Controlled Semihydrogenation of Aminoalkynes Using Ethylenediamine as a Poison of Lindlar's Catalyst

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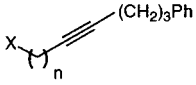
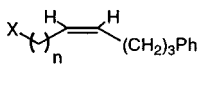
Introduction

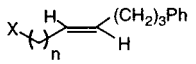
Lindlar's catalyst is the most ubiquitous reagent employed for the stereoselective reduction of alkynes to (*Z*)-alkenes with low levels of *Z*/*E* isomerization and overreduction.[1] Although alkynes containing diverse functionality have been successfully reduced in this reaction,[2] most substrates containing amines are protected before a half-reduction is performed.[3] We report that a primary amine functionality in the vicinity of an alkyne accelerates the rate of overreduction using Lindlar's catalyst to the point where the reaction is no longer chemoselective; however, addition of approximately 1 equiv of ethylenediamine (EDA) to the hydrogenation mixture affords a well-controlled reduction that produces ≤0.5% of the overreduced impurity.



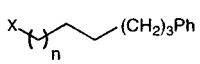
X = OH, n=3 (**1a**)
X = NH_2 n=1 (**2a**)
X = NH_2 n=2 (**3a**)
X = NH_2 n=3 (**4a**)
X = NH_2 n=4 (**5a**)



X = OH, n=3 (**1b**)
X = NH_2 n=1 (**2b**)
X = NH_2 n=2 (**3b**)
X = NH_2 n=3 (**4b**)
X = NH_2 n=4 (**5b**)



X = OH, n=3 (**1c**)
X = NH_2 n=1 (**2c**)
X = NH_2 n=2 (**3c**)
X = NH_2 n=3 (**4c**)
X = NH_2 n=4 (**5c**)

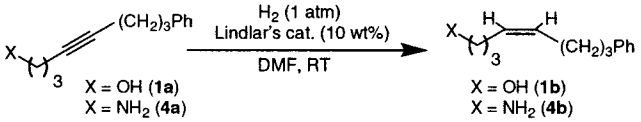


X = OH, n=3 (**1d**)
X = NH_2 n=1 (**2d**)
X = NH_2 n=2 (**3d**)
X = NH_2 n=3 (**4d**)
X = NH_2 n=4 (**5d**)

Results and Discussion

In our pursuits to synthesize (*Z*)-aminoalkene **4b** (*n* = 3), we discovered a dramatic difference in rate and chemoselectivity between the Lindlar reduction of hydroxyalkyne (**1a**) and its aminoalkyne counterpart (**4a**, Table 1). With low catalyst loading (10 wt %) in DMF,[4] the hydrogenation of **1a** with Lindlar's catalyst proceeded to completion in 18 h to afford (*Z*)-hydroxyalkene **1b** with typical levels (8%) of the trans isomer (**1c**) and 0.7% of the overreduced product (**1d**). In contrast, under the same conditions, the half-reduction of **4a** was complete in less than 1 h with significant isomerization to the (*E*)-aminoalkene **4c** and overreduction to the aminoalkane **4d**.[5,6] Moreover, the overreduction was completely uncontrolled, continuing until **4d** was the sole product of the reaction. The increased rate of reaction of **4a** versus that of **1a** could be attributed to preassociation of the amine functionality in **4a** to the catalyst surface.[7] This accelerated reaction rate would also be observed for the product **5b**, causing overreduction to be a significant side reaction.[8]

Table 1. Semihydrogenation of Hydroxyalkyne 1a versus Aminoalkyne 4a[a]



time (h)	**1a** : **1b** : **1c** : **1d**[b]	**4a** : **4b** : **4c** : **4d**[b]
1	39 : 57 : 3.5 : 0.5	0 : 88 : 8.1 : 3.8
2	22 : 72 : 5.5 : 0.5	0 : 70.1 : 17.8 : 12.1
4	4 : 89 : 6.4 : 0.6	0 : 30.7 : 36.3 : 33.0
8	2 : 90.4 : 7 : 0.6	0 : 10.0 : 40.1 : 49.9
18	0 : 91.3 : 8 : 0.7	0 : 0 : 0 : 100

[a] All reactions were carried out in DMF (0.5 M in substrate) at rt. [b] Ratio of products determined by HPLC analysis. See Supporting Information for details.

Closer investigation of the hydrogenation of **4a** at lower catalyst loadings (4 wt %) revealed that overreduction was only significant AFTER the alkyne was completely consumed.[9] Although it is theoretically possible to stop the hydrogenation at a point where **4a** is consumed and **4d** has not been formed in significant quantity, this solution is irreproducible, unreliable, and poorly con-

(1) Lindlar, H.; Dubuis, R. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, pp 880−883.

(2) (a) Evans, D. A.; Fitch, D. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2536−2540. (b) Nicolaou, K. C.; Xu, J.-Y., Kim, S.; Ohshima, T.; Hosokawa, S.; Pfefferkorn, J. *J. Am. Chem. Soc.* **1997**, *119*, 11353−11354. (c) Rzasa, R. M.; Shea, H. A.; Romo, D. *J. Am. Chem. Soc.* **1998**, *120*, 591−592. (d) Noyori, R.; Suzuki, M. *Angew. Chem., Int. Ed. Engl.* **1984**, ***23***, 847−850. (e) Yanagisawa, A.; Habaue, S.; Yamamoto, H. *Tetrahedron* **1992**, *48*, 1969−1980. (f) Zhou, W.-S.; Shen, Z.-W. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2827−2830.

(3) (a) Fujita, M.; Chiba, K.; Nakano, J.; Tominaga, Y.; Matsumoto, J. *Chem. Pharm. Bull.* **1998**, *46*, 631−638. (b) Li, S.; Kosemura, S.; Yamamura, S. *Tetrahedron Lett.* **1994**, *35*, 8217−8220. (c) Walters, M. A.; Hoern, A. B. *J. Org. Chem.* **1994**, *59*, 2645−2647. (d) Knight, D. W.; Little, P. B. *Tetrahedron Lett.* **1998**, *39*, 5105−5108. (e) Koskinen, A. M. P.; Paul, J. M. *Tetrahedron Lett.* **1992**, *33*, 6853−6856. (f) Altenbach, H.-J.; Himmeldirk, K. *Tetrahedron: Asymmetry* **1995**, *6*, 1077−1080. (g) Hamprecht, D.; Josten, J.; Steglich, W. *Tetrahedron* **1996**, *52*, 10883−10902. (h) Examples containing nitrogen in a pyridine ring do not appear to require protection. See: Taylor, E. C.; Yoon, C. *J. Org. Chem.* **1994**, *59*, 7096−7098. Teubner, A.; Gerlach, H. *Leibigs Ann. Chem.* **1993**, 161−165.

(4) Typical solvents for Lindlar's half-reduction (ethyl acetate, heptane, toluene, or acetone) afforded more overreduction and *Z*/*E* isomerization.

(5) Significant overreduction has been observed with other substrates containing unprotected amines. (a) Lindel, T.; Hochguertel, M. *Tetrahedron Lett.* **1998**, *39*, 2541−2544. (b) Sagi, G.; Oetvoes, L.; Ikeda, S.; Andrei, G.; Snoeck, R.; De Clerq, E. *J. Med. Chem.* **1994**, *37*, 1307−1311. (c) Merino, P.; Castillo, E.; Franco, S.; Merchan, F. L.; Tejero, T. *Tetrahedron: Asymmetry* **1998**, *9*,1759−1769. (d) Cliff, M. D.; Pyne, S. G. *J. Org. Chem.* **1997**, *62*, 1023−1032.

(6) Hydrogenation of **4a** as the HCl salt was unsuccessful, affording only 20% conversion; however, hydrogenation of **4a** NBoc derivative was clean with <1% overreduced product and minor *Z*/*E* isomerization.

(7) The preassociation of an amine to a catalyst surface (Pd/C) has been previously reported to account for surprising selectivities in olefin hydrogenations. See: Thompson, H. W.; Wong, J. K. *J. Org. Chem.* **1985**, *50*, 4270−4276.

(8) On the basis of this model, highly polar, aprotic solvents such as DMF would reduce the reaction rate, whereas less polar solvents such as heptane or ethyl acetate would favor substrate/catalyst interactions, leading to increased reaction rates. This is in accord with our experimental data (ref 4).

(9) With only 4 wt % catalyst, the hydrogenation was complete in less than 2 h. At the end of the reaction, the ratio of **4b**:**4c**:**4d** was 94:4:2; however, by the time that the ratio had been determined by HPLC (25 min), the ratio had already changed to 91:5:4.

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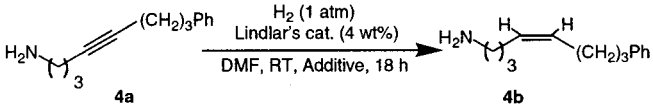
Table 2. Semihydrogenation of Aminoalkyne 4a with Amine Additives[a]



entry	additive (1.2 equiv)	**4b** : **4c** : **4d**[b]
1	pyridine	70 : 20 : 10
2	quinoline	80 : 13 : 7
3	ethylenediamine	97.6 : 2.0 : 0.4
4	propylenediamine	96.7 : 2.5 : 0.7
5	1,10-phenanthroline	97.0 : 2.5 : 0.5
6	diethylenetriamine	97.3 : 2.3 : 0.4

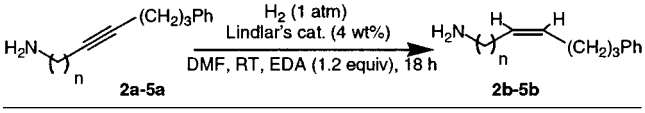
[a] All reactions were carried out in DMF (0.5 M in substrate) at rt. [b] Ratio of products determined by HPLC analysis. See Supporting Information for details.

trolled. A more reliable solution to the problem was to attempt to control overreduction through the use of an additive.

The fact that the rate of reduction of **4b** only becomes significant after complete consumption of **4a** suggests that the preassociation of the catalyst surface is stronger to **4a** than to **4b**.[10] One might expect, on the basis of this model, that the most suitable additive to attenuate the reactivity of **4b** would be a bidentate ligand to compete for catalyst surface association. As expected, monodentate amines such as pyridine or quinoline were ineffective at preventing overreduction (Table 2);[11] however a number of bidentate amines were highly effective, reducing the amount of **4d** to ≤0.7%.[12] Of the diamines investigated, ethylenediamine (EDA) afforded the least overreduction and *Z*/*E* isomerization.[13]

To test the generality of this method, a variety of aminoalkyne substrates were prepared with different tether lengths between the amine and the alkyne functionalities.[14] Under conditions without EDA, all of these substrates showed significant *Z*/*E* isomerization and overreduction; however with 1.2 equiv of EDA, the half-reduction proceeded smoothly to the desired (*Z*)-aminoalkenes (**2b**−**5b**) with only 2% of the *E* isomers (**2c**−**5c**) and approximately 0.5% alkane impurities (**2d**−**5d**)

Table 3. Semihydrogenation of Aminoalkynes 2a−5a Using Ethylenediamine as a Catalyst Poison[a]



n (substrate)	*Z* isomer : *E* isomer : alkane[b]
1 (**2a**)[c]	91.5 : 5.0 : 3.5 (**2b** : **2c** : **2d**)
2 (**3a**)	97.0 : 2.5 : 0.5 (**3b** : **3c** : **3d**)
3 (**4a**)	97.1 : 2.6 : 0.3 (**4b** : **4c** : **4d**)
4 (**5a**)	97.4 : 2.1 : 0.5 (**5b** : **5c** : **5d**)

[a] All reactions were carried out in DMF (0.5 M in substrate) at rt. [b] Ratio of products determined by HPLC analysis. See Supporting Information for details. [c] This substrate required 2.5 equiv of EDA.

even after stirring for 18 h under a hydrogen atmosphere (Table 3).[15] Aminoalkyne **2a** required more EDA than the other substrates and still afforded more of both the *E* isomer and the alkane impurities; however, in the absence of EDA, the (*Z*)-aminoalkene **2b** was rapidly reduced to the alkane.

In conclusion, the use of EDA to poison Lindlar's catalyst allows one to cleanly perform a well-controlled semihydrogenation of a variety of aminoalkynes with minimal *Z*/*E* isomerization and almost no overreduction. These conditions provide a reliable method for the synthesis of (*Z*)-aminoalkenes and may prove to be generally useful for more reactive alkynes. Studies toward the application of this methodology to other systems are ongoing.

Experimental Section

NMR spectra (^{1}H, ^{13}C) were recorded with a Bruker AM-400 with $CDCl_3$ as solvent. The reactions and products were assayed by HPLC (Hewlett-Packard series 1100) using a Supelcosil ABZ-Plus column with water and acetonitrile as eluting solvents. Anhydrous DMF, EDA, and Lindlar's catalyst were all purchased from Aldrich and used without further purification. The reactions were run under a balloon of hydrogen, and all reactions were degassed by vacuum and then purged with hydrogen.

General Hydrogenation Procedure. To a solution of **4a** (2.50 g, 12.4 mmol) in DMF (25 mL) was added EDA (1.0 mL, 15 mmol) followed by Lindlar's catalyst (100 mg). The reaction flask was evacuated, purged with hydrogen five times, and then stirred under a hydrogen atmosphere for 4 h. The reaction was filtered over Celite and washed with isopropyl acetate (IPAC) (25 mL). The resulting solution was washed with 2 wt % NH_4Cl (37 mL) and then twice with water (2 × 25 mL). The organic solution was concentrated to yield the desired (*Z*)-aminoalkene (**4b**) as an oil (2.45 g, 97% assay yield by HPLC, 200 nm). The chemical purity of this material was 95−97 area % with two major impurities identified as the (*E*)-aminoalkene (**4c**, 2.5%) and the aminoalkane (**4d**, 0.5%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.26 (m, 2H), 7.22−7.17 (m, 3H), 5.42 (m, 2H), 2.67 (t, J = 7.0 Hz, 2H), 2.63 (t, J = 7.6 Hz, 2H), 2.08 (m, 4H), 1.69 (quint, J = 7.5 Hz, 2H), 1.50 (quint, J = 7.1 Hz, 2H), 1.36 (brs, 2H); ^{13}C NMR (100 MHz $CDCl_3$) δ 142.4, 129.7, 129.6, 128.3, 128.2, 125.6, 41.8, 35.4, 33.7, 31.3, 26.7, 24.6; LC-MS ($M^+ + 1$) calcd 204.17, found 204.20. The ratio of **4a**:**4b**:**4c**:**4d** was determined by HPLC analysis Supelcosil ABZ plus column (1.5 mL/min, 80:20 (0.1% $HClO_4$(aq)/MeCN) to 50:50 over 20 min. T_r(**4a**) = 12.0 min, T_r(**4b**) = 14.0 min, T_r(**4c**) = 14.4 min, T_r(**4d**) = 16.0 min.

Supporting Information Available: Detailed experimental procedures, compound characterization data, and HPLC separation methods. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) This is in accord with the relative coordination strength of an alkyne to palladium versus that of an olefin. Typically, the metal−carbon bonds in alkyne complexes are 0.1 Å shorter than those with their olefin counterparts. (a) Redhouse, A. D. In *The Chemistry of the Metal−Carbon Bond*; Hartley, F. R., Patai, S., Eds.; John Wiley and Sons: New York, 1982; Vol. 1, Chapter 1, pp 18−20. (b) Davies, J. A. In *Comprehensive Organometallic Chemistry*; Puddephatt, R. J. Ed.; Pergamon Press: New York, 1986; Vol. 9, Chapter 6, pp 293−320.

(11) Diphenylphosphinoethane was used as a catalyst poison as well (0.1 mol %); however, this was too effective a poison, affording no hydrogenation over 24 h.

(12) The hydrogenations were complete in 2−3 h; however, to test the robustness of the process, the reactions were allowed to stir for 18 h with no increase in the amount of the aminoalkane impurity. The catalyst level could be increased up to 10 wt % with very little change in the amount of overreduction observed (4 wt %, 0.7% alkane; 10 wt % 0.9% alkane).

(13) Ethylenediamine has been reported to be a catalyst poison for other Pd catalysts. (a) Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron Lett.* **2000**, *41*, 5711−5714. (c) Enders, D.; Schankat, J. *Helv. Chim. Acta* **1995**, *78*, 970−992. (c) Savoia, D.; Trombini, C.; Umani-Ronchi, A.; Verardo, G. *J. Chem. Soc., Chem. Commun.* **1981**, 540−541.

(14) These substrates were synthesized from the parent monosubstituted hydroxyalkyne using standard methods (i.e., protection, alkylation, deprotection, activation, displacement with NH_3) in 55% overall yield.

(15) It is noteworthy that after the reaction is complete, the color of the catalyst bleaches, affording an opaque white solution. After this color change, no further reaction was ever observed.