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A Practical Buchwald−Hartwig Amination of 2-Bromopyridines with Volatile Amines

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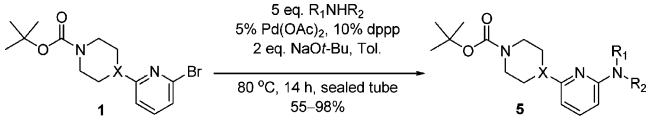
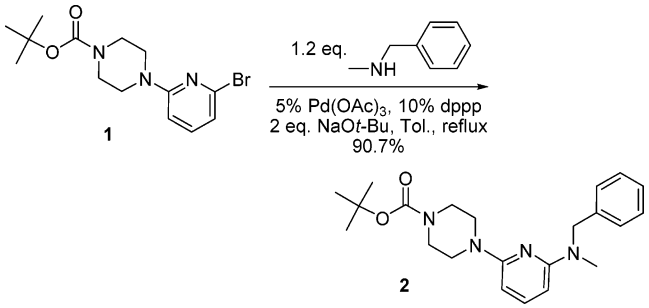


A practical Buchwald−Hartwig amination of 2-bromopyridines with volatile amines is developed in sealed tubes. The method provides an expedient entry to a variety of secondary and tertiary aminopyridines that are otherwise not readily synthesized.

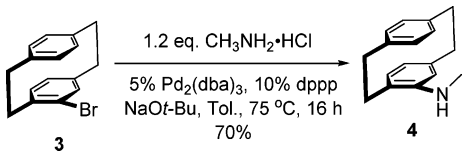
Heterocycles are of paramount importance in medicinal chemistry. Applications of palladium catalysis in heterocyclic chemistry have grown exponentially.[1] In particular, the Buchwald−Hartwig amination has seen widespread use in heterocyclic chemistry.[2,3] The palladium-catalyzed carbon−nitrogen bond formation reaction enables assembly of a variety of aminopyridines. Wagaw and Buchwald systematically investigated the synthesis of aminopyridines employing palladium-catalyzed carbon−nitrogen bond formation.[4] By utilizing chelating bis(phosphine) ligands, they overcame the chelation effect of pyridine on the palladium catalysts. The chelating bidentate ligands also inhibit side reactions such as β-hydride elimination from an amidopalladium intermediate and the formation of bis(amine) complexes that lead to products of hydrodebromination. Recently, Hartwig described mild, palladium-catalyzed coupling of aryl halides with ammonia in a Parr bomb to form primary arylamines as the major product.[5]

However, formation of a methylamine (boiling point, −6.2 °C) using the Buchwald−Hartwig amination reaction does not work because of its volatility. Dimethylamine (bp, 7 °C), ethylamine (bp, 16.6 °C), isopropylamine (bp, 33.5 °C), propylamine (bp, 48.0 °C), and cyclopropylamine (bp, 49.5 °C) all suffer similar demise. A common method of circumventing the problem of volatility is the use of benzylmethylamine. As illustrated in Scheme 1, the transformation of 2-bromopyridine

SCHEME 1. The Buchwald−Hartwig Amination Using Benzylmethylamine



SCHEME 2. Palladium-Catalyzed Methylamination Using Methylammonium Chloride



1 to the amination product **2** was achieved in good yield. Unfortunately, debenzylation of **2**, like many similar cases, proved to be challenging without destroying the integrity of the molecule.

Another method of installing methylamine is the use of methylammonium chloride as illustrated by the transformation of 4-bromo[2,2]paracyclophane (**3**) to its corresponding methylamine **4**.[6] The method uses an excess amount of sodium *tert*-butoxide and cannot be applied to free amines (Scheme 2).

Herein, we have developed a methodology for palladium-catalyzed amination of 2-bromopyridines with volatile amines in sealed tubes. This simple and practical method applies to all volatile amines such as methylamine, ethylamine, isopropylamine, propylamine, and cyclopropylamine. It has been successfully applied to a variety of 2-bromopyridines.

Although the aminations of 2-bromopyridines failed for volatile amines under the classic Buchwald−Hartwig amination conditions under normal pressure, they consistently worked well in sealed tubes. Therefore, the mixture of 1 equiv of the substrate, such as **1**, 5 equiv of the amine (methylamine and dimethylamine gases were cooled to −78 °C and added as liquid), 5% of $Pd(OAc)_2$, 10% 1,3-bis(diphenylphosphino)-propane (dppp), and 2 equiv of NaO*t*-Bu in toluene was added to a sealed tube and heated at 80 °C overnight (14 h). Methylamine has the highest volatility with a vapor pressure of 20 atm at 80 °C. The volatility at 80 °C of other volatile amines is 10 atm for dimethylamine, 7.5 atm for ethylamine, and 3.5 atm for propylamine and cyclopropylamine. The reaction gave moderate (55% for entry 2) to almost quantitative (98% for entry 5) yield for all of the volatile amines that we investigated.

As depicted in Table 1, secondary amines generally worked better in synthesis than the primary amines with an exception for entry 8. The yields were often better and the products were consistently cleaner as well when secondary amines were used.

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(1) *Palladium in Heterocyclic Chemistry: A Guide for the Synthetic Chemist*, 2nd ed.; Li, J. J., Gribble, G. W., Eds.; Elsevier: Oxford, UK, 2006.

(2) Janey, J. M. Buchwald−Hartwig Amination. In *Name Reactions for Functional Group Transformations*; Li, J. J., Ed.; John Wiley & Sons: Hoboken, NJ, 2007; pp 566−611.

(3) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599−1626.

(4) Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7240−7241.

(5) Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 10028−10029.

(6) Kreis, M.; Friedmann, C. J.; Braese, S. *Chem.−Eur. J.* **2005**, *11*, 7387−7394.

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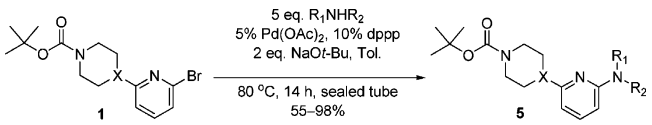
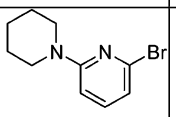
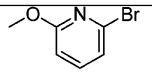
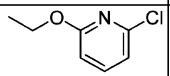
TABLE 1. The Buchwald−Hartwig Amination of 2-Halopyridines



entry	**1**, X	R_1NHR_2	yield[a]
1	**1a**, N	CH_3NH_2	77
2	1a, N		55
3	1a, N	$(CH_3)_2NH$	76
4	**1a**, C	$(CH_3)_2CHNH_2$	93
5	**1b**, C	$(CH_3)_2NH$	98
6	**1b**, C	$CH_3CH_2NH_2$	70
7	**1b**, C	$CH_3CH_2CH_2NH_2$	73
8		$CH_3CH_2NH_2$	94
9		$(CH_3)_2NH$	95
10		$(CH_3)_2NH$	28

[a] Yields were not optimized.

One reason could be that side reactions were impossible because the products from the first amination did not have a free amine that was available for further complications. Another reason might be that the resulting tertiary amines were immune to further oxidation reaction that plagued some resulting secondary amines, which were slowly oxidized under light, and the color of some secondary amine products tended to darken after exposure to light over extended time.

The methodology described above worked well for all 2-bromopyridines that we tried. However, the corresponding 2-chloropyridines worked but with lower yields. For instance, 6-ethoxy-*N*,*N*-dimethylpyridin-2-amine was obtained in only 28% yield from the reaction of 2-chloro-6-ethoxypyridine with dimethylamine under similar reaction conditions. Extension of this methodology to 2-chloropyrimidine and 2-bromopyrimidine failed to yield detectable amount of the Buchwald−Hartwig amination with volatile amines under the sealed-tube conditions.

In summary, carrying out the Buchwald−Hartwig amination of 2-bromopyridines with volatile amines in sealed tubes provides an expedient entry to a variety of novel secondary and tertiary amines that are otherwise not straightforward to synthesize and not found in the literature.

Experimental Section

Typical Procedure: 4-(6-Cyclopropylaminopyridin-2-yl)piperazine-1-carboxylic Acid *tert*-Butyl Ester (5b, Entry 2): To an Ace-Thred sealed tube (the sealed tube is rated 150 PSI at 120 °C) was added **1b** (1.0 g, 2.92 mmol) in toluene (10 mL), followed by cyclopropylamine (0.84 g, 14.61 mmol), $Pd(OAc)_2$ (33 mg, 0.15 mmol), dppp (0.12 g, 0.29 mmol), and NaO*t*-Bu (0.56 g, 5.84 mmol). The tube was then sealed and heated in an electronically controlled pipe heater, which was operated behind heavy shielding, at 80 °C overnight (14 h) with mechanical shaking. (*CAUTION: The reaction must be carried out in a fume-hood with shield protection!*) After cooling to room temperature, the resulting black suspension was directly submitted to flash chromatography eluting with 2:1 hexanes/EtOAc to give the desired amination product **5b** as gray flaky crystals after recrystallization from ethanol (0.515 g, 55.4%): mp = 95.3 °C; ^{1}H NMR ($CDCl_3$) δ (ppm) 7.36 (dd, J_1 = 7.8 Hz, J_2 = 8.2 Hz, 1H), 6.38 (d, J = 7.8 Hz, 1H), 6.18 (d, J = 7.8 Hz, 1H), 4.73 (s, 1H, NH), 3.50−3.41 (m, 8H), 2.46 (m, 1H), 0.72 (m, 2H), 0.53 (m, 2H); MS (APCI), *m/z* (M + 1) calcd, 319.20; found, 319.22; $C_{17}H_{26}N_4O_2$ calcd, C, 64.12; H, 8.23; N, 17.60; found, C, 64.05; H, 8.53; N, 17.55.

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Supporting Information Available: ^{1}H NMR spectra and data, MS(APCI) data of all amination products, and melting points and CHN elemental analysis data for all solid samples. ^{13}C NMR spectrum and IR for the new compound **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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