The Lindlar Catalyst Revitalized: A Highly Chemoselective Method for the Direct Conversion of Azides to *N*-(*tert*-Butoxycarbonyl)amines

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An exceptionally chemoselective method for the direct conversion of azides to *N*-(*tert*-butoxycarbonyl)-protected amines under catalytic transfer-hydrogenation conditions, using the Lindlar catalyst, is reported. The extremely labile functional groups such as *N*-Cbz, benzyl ester are shown to be inert under the reaction conditions. The present method allows us to synthesize orthogonally protected (*N*-Cbz & *N*-Boc) 1,2-diamino systems, which will be immensely useful in organic synthesis.

Introduction

In recent years a great deal of success has been achieved in the field of asymmetric catalysis in which the development of effective chiral catalysts plays a major role.[1] A variety of catalytic systems employing new chiral ligands have been developed. Among these, those systems containing nitrogen ligands exhibit a remarkable enantioselectivity.[2] Chiral vicinal 1,2-diamine and 1,2-amino alcohol derivatives have gained particular attention, since they are not only useful as powerful coordinating ligands for asymmetric catalysis but also as chiral auxiliaries, chiral reagents, chiral solvating agents and key intermediates of pharmaceutical importance.[1] Organic azides offer an easy access to enantiomerically pure amino alcohols by either asymmetric ring opening of epoxides using Jacobsen's catalyst[3] or by opening of chiral cyclic sulfates/carbonates[4] with azides. On the other hand, chiral aziridinium ions[5] afford α-amino azides by nucleophilic ring opening with an azide ion. These chiral azides, upon reduction and subsequent protection of the amines, provide *N*-protected vicinal amino alcohols[6] and 1,2-diamines[7] respectively, known for their application in stereoselective synthesis. Among the wide variety of protecting groups, the *tert*-butoxycarbonyl (Boc) group occupies a significant place due to its chemical stability and ease of removal.[8] Many methodologies and reagent systems have been reported in the literature for the direct conversion of azides to the corresponding *N*-Boc-protected amines. Among them, the catalytic hydrogenation method[9] and a phosphane-based approach[10] are widely used. Although, catalytic hydrogenation over Pd/C is operationally simple, this protocol precludes a variety of substrates containing sensitive groups such as *N*-benzyloxycarbonyl (*N*-Cbz), benzyl ester, benzyl ether, benzyloxy phenyl, *N*-benzyl, alkenes and other reducible functional groups. On the other hand, the phosphane method (Staudinger reaction) involves either basic or acidic conditions for the hydrolysis of iminophosphoranes, which makes the work up process rather tedious. Hence, an exceptionally chemoselective and operationally very simple procedure is much sought after for effecting this important transformation which will be of immense use in asymmetric as well as in natural product synthesis.

Results and Discussion

During the course of our studies on the synthesis of chiral C_2-symmetric amino alcohol derivatives as novel HIV-1 protease inhibitors,[11] we encountered the problem of effecting a chemoselective reductive transformation of polyfunctional azides into *N*-Boc-protected amines. After surveying several reagent systems we found, to our delight, that the use of Lindlar catalyst along with Boc_2O chemoselectively reduces azide **1a** to the corresponding *N*-Boc-protected amine **2a** in excellent yield (Scheme 1).[12] In a typical experimental procedure, a mixture of azide, Lindlar catalyst and Boc_2O was stirred in methanol at room temperature under one atmosphere of hydrogen (balloon) until the reaction went to completion (as indicated by TLC). After removal of the catalyst by simple filtration, the crude product was purified by column chromatography to furnish the *N*-Boc-protected amine in excellent yield. In general, 20% of

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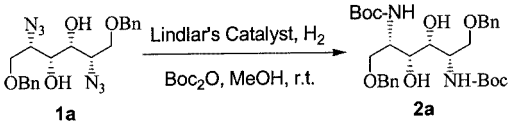
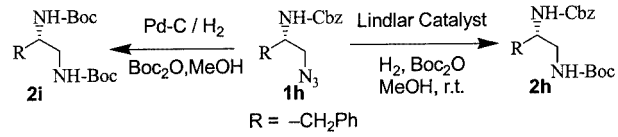


Scheme 1. Chemoselective reduction of azides to *N*-(Boc) amines

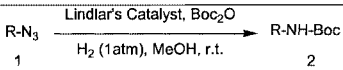


Scheme 2. Chemoselective reduction of azides in the presence of an *N*-(Cbz) protecting group

Lindlar catalyst (by weight) and 1.1 equivalents of Boc_2O are found to give the best results.[13]

The unique ability of Lindlar catalyst to mediate a chemoselective transformation has inspired us to investigate the usefulness of this reagent system with other azides possessing exceptionally labile functional groups. Thus, the *N*-Cbz-protected chiral vicinal amino azide **1h** was treated with Lindlar catalyst and Boc_2O under hydrogen atmosphere for 1 h and the corresponding *N*-Boc, *N*′-Cbz-protected vicinal diamino derivative **2h** was isolated in 95% yield (Scheme 2). Surprisingly, we did not observe any de-

Table 1. Reductive transformation of azides to *N*-Boc-protected amines



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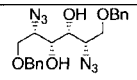
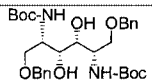
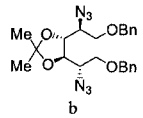
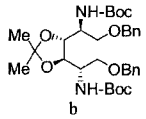
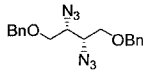
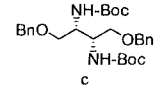
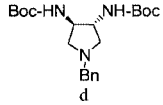
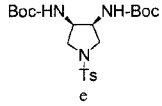
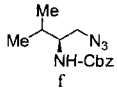
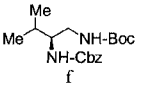
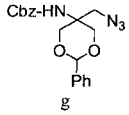
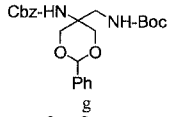
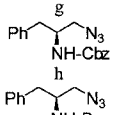
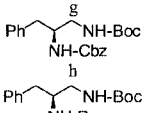
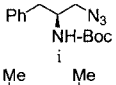
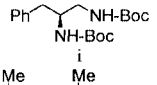
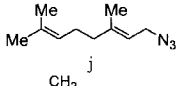
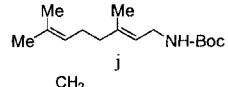
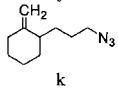
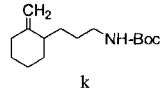
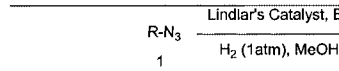
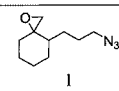
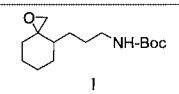
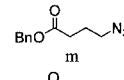
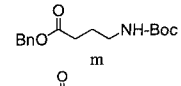
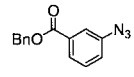
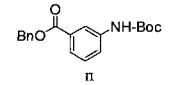
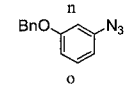
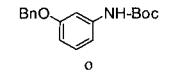
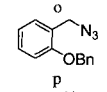
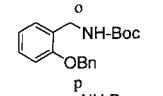
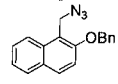
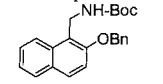
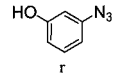
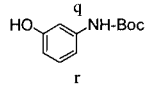
1	 a	2	 a	91
2	 b	5	 b	82
3	 c	3	 c	78
4	 d	2	 d	86
5	 e	1.5	 e	89
6	 f	1.5	 f	88
7	 g	2	 g	85
8	 h	1	 h	95
9	 i	1	 i	90
10	 j	6.5	 j	89
11	 k	0.5	 k	90



Entry	Substrate 1	Time [h]	Product 2[a]	Yield[b] (%)
12	 l	0.5	 l	91
13	 m	1	 m	91
14	 n	36	 n	82
15	 o	6	 o	89[c]
16	 p	2	 p	94
17	 q	1.5	 q	89
18	 r	6	 r	89
19	s	2	s	96
20	t	36	t	96
21	u	36	u	81
22	R=1-morpholinyl v	3	R=1-morpholinyl v	95
23	R =1-[4-(N-(cbz) piperazinyl] w	4	R =1-[4-(N-(cbz) piperazinyl] w	81
24	x	7.5	x	95

[a] All the products gave satisfactory spectroscopic data. [b] Isolated yields. [c] 40% (by weight) of the catalyst was used.

protection of the *N*-Cbz protecting group or formation of the *N*,*N*′-di(Boc)-1,2-diamino derivative **2i** under our reaction conditions.[14] Using this newly found methodology of one-pot conversion of azides to *N*-Boc amines, we have found an avenue for the synthesis of orthogonally protected diamino systems, which is a rarity in organic synthesis (Scheme 2). The contrasting chemical stability of the protecting groups in an orthogonally protected diamino system offers scope for planning a synthetic strategy in multi-step syntheses.[1]

The versatility of this one step transformation has been exhaustively studied with azides bearing different sensitive functional groups. The results are summarized in Table 1. The remarkable selectivity and mildness of this very useful transformation was further tested with other substrates bearing the *N*-Cbz protecting group (entries 6, 7 & 23[15]). As expected, azides possesing olefin functional groups were smoothly converted into the corresponding *N*-Boc-protected amines (entries 10 & 11) in excellent yields without affecting the carbon-carbon double bonds.[12] Similarly, the epoxy azide **1l** (entry 12) afforded the corresponding *N*-Boc-protected amine **2l** in 91% yield, emphasizing the mildness of the reaction conditions. The exceptional chemoselectivity of our method is further exemplified in the case of entries 13 & 14, where the highly labile benzyl esters were found to be stable under the reaction conditions.[16] Protective groups such as benzylidene acetal (entry 7), phenolic benzyl ethers (entries 15 & 16), *O*-benzyl ethers (entries 1, 2 & 3[17]), *N*-benzylamine (entry 4[18]), *N*-tosylamine (entry 5) and *N*-Fmoc amine (entry 24) were also found to be compatible with the reaction conditions. The *tert*-butyldimethylsilyl ether (OTBS) protective group is known to undergo hydrogenolysis under catalytic hydrogenation,[19] however under our reaction conditions it is found to be intact even after 36 h (entry 20). The highly functionalized *N*-aryl-1,3-oxazine-3-one azide derivative **1v**[20] was smoothly converted into the corresponding *N*-Boc-protected amine **2v** in 95% yield. Unlike aryl azides, the rate of reduction of aliphatic azides was found to be much faster (1−5 h).

Conclusion

In conclusion, an exceptionally chemoselective and convenient procedure for transforming azides into *N*-Boc-protected amines under very mild reaction conditions has been developed. We believe that the reagent system reported here has tremendous potential for use in asymmetric and natural product synthesis due to its simplicity, efficiency and high chemoselectivity.

Experimental Section

General Remarks: Melting points were determined on a Toshniwal melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR-470 spectrometer. NMR spectra were recorded on JEOL GSX − 400 FT NMR spectrometer. ^{1}H & ^{13}C chemical shifts are reported in ppm relative to tetramethylsilane as an internal standard. Mass spectra were recorded on Finnigan − MAT TSQ 70 B. Optical rotations were obtained on Jasco-DIP 200 digital polarimeter. TLC was carried out on E. Merck pre-coated aluminum silica gel plates (60 F-254).

Typical Experimental Procedure: Boc_2O (92 mg, 0.42 mmol) and Lindlar catalyst (20 mg, 20% by wt.) were added successively to a stirred solution of azide **1f** (100 mg, 0.38 mmol) in methanol (3 mL). The reaction flask was evacuated and flushed with hydrogen gas. The resultant mixture was stirred under hydrogen atmosphere (balloon) at room temperature for 1.5 h. After completion of the reaction, the catalyst was filtered through a pad of Celite, the filter cake was washed with methanol (10 mL) and the filtrate was concentrated under reduced pressure. The residue was purified over silica gel (100−200 mesh) using 5−15% EtOAc in hexane solvent gradient as eluent to afford pure compound **2f** (113 mg, 88%) as a white solid. R_f = 0.5 (silica gel; EtOAc/hexane, 4:6); m.p. 89−90 °C. IR (KBr): $\tilde{\nu}$ = 3366, 2973, 1686, 1540, 1304 cm^{-1}. $[\alpha]_D^{25}$ = 20.6 (c = 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.91 (d, J = 6.8 Hz, 3 H), 0.94 (d, J = 6.8 Hz, 3 H), 1.40 (s, 9 H), 1.76 (m, 1 H), 3.20 (m, 2 H), 3.55 (m, 1 H), 4.85 (br. s, 1 H), 4.98 (br. s, 1 H), 5.09 (s, 2 H), 7.34 (s, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.3, 19.5, 28.6, 30.9, 42.9, 57.5, 67.0, 79.8, 128.3, 128.4, 128.8, 136.8, 156.9, 157.3 ppm. MS (EI, 70 eV): m/z (%) = 337 (2.5), 281 (45), 237 (100).

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[1] *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz H. Yamamoto) Springer, Heidelberg, **1999**.
[2] [2a] I. Ojima, *Catalytic Asymmetric Synthesis*, 2nd ed. VCH, Weinheim **2000**. [2b] R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York **1994**. [2c] H. Brunner, W. Zettlmeier, *Handbook for Enantioselective Catalysis*, VCH, Weinheim **1993**. [2d] M. Beller, C. Bolm, *Transition Metals for Organic Synthesis*, Wiley-VCH, Weinheim, **1998**.
[3] [3a] L. E. Martinez, J. L. Leighton, D. H. Carsten, E. N. Jacobsen, *J. Am. Chem. Soc.* **1995**, *117*, 5897−5898. [3b] J. F. Larrow, S. E. Schaus, E. N. Jacobsen, *J. Am. Chem. Soc.* **1996**, *118*, 7420−7421.
[4] [4a] Y. Gao, K. B. Sharpless, *J. Am. Chem. Soc.* **1988**, *110*, 7538−7539. [4b] H.-T. Chang, K. B. Sharpless, *Tetrahedron Lett.* **1996**, *37*, 3219−3222.
[5] B. B. Lohray, Y. Gao, K. B. Sharpless, *Tetrahedron Lett.* **1989**, *30*, 2623−2626.
[6] [6a] D. J. Ager, I. Prakash, D. R. Schaad, *Chem. Rev.* **1996**, *96*, 835−875. [6b] F. Fache, E. Schulz, M. L. Tommasino, M. Lemaire, *Chem. Rev.* **2000**, *100*, 2159−2232.
[7] D. Lucet, T. Le Gall, C. Mioskowski, *Angew. Chem.* **1998**, *110*, 2724−2772; *Angew. Chem. Int. Ed.* **1998**, *37*, 2580−2627.
[8] T. W. Greene, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, Wiley: New York, **1999**.
[9] [9a] S. Saito, H. Nakajima, M. Inaba, T. Moriwake, *Tetrahedron Lett.* **1989**, *30*, 837−838. [9b] H. Kotsuki, T. Ohishi, T. Araki, *Tetrahedron Lett.* **1997**, *38*, 2129−2132.
[10] [10a] C. A. M. Afonso, *Tetrahedron Lett.* **1995**, *36*, 8857−8858. [10b] X. Ariza, O. Pineda, F. Urpi, J. Vilarrasa, *Tetrahedron Lett.* **2001**, *42*, 4995−4999.

[11] [11a] D. A. Nugiel, K. Jacobs, T. Worley; M. Patel, R. F. Kaltenbach, D. T. Meyer, P. K. Jadhav, G. V. De Lucca, T. E. Smyser, R. M. Klabe, L. T. Bacheler, M. M. Rayner, S. P. Seitz, *J. Med. Chem.* **1996**, *39*, 2156−2169. [11b] J. Hulten, N. M. Bonham, U. Nillroth, T. Hansson, G. Zuccarello, A. Bouzide, J. Aqvist, B. Classon, U. H. Danielson, A. Karlen, I. Kvarnstrom, B. Samuelsson, A. Hallberg, *J. Med. Chem.* **1997**, *40*, 885−897.

[12] [12a] Lindlar catalyst mediated selective reduction of azides to primary amines, in the presence of double bonds and benzyl ether, has been reported previously: E. J. Corey, K. C. Nicolaou, R. D. Balanson, Y. Machida, *Synthesis* **1975**, 590−591. [12b] Reduction of azide to amine without affecting the *N*-Cbz protecting group has been observed: D. C. Horwell, J. Hughes, J. C. Hunter, M. C. Pritchard, R. S. Richardson, E. Roberts, G. N. Woodruff, *J. Med. Chem.* **1991**, *34*, 404−414. [12c] However, hydrogenolysis of na *N*-Cbz protecting group has been reported with Lindlar catalyst: A. K. Ghosh, K. Krishnan, *Tetrahedron Lett.* **1988**, *39*, 947−948.

[13] Different batches of Lindlar catalyst procured from different sources (Merck and Aldrich) were found to give the same results.

[14] Interestingly, a one-pot direct conversion of *N*-Cbz to *N*-Boc has been reported under mild conditions using a Pd/C/H_2-Boc_2O reagent system: M. Sakaitani, K. Hori, Y. Ohfune, *Tetrahedron Lett.* **1988**, *29*, 2983−2984.

[15] B. B. Lohray, S. Baskaran, B. S. Rao, B. Y. Reddy, I. N. Rao, *Tetrahedron Lett.* **1999**, *40*, 4855−4856.

[16] Several modified palladium catalysts have been reported for the selective hydrogenation/hydrogenolysis of *N*-Cbz, benzyl ester and azide in the presence of aliphatic and phenolic *O*-benzyl protecting groups. [16a] J. S. Bajwa, *Tetrahedron Lett.* **1992**, *33*, 2299−2302. [16b] H. Sajiki, H. Kuno, K. Hirota, *Tetrahedron Lett.* **1997**, *38*, 399−402. [16c] Y. Shi, L. F. Peng, Y. Kishi, *J. Org. Chem.* **1997**, *62*, 5666−5667. [16d] H. Sajiki, K. Hirota, *Tetrahedron* **1998**, *54*, 13981−13996.

[17] A. Scheurer, P. Mosset, R. W. Saalfrank, *Tetrahedron: Asymmetry* **1997**, *8*, 1243−1251.

[18] B. B. Lohray, S. Baskaran, B. S. Rao, B. Mallesham, K. S. N. Bharath, B. Y. Reddy, S. Venkateswarlu, A. K. Sadhukhan, M. S. Kumar, H. M. Sarnaik, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 525−528.

[19] K. Hattori, H. Sajiki, K. Hirota, *Tetrahedron Lett.* **2000**, *41*, 5711−5714.

[20] B. B. Lohray, S. Baskaran, B. Y. Reddy, K. S. Rao, *Tetrahedron Lett.* **1998**, *39*, 6555−6556.

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