *J* = 250 Hz), 133.2 (d, *J* = 3.5 Hz), 126.4 (d, *J* = 11 Hz), 125.4 (s), 124.1 (d, *J* = 22 Hz), 87.0 (d, J = 7.1 Hz), 23.6 (s).



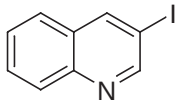
5-Iodoindole (4i). Following the general procedure, 5-bromoindole (197 mg, 1.00 mmol) was converted into 5-iodoindole. Purification of the crude product by column chromatography on silica gel (hexane-ethyl acetate 10:1 followed by hexane-ethyl acetate 3:1) provided the desired product as a white solid (238 mg, 98% yield). Mp: 99-100 °C (lit. 99-102 °C).[9] The ^{1}H spectrum matched the one reported by Somei, et al.[10] ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.7, 130.4, 130.2, 129.5, 124.9, 112.9, 101.9, 83.2.



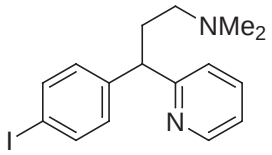
2-Amino-5-iodopyridine (4j). Following the general procedure, 2-amino-5-bromopyridine (173 mg, 1.00 mmol) was converted into 2-amino-5-iodopyridine. Purification of the crude product by column chromatography on silica gel (hexane-ethyl acetate 2:3) provided the desired product

[8] Krueger, G.; Keck, J.; Noll, K.; Pieper, H. *Arzneim.-Forsch.* **1984**, *34*, 1612.
[9] Hydorn, A. E. *J. Org. Chem.* **1967**, *32*, 4100.
[10] Somei, M.; Saida, Y.; Funamoto, T.; Ohta, T. *Chem. Pharm. Bull.* **1987**, *35*, 3146.

as a pale tan solid (209 mg, 95% yield). Mp: 128-129 °C (lit. 126-128 °C).[11] The ^{1}H spectrum matched the one reported by Trapani, et al.[12] ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.2, 153.8, 145.3, 110.8, 77.9.



3-Iodoquinoline (4k). Following the general procedure, 3-bromoquinoline (136 μL, 1.00 mmol) was converted into 3-iodoquinoline. Purification of the crude product by column chromatography on silica gel (hexane-ethyl acetate 8:1) provided the desired product as a pale yellow solid (248 mg, 97% yield). Mp: 58-59 °C (lit. 61-62 °C).[13] ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.03 (d, J = 2.1 Hz, 1H), 8.52 (d, J = 2.1 Hz, 1H), 8.06 (d, J = 8.9 Hz, 1H), 7.75-7.66 (m, 2H), 7.58-7.52 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5, 146.2, 143.6, 130.0, 129.8, 129.4, 127.3, 126.7, 89.8.



(±)-1-(4-Iodophenyl)-1-(2-pyridyl)-3-dimethylaminopropane (4l). Following the general procedure, (±)-1-(4-bromophenyl)-1-(2-pyridyl)-3-dimethylaminopropane[14] (256 μL, 1.00 mmol) was converted into (±)-1-(4-iodophenyl)-1-(2-pyridyl)-3-dimethylaminopropane. Purification of the crude product by column chromatography on silica gel (dichloromethane - dichloromethane (saturated with 30% aq ammonia) - methanol 30:20:2) provided the desired product as a pale tan oil (365 mg, 100% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.56 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H), 7.63-7.57 (m, 2H), 7.55 (td, J = 7.7, 1.8 Hz, 1H), 7.16-7.06 (m, 4H), 2.46-2.32 (m, 1H), 2.24-2.10 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.9, 149.4, 143.4, 137.4, 136.4, 130.1, 122.7, 121.4, 91.8, 57.6, 50.7, 45.5, 32.8. IR (neat, cm^{-1}): 1590, 1569, 1482, 1471, 1432, 1006, 749. HRMS-EI calcd for $C_{16}H_{20}IN_2$ ($M+H^+$), 367.0665; found, 367.0679.

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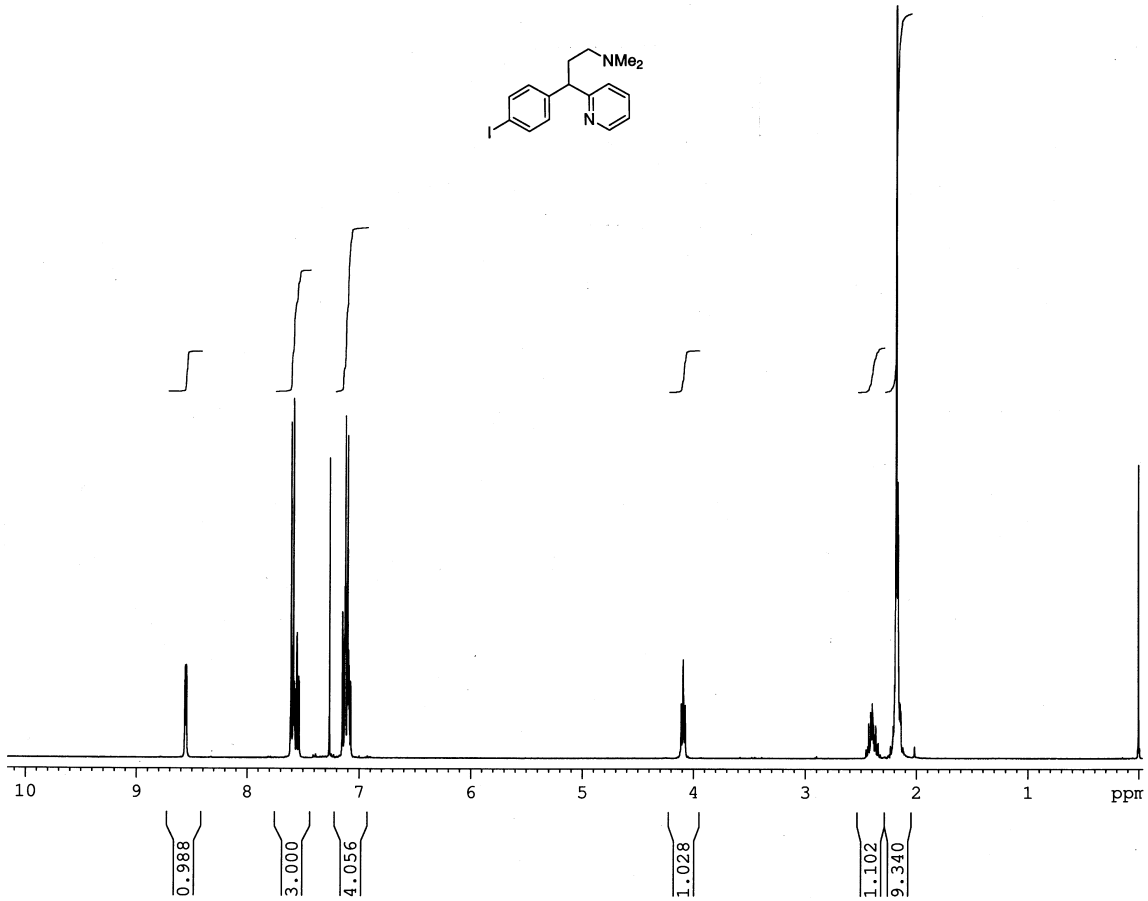
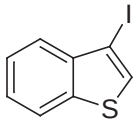
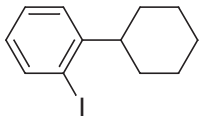
[14] Obtained by extracting a basified solution of the corresponding maleate salt (Sigma) with dichloromethane.



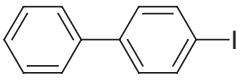


Preparation of 3-iodobenzo[b]thiophene (4m) using *m*-xylene-diglyme solvent mixture. A Schlenk tube was charged with CuI (9.6 mg, 0.050 mmol, 5.0 mol%), NaI (300 mg, 2.00 mmol), evacuated and backfilled with argon. Racemic *trans-N,N'*-dimethyl-1,2-cyclohexanediamine (16 μL, 0.10 mmol, 10 mol%), 3-bromobenzo[*b*]thiophene (131 μL, 1.00 mmol), *m*-xylene (0.80 mL), and diglyme (0.20 mL) were added under argon. The Schlenk tube was sealed with a Teflon valve and the reaction mixture was stirred at 130 °C for 22 h. The resulting suspension was allowed to reach room temperature, diluted with hexane (10 mL), and filtered through silica gel (2×2 cm) eluting with hexane (50 mL). The filtrate was concentrated, and the residue was purified by flash chromatography on silica gel (hexane) to provide 3-iodobenzo[*b*]thiophene (243 mg, 93% yield) as a pale yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, J = 8.0 Hz,

1H), 7.80 (d, J = 7.9 Hz, 1H), 7.64 (s, 1H), 7.53-7.40 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.2, 138.3, 129.1, 125.22, 125.16, 122.4, 78.2. IR (neat, cm^{-1}): 1416, 1305, 1251, 749, 723. Anal. Calcd. for C_8H_5IS: C, 36.94; H, 1.94. Found: C, 37.14; H, 1.98.



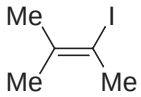
Preparation of 1-iodo-2-cyclohexylbenzene (4n) using *n*-pentanol as the solvent. A Schlenk tube was charged with CuI (9.6 mg, 0.050 mmol, 5.0 mol%), NaI (300 mg, 2.00 mmol), evacuated and backfilled with argon. Racemic *trans-N,N'*-dimethyl-1,2-cyclohexanediamine (16 μL, 0.10 mmol, 10 mol%), 1-bromo-2-cyclohexylbenzene (97% pure;[15] Lancaster; 186 μL, 1.00 mmol), *n*-pentanol (1 mL) were added under argon. The Schlenk tube was sealed with a Teflon valve and the reaction mixture was stirred at 130 °C for 40 h. The resulting suspension was allowed to reach room temperature and filtered through silica gel (1×0.5 cm) eluting with hexane (50 mL). The filtrate was concentrated, and the residue was purified by flash chromatography on silica gel (hexane) to provide the known[16] 1-iodo-2-cyclohexylbenzene (283 mg, 99% yield; ca. 97% pure) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (dd, J = 7.5, 1.2 Hz, 1H), 7.32 (td, J = 7.5, 1.2 Hz, 1H), 7.23 (dd, J = 7.5, 1.7 Hz, 1H), 6.90 (td, J = 7.5, 1.7 Hz, 1H), 2.81 (tt, J = 11.7, 3.0 Hz, 1H), 1.97-1.74 (m, 5H), 1.55-1.23 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.3, 139.5, 128.4, 127.6, 126.6, 101.5, 48.5, 33.4, 26.8, 26.1.



Preparation of 4-iodobiphenyl (4o) using 1,3-propanediamine as the ligand. A Schlenk tube was charged with CuI (9.6 mg, 0.050 mmol, 5.0 mol%), 4-bromobiphenyl (234 mg, 1.00 mmol), NaI (300 mg, 2.00 mmol), evacuated and backfilled with argon. 1,3-Propanediamine (8.4 μL, 0.10 mmol, 10 mol%) and *n*-pentanol (1.0 mL) were added under argon. The Schlenk tube was sealed with a Teflon valve and the reaction mixture was stirred at 130 °C for 22 h. The resulting suspension was allowed to reach room temperature, diluted with 30% aq ammonia (2 mL), poured into water (20 mL), and extracted with dichloromethane (3×15 mL). The combined organic phases were dried ($MgSO_4$), concentrated, and the residue was purified by flash

[15] The ^{1}H NMR spectrum of the commercial sample indicates ca. 3% of an impurity, presumably 1-bromo-4-cyclohexylbenzene.

chromatography on silica gel (hexane) to provide 269 mg (96% yield) of 4-iodobiphenyl as a white solid. Mp: 113-114 °C (lit. 112.5-113.5 °C).[17] The ^{1}H and ^{13}C spectra matched those reported by Dektar, et al.[18]



2-Iodo-3-methyl-2-butene. A 50 mL Schlenk tube was charged with CuI (382 mg, 2.01 mmol, 5.0 mol%), NaI (9.00 g, 60.0 mmol), evacuated and backfilled with argon. *N,N'*-Dimethylethylenediamine (426 μL, 4.00 mmol, 10 mol%), 2-bromo-3-methyl-2-butene (4.65 mL, 40.1 mmol), and *n*-butanol (20 mL) were added under argon. The Schlenk tube was sealed with a Teflon valve and the reaction mixture was stirred at 120 °C for 24 h. The resulting tan suspension was allowed to reach room temperature, poured into pentane (200 mL) and washed with a solution of 30% aq ammonia (10 mL) in water (200 mL), followed by water (3×200 mL). The organic phase was dried ($MgSO_4$) and concentrated to ~10 mL volume. The residue was distilled collecting the fraction boiling at 120-140 °C to give 6.08 g (77% yield) of 2-iodo-3-methyl-2-butene as a colorless liquid (>95% pure). The ^{1}H spectrum matched the one reported by Sherrod, et al.[19] ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.9, 93.2, 31.4, 30.3, 18.9.

Partial conversion of 4-chlorotoluene into 4-iodotoluene. A Schlenk tube was charged with CuI (19.5 mg, 0.102 mmol, 5.0 mol%), NaI (450 mg, 3.00 mmol), evacuated and backfilled with argon. Racemic *trans-N,N'*-dimethyl-1,2-cyclohexanediamine (31.5 μL, 0.200 mmol, 10 mol%), 4-chlorotoluene (237 μL, 2.00 mmol), and *n*-pentanol (0.50 mL) were added under argon. The Schlenk tube was sealed with a Teflon valve and the reaction mixture was stirred at 130 °C for 24 h. The resulting dark green-gray suspension was allowed to reach room temperature. Ethyl acetate (3 mL) and dodecane (internal GC standard, 460 μL) were added to the reaction mixture. A 50 μL sample of the supernatant solution was diluted with ethyl acetate (1 mL) and analyzed by GC to provide 35% conversion of 4-chlorotoluene and 33% yield of 4-iodotoluene.

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Conversion of 5-Bromo-*m*-xylene into 5-Iodo-*m*-xylene Using NaI or KI in *n*-BuOH or DMF (Figure 1a)

Four Schlenk tubes were charged with CuI (19.5 mg, 0.102 mmol, 5.0 mol%) and sodium iodide (600 mg, 4.00 mmol) or potassium iodide (665 mg, 4.01 mmol). The Schlenk tubes were evacuated and backfilled with argon. Racemic *trans*-*N,N'*-dimethyl-1,2-cyclohexanediamine (31.5 μL, 0.200 mmol, 10 mol%), 5-bromo-*m*-xylene (272 μL, 2.00 mmol), *sec*-butylbenzene (62 μL, internal GC standard), and *n*-butanol (2.0 mL) or DMF (2.0 mL) were added to each Schlenk tube. The reaction mixtures were stirred at 110 °C in an oil bath. After certain time intervals, the Schlenk tubes were briefly (ca. 1-2 min) removed from the oil bath, the Teflon valve was removed under a positive pressure of argon, and a sample (ca. 10-50 μL) was taken with a Pasteur pipette under a positive pressure of argon (the sample was drawn into the pipette by the capillary forces). The Teflon valve was then quickly replaced, and heating of the reaction mixture was continued. The sample taken with the Pasteur pipette was diluted with ethyl acetate (1 mL) and analyzed by GC. The results are compiled in Figure 1a, and represent averaged data from two runs.

Halogen Exchange in 5-Bromo-*m*-xylene or 5-Iodo-*m*-xylene Using Different Halide Sources (Figure 1b)

Conversion of 5-bromo-*m*-xylene into 5-iodo-*m*-xylene. Two Schlenk tubes were charged with CuI (19.5 mg, 0.102 mmol, 5.0 mol%) and sodium iodide (300 mg, 2.00 mmol) or tetrabutylammonium iodide (740 mg, 2.00 mmol). The Schlenk tubes were evacuated and backfilled with argon. Racemic *trans*-*N,N'*-dimethyl-1,2-cyclohexanediamine (31.5 μL, 0.200 mmol, 10 mol%), 5-bromo-*m*-xylene (272 μL, 2.00 mmol), *sec*-butylbenzene (62 μL, internal GC standard), and DMF (2.0 mL) were added to each Schlenk tube. The reaction mixtures were stirred at 110 °C in an oil bath. After certain time intervals, the Schlenk tubes were briefly (ca. 1-2 min) removed from the oil bath, the Teflon valve was removed under a positive pressure of argon, and a sample (ca. 10-50 μL) was taken with a Pasteur pipette under a positive pressure of

argon (the sample was drawn into the pipette by the capillary forces). The Teflon valve was then quickly replaced, and heating of the reaction mixture was continued. The sample taken with the Pasteur pipette was diluted with ethyl acetate (1 mL) and analyzed by GC. The results are compiled in Figure 1b, and represent averaged data from two runs.

Conversion of 5-iodo-*m*-xylene into 5-bromo-*m*-xylene. Two Schlenk tubes were charged with CuI (19.5 mg, 0.102 mmol, 5.0 mol%) and sodium bromide (206 mg, 2.00 mmol) or tetrabutylammonium bromide (645 mg, 2.00 mmol). The Schlenk tubes were evacuated and backfilled with argon. Racemic *trans-N,N'*-dimethyl-1,2-cyclohexanediamine (31.5 μL, 0.200 mmol, 10 mol%), 5-iodo-*m*-xylene (290 μL, 2.01 mmol), *sec*-butylbenzene (62 μL, internal GC standard), and DMF (2.0 mL) were added to each Schlenk tube. The reaction mixtures were stirred at 110 °C in an oil bath. After certain time intervals, the Schlenk tubes were briefly (ca. 1-2 min) removed from the oil bath, the Teflon valve was removed under a positive pressure of argon, and a sample (ca. 10-50 μL) was taken with a Pasteur pipette under a positive pressure of argon (the sample was drawn into the pipette by the capillary forces). The Teflon valve was then quickly replaced, and heating of the reaction mixture was continued. The sample taken with the Pasteur pipette was diluted with ethyl acetate (1 mL) and analyzed by GC. The results are compiled in Figure 1b, and represent averaged data from two runs.

Halogen Exchange Reaction Performed in a *m*-Xylene/Diglyme Solvent Mixture of Variable Composition (Figure 2)

Nine Schlenk tubes were charged with CuI (9.6 mg, 0.050 mmol, 5.0 mol%), sodium iodide (300 mg, 2.00 mmol), evacuated and backfilled with argon. Racemic *trans-N,N'*-dimethyl-1,2-cyclohexanediamine (16 μL, 0.10 mmol, 10 mol%), 2-bromotoluene (121 μL, 1.01 mmol), *m*-xylene (0-1.0 mL), and diglyme (0-1.0 mL) were added to each Schlenk tube. The reaction mixtures were stirred at 130 °C for 15 h. The resulting suspensions were allowed to reach room temperature. Ethyl acetate (2 mL) and dodecane (230 μL, internal GC standard) were added to each reaction mixture. A 50 μL sample of the supernatant solution was diluted with ethyl acetate

(1 mL) and analyzed by GC. The results are compiled in Figure 2, and represent averaged data from two runs.