Promazine Synthesis

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Palladium-Catalyzed Three-Component Approach to Promazine with Formation of One Carbon–Sulfur and Two Carbon–Nitrogen Bonds

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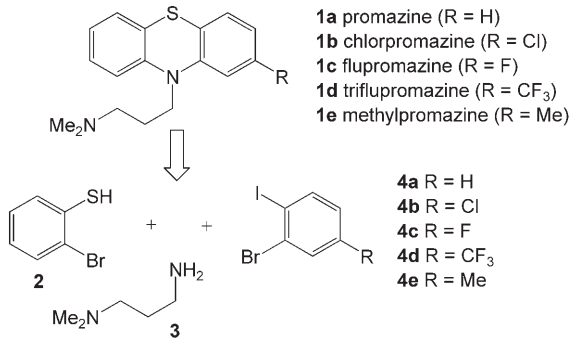
The formation of aromatic carbon–heteroatom bonds has traditionally been achieved by nucleophilic aromatic substitution or by the copper-mediated Ullman reaction.[1] The former type of chemistry is generally limited to activated substrates, whereas the latter often requires prolonged heating in the presence of excess copper salts. The palladium-catalyzed formation of aromatic C–N bonds,[2] extensively developed by the groups of Hartwig and Buchwald, has provided a powerful alternative.[3] Whereas aryl amination has been optimized so that it is even applicable to aryl chlorides and activated phenols, the analogous formation of C–O and C–S bonds has attracted less attention. For a medicinal chemistry project, we have identified conditions that enable the formation of C–S bonds from thiophenols and aryl iodides, and C–N bonds from amines and aryl bromides using the same catalyst in a one-pot reaction. We now report the application of this discovery to the synthesis of the promazine class of antipsychotics.[4]

Our attention was drawn to the phenothiazine backbone of the promazine series **1a–e** as a suitable model system for the controlled construction of three carbon–heteroatom bonds in a single synthetic operation (Scheme 1). This synthesis would require that either C–S or C–N bond formation occur initially with subsequent cyclization to the phenothiazine nucleus. This disconnection of the promazines leads to the precursors 2-bromothiophenol (**2**), primary amine **3**, and an appropriately substituted 1-bromo-2-iodobenzene **4a–e**.



Scheme 1. Retrosynthetic analysis for the promazines.

From reported literature and our experience with reactions involving dppf,[5] binap,[6] dpephos,[7] and xantphos,[8] the formation of the C–S bond was expected to precede the amination steps.[9] Indeed, clean formation of diaryl sulfide **6** was observed when a mixture of **2**, **3**, **4a**, and NaO*t*Bu was treated with [Pd_2dba_3] and dppf at 60 °C for 20 minutes, and **1a** was formed in high yield after 2 hours at 160 °C under microwave (MW) irradiation. These conditions were mimicked in a ligand optimization study using oil-bath heating (Figure 1).[10]

Figure 1 summarizes results obtained with commercially available and easily handled ligands reported for C–S and C–N coupling reactions. Ferrocene ligands such as dppf gave mainly the desired product (**1a**) in addition to the noncyclized intermediate **7**. Significant amounts of aniline **5** were observed with davephos, x-phos, and binap.[11] Noncyclized promazine **7** was the major product with dpephos and xantphos. Trace amounts of the desired product were formed with PPh_3, P(*o*-tol)$_3$, P(*t*Bu)$_3$,[12,13] or the carbene ligand.[14] Low conversion of **4a** occurred with diaryl sulfide **6** as the only detectable product in the absence of palladium and ligand, whereas small amounts of **6** and bromobenzene were formed without the ligand.[15]

The reaction appears to proceed in a stepwise fashion from diaryl sulfide **6** (only product with one equivalent of NaO*t*Bu), to aniline **7** (only product with two equivalents of NaO*t*Bu), to **1a** (74 % yield; Table 1) under MW conditions.

The three-component reaction worked well for the parent promazines **1a–e** with yields of the isolated products ranging from 50 % to 76 %, and an average yield of greater than 75 % for each of the three bonds formed (Table 1). The reaction with allyl amine[16] gave a complex mixture of unidentified products.[17] Benzyl amines were good substrates and the scope of the reaction was extended to include anilines;[18] 2,6-disubstituted anilines participated in the reaction, albeit with reduced yields as the steric hindrance around the nitrogen atom increased.

The microwave method was relatively slow as the reagents had to be mixed immediately before starting the reactions to avoid catalyst deactivation. Conveniently, the reaction was performed with conventional heating, warming from room temperature to 160 °C over approximately 0.5 hours, with subsequent stirring at 160 °C overnight (reaction times have not been optimized).

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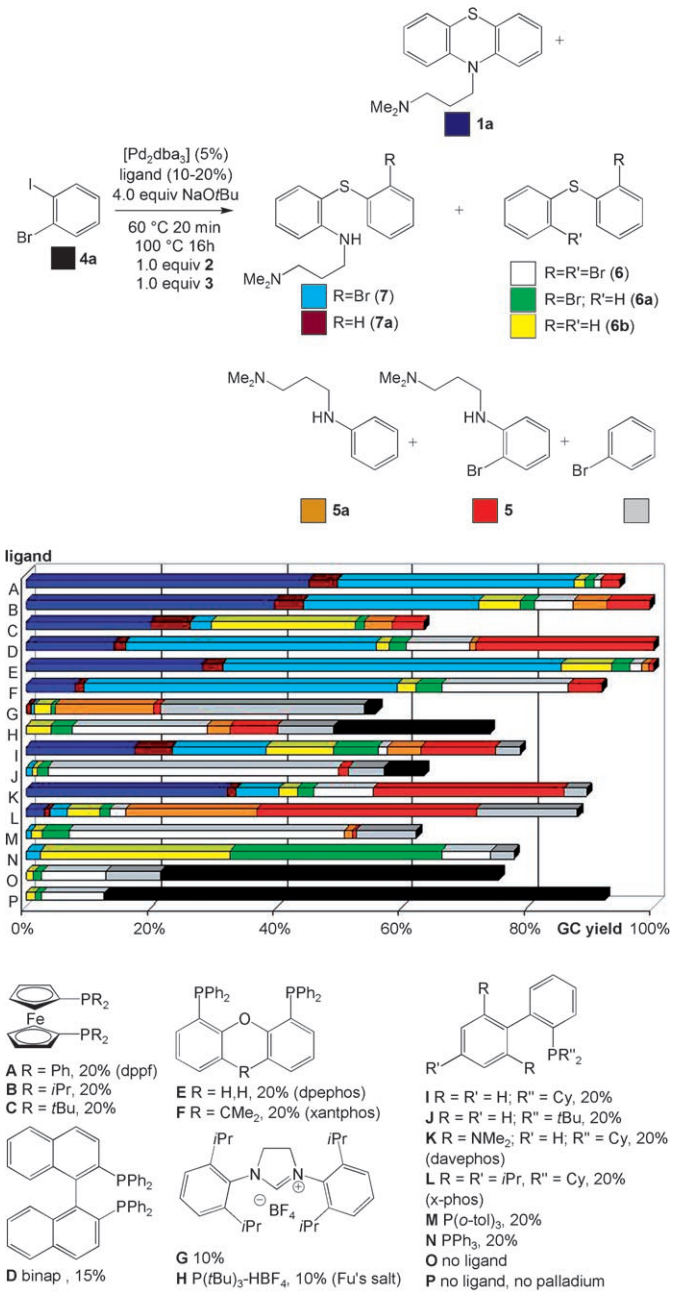
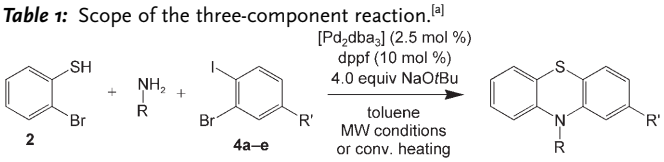


Figure 1. Ligand screening. Reactions were performed on 0.26-mmol scale using 5% [Pd_2dba_3] and 10–20% ligand in toluene (2 mL). The colors in the chart indicate the product distribution across the range of ligands (A–N) studied in addition to two control experiments (O and P). Cy = cyclohexyl; tol = tolyl.

The use of 1-bromo-2-iodobenzenes (**4a–e**) controlled the regiochemistry with C–S bond formation exclusively at the aryl iodide. Replacing **4a** with 1,2-dibromobenzene led to a much lower yield of **1a**. This difference in yield means that the reaction scope is limited to 1-bromo-2-iodobenzenes.

Toluene is a relatively poor solvent for microwave chemistry, and often MW heating to 160 °C failed. However, toluene/DMF or 1,2-dichlorobenzene were good solvents for the reaction (Table 2). No product was observed when toluene was doped with the ionic liquids bmimCl and

Table 1: Scope of the three-component reaction.[a]



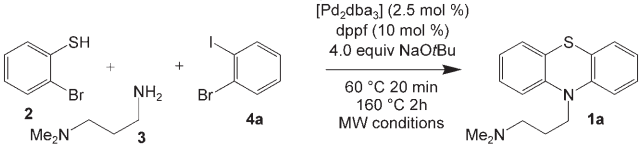
Entry	Amine	Aryl halide		Product Yield
1	Me_2N NH_2	X Br	X = I	74%, 73%,[c]
			X = Br	66%[e]
				17%[e]
2	Me_2N NH_2	I Br R'	R' = Cl	50%[b]
			R' = F	62%[b]
			R' = CF_3	59%[b]
			R' = Me	76%[b]
3	NH_2 R	I Br	R = H	76%,[b] 91%[d,e]
			R = OMe	61%,[b] 68%[e]
4	NH_2 R	I Br	R = H	91%[b,d]
			R = Me	78%[e]
			R = F	92%[d,e]
			R = Cl	89%[d,e]
5	R NH_2 R	I Br	R = Me	56%[d,e]
			R = *i*Pr	21%[d,e]
6	NH_2 R	I Br	R = F	88%[e]
			R = Cl	83%[e]
			R = OMe	65%[b]
7	R NH_2	I Br	R = F	89%[d,e]
			R = Cl	82%[e]

[a] Reactions were performed on 3.0-mmol scale. [b] Microwave heating at 60 °C for 20 min, then 160 °C for 2 h. [c] Performed in screw-cap vials, which were inserted into an oil bath preheated to 60 °C for 20 min then heated to 160 °C for 2 h. [d] 5 mol% [Pd_2dba_3] and 20 mol% dppf. [e] Conventional heating from room temperature to 160 °C overnight.

$bmimPF_6$.[9] The reaction was scaled to produce multigram quantities of **1a**.

In conclusion, we have developed an efficient catalyst system for the formation of one C–S and two C–N bonds in a

Table 2: Solvent effects and scale up of microwave reactions.[a]



Entry	Solvent	Heating rate [°C s^{-1}]	Yield **1a** [%]
1	toluene	0.53	74
2	toluene/DMF (95:5)	1.12	61
3	toluene/bmimCl (95:5)	0.82	0
4	toluene/$bmimPF_6$ (95:5)	1.28	0
5	1,2-dichlorobenzene	1.25	60
6[b]	toluene/DMF (95:5)	NA	68 (17.9 g)

[a] Reactions were performed on 3-mmol scale using 2.5 mol% [Pd_2dba_3] and 10 mol% dppf in dry solvent (15 mL). Heating rates were determined at a constant MW output of 300 W. [b] Reaction performed on 90-mmol scale using 2.5 mol% [Pd_2dba_3] and 10 mol% dppf in dry toluene/DMF (95:5; 450 mL). NA = not applicable.

three-component reaction leading to phenothiazines in a single reaction flask. The transformation requires either microwave or conventional heating.

Experimental Section

General procedure: [Pd_2dba_3] (69 mg, 0.075 mmol), dppf (166 mg, 0.10 mmol), and NaO*t*Bu (1.15 g, 12.0 mmol) were added to a MW vial and mixed with toluene (15 mL), **2** (567 mg, 3.0 mmol), **4a** (849 mg, 3.0 mmol), and **3** (307 mg, 3.0 mmol). The mixture was heated at 60 °C for 20 min and then heated to 160 °C for 2 h under MW conditions. The mixture was purified by chromatography.

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[1] a) J. March, *Advanced Organic Chemistry*, 4th ed., Wiley, New York, **1992**, chap. 13; b) S. V. Ley, A. W. Thomas, *Angew. Chem.* **2003**, *115*, 5558 – 5607; *Angew. Chem. Int. Ed.* **2003**, *42*, 5400 – 5449; c) T. Kondo, T. Mitsudo, *Chem. Rev.* **2000**, *100*, 3205 – 3220.

[2] This reaction was first reported in a catalytic version in 1986: N. V. Kondratenko, A. Kolomeitsev, V. O. Mogilevskaya, N. M. Varlamova, L. M. Yagupol'skii, *Zh. Org. Khim.* **1986**, *8*, 1721 – 1729 (English translation: *J. Org. Chem. USSR* **1986**, *22*, 1547–1554).

[3] a) J. Louie, J. F. Hartwig, *Tetrahedron Lett.* **1995**, *36*, 3609 – 3612; b) A. S. Guram, R. A. Rennels, S. L. Buchwald, *Angew. Chem.* **1995**, *107*, 1456 – 1459; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1348 – 1350. For a review, see: B. Schlummer, U. Scholz, *Adv. Synth. Catal.* **2004**, *346*, 1599 – 1626.

[4] For a general discussion, see: K. P. Bøgesø, B. Bang-Andersen in *Textbook of Drug Design and Discovery*, 3rd ed. (Eds.: P. Krogsgaard-Larsen, T. Liljefors, U. Madsen), Taylor and Francis, London, UK, **2002**, chap. 11.

[5] a) G. Mann, D. Barano, J. F. Hartwig, A. L. Rheingold, I. A. Guzei, *J. Am. Chem. Soc.* **1998**, *120*, 9205 – 9219; b) M. S. Driver, J. F. Hartwig, *J. Am. Chem. Soc.* **1997**, *119*, 8232 – 8245.

[6] a) J. P. Wolfe, S. Wagaw, S. L. Buchwald, *J. Am. Chem. Soc.* **1996**, *118*, 7215 – 7216; b) J. P. Wolfe, S. L. Buchwald, *J. Org. Chem.* **2000**, *65*, 1144 – 1157.

[7] a) U. Schofper, A. Schlapbach, *Tetrahedron* **2001**, *57*, 3069 – 3073; b) Y. Guari, G. P. F. van Strijdonck, M. D. K. Boele, J. N. H. Reek, P. C. J. Kramer, P. W. N. M. van Leeuwen, *Chem. Eur. J.* **2001**, *7*, 475 – 482.

[8] Y. Guari, D. S. van Es, J. N. H. Reek, P. C. J. Kamer, P. W. N. M. van Leeuwen, *Tetrahedron Lett.* **1999**, *40*, 3789 – 3790.

[9] Abbreviations: bmim = (*n*-butyl)methyl imidazolium; binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl; davephos = 2-dicyclohexylphosphanyl-2′-(*N*,*N*-dimethylamino)biphenyl; dba = dibenzylidine acetone; dpephos = bis(2-diphenylphosphanyl)-ether; dppf = 1,1′-bis(diphenylphosphanyl)ferrocene; xantphos = 4,5-bis(diphenylphosphanyl)-9,9-dimethylxanthene; x-phos = 2-dicyclohexylphosphanyl-2′,4′-6′-triisopropyl-1,1′-biphenyl.

[10] The reagents had to be mixed immediately before starting the reactions to avoid catalyst deactivation. Therefore, the classic oil bath conditions were more practical for ligand screening experiments (see the Supporting Information for details). All chemicals were weighed out in air without precautions to exclude air from the reaction mixture.

[11] a) J. P. Wolfe, H. Tomori, J. P. Sadighi, J. Yin, S. L. Buchwald, *J. Org. Chem.* **2000**, *65*, 1158 – 1174; b) E. R. Strieter, D. G. Blackwood, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 13978 – 13980.

[12] a) M. Nishiyama, T. Yamamoto, Y. Koie, *Tetrahedron Lett.* **1998**, *39*, 617 – 620; b) J. F. Hartwig, M. Kawatsura, S. I. Hauck, K. H. Shaughnessy, L. M. Alcazar-Roman, *J. Org. Chem.* **1999**, *64*, 5575 – 5580.

[13] M. R. Netherton, G. C. Fu, *Org. Lett.* **2001**, *3*, 4295 – 4298.

[14] a) J. Huang, G. Grasa, S. P. Nolan, *Org. Lett.* **1999**, *1*, 1307 – 1309; b) S. R. Stauffer, S. Lee, J. P. Stambuli, S. I. Hauck, J. F. Hartwig, *Org. Lett.* **2000**, *2*, 1423 – 1426; c) M. S. Viciu, R. M. Kissling, E. D. Stevens, S. P. Nolan, *Org. Lett.* **2002**, *4*, 2229 – 2231.

[15] Side-by-side comparisons of $Pd(OAc)_2$, [$Pddba_2$], or [Pd_2dba_3] in combination with dppf established that a 1:4 mixture of [Pd_2dba_3] and dppf was superior for the synthesis of **1a**. The desired product was not observed when using [Pd(dppf)Cl_2·CH_2Cl_2].

[16] S. Jaime-Figueroa, Y. Liu, J. M. Muchowski, D. G. Putman, *Tetrahedron Lett.* **1998**, *39*, 1313 – 1316.

[17] 5% of 3-methylindole is formed under these reaction conditions. We have optimized this serendipitous finding to a one-flask approach to 3-substituted indoles. T. Jensen, H. Pedersen, B. Bang-Andersen, R. Madsen, M. Jørgensen, *Angew. Chem.* **2008**,*120*, 902 – 904; *Angew. Chem. Int. Ed.* **2008**, *47*, 880 – 890..

[18] No amination products formed with 4-(trifluoromethyl)aniline, 4-amino-benzoic acid ethyl ester, or 4-(dimethylamino)aniline.

