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Selective Catalytic Hydrogenation of Nitro Groups in the Presence of Activated Heteroaryl Halides

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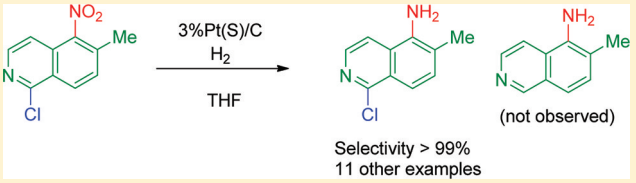
Supporting Information

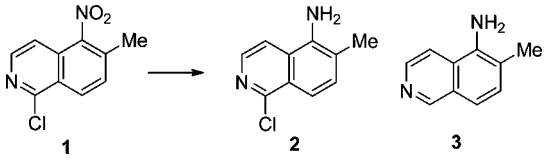
ABSTRACT: Chemoselective reduction of nitro groups in the presence of activated heteroaryl halides was achieved via catalytic hydrogenation with a commercially available sulfided platinum catalyst. The optimized conditions employ low temperature, pressure, and catalyst loading (<0.1 mol % Pt) to afford heteroaromatic amines with minimal hydrodehalogenation byproducts.



The reduction of heteroaromatic nitro groups to the corresponding anilines is an important transformation in the pharmaceutical industry for the synthesis of key intermediates and active pharmaceutical ingredients.[1] Typical aryl nitro reduction methods require stoichiometric reductants such as zinc,[2] tin,[3] and iron[4] or employ transition metal catalysts such as palladium, platinum, and nickel.[5] The use of stoichiometric metals often necessitates laborious work up procedures that require high solvent volumes and generate large amounts of waste. On the other hand, work up procedures for heterogeneous catalytic reductions are relatively simple, typically consisting of the removal of the metal supported catalyst by filtration and concentration of the filtrate to isolate the product. This simplified process and reduced waste represents a greener alternative.[6] Although reductions of nitro aromatics in the presence of other reducible functional groups such as Cl, I, OCH_2Ph, $NHCH_2Ph$, CN, etc. are well-known in the literature,[7] the selective hydrogenation of nitro groups in the presence of electronically activated heteroaryl halides[8] remains challenging. This is because the most common nitro reduction catalysts (Pd, Ni, Pt, Rh) are also known to promote hydrodehalogenation,[9] which is often more pronounced in the case of heteroaryl halide substrates. The extent of hydrodehalogenation depends upon halogen type (I, Br, Cl), position on the aromatic ring, and reaction parameters such as temperature, pressure, solvent, and the catalyst employed.[10] In some cases, additives have been shown to attenuate hydrodehalogenation; however, they can also diminish catalytic activity toward the reduction of nitro group, necessitating higher reaction temperature and pressure.[11] Thus, selection of the ideal catalyst and additive remains a largely empirical process, and there is a continuing need for more general and selective catalyst systems.[12]

As part of a program to develop an improved synthesis of a B-raf kinase inhibitor,[13] we required a selective reduction of the nitro group of **1** in the presence of an activated chloroisoquinoline (Scheme 1). Although a stoichiometric iron-mediated reduction was successful in effecting the desired transformation, the product **2** was isolated in poor yield (~40%).

Scheme 1. Chemoselective Nitro Reduction of 1 to 2



Catalytic reduction provided a more attractive approach; however, various conventional palladium catalysts (e.g., Pd/C, Pd/Al_2O_3, Pd/SiO_2, $Pd/CaCO_3$, $Pd(OH)_2$) produced high levels of concomitant hydrodechlorination (3.5−20%[14]). Selectivity was particularly critical in this case, as the dechlorination byproduct **3** was difficult to reject in the crystallization process used to purify the product. As a result, we screened numerous catalytic conditions for reduction of **1** and now report a selective and general procedure for the reduction of nitro groups in the presence of activated heteroaryl halides.

Our screen of heterogeneous catalysts for selective reduction of **1** included palladium and platinum metals with various supports (C, Al_2O_3, SiO_2, $CaCO_3$), additives, and poisons (S, V, Fe, Pb, Cu), as well as bimetallic systems (e.g., Pd/Pt, Pd/Pb). More than 100 conditions were examined, and although many catalysts were successful at reducing the nitro group, very few catalysts provided the desired selectivity. A representative summary of the screening results are listed in Table 1.

Use of palladium catalysts led to significant levels of hydrodechlorination byproduct **3** (entries 1−2, Table 1), and results varied when using the same metal source and support depending on the lot employed. Some palladium catalysts resulted in over-reduction of the isoquinoline ring. Reaction rates were generally slower with platinum catalysts, but the

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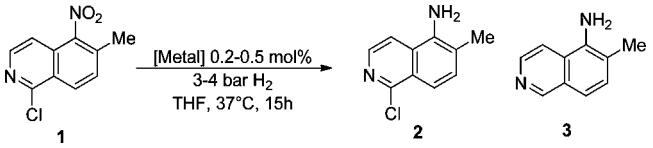
Table 1. Summary of Catalyst Screen for the Reduction of 1



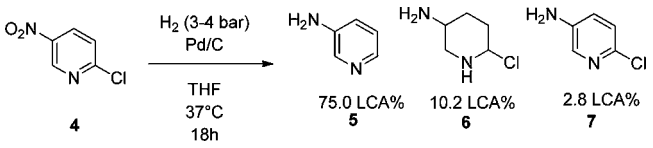
entry	catalyst	% 2[a]	% 3[b]
1	5% Pd/C[c]	91.8	8.2
2	5% Pd/C[c]	84.4	15.6
3	3% Pt/C	97.9	1.2
4	1% Pt/C V doped	50.7	1.3
5	3% Pt(S)/C	99.9	0.0

[a]% **2** refers to liquid chromatography area % 5-amino-1-chloro-6-methyl isoqionoline. [b]% **3** refers to liquid chromatography area % 5-amino-6-methyl isoquinoline. [c]5% Pd/C refers to Johnson Matthey's A503023-5 catalyst.

selectivity improved. In particular, use of the sulfided platinum catalyst Pt(S)/C completely suppressed the formation of **3** (entry 5, Table 1). Further optimization revealed that the Pt(S)/C catalyst loading could be reduced to 0.09 mol %, providing full conversion at room temperature in THF under 3 bar H_2 in 18 h. At the end of the reaction, the mixture was filtered to remove the catalyst and the product isolated via crystallization (91% yield, 99% purity on 45 g scale). Since the crystallized product **2** contained very low levels of residual metal (15 ppm Pt, 5 ppm S), a separate metal scavenging step was avoided.

To further demonstrate the challenges associated with nitro reduction selectivity for activated substrates, a six membered heterocycle (**4**) was reduced using a conventional Pd/C catalyst (Scheme 2).

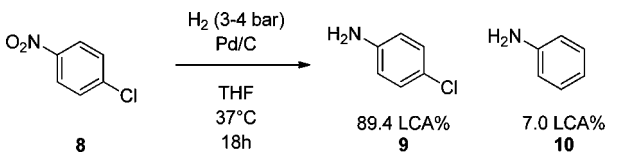
Scheme 2. Hydrogenation of 4 Using 5% Pd/C, 3−4 bar H_2, 37°C, THF, 18 h



The major products formed (**5** and **6**) were the result of unselective reduction, and the desired aniline **7** was observed only as a minor product.

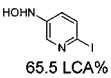
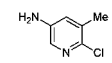
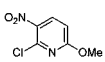
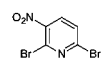
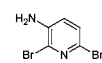
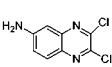
On the other hand, when the same reaction conditions were applied to the non-heterocyclic substrate **8** (Scheme 3), the major product was the aniline **9** accompanied by some of the hydrodechlorination product **10**.

Scheme 3. Hydrogenation of 5 Using 5% Pd/C, 3−4 bar H_2, 37°C, THF, 18h



The scope and generality of the selective reduction process using 3% Pt(S)/C was subsequently examined with a variety of substrates (Table 2). For simple 2-chloro and 2-bromo substituted nitro pyridines, such as compound **4**, high yields

Table 2. Hydrogenation of Various Nitro Halo Aromatics

Entry	Substrate	Product	Yield %[a]	Hydrodehalogenation %[b]	Time (h)
1			95	2.4	8
2			92	1.9	18
3		 11.5 LCA%  65.5 LCA%  13.8 LCA%  8.1 LCA%			12
4			92	2.4	36
5			94	0	8
6			93	4.9	12
7			92	0	16
8			93	0	42
9			92	0	18
10			95	0	12
11			93	0	6

[a]Yields refer to isolated products characterized by ^{1}H and ^{13}C NMR spectroscopic data, HRMS. [b]Hydrodehalogenation % refers to LCA% hydrodehalogenated aniline by products. All products (entries 1−11, excluding entry 3) were isolated in greater than 95% purity by LC and NMR analysis, and all reactions were carried out using 1 mmol substrate, 0.1 mol % Pt(S)/C in THF (4 mL), at 37 °C under H_2 (3.5 bar)

of the corresponding anilines were obtained with minor dehalogenation (entries 1 and 2, Table 2). In contrast to the high selectivity observed for bromo- and chloro-nitropyridines, reduction of 2-iodo-5-nitropyridine proceeded with poor selectivity, presumably because of the weaker C−I bond (entry 3, Table 2).[15] The reaction profiles for the series of 2-halo-5-nitropyridines are illustrated in Figure 1 and indicate

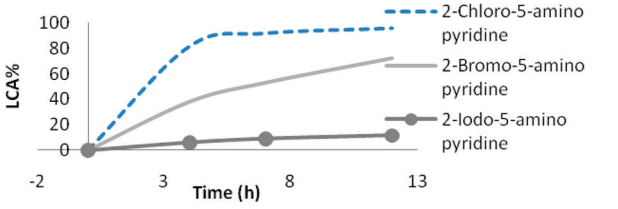


Figure 1. Reaction profiles for reduction of 2-halo-5-nitropyridines using 3% Pt(S)/C (0.09 mol %), 3 bar H_2, THF, 37 °C.

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that the relative rate of product formation increases in the order 2-Cl > 2-Br > 2-I. Consistent with data from Table 2 (entries 1−3), 2-iodo-5-nitropyridine reacts the slowest, and significant amounts of the intermediate hydroxylamine and hydrodeiodination side products were observed. Thus, a combination of lower reactivity and product stability contributes to much higher levels of hydrodehalogenation in the case of the 2-I substrate.[16]

Chloro-nitropyridines with alternative substitution patterns and substituents were also reduced with high selectivity (entries 4−6, Table 2). In the case of nitropyridines possessing multiple halide substituents, including iodides, high selectivities were observed with conversion to the corresponding dihaloamino pyridines in excellent yield (entries 7−11, Table 2). The high chemoselectivity of the platinum sulfided catalyst is believed to be due to the poisoning effect of the sulfur, which occupies the most active sites on the platinum surface, thereby enhancing the selectivity of the process.[17]

In conclusion, a convenient and selective process for the catalytic hydrogenation of nitro groups in the presence of heteroaryl halides has been demonstrated, making use of a readily available sulfided platinum catalyst. The method is efficient, employs low catalyst loading (<0.10 mol %) and mild reaction temperatures (<40 °C) and pressures (3−4 bar H_2), and can eliminate the need for screening additives in order to obtain high selectivity in many cases. In addition, the method is operationally convenient and minimizes waste, which represents a greener alternative to other reducing conditions.

■ EXPERIMENTAL SECTION

General Experimental Procedures. ^{1}H NMR and ^{13}C NMR were obtained at 400 and 100 MHz respectively, with $CDCl_3$ (for compound 2) and DMSO-d_6 (for entries 1, 2, 4−11, Table 2) as solvents. In the ^{1}HNMR spectra of entries 1, 5, 6, 10, and 11, Table 2, signals between 3.15 and 3.33 ppm originate from water in DMSO-d_6 solvents and in entry 4, signals 3.32 and 1.36 ppm originate from residual THF from the reaction. High resolution mass spectrometry (HRMS) was conducted using positive mode electrospray ionization (ESI) and produced spectra with less than 5 ppm mass accuracy. LC chromatograms were obtained using an Agilent 3.0 × 150 mm Eclipse XDB-Phenyl column.

General Procedures for Nitro Reduction. A mixture of nitro starting material (substrates 1−11, Table 2) and 3% Pt(S)/C (B109032-3, 62.80% wet, 0.09 mol %) in THF (4 mL/mmol substrate) was purged with three nitrogen cycles followed by three hydrogen cycles before pressurizing to 3 bar hydrogen pressure and then heated at 37 °C. Upon reaction completion, the mixture was cooled to rt, and the hydrogen was replaced with argon gas (via three evacuation−backfill cycles). The mixture was vacuum filtered using a fine glass frit to remove the catalyst, the filtrate was concentrated, and the resulting solid was further dried in a vacuum oven (<45 Torr) for 18 h to afford the product.

5-Amino-1-chloro-6-methyl isoquinoline (2). 1-Chloro-6-methyl-5-nitroisoquinoline (50.5 g, 0.22 mol), 3% Pt(S)/C (3.5 g, 0.09 mol % Pt, type: JM B109032-3, 62.80% water), and THF (250 mL) were charged to a 450 mL Parr reactor. The mixture was purged with three evacuation−backfill cycles with nitrogen followed by three cycles of hydrogen before pressurizing to 3 bar hydrogen pressure at rt. The progress of the reaction was monitored by LC/MS analysis. Upon completion (after 18 h), the catalyst was filtered, rinsing with THF (150 mL). The filtrate was concentrated to 160 mL via distillation under reduced pressure at 50 °C. The reaction mixture was then cooled to rt and seeded (with 0.5 g 2). The mixture was aged for 1 h, followed by addition of heptane (750 mL) over 2 h. The product was collected via filtration, and the cake was washed with a mixture of heptane (55 mL) and THF (10 mL). The product was dried in a vacuum oven (<45 Torr) at rt for 18 h. The dry product 2 was obtained as a white solid (41.5 g, 90.1% yield, 99.1 LC purity, 94.5 wt %, residual metal content: Pt, 15 ppm; S, 5 ppm, 4.4% mother liquor loss): ^{1}H NMR (400 MHz, chloroform-d) δ ppm 2.38 (s, 3 H), 7.41 (s, 1 H), 7.52 (s, 1 H), 7.73 (s, 1 H), 8.20 (s, 1 H); ^{13}C NMR (101 MHz, chloroform-d) δ ppm 113.9 (s, 1 C), 116.1 (s, 1 C), 121.5 (s, 1 C), 126.4 (s, 1 C), 127.2 (s, 1 C), 131.7 (s, 1 C), 139.0 (s, 1 C), 140.2 (s, 1 C), 152.2 (s, 1 C). HRMS m/z calcd for $C_{10}H_{10}ClN_2$ 193.0527 (M + H), found 193.0537.

5-Amino-2-chloro Pyridine (Entry 1, Table 2). Product 1, Table 2 was prepared from commercially available 2-chloro-5-nitro pyridine (161 mg, 1.25 mmol) as described in General Procedures for Nitro Reduction. The reaction reached full conversion after 8 h. A brown solid (121.5 mg, 95% yield, 96.6 LC purity containing 2.8 LCAP hydrodechlorination product) was obtained: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 5.48 (s, 1 H), 6.98 (s, 1 H), 7.09 (s, 1 H), 7.70 (s, 2 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 123.7 (s, 1 C), 123.8 (s, 1 C), 135.1 (s, 1 C), 136.0 (s, 1 C), 144.5 (s, 1 C). HRMS m/z calcd for $C_5H_6ClN_2$ 129.0214 (M + H), found 129.0214.

5-Amino-2-bromo Pyridine (Entry 2, Table 2). Product 2, Table 2 was prepared from commercially available 2-bromo-5-nitro pyridine (201.1 mg, 0.99 mmol) as described in General Procedures for Nitro Reduction. The reaction reached full conversion after 18 h. A brown solid (159.2 mg, 92% yield, 96.0 LC purity containing 1.9% hydrodebromination product) was obtained: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.37 (s, 2 H), 7.99 (s, 1 H), 8.52 (s, 1 H), 9.22 (s, 1 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 123.9 (s, 1 C), 125.2 (s, 1 C), 132.4 (s, 1 C), 133.3 (s, 1 C), 141.2 (s, 1 C). HRMS m/z calcd for $C_5H_6BrN_2$ 172.9709 (M + H), found 172.9706.

3-Amino-2-chloro Pyridine (Entry 4, Table 2). Product 4, Table 2 was prepared from commercially available 2-chloro-3-nitro pyridine (162.3 mg, 1.02 mmol) as described in General Procedures for Nitro Reduction. The reaction reached full conversion after 36 h. A dark colored solid (120.9 mg, 92% yield, 95.4 LC purity containing 2.4% hydrodechlorination product) was obtained: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 5.54 (s, 2 H), 7.11 (s, 1 H), 7.58 (s, 1 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 121.8 (s, 1 C), 123.7 (s, 1 C), 135.0 (s, 1 C), 136.0 (s, 1 C), 141.5 (s, 1 C). HRMS m/z calcd for $C_5H_6ClN_2$ 129.0214 (M + H), found 129.0211.

5-Amino-2-chloro-3-methyl Pyridine (Entry 5, Table 2). Product 5, Table 2 was prepared from commercially available 2-chloro-3-methyl-5-nitro pyridine (173.0 mg, 1.00 mmol) as described in General Procedures for Nitro Reduction. The reaction reached full conversion after 8 h. A brown solid (121.5 mg, 93.8% yield, 98.9 LC purity) was obtained: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.00 (s, 3 H), 5.21 (s, 2 H), 6.73 (d, J = 2.35 Hz, 1 H), 7.37 (d, J = 2.74 Hz, 1 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 124.1 (s, 1 C), 131.2 (s, 1 C), 132.8 (s, 1 C), 136.5 (s, 1 C), 144.7 (s, 1 C). HRMS m/z calcd for $C_6H_8ClN_2$ 143.0370 (M + H), found 143.0370.

5-Amino-6-chloro-3-methoxy Pyridine (Entry 6, Table 2). Product 6, Table 2 was prepared from commercially available 2-chloro-6-methoxy-3-nitro pyridine (202.1 mg, 1.07 mmol) as described in General Procedures for Nitro Reduction. The reaction reached full conversion after 12 h. A red-brown oil (157.81 mg, 93% yield, 95.1 LC purity containing 4.9% hydrodechlorination product) was obtained: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.72 (s, 3 H), 4.97 (s, 2 H), 6.64 (s, 1 H), 7.22 (s, 1 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 53.3 (s, 1 C), 109.9 (s, 1 C), 127.9 (s, 1 C), 129.6 (s, 1 C), 135.5 (s, 1 C), 154.2 (s, 1 C). HRMS m/z calcd for $C_6H_8OClN_2$ 159.0320 (M + H), found 159.0315.

5-Amino-2,6-dichloro Pyridine (Entry 7, Table 2). Product 2, Table 2 was prepared from commercially available 2-bromo-5-nitro pyridine (197.6 mg, 1.02 mmol) as described in General Procedures for Nitro Reduction. The reaction reached full conversion after 16 h. A light brown solid (166.27 mg, 92% yield, 98.8 LC purity) was obtained: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 5.84 (s, 2 H), 7.26 (s, 2 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 123.9 (s, 1 C), 125.2 (s, 1 C), 132.4 (s, 1 C), 133.3 (s, 1 C), 141.2 (s, 1 C). HRMS m/z calcd for $C_5H_5Cl_2N_2$ 162.9824 (M + H), found 162.9823.

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5-Amino-2,6-dibromo Pyridine (Entry 8, Table 2). Product 8, Table 2 was prepared from commercially available 2,6-dibromo-5-nitro pyridine (281.9 mg, 1.00 mmol) as described in General Procedures for Nitro Reduction. The reaction reached full conversion after 42 h. A dark red-brown solid (234.0 mg, 93% yield, 95.0 LC purity) was obtained: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 5.52 (s, 2 H), 6.91 (s, 1 H), 7.19 (s, 1 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 122.6 (s, 1 C), 124.7 (s, 1 C), 125.1 (s, 1 C), 127.7 (s, 1 C), 143.3 (s, 1 C). HRMS m/z calcd for $C_5H_5Br_2N_2$ 250.8814 (M + H), found 250.8810.

5-Amino-3-bromo-2-chloro Pyridine (Entry 9, Table 2). Product 9, Table 2 was prepared from commercially available 3-bromo-2-chloro-5-nitro pyridine (240.0 mg, 1.01 mmol) as described in General Procedures for Nitro Reduction. The reaction reached full conversion after 18 h. A light brown solid (189.5 mg, 92% yield, 98.6 LC purity) was obtained: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 5.77 (s, 2 H), 7.32 (s, 1 H), 7.72 (s, 1 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 113.6 (s, 1 C), 118.6 (s, 1 C), 125.5 (s, 1 C), 134.1 (s, 1 C), 145.8 (s, 1 C). HRMS m/z calcd for $C_5H_5ClBrN_2$ 206.9319 (M + H), found 206.9318.

5-Amino-6-chloro-3-iodo Pyridine (Entry 10, Table 2). Product 10, Table 2 was prepared from commercially available 2-chloro-5-iodo-3-nitro pyridine (286 mg, 1.00 mmol) as described in General Procedures for Nitro Reduction. The reaction reached full conversion after 12 h. A tan colored solid (239.9 mg, 95% yield, 98.6 LC purity) was obtained: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.00 (s, 1 H), 9.05 (s, 1 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 92.7 (s, 1 C), 140.7 (s, 1 C), 142.1 (s, 1 C), 144.6 (s, 1 C), 158.5 (s, 1 C). HRMS m/z calcd for $C_5H_5ICIN_2$ 254.9180 (M + H), found 254.9178.

6-Amino-2,3-dichloro-quinoxaline (Entry 11, Table 2). Product 11, Table 2 was prepared from commercially available 2,3-dichloro-6-nitro quinoxaline (238 mg, 0.97 mmol) as described in General Procedures for Nitro Reduction. The reaction reached full conversion after 6 h. The product (193.3 mg, 93% yield, 98.4 LC purity) was obtained: ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.45 (s, 2 H), 6.84 (s, 1 H), 7.30 (s, 1 H), 7.73 (s, 1 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 103.42 (s, 1 C), 123.54 (s, 1 C), 128.56 (s, 1 C), 133.93 (s, 1 C), 136.92 (s, 1 C), 143.06 (s, 1 C), 143.69 (s, 1 C), 152.26 (s, 1 C). HRMS m/z calcd for $C_8H_6Cl_2N_3$ 213.9933 (M + H), found 213.9933.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR, ^{13}C NMR, and HRMS for 5-amino-2-chloro-6-methyl isoquinoline (**2**) and the products in Table 2, entries 1, 2, 4−11. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) (a) Downing, R. S.; Kunkeler, P. J.; van Bekkum, H. *Catal. Today* **1997**, *37*, 121. (b) Dale, D. J.; Dunn, P. J.; Golightly, C.; Hughes, M. L.; Levett, P. C.; Pearce, A. K.; Searle, P. M.; Ward, G.; Wood, A. S. *Org. Process Res. Dev.* **2000**, *4*, 17. (c) Couturier, M.; Andresen, B. M.; Jorgensen, J. B.; Tucker, J. L.; Busch, F. R.; Brenek, S. J.; Dube, P.; Ende, D. J.; Negri, J. T. *Org. Process Res. Dev.* **2002**, *6*, 42.

(2) Sundberg, R. J.; Pitts, W. J. *J. Org. Chem.* **1991**, *56*, 3048.

(3) Hartman, W. W. *Org. Synth.* **1943**, *II*, 175.

(4) (a) Junge, K.; Wendt, B.; Shaikh, N.; Beller, M. *Chem. Commun.* **2010**, *46*, 1769. (b) Sharma, U.; Verma, P. K; Kumar, N.; Kumar, V.; Bala, M.; Singh, B. *Chem.—Eur. J.* **2011**, *17*, 5903. (c) Sonavane, S. U.; Mohapatra, S. K.; Jayaram, R. V.; Sclvam, P. *Chem. Lett.* **2003**, *32*, 142.

(5) (a) Augustine, R. L. *Heterogeneous Catalysis for the Synthetic Chemist*; Marcel Dekker: New York, 1996. (b) Nishimura, S. *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*; Wiley & Sons: New York, 2001.

(6) Anastas, P. T. *Green Chemistry: Designing Chemistry for the Environment*; Developed from a symposium sponsored by the Division of Environmental Chemistry, Inc., at the 208th National Meeting of the American Chemical Society, Washington D.C., August 21−25, 1994.

(7) (a) Hoogenraad, M.; van der Linden, J. B.; Smith, A. A.; Hughes, B.; Derrick, A. M.; Harris, L. J.; Higginson, P. D.; Pettman, A. J. *Org. Process Res. Dev.* **2004**, *8*, 469. (b) Chandregowda, V.; Rao, G. V.; Reddy, G. C. *Org. Process Res. Dev.* **2007**, *11*, 813. (c) Saha, A.; Ranu, B. *J. Org. Chem.* **2008**, *73*, 6867.

(8) Joule, J. A. *Heterocyclic Chemistry*, 4th ed.; Blackwell Science: Hoboken, NJ, 2000.

(9) (a) Sonavane, S. U.; Mohapatra, S. K.; Jayaram, R. V.; Sclvam, P. *Chem. Lett.* **2003**, *32*, 142. (b) Kosak, J. R.; *Catalysis in Organic Synthesis*; Academic Press: New York, 1980; p 107. (c) Cellier, P. P.; Spindler, J.-F.; Taillefer, M.; Cristau, H.-J. *Tetrahedron Lett.* **2003**, *44*, 7191. (d) Monguchi, Y.; Ishihara, S.; Ido, A.; Niikawa, M.; Kamiya, K.; Sawama, Y.; Nagase, H.; Sajiki, H. *Org. Process Res. Dev.* **2010**, *14*, 1140.

(10) (a) Kosak, J. R.; *Catalysis in Organic Synthesis*; Academic Press: New York, 1980; p 107. (b) Nishimura, S. *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*; Wiley & Sons: New York, 2001.

(11) Takasagi, M.; Motoyama, Y.; Higashi, K.; Yoon, S. H. *Org. Lett.* **2008**, *10*, 1601.

(12) For a recent review on the selective heterogeneous catalytic hydrogenation of nitroarenes see: Blaser, H. U.; Steiner, H.; Studer, M. *ChemCatChem* **2009**, *1*, 210.

(13) Smith, A. L.; De Morin, F. F.; Paras, N. A.; Huang, Q.; Petkus, J. K.; Doherty, E. M.; Nixey, T.; Kim, J. L.; Whittington, D. A.; Epstein, L. F.; Lee, M. R.; Rose, M. J.; Babij, C.; Fernando, M.; Hess, K.; Le, Q.; Beltran, P.; Carnahan, J. *J. Med. Chem.* **2009**, *52*, 6189.

(14) Purity refers to liquid chromatography area percent.

(15) Reductions of such substrates are typically carried out with stoichiometric reductants: Seton, A. W.; Stevens, M. F. G.; Westwell, A. D. *J. Chem. Res., Synop.* **2001**, 546.

(16) Subjection of the product 2-iodo-5-aminopyridine to the reduction conditions for 10 h resulted in 8.1% hydrodeiodination. Thus, relative to the corresponding 2-Cl and 2-Br aminopyridines, the iodide product is also less stable under the reaction conditions.

(17) Blaser, H. U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv .Synth. Catal.* **2003**, *345*, 103.