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Selective Synthesis of *N*-Alkyl Hydroxylamines by Hydrogenation of Nitroalkanes using Supported Palladium Catalysts

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Organic hydroxylamines are useful compounds in a wide range of applications, including intermediates in the synthesis of biologically active substances,[1] reagents for organic synthesis,[2] raw materials for polymerization inhibitors,[3] and release agents for photoresists.[4] A number of different synthetic routes to hydroxylamines have been reported. Examples include the alkylation of hydroxylamines;[5] the stoichiometric (with zinc, tin, samarium diiodide, boron hydrides, silicon hydrides, or hydrazine),[6] electrochemical,[7] and electron-transfer reduction of nitro compounds;[8] and biosynthesis by using bakers' yeast.[9] However, these processes are not necessarily environmentally benign and cost-efficient. In addition, some of these routes have disadvantages when they are scaled up and/or applied industrially. Thus, the development of methods that are more efficient, greener, and more practical is desirable.

Because H_2 is a clean and relatively cheap reductant, the selective catalytic hydrogenation of nitro compounds is an ideal process for the production of hydroxylamines. Although several groups have reported the synthesis of *N*-aryl hydroxylamines through the hydrogenation of nitroaromatics,[10] the yields and selectivities were insufficient because suppressing overhydrogenation was difficult. We have recently reported that by using supported platinum catalysts and small amounts of additives, *N*-aryl hydroxylamines can be successfully produced in high yields (up to 99%) under atmospheric pressure and temperature.[11] Unfortunately, this method cannot be applied to the synthesis of aliphatic hydroxylamines. More recently, Lu et al. have reported that *N*-aryl hydroxylamines can be selectively formed via additive-free hydrogenation in THF using carbon-supported platinum colloid catalysts.[12] However, the substrates for this reaction were limited to aromatic nitro compounds with an electron-withdrawing substituent, such as *o*-, *m*-, *p*-dinitrobenzene and 1-(4-nitrophenyl)ethanone.

For aliphatic nitro compounds, some patents have claimed that for the hydrogenation of nitroalkanes over supported palladium catalysts, the addition of oxalic acid,[13a] sulfuric acid,[13b,c,e] metal cations such as iron, nickel, and cobalt ions,[13d] or ethylenediaminetetraacetic acid (EDTA)[13f] effectively increases the yield of *N*-alkyl hydroxylamines. However, these processes require the separation of these additives and/or the purification of the hydroxylamines. Herein, we report that by using supported palladium catalysts, genuine *N*-alkyl hydroxylamines (R-NHOH) can be obtained in high yields (up to 98%) through hydrogenation of nitroalkanes (R-NO$_2$) without the need for selectivity-improving additives.

Adding small amounts of dimethyl sulfoxide (DMSO) and amines, which serve as inhibitor and promoter, respectively, to the reaction mixture during the selective hydrogenation of nitroaromatics over supported platinum catalysts such as Pt/SiO$_2$ realizes the fast and highly selective formation of the corresponding *N*-aryl hydroxylamines.[11] In contrast, a Pd/SiO$_2$ catalyst was found to be nonselective for the hydrogenation of nitrobenzene, even in the presence of DMSO and amine; the major product was aniline.[11] Thus, we initially attempted the hydrogenation of 1-nitrohexane (^{n}Hex-NO$_2$) by using a commercial Pt/SiO$_2$ catalyst. The hydrogenation in isopropyl alcohol (IPA) under a H_2 pressure of 1 bar at room temperature exclusively afforded 1-hexylamine (^{n}Hex-NH$_2$) (Table 1, entry 1). However, in the case of ^{n}Hex-NO$_2$, adding DMSO and triethylamine was ineffective for the selective formation of *N*-hexyl hydroxylamine (^{n}Hex-NHOH). On the other hand, when Pt/SiO$_2$ was replaced with a commercial Pd/SiO$_2$ catalyst, ^{n}Hex-NO$_2$ was selectively and smoothly hydrogenated to give ^{n}Hex-NHOH in a high yield (90%) without additives. Likewise, the two types of palladium on silica (Pd/SIO-1 and Pd/SIO-2) catalysts prepared in this study as well as commercial Pd/C and Pd/Al$_2$O$_3$ catalysts afforded ^{n}Hex-NHOH in excellent yields (up to 96%). ^{n}Hex-NO$_2$ was also hydrogenated selectively by using palladium acetate as a homogeneous catalyst, but palladium acetate formed pal-

Table 1. Selective hydrogenation of 1-nitrohexane

$$^{n}\text{Hex-NO}_2 \xrightarrow[\text{H}_2\text{ (1 bar), IPA, RT}]{\text{Catalyst}} \underset{\mathbf{1}}{^{n}\text{Hex-NHOH}} + \underset{\mathbf{2}}{^{n}\text{Hex-NH}_2}$$

Entry	Catalyst	*t* [h]	Conv.[b] [%]	Yield **1**[b] [%]	Yield **2**[b] [%]	Select.[b] [%]
1	Pt/SiO$_2$	6	92	0	92	0
2[c]	Pt/SiO$_2$	24	0	0	0	0
3[d]	Pt/SiO$_2$	24	0	0	0	0
4	Pd/SiO$_2$	2	90	90	trace	>99
5	Pd/SIO-1	2	>99	94	6	94
6	Pd/SIO-2	1	64	62	2	97
7	Pd/SIO-2	2	>99	96 (95[e])	4	96
8	Pd/C	2	>99	94	6	94
9	Pd/Al$_2$O$_3$	2	>99	94	6	94
10[f]	Pd(OAc)$_2$	2	33	31	2	94

[a] 2 mmol ^{n}Hex-NO$_2$, 20 mg catalyst, 2 mL catalyst. [b] Determined by ^{1}H NMR with 1,3,5-trimethyl benzene as an internal standard. [c] 0.030 mL DMSO. [d] 0.030 mL DMSO, 0.010 mL triethylamine. [e] Isolated yield. [f] 0.5 mol% Pd(OAc)$_2$.

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ladium black during the reaction, resulting in giving ^{n}Hex-NHOH in a low yield (31 %; Table 1, entry 10).

We then investigated the reaction conditions using the Pd/SIO-2 catalyst. The hydrogenation proceeded significantly faster when the H_2 pressure was increased to 2 bar, while a high ^{n}Hex-NHOH selectivity was maintained (97 %; Table 2, entry 1). Further increasing the H_2 pressure slightly decreased the selectivity (87 %). On the other hand, when the reaction temperature was increased from room temperature to 50 °C, the rate of hydrogenation of ^{n}Hex-NO_2 increased, but further hydrogenation of ^{n}Hex-NHOH was accelerated, which decreased the ^{n}Hex-NHOH yield to 49 % (Table 2, entry 3). Sherwin et al. performed the hydrogenation of 2-nitropropane with Pd/Al_2O_3 catalysts under hydrogen pressures of 2–5 bar at 50–70 °C in the absence of a promoter (i.e., EDTA), and reported a medium *N*-isopropyl hydroxylamine selectivity (56–89 %),[13f] consistent with our results. Hence, these observations demonstrate that controlling the reaction temperature is key to achieving a high selectivity in the formation of ^{n}Hex-NHOH.

Table 2. Effect of reaction conditions.[a]

Entry	*P* [bar]	*T* [°C]	*t* [min]	Conv.[b] [%]	Yield **1**[b] [%]	Yield **2**[b] [%]	Select.[b] [%]
1	2	RT	30	97	94 (90[c])	3	97
2	5	RT	24	88	77	11	87
3	1	50	30	83	49	34	59

[a] 2 mmol ^{n}Hex-NO_2, 20 mg Pd/SIO-2, 2 mL IPA. [b] Determined by ^{1}H NMR with 1,3,5-trimethyl benzene as an internal standard. [c] Isolated yield.

We then examined the effect of solvent. Table 3 compares the reaction times required for the conversion of ^{n}Hex-NO_2 to exceed 95 %. Alcoholic solvents such as IPA and ethanol produced ^{n}Hex-NHOH in high yields within a short reaction time (105 min) (Table 3, entries 1 and 2). Although employing low-polarity solvents such as toluene or dichloromethane required somewhat longer reaction times, ^{n}Hex-NHOH was produced selectively.

Table 3. Effect of solvent.[a]

Entry	Solvent	*t* [min]	Conv.[b] [%]	Yield **1**[b] [%]]	Yield **2**[b] [%]	Select.[b] [%]
1	IPA	105	98	95	3	97
2	EtOH	105	95	93	2	98
3	Et_2O	135	99	96	3	97
4	THF	210	99	95	4	96
5	Toluene	210	99	95	4	96
6	CH_2Cl_2	240	98	92	6	94

[a] 2 mmol ^{n}Hex-NO_2, 20 mg Pd/SIO-2, 2 mL solvent. [b] Determined by ^{1}H NMR with 1,3,5-trimethyl benzene as an internal standard.

The synthesis of R-NHOH through selective hydrogenation using palladium on silica catalysts is applicable to various R-NO_2 substrates, as summarized in Table 4. Similar to ^{n}Hex-NO_2, primary R-NO_2 compounds such as nitroethane and 1-nitropropane were hydrogenated using the Pd/SIO-2 catalyst into the corresponding R-NHOH compounds in yields greater than 90 % (Table 4, entries 1 and 2). Sterically hindered R-NO_2 substrates such as 2-nitropropane (nitro-*iso*-propane), nitro-*cyclo*-pentane, and 2-methyl-2-nitropropane (nitro-*tert*-butane) were also hydrogenated selectively to the corresponding R-NHOH analogues, but a longer reaction time was necessary.

Table 4. Selective hydrogenation of nitroalkanes

$$\mathrm{R{-}NO_2} \xrightarrow[\mathrm{H_2\ (1\ bar),\ IPA,\ RT}]{\mathrm{Pd/SIO\text{-}2}} \mathrm{R{-}NHOH} \quad + \quad \mathrm{R{-}NH_2}$$

Entry	R	*t* [h]	Conv.[b] [%]	Yield R-NHOH[b] [%]	Yield R-NH_2[b] [%]	Select.[b] [%]
1	Et	2	> 99	91	9	91
2	1-Pr	2	> 99	97	3	97
3	2-Pr	2	98	98	trace	> 99
4	*cyclo*-Pen	12	> 99	98	2	98
5	*tert*-Bu	30	98	89	9	91

[a] 2 mmol R-NO_2, 20 mg Pd/SIO-2, 2 mL IPA. [b] Determined by ^{1}H NMR with 1,3,5-trimethyl benzene as an internal standard.

Finally, we investigated the recyclability of the Pd/SIO-2 catalyst in the selective hydrogenation of ^{n}Hex-NO_2. After each run, the catalyst was separated by filtration, washed with IPA, dried in vacuum at room temperature, and pretreated in a H_2 stream at 200 °C for 1 h. The catalyst was then reused in a subsequent run. By using this process, the recovered catalyst could be recycled at least five times without a loss in the yield of ^{n}Hex-NHOH (Table 5). When comparing the catalytic activity of the Pd/SIO-2 in the sixth recycling experiment to that of the fresh Pd/SIO-2, no significant deactivation can be observed (Table 5, entry 7 vs. Table 1, entry 6). In addition, when ICP–AES measurements of the filtrates obtained from the runs in entries 1 and 6 in Table 5 indicated that the palladium content was below the detection limit (0.01 ppm). These results demonstrate that Pd/SIO-2 is a sufficiently stable heterogeneous catalyst for the selective hydrogenation of R-NO_2.

In summary, we have developed a highly efficient synthetic method for preparing R-NHOH by selectively hydrogenation of

Table 5. Catalyst recycling in the selective hydrogenation of 1-nitrohexane.[a]

Entry	Catalyst	*t* [h]	Conv.[b] [%]	Yield **1**[b] [%]]	Yield **2**[b] [%]	Select.[b] [%]
1c]	Pd/SIO-2	2	> 99	96	4	96
2	1st reuse	2	> 99	98	2	98
3	2nd reuse	2	> 99	98	2	98
4	3rd reuse	2	> 99	97	3	97
5	4th reuse	2	> 99	98	2	98
6[c]	5th reuse	2	> 99	98	2	98
7	6th reuse	1	59	58	1	98

[a] 2 mmol ^{n}Hex-NO_2, 20 mg catalyst, 2 mL IPA. [b] Determined by ^{1}H NMR with 1,3,5-trimethyl benzene as an internal standard. [c] The palladium content of the filtrates was measured by ICP–AES.

$R\text{-}NO_2$ with supported palladium catalysts. This method has the following advantageous and attractive aspects: (1) the selective hydrogenation proceeds efficiently under an atmospheric pressure of H_2 at room temperature and does not require additives; (2) the hydrogenation method can be applied to a wide range of $R\text{-}NO_2$ substrates, and organic solvents; and (3) the palladium on silica catalyst can be recycled at least five times. The presented synthetic procedure towards R-NHOH can be considered green and practical.

Experimental Section

All nitroalkanes, solvents, and H_2 (99.99999%) were used without further purification. Solvents were degassed with Ar bubbling for 1 h prior to use. 5 wt% Pt/SiO_2 (BASF/Engelhard, Escat 2351) and 5 wt% Pd/SiO_2 (BASF/Engelhard, Escat 1351) catalysts were obtained from Strem Chemicals Inc. 5 wt% Pd/C and 5 wt% Pd/Al_2O_3 catalysts were purchased from Sigma–Aldrich Co. Amorphous silica (SIO-1, CARiACT Q-10, BET surface area: 275 $m^2 g^{-1}$, pore volume: 1.23 $cm^3 g^{-1}$) was supplied by Fuji Silysia Chemical Ltd. Mesoporous silica with a wormhole-like structure[14] (SIO-2, TMPS-10, BET surface area: 571 $m^2 g^{-1}$, pore volume: 1.62 $cm^3 g^{-1}$, average pore size 10.9 nm) was supplied by Taiyo Kagaku Co. Ltd. ^1H and ^{13}C NMR spectra were recorded on a Bruker-AV400 superconducting high-resolution spectrometer (400 MHz for ^1H NMR).

Catalyst preparation: An incipient wetness impregnation method with $[Pd(NH_3)_4](NO_3)_2$ as the Pd precursor was used to prepare 5 wt% Pd on silica (SIO-1 and SIO-2) catalysts. An aqueous solution containing $[Pd(NH_3)_4](NO_3)_2$ was added dropwise to the silica. The impregnated sample was dried at 60 °C under reduced pressure and then calcined at 300 °C for 3 h in air. The resulting samples, denoted as Pd/SIO-1 and Pd/SIO-2, were stored in a dry box. Reduction of the Pd/SIO-1 and Pd/SIO-2 catalysts by H_2 was performed prior to use in the reaction.

Selective hydrogenation of nitroalkanes: The selective hydrogenation of nitroalkanes was conducted in a Schlenk flask (20 mL). A typical procedure was as follows: a catalyst (20 mg) was placed in a flask and reduced in a H_2 stream (30 $cm^3 min^{-1}$) at 200 °C for 1 h. After cooling to room temperature, the H_2 stream was replaced by an Ar stream. A Teflon-coated magnetic stirrer bar, solvent (2 mL), and nitroalkanes (2 mmol) were successively placed in the flask, and the suspension was purged with H_2. The reaction mixture was then stirred at 1500 rpm under 1 bar of H_2 at room temperature. During the reaction H_2 was continuously supplied to maintain the pressure at 1 bar. The reaction mixture was periodically sampled to determine the conversion and yield by ^1H NMR analysis using 1,3,5-trimethylbenzene as an internal standard. After the reaction, the catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The identities of the hydrogenation products were confirmed by comparing their ^1H and ^{13}C NMR spectra to those of authentic samples.

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