Published in final edited form as:

Synthesis (Stuttg). 2007 November 16; (22): 3519–3527. doi:10.1055/s-2007-990875.

Regioselective Copper-catalyzed C-N and C-S Bond Formation using Amines, Thiols and Halobenzoic Acids

Shuanglong Liu, John Paul C. Pestano, and Christian Wolf*

Department of Chemistry, Georgetown University, Washington, DC 20057

Abstract

A regioselective method for highly efficient C-N and C-S bond formation with 2-halobenzoic acids is described. The Cu/Cu₂O-catalyzed reaction is carried out in 2-ethoxyethanol or ethylene glycol diethyl ether and does not require the use of strong base or other additives. This procedure eliminates the need for acid protection, tolerates a wide range of functional groups and provides aromatic and aliphatic amines and sulfides in 81 to 99% yield.

Keywords

Amines; thiols; halobenzoic acids; carbon-heteroatom bond formation

The synthesis of flufenamic, mefenamic and other anthranilic acids has received increasing attention due to important biomedical applications.¹ Some aromatic amino acids possess anti-inflammatory properties and have been identified as promising candidates for the therapy of neurodegenerative disorders and amyloid diseases.² Incorporation of achiral amino acids into peptides has become a widespread tool to modify secondary protein structures and biochemical properties or to investigate peptide folding and chiral amplification.³ The synthesis of anthranilic acids from unprotected 2-chlorobenzoic acid was first reported by Ullmann.⁴ Since then, copper-catalyzed amination of a range of 2-halobenzoic acids has been accomplished⁵ and few cases of palladium-catalyzed amination of aryl halides bearing free carboxylic acid groups in meta and para position have been identified.^{5a,6} To date, anthranilic acids have mostly been prepared either by Ullmann-Jourdan coupling which suffers from poor substrate scope and often involves high temperatures and stoichiometric amounts of copper reagents or by Buchwald-Hartwig amination with alkyl 2-halobenzoates and subsequent ester cleavage.⁷ Despite the significance of arylthiobenzoic acids to the pharmaceutical industry,⁸ few examples of catalytic C-S bond formation with free benzoic acids are known.⁹ Copper-catalyzed coupling of thiophenols with 2-halobenzamides¹⁰ and chlorobenzoic acids¹¹ has been described. Recently, our laboratory decided to reinvestigate the scope of copper-catalyzed C-N bond formation using unprotected 2-halobenzoic acid and aniline derivatives.¹² We now wish to report a general approach to N-alkyl anthranilic acids and C-S bond formation with aliphatic and aromatic thiols.

In previous studies we learned that amination of 2-halobenzoic acids with aromatic amines in the presence of catalytic amounts of copper and copper(I) oxide proceeds with high yields when ethoxyethanol is used as solvent whereas formation of *N*-alkyl anthranilic acids proved more difficult. For example, 2-chlorobenzoic acid, **1**, and aminocyclohexane, **2**, gave *N*-cyclohexyl anthranilic acid, **3**, in only 58% yield (Scheme 1). Chromatographic separation and NMR spectroscopic analysis of by-products revealed that 35% of ether **4** was formed and similar results were obtained when 2-bromobenzoic acid, **5**, was employed in the same reaction. In order to extend the copper-catalyzed amination procedure to aliphatic amines, we decided to replace 2-ethoxyethanol with ethylene glycol diethyl ether and optimized catalyst amount and composition as well as temperature and reaction time. The best results were obtained when a solution of benzoic acid **1** and two equivalents of aliphatic amine **2** was heated to 130 °C for 24 hours in the presence of 4 mol% of copper(I) oxide, 9 mol% of copper powder and stoichiometric amounts of potassium carbonate. Under these conditions, anthranilic acid **3** was obtained in 93% yield (Table 1). The reaction can also be conducted at lower temperatures although longer reaction times are required. We found that starting materials are not fully consumed after 24 hours when the Cu/Cu₂O-catalyzed coupling of **1** and **2** is carried out at 80 °C but **3** was still isolated in remarkable 85% yield (entry 1). Reaction of acid **1** with other aliphatic amines furnished anthranilic acids **7**, **9** and **11** in 85 to 99% yield (entries 2-4). Incorporation of electron-deficient and electron-rich substituents into 2-chlorobenzoic acid does not significantly affect the results (entries 5-10): 3-chloro-4-nitrobenzoic acid, **14**, and 3,4-dimethoxy-2-chlorobenzoic acid, **16**, afford the corresponding amino acids **15** and **17** in 86 and 84% yield, respectively. The copper-catalyzed C-N bond formation proceeds with excellent regioselectivity. We found that only the chloride adjacent to the carboxylate group is replaced while halides located in meta and para position do not react (entries 5, 8 and 10). This is consistent with previous reports from our laboratories and others.^{12,13} While excellent results were obtained with primary amines, we obtained only moderate yields when secondary amines were employed in the same reaction. For example, coupling of 2-chlorobenzoic acid with *N*-methyl benzylamine and piperidine gave the corresponding tertiary amines in only 40 and 45% yield, respectively.¹⁴

The same conditions were successfully applied to bromobenzoic acids. As discussed above for the formation of *N*-alkyl anthranilic acids from chlorobenzoic acids, the amination was found to proceed with high regioselectivity and proved insensitive to the presence of electron-donating and electron-withdrawing groups in the aromatic ring (Table 2, entries 4, 6, 8, and 9). Our method affords significantly higher yields than other amination protocols. For example, anthranilic acid **7** can be prepared in quantitative amounts within 24 hours from both **1** and **5** (entry 2 in Table 1 and 2) which compares favorably with a previously reported CuI-catalyzed procedure providing **7** from 2-chloro- and 2-bromobenzoic acid in only 48 and 53% yield, respectively, after 48 to 72 hours.^{5a}

The same catalytic system is suitable for construction of carbon-sulfur bonds with both aliphatic and aromatic thiols. We found that Cu/Cu₂O-catalyzed coupling of 2-bromobenzoic acids with thiols is considerably faster than C-N and C-O bond formation and aryl ether by-products such as **4** are not observed when the reaction is carried out in 2-ethoxyethanol. Product purification can be conveniently accomplished by precipitation from aqueous solution when 2-ethoxyethanol is used as solvent whereas chromatographic work-up is usually required when the coupling reaction is conducted in ethylene glycol diethyl ether. Although aliphatic thiols react more slowly than thiophenols, both diaryl and alkyl aryl sulfides were obtained in more than 90% yields (Table 3).¹⁵ Noteworthy, coupling products **34**, **38**, **44**, and **50** were isolated in quantitative amounts (entries 1, 3, 6, and 9) which underscores that our procedure provides a valuable alternative to methods based on alkylation and arylation of thiosalicylic acid.¹⁶

In summary, we have developed a method for highly efficient Cu/Cu₂O-catalyzed C-N and C-S bond formation with 2-halobenzoic acids. The reaction tolerates a wide range of functional groups and provides aromatic and aliphatic amines and sulfides in 81 to 99% yield. The remarkable regioselectivity, experimental simplicity, and the low cost of the catalytic system are attractive features of this procedure which may prove useful for the synthesis of pharmaceutically relevant anthranilic acids and benzoic acid-derived sulfides.

General Procedure for Coupling with Amines

A mixture of an amine (17.6 mmol), 2-halobenzoic acid (8.8 mmol), K₂CO₃ (1.21 g, 8.8 mmol), Cu powder (51 mg, 0.8 mmol), Cu₂O (38 mg, 0.4 mmol) and 3 mL of ethylene glycol diethyl ether was heated to 130 °C for 24 hours under nitrogen. The reaction was cooled to room temperature and the solvent was removed under reduced pressure. This residue was poured into 30 mL of water, treated with charcoal and the mixture was filtrated through celite. Acidification of the filtrate to pH 5 with diluted HCl gave a precipitate, which was dissolved in 100 mL of 5% aqueous Na₂CO₃ and the solution was filtrated through celite and subjected to precipitation as described above. Flash chromatography (30% ethyl acetate in hexanes) afforded the desired *N*-alkyl anthranilic acids.

N-Cyclohexyl anthranilic acid (3)^{12b}

¹H NMR (300 MHz, CDCl₃) δ = 1.28-1.44 (m, 5H), 1.62-1.65 (m, 1H), 1.76-1.80 (m, 2H), 2.02-2.05 (m, 2H), 3.35-3.43 (m, 1H), 6.56 (ddd, *J* = 8.6 Hz, 8.1 Hz, 1.0 Hz, 1H), 6.71 (d, *J* = 8.6 Hz, 1H), 7.34 (ddd, *J* = 8.6 Hz, 8.1 Hz, 1.7 Hz, 1H), 7.98 (dd, *J* = 8.1 Hz, 1.7 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃) δ = 25.0, 26.1, 33.2, 50.9, 108.6, 112.1, 114.4, 133.2, 135.8, 151.3, 174.7.

N-Benzyl anthranilic acid (7)^{12b}

¹H NMR (300 MHz, CDCl₃) δ = 4.48 (s, 2H), 6.18 (dd, *J* = 8.3 Hz, 8.3 Hz, 2H), 7.26-7.35 (m, 6H), 7.98 (dd, *J* = 7.8 Hz, 1.2 Hz, 1H), 8.05 (bs, 1H). ¹³C NMR (75 MHz, CDCl₃) δ = 46.9, 109.0, 111.9, 115.1, 126.9, 127.2, 128.7, 132.6, 135.6, 138.7, 151.6, 173.5.

N-Pentyl anthranilic acid (9)¹⁷

¹H NMR (300 MHz, CDCl₃) δ = 0.95 (t, *J* = 5.4 Hz, 3H), 1.37-1.41 (m, 4H), 1.66-1.72 (m, 2H), 3.19 (t, *J* = 7.1 Hz, 2H), 6.58 (ddd, *J* = 8.1 Hz, 6.8 Hz, 1.2 Hz, 1H), 6.68 (d, *J* = 8.1 Hz, 1H), 7.48 (ddd, *J* = 8.1 Hz, 6.8 Hz, 1.7 Hz, 1H), 7.98 (dd, *J* = 8.1 Hz, 1.7 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃) δ = 14.7, 23.1, 29.5, 30.0, 43.5, 109.1, 112.0, 115.0, 133.4, 136.3, 152.6, 175.0.

N-Phenethyl anthranilic acid (11)^{12b}

¹H NMR (300 MHz, CDCl₃) δ = 2.98 (t, *J* = 7.1, 2H), 3.47 (t, *J* = 7.1 Hz, 2H), 6.60 (ddd, *J* = 9.5 Hz, 7.1 Hz, 1.0 Hz, 1H), 6.71 (d, *J* = 8.6 Hz, 1H), 7.22-7.42 (m, 6H), 8.00 (dd, *J* = 1.7 Hz, 8.1 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃) δ = 35.9, 44.8, 109.1, 111.7, 115.1, 126.9, 129.0, 129.2, 133.1, 136.0, 139.4, 151.9, 174.7.

5-Chloro-*N*-phenethyl anthranilic acid (13)

¹H NMR (300 MHz, CDCl₃) δ = 2.95 (t, *J* = 6.8 Hz, 2H), 3.40 (t, *J* = 6.8 Hz, 2H), 6.64 (d, *J* = 9.0 Hz, 1H), 7.19-7.35 (m, 6H), 7.90 (s, 1H). ¹³C NMR (75 MHz, CDCl₃) δ = 36.0, 45.1, 110.1, 113.5, 119.9, 127.3, 129.3, 129.4, 132.3, 136.2, 139.4, 150.7, 173.9. Anal. Calcd for C₁₅H₁₄ClNO₂: C, 65.34; H, 5.12; N, 5.08. Found: C, 65.28; H, 5.21; N, 5.02.

4-Nitro-*N*-phenethyl anthranilic acid (15)¹⁸

¹H NMR (300 MHz, methanol-*d*₄) δ = 3.16 (t, *J* = 6.8 Hz, 2H), 3.54 (s, 1H), 3.72 (t, *J* = 6.8 Hz, 2H), 7.38 (m, 1H), 7.44-7.48 (m, 5H), 7.66 (d, *J* = 2.2 Hz, 1H), 8.23 (d, *J* = 8.8 Hz, 1H). ¹³C NMR (75 MHz, methanol-*d*₄) δ = 35.1, 44.2, 105.3, 107.8, 114.9, 126.4, 128.5, 128.7, 133.5, 139.2, 151.5, 152.0, 169.2.

3,4-Dimethoxy-*N*-phenethyl anthranilic acid (17)

¹H NMR (300 MHz, CDCl₃) δ = 2.90 (t, *J* = 7.3 Hz, 2H), 3.67 (t, *J* = 7.3 Hz, 2H), 3.72 (s, 3H), 3.90 (s, 3H), 6.43 (d, *J* = 9.0 Hz, 1H), 7.19-7.30 (m, 5H), 7.84 (d, *J* = 9.0 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃) δ = 37.7, 49.0, 56.5, 60.7, 103.3, 109.6, 126.9, 129.1, 129.5, 129.8, 138.8, 139.9, 146.4, 158.6, 173.0. Anal. Calcd for C₁₇H₁₉NO₄: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.43; H, 6.67; N, 4.60.

4-Chloro-*N*-phenethyl anthranilic acid (19)

¹H NMR (300 MHz, CDCl₃) δ = 2.98 (t, *J* = 7.1 Hz, 2H), 3.44 (t, *J* = 7.1 Hz, 2H), 6.58 (dd, *J* = 8.6 Hz, 2.0 Hz, 1H), 6.68 (d, *J* = 2.0 Hz, 1H), 7.22-7.28 (m, 3H), 7.31-7.37 (m, 2H), 7.73 (bs, 1H), 7.88 (d, *J* = 8.8 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃) δ = 36.0, 45.1, 107.9, 111.8, 115.9, 127.4, 129.4, 129.5, 134.6, 139.3, 142.7, 152.8, 173.9. Anal. Calcd for C₁₅H₁₄ClNO₂: C, 65.34; H, 5.12; N, 5.08. Found: C, 65.01, H, 5.50, N, 5.00.

5-Bromo-*N*-phenethyl anthranilic acid (21)

¹H NMR (300 MHz, CDCl₃) δ = 2.99 (t, *J* = 7.3 Hz, 2H), 3.48 (t, *J* = 7.3 Hz, 2H), 6.60 (ddd, *J* = 7.3 Hz, 7.1 Hz, 1.0 Hz, 1H), 6.72 (d, *J* = 8.3 Hz, 1H), 7.20-7.43 (m, 5H), 7.99 (dd, *J* = 8.1 Hz, 1.7 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃) δ = 36.1, 45.0, 109.4, 112.0, 115.4, 127.2, 129.3, 129.5, 133.3, 136.3, 139.7, 152.2, 175.0. Anal. Calcd for C₁₅H₁₄BrNO₂: C, 56.27; H, 4.41; N, 4.37. Found: C, 56.10; H, 4.80; N, 4.05.

4-Fluoro-*N*-benzyl anthranilic acid (23)

¹H NMR (300 MHz, CDCl₃) δ = 4.44 (d, *J* = 4.6 Hz, 2H), 6.27-6.36 (m 2H), 7.29-7.37 (m, 5H), 8.00 (dd, *J* = 9.0 Hz, 6.8 Hz, 1H), 8.11 (bs, 1H). ¹³C NMR (75 MHz, CDCl₃) δ = 47.7, 98.8 (d, *J*_{C,F} = 25.7 Hz), 103.9 (d, *J*_{C,F} = 22.7 Hz), 106.4 (d, *J*_{C,F} = 1.5 Hz), 127.6, 128.1, 129.5, 136.1 (d, *J*_{C,F} = 11.8 Hz), 138.6, 154.4 (d, *J*_{C,F} = 12.8 Hz), 168.6 (d, *J*_{C,F} = 253.1 Hz), 174.0. Anal. Calcd for C₁₄H₁₂FNO₂: C, 68.56; H, 4.93; N, 5.71. Found: C, 68.11; H, 4.92; N, 5.98.

5-Methoxy-*N*-benzyl anthranilic acid (27)

¹H NMR (300 MHz, methanol-*d*₄) δ = 3.75 (s, 3H), 4.51 (s, 2H), 6.73 (d, *J* = 9.3 Hz, 1H), 7.09 (dd, *J* = 9.0 Hz, 3.2 Hz, 1H), 7.33 (m, 1H), 7.36-7.40 (m, 4H), 7.48 (d, *J* = 3.2 Hz, 1H). ¹³C NMR (75 MHz, DMSO-*d*₆) δ = 46.3, 55.4, 110.4, 113.2, 114.6, 122.5, 126.9, 127.0, 128.5, 139.7, 145.7, 148.9, 169.7. Anal. Calcd for C₁₅H₁₅NO₃: C, 70.02; H, 5.88; N, 5.44. Found: C, 69.88; H, 6.01; N, 5.47.

5-Carboxy-*N*-benzyl anthranilic acid (29)

¹H NMR (300 MHz, DMSO-*d*₆) δ = 4.63 (s, 2H), 6.83 (d, *J* = 8.8 Hz, 1H), 7.35-7.44 (m, 5H), 7.90 (d, *J* = 8.8 Hz, 1H), 8.54 (s, 1H), 8.89 (bs, 1H). ¹³C NMR (75 MHz, DMSO-*d*₆) δ = 45.7, 110.1, 111.4, 116.3, 127.1, 128.6, 134.1, 134.9, 138.7, 153.4, 166.8, 169.6. Anal. Calcd for C₁₅H₁₃NO₄: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.13; H, 4.96; N, 5.02.

5-Nitro-*N*-benzyl anthranilic acid (31)¹⁹

¹H NMR (300 MHz, methanol-d₄) δ = 4.77 (s, 2H), 6.99 (d, J = 9.3 Hz, 1H), 7.46-7.55 (m, 5H), 8.28 (d, J = 9.0 Hz, 1H), 8.99 (bs, 1H). ¹³C NMR (75 MHz, DMSO-d₆) δ = 45.8, 112.0, 127.0, 127.2, 128.6, 129.1, 135.2, 137.9, 154.5.

General Procedure for Coupling with Thiols

A mixture of a thiol (11.4 mmol), 2-bromobenzoic acid (8.8 mmol), K₂CO₃ (1.21 g, 8.8 mmol), Cu powder (51 mg, 0.8 mmol), Cu₂O (38 mg, 0.4 mmol) and 3 mL of 2-ethoxyethanol was heated to 130 °C for 4 h. The reaction was cooled to room temperature and the solvent was removed under reduced pressure. The residue was poured into 30 mL of water, treated with charcoal and the mixture was filtrated through celite. Acidification of the filtrate to pH 5 with diluted HCl gave a precipitate, which was dissolved in 100 mL of 5% aqueous Na₂CO₃ and the solution was filtrated through celite and subjected to precipitation as described above. Precipitation upon acidification gave pure sulfides.

2-(Phenylthio)benzoic acid (34)²⁰

¹H NMR (300 MHz, CDCl₃) δ = 6.84 (d, J = 8.1 Hz, 1H), 7.18 (dd, J = 7.7 Hz, 7.7 Hz, 1H), 7.31 (ddd, J = 7.3 Hz, 7.3 Hz, 1.5 Hz, 1H), 7.45-7.49 (m, 3H), 7.59-7.65 (m, 2H), 8.17 (dd, J = 7.7 Hz, 1.2 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃) δ = 124.9, 125.9, 127.8, 130.0, 130.5, 132.7, 132.9, 133.9, 136.5, 145.4, 172.7.

2-(4-Fluorophenylthio)benzoic acid (36)

¹H NMR (300 MHz, DMSO-d₆) δ = 6.78 (dd, J = 8.3 Hz, 1.0 Hz, 1H), 7.30 (ddd, J = 7.6 Hz, 7.6 Hz, 1.0 Hz, 1H), 7.40-7.50 (m, 3H), 7.65-7.72 (m, 2H), 8.02 (dd, J = 7.8 Hz, 1.5 Hz, 1H). ¹³C NMR (75 MHz, DMSO-d₆) δ = 117.2 (d, $J_{C,F}$ = 21.7 Hz), 124.6, 126.4, 127.3, 127.7 (d, $J_{C,F}$ = 3.0 Hz), 130.9, 132.5, 137.9 (d, $J_{C,F}$ = 8.6 Hz), 142.0, 163.2 (d, $J_{C,F}$ = 247.8 Hz), 167.3. Anal. Calcd for C₁₃H₉FO₂S: C, 62.89; H, 3.65. Found: C, 62.78; H, 3.81.

2-(4-Methoxyphenylthio)benzoic acid (38)²¹

¹H NMR (300 MHz, DMSO-d₆) δ = 3.91 (s, 3H), 6.74 (d, J = 8.1 Hz, 1H), 7.16 (d, J = 8.5 Hz, 2H), 7.25 (dd, J = 7.3 Hz, 7.3 Hz, 1H), 7.43 (dd, J = 7.3 Hz, 7.3 Hz, 1H), 7.56 (d, J = 8.5 Hz, 2H), 8.01 (d, J = 7.6 Hz, 1H). ¹³C NMR (75 MHz, DMSO-d₆) δ = 55.4, 115.7, 122.0, 124.1, 125.9, 126.8, 130.9, 132.3, 137.4, 143.4, 160.3, 167.3.

2-(2,6-Dimethylphenylthio)benzoic acid (40)

¹H NMR (300 MHz, DMSO-d₆) δ = 2.40 (s, 6H), 6.49 (d, J = 8.1 Hz, 1H), 7.26 (dd, J = 7.3 Hz, 7.3 Hz, 1H), 7.36-7.44 (m, 4H), 8.04 (dd, J = 7.6 Hz, 1.2 Hz, 1H). ¹³C NMR (75 MHz, DMSO-d₆) δ = 21.1, 124.0, 124.2, 127.7, 128.7, 129.7, 130.4, 131.3, 132.4, 140.8, 143.3, 167.5. Anal. Calcd for C₁₅H₁₄SO₂: C, 69.74; H, 5.46. Found: C, 69.57; H, 5.66.

5-Bromo-2-(phenylthio)benzoic acid (42)

¹H NMR (300 MHz, CDCl₃) δ = 6.67 (d, J = 8.8 Hz, 1H), 7.37 (dd, J = 8.8 Hz, 2.2 Hz, 1H), 7.44-7.50 (m, 3H), 7.54-7.60 (m, 2H), 8.25 (d, J = 2.4 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃) δ = 118.3, 127.2, 129.5, 130.3, 130.7, 132.1, 135.3, 136.5, 136.7, 144.8, 171.2. Anal. Calcd for C₁₃H₉BrO₂S: C, 50.50; H, 2.93. Found: C, 50.12; H, 3.21.

2-(Phenylthio)-5-methoxybenzoic acid (44)

¹H NMR (300 MHz, CDCl₃) δ = 3.85 (s, 3H), 6.93 (dd, J = 13.4 Hz, 9.0 Hz, 2H), 7.41-7.53 (m, 3H), 7.54-7.56 (m, 2H), 7.69 (s, 1H). ¹³C NMR (75 MHz, CDCl₃) δ = 56.2, 116.6, 121.1,

128.1, 129.3, 130.3, 131.0, 134.2, 134.5, 135.2, 157.9, 171.9. Anal. Calcd for $C_{14}H_{12}O_3S$: C, 64.60; H, 4.65. Found: C, 64.48; H, 4.88.

2-(Phenylthio)-5-nitrobenzoic acid (46)²²

1H NMR (300 MHz, DMSO- d_6) δ = 6.96 (d, J = 9.0 Hz, 1H), 7.68-7.74 (m, 5H), 8.27 (d, J = 8.8 Hz, 1H), 8.75 (s, 1H). ^{13}C NMR (75 MHz, DMSO- d_6) δ = 125.7, 126.5, 127.0, 127.1, 130.1, 130.4, 130.5, 135.6, 143.8, 151.8, 165.8.

2-(Phenylthio)-4-fluorobenzoic acid (48)

1H NMR (300 MHz, DMSO- d_6) δ = 6.38 (dd, J = 10.5 Hz, 2.4 Hz, 1H), 7.13 (ddd, J = 8.1 Hz, 8.1 Hz, 2.7 Hz, 1H), 7.63-7.71 (m, 5H), 8.12 (dd, J = 8.8 Hz, 6.1 Hz, 1H). ^{13}C NMR (75 MHz, DMSO- d_6) δ = 111.8 (d, $J_{C,F}$ = 21.7 Hz), 112.8 (d, $J_{C,F}$ = 25.7 Hz), 130.0, 130.3, 131.3, 135.6, 147.0, 164.2 (d, $J_{C,F}$ = 251.8 Hz). Anal. Calcd for $C_{13}H_9O_2S$: C, 62.89; H, 3.65. Found: C, 62.63; H, 3.99.

2-(Hexylthio)benzoic acid (50)

1H NMR (300 MHz, $CDCl_3$) δ = 0.90 (t, J = 6.8 Hz, 3H), 1.29-1.35 (m, 4H), 1.44-1.53 (m, 2H), 1.69-1.80 (m, 2H), 2.93 (t, J = 7.3 Hz, 2H), 7.18 (ddd, J = 7.7 Hz, 7.3 Hz, 1.2 Hz, 1H), 7.33 (d, J = 7.7 Hz, 1H), 7.48 (ddd, J = 8.1 Hz, 7.3 Hz, 1.5 Hz, 1H), 8.13 (dd, J = 8.1 Hz, 1.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 15.1, 23.6, 29.2, 30.0, 32.5, 33.3, 124.8, 126.7, 127.3, 133.7, 134.2, 144.4, 172.9. Anal. Calcd for $C_{13}H_{18}O_2S$: C, 65.51; H, 7.61. Found: C, 65.22; H, 7.92.

2-(Phenethylthio)benzoic acid (52)²³

1H NMR (300 MHz, DMSO- d_6) δ = 3.01 (t, J = 7.1 Hz, 2H), 3.28 (t, J = 7.1 Hz, 2H), 7.28-7.34 (m, 2H), 7.37-7.41 (m, 4H), 7.55 (d, J = 7.8 Hz, 1H), 7.61 (ddd, J = 6.8 Hz, 6.8 Hz, 1.5 Hz, 1H), 7.98 (dd, J = 7.8 Hz, 1.5 Hz, 1H). ^{13}C NMR (75 MHz, DMSO- d_6) δ = 32.3, 33.9, 123.8, 125.6, 126.3, 128.4, 130.9, 132.3, 139.8, 140.2, 140.6, 167.5.

2-(Benzylthio)benzoic acid (54)^{16d}

1H NMR (300 MHz, DMSO- d_6) δ = 4.30 (s, 2H), 7.31 (m, 1H), 7.37 (d, J = 7.1 Hz, 1H), 7.43 (dd, J = 7.3 Hz, 7.3 Hz, 2H), 7.51-7.60 (m, 4H), 8.01 (d, J = 8.1 Hz, 1H). ^{13}C NMR (75 MHz, DMSO- d_6) δ = 35.5, 123.7, 125.4, 126.9, 127.4, 128.2, 128.9, 130.7, 132.1, 136.3, 141.0, 167.2.

2-(Cyclohexylthio)benzoic acid (56)

1H NMR (300 MHz, DMSO- d_6) δ = 1.33-1.51 (m, 5H), 1.69 (m, 1H), 1.79-1.83 (m, 2H), 2.03-2.07 (m, 2H), 3.44 (m, 1H), 7.29 (ddd, J = 2.4 Hz, 6.1 Hz, 8.1 Hz, 1H), 7.53-7.60 (m, 2H), 7.87 (d, J = 7.3 Hz, 1H). ^{13}C NMR (75 MHz, DMSO- d_6) δ = 25.3, 25.4, 32.4, 42.6, 124.2, 127.3, 130.4, 131.7, 138.4, 167.7. Anal. Calcd for $C_{13}H_{16}O_2S$: C, 66.07; H, 6.82. Found: C, 65.99; H, 7.02.

Acknowledgements

We gratefully acknowledge the National Institutes of Health (R01 AI060792) for financial support.

5. References and Notes

- (a) Ottolia M, Toro L. *Biophys J* 1994;67:2272–2279. [PubMed: 7535111] (b) Farrugia G, Nitecki S, Harty GJ, Camilleri M, Szurszewski JH. *GUT* 1998;42:258–265. [PubMed: 9536952]
- (a) Green NS, Palaninathan SK, Sacchettini JC, Kelly JW. *J Am Chem Soc* 2003;125:13404–13414. [PubMed: 14583036] (b) Klabunde T, Petrassi HM, Oza VB, Raman P, Kelly JW, Sacchettini JC. *Nature*

- Struct Biol 2000;7:312–321. [PubMed: 10742177] (c) Oza VB, Smith C, Raman B, Koepf EK, Lashuel HA, Petrassi HM, Chiang KP, Powers ET, Sachettinni J, Kelly JW. J Med Chem 2002;45:321–332. [PubMed: 11784137]
3. (a) Inai Y, Kurokawa Y, Ida A, Hirabayashi T. Bull Chem Soc Jpn 1999;72:55–61. (b) Ramesh K, Balaram P. Bioorgan Med Chem 1999;7:105–117. (c) Abele S, Seebach D. Eur J Org Chem 2000;1:1–15. (d) Inai Y, Tagawa K, Takasu A, Hirabayashi T, Oshikawa T, Yamashita M. J Am Chem Soc 2000;122:11731–11732. (e) Inai Y, Ousaka N, Okabe T. J Am Chem Soc 2003;125:8151–8162. [PubMed: 12837085]
4. Ullmann F. Ber dt chem Ges 1903;36:2382–2384.
5. (a) Kwong FY, Klapars A, Buchwald SL. Org Lett 2002;4:581–584. [PubMed: 11843596] (b) Wolf C, Mei X. J Am Chem Soc 2003;125:10651–10658. [PubMed: 12940749] (c) Docampo Palacios ML, Pellon Comdom RF. Synth Commun 2003;33:1771–1775. (d) Kunz K, Scholz U, Ganzer D. Synlett 2003:2428–2439. (e) Huang X, Anderson KW, Zim D, Jiang L, Klapars A, Buchwald SL. J Am Chem Soc 2003;125:6653–6655. [PubMed: 12769573] (f) Dokorou V, Kovala-Demertzi D, Jasinski JP, Galani A, Demertzi MA. Helv Chim Acta 2004;87:1940–1950. (g) Mei X, Wolf C. Chem Comm 2004:2078–2079. [PubMed: 15367983] (h) Mei X, Wolf C. J Am Chem Soc 2004;126:14736–14737. [PubMed: 15535695] (i) Mei X, Wolf C. J Org Chem 2005;70:2299–2305. [PubMed: 15760218]
6. Stauffer SR, Steinbeiser MA. Tetrahedron Lett 2005;46:2571–2575.
7. Csuk R, Barthel A, Raschke C. Tetrahedron 2004;60:5737–5750.
8. (a) Beard RL, Colon DF, Song TK, Davies PJA, Kochhar DM, Chandraratna RAS. J Med Chem 1996;39:3556–3563. [PubMed: 8784454] (b) Potin D, Parnet V, Teulon JM, Camborde F, Caussade F, Meignen J, Provost D, Cloarec A. Bioorg Med Chem Lett 2000;10:805–809. [PubMed: 10782691]
9. (a) Kwong FY, Buchwald SL. Org Lett 2002;4:3517–3520. [PubMed: 12323058] (b) Fernandez-Rodriguez MA, Shen Q, Hartwig JF. J Am Chem Soc 2006;128:2180–2181. [PubMed: 16478149]
10. Kalinin AV, Bower JF, Riebel P, Snieckus V. J Org Chem 1999;64:2986–2987. [PubMed: 11674386]
11. Geertsma EM, Hoen R, Meetsma A, Feringa BL. Eur J Org Chem 2006:3596–3605.
12. (a) Mei X, August AT, Wolf C. J Org Chem 2006;71:142–149. [PubMed: 16388629] (b) Wolf C, Liu S, Mei X, August AT, Casimir MD. J Org Chem 2006;71:3270–3273. [PubMed: 16599627]
13. (a) Maradolla MB, Amaravathi M, Kumar VN, Mouli GVPC. J Mol Catal A 2007;266:47–49. (b) Rodriguez-Dominguez JC, Balbuzano-Deus A, Lopez-Lopez MA, Kirsch G. J Heterocycl Chem 2007;44:273–275.
14. No product formation was observed in the absence of a copper catalyst.
15. Carbon–sulfide bond formation with 2-iodobenzoic acids proved to be complete within 2 hours while 2-chlorobenzoic acids gave low yields under the conditions described.
16. (a) Luyt LG, Katzenellenbogen JA. Bioconjugate Chem 2002;13:1140–1145. (b) Zarghi A, Faizi M, Shafaghi B, Ahadian A, Khojastehpoor HR, Zanganeh V, Tabatabai SA, Shafiee A. Bioorg Med Chem Lett 2005;15:3126–3129. [PubMed: 15876530] (c) Khan S, Bernad PL, Korshun VA, Southern EM, Shchepinov MS. Synlett 2005:2453–2456. (d) Ko J, Ham J, Yang I, Chin J, Nam S, Kang H. Tetrahedron Lett 2006;47:7101–7106.
17. Pellon RF, Estevez-Braun A, Docampo ML, Martin A, Ravelo AG. Synlett 2005:1606–1608.
18. Kirk K, Horner HA. Biochem J 1995;311:761–768. [PubMed: 7487930]
19. Kohno Y, Awano K, Miyashita M, Fujimori S, Kuriyama K, Sakoe Y, Kudoh S, Saito K, Kojima E. Bioorg Med Chem Lett 1997;7:1515–1518.
20. Hiroi K, Suzuki Y, Abe I. Tetrahedron: Asymm 1999;10:1173–1188.
21. Liao Y, Venhuis BJ, Rodenhuis N, Timmerman W, Wikstroem H, Meier E, Bartoszyk GD, Boettcher H, Seyfried CA, Sundell S. J Med Chem 1999;42:2235–2244. [PubMed: 10377229]
22. Parlow JJ, Stevens AM, Stegeman RA, Stallings WC, Kurumbail RG, South MS. J Med Chem 2003;46:4297–4312. [PubMed: 13678408]
23. Arya VP, Sudarsanam V. Indian J Chem, Sect B 1977;15B:145–147.

Scheme 1.
Copper-catalyzed amination of **1** using **2** in ethoxyethanol.

Table 1
Copper-catalyzed C-N Bond Formation with 2-Chlorobenzoic Acids

entry	aryl chloride	amine	product	yield (%)
1				93 (85) ^a
2				>99
3				85
4				91
5				94
6				86
7				84 ^b
8				82
9				84

entry	aryl chloride	amine	product	yield (%)
10	<p>22</p>	<p>6</p>	<p>23</p>	92

Reaction conditions: A mixture of a 2-chlorobenzoic acid (8.8 mmol), amine (17.6 mmol), K₂CO₃ (8.8 mmol), Cu (0.8 mmol), Cu₂O (0.4 mmol) in 3 mL of ethylene glycol diethyl ether (EGDE) was heated to 130 °C for 24 h.

^a 80 °C.

^b 12 h.

Table 2
Copper-catalyzed C-N Bond Formation with 2-Bromobenzoic Acids

entry	aryl bromide	amine	product	yield (%)
1				82
2				95
3				91
4				94
5				90
6				85
7				91
8				81
9				88
10				97

entry	aryl bromide	amine	product	yield (%)
-------	--------------	-------	---------	-----------

Reaction conditions: A mixture of a 2-bromobenzoic acid (8.8 mmol), amine (17.6 mmol), K_2CO_3 (8.8 mmol), Cu (0.8 mmol), Cu_2O (0.4 mmol) in 3 mL of EGDE was heated to 130°C for 24 h.

Table 3
Copper-catalyzed C-S Bond Formation with 2-Bromobenzoic Acids

entry	aryl bromide	thiol	product	yield (%)
1				99
2				92
3				>99
4				94 ^a
5				92
6				>99
7				92
8				90
9				>99 ^b
10				95 ^b

entry	aryl bromide	thiol	product	yield (%)
11				97 ^b
12				92 ^b

Reaction conditions: A mixture of 2-bromobenzoic acid (8.8 mmol), thiol (8.8 mmol), K₂CO₃ (8.8 mmol), Cu (0.8 mmol), Cu₂O (0.4 mmol) in 3 mL of ethoxyethanol was heated to 130 °C for 4 h.

^a 6 h.

^b 12 h.