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Highly Chemoselective Pd−C Catalytic Hydrodechlorination Leading to the Highly Efficient *N*-Debenzylation of Benzylamines

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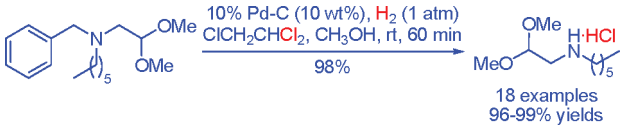
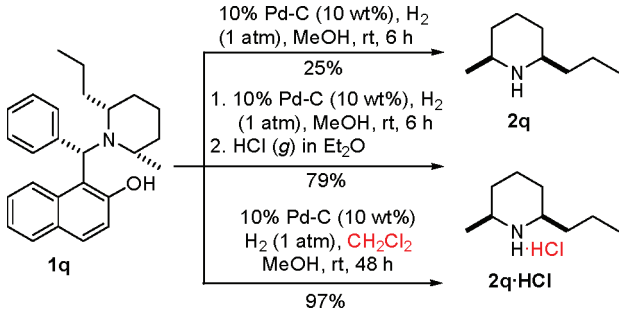


In the presence of 1,1,2-trichloroethane, a novel procedure for the Pd−C catalytic *N*-debenzylation of benzylamines was established. The method proceeded in a synergistic catalytic system and directly gave the products as crystal amine hydrochlorides in practically quantitative yields.

N-Debenzylation of benzylamines is a fundamental transformation in modern organic syntheses. For example, benzylamines are major protective groups for amines in multistep syntheses, where *N*-debenzylation is an essential conversion for the deprotection.[1,2] In recent years, many chiral benzylamines served as excellent chiral auxiliaries in asymmetric syntheses, in which *N*-debenzylation is a necessary step to remove the auxiliary residue from the induced molecules.[3,4]

SCHEME 1



Pd−C catalytic hydrogenolysis is one of the most favored methods for *N*-debenzylation of benzylamines, characterized by mild conditions (room temperature and atmospheric pressure), high conversion, and clean product. However, the method suffers from poor isolated yields for many biologically important amine products with low molecular weights and multihydrophilic groups, because the former are highly volatile and the latter are water-soluble. One of the best improvements is to convert them into amine hydrochlorides by treatment with aqueous HCl or saturated solution of HCl (*g*) in an anhydrous organic solvent.[5,6] In our previous work, the natural product (2*S*,6*R*)-dihydropinidine (**2q**) was isolated in 25% yield, whereas the crystal **2q·HCl** was obtained in 79% yield from the same Pd−C catalytic hydrogenolysis of **1q** (Scheme 1).[4] However, this improvement usually was incompatible with many acid-sensitive functional groups and was associated with tedious operations.

It is well-known that C−Cl bonds in organochlorides can be cleaved to release HCl in Pd−C catalyzed hydrodechlorination,[7] in which a base (inorganic bases or tertiary amines) usually is employed as both HCl acceptor and reaction promoter.[8]

(1) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons, Inc.: New York, 1999.

(2) For selected references, see: (a) Asahina, Y.; Takei, M.; Kimura, T.; Fukuda, Y. *J. Med. Chem.* **2008**, *51*, 3238–3249. (b) Gonzlez-Sabn, J.; Gotor, V.; Rebolledo, F. *J. Org. Chem.* **2007**, *72*, 1309–1314. (c) Faler, C. A.; Joulli, M. M. *Org. Lett.* **2007**, *9*, 1987–1990. (d) Arefalk, A.; Larhed, M.; Hallberg, A. *J. Org. Chem.* **2005**, *70*, 938–942. (e) White, K. N.; Konopelski, J. P. *Org. Lett.* **2005**, *7*, 4111–4112. (f) Wang, X. J.; Hart, S. A.; Xu, B.; Mason, M. D.; Goodell, J. R.; Etzkorn, F. A. *J. Org. Chem.* **2003**, *68*, 2343–2349. (g) Kuehne, M. E.; Cowen, S. D.; Xu, F.; Borman, L. *J. Org. Chem.* **2001**, *66*, 5303–5316. (h) Liras, S.; Lynch, C. L.; Fryer, A. M.; Vu, B. T.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 5918–5924.

(3) For selected references, see: (a) Resek, J. E. *J. Org. Chem.* **2008**, *73*, 9792–9794. (b) Amat, M.; Perez, M.; Minaglia, A. T.; Bosch, J. *J. Org. Chem.* **2008**, *73*, 6920–6923. (c) Santarem, M.; Vanucci-Bacque, C.; Lhommet, G. *J. Org. Chem.* **2008**, *73*, 6466–6469. (d) Amat, M.; Griera, R.; Fabregat, R.; Molins, E.; Bosch, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 3348–3351. (e) Noel, R.; Vanucci-Bacqué, C.; Fargeau-Bellassoued, M.-C.; Lhommet, G. *Eur. J. Org. Chem.* **2007**, 476–486. (f) Chi, Y.; English, E. P.; Pomerantz, W. C.; Seth Horne, W.; Joyce, L. A.; Alexander, L. R.; Fleming, W. S.; Hopkins, E. A.; Gellman, S. H. *J. Am. Chem. Soc.* **2007**, *129*, 6050–6055. (g) Amat, M.; Bassas, O.; Llor, N.; Cantl, M.; Prez, M.; Molins, E.; Bosch, J. *Chem.—Eur. J.* **2006**, *12*, 7872–7881. (h) Fujita, K.-i.; Fujii, T.; Yamaguchi, R. *Org. Lett.* **2004**, *6*, 3525–3528. (i) Bunnage, M. E.; Davies, S. D.; Roberts, P. M.; Smith, A. D.; Withey, J. M. *Org. Biomol. Chem.* **2004**, *2*, 2763–2776.

(4) Wang, X.; Dong, Y.; Sun, J.; Xu, X.; Li, R.; Hu, Y. *J. Org. Chem.* **2005**, *70*, 1897–1900.

(5) For amine products with small molecular weights, see: (a) Evans, G. B.; Furneaux, R. H.; Greatrex, B.; Murkin, A. S.; Schramm, V. L.; Tyler, P. C. *J. Med. Chem.* **2008**, *51*, 948–956. (b) Davies, S. G.; Garner, A. C.; Goddard, E. C.; Kruchinin, D.; Roberts, P. M.; Rodriguez-Solla, H.; Smith, A. D. *Chem. Commun.* **2006**, 2664–2666. (c) Kaur, K.; Aeron, S.; Bruhaspathy, M.; Shetty, S. J.; Gupta, S.; Hegde, L. H.; Silamkoti, A. D. V.; Mehta, A.; Chugh, A.; Gupta, J. B.; Sarmaa, P. K. S.; Kumara, N. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2093–2096. (d) Hulin, B.; Cabral, S.; Lopaze, M. G.; Van Volkenburg, M. A.; Andrews, K. M.; Parker, J. C. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4770–4773.

(6) For amine products with multihydrophilic groups, see: (a) Pandey, G.; Bharadwaj, K. C.; Khan, M. I.; Shashidhara, K. S.; Puranik, V. G. *Org. Biomol. Chem.* **2008**, *6*, 2587–2595. (b) Carreño, M. C.; Hernández-Torres, G.; Urbano, A.; Colobert, F. *Eur. J. Org. Chem.* **2008**, 2035–2038. (c) Gelmi, M. L.; Cattaneo, C.; Pellegrino, S.; Clerici, F.; Montali, M.; Martini, C. *J. Org. Chem.* **2007**, *72*, 9811–9814. (d) Galeazzi, R.; Martelli, G.; Mobbili, G.; Orena, M.; Rinaldi, S. *Tetrahedron: Asymmetry* **2004**, *15*, 3249–3256. (e) Pandey, G.; Kapur, M. *Org. Lett.* **2002**, *4*, 3883–3886. (f) Mehta, G.; Lakshminath, S. *Tetrahedron Lett.* **2002**, *43*, 331–334. (g) Amat, M.; Llor, N.; Huguet, M.; Molins, E.; Espinosa, E.; Bosch, J. *Org. Lett.* **2001**, *3*, 3257–3260.

(7) (a) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2002**, *102*, 4009–4092. (b) Nishimura, S. *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*; John Wiley & Sons, Inc.: New York, 2001; pp 623−639. (c) Rylander, P. N. *Hydrogenation Methods*; Academic Press: London, 1985; pp 148−156.

(8) (a) Xia, C.; Liu, Y.; Xu, J.; Yu, J.; Qin, W.; Liang, X. *Catal. Commun.* **2009**, *10*, 456–458. (b) Kume, A.; Monguchi, Y.; Hattori, K.; Nagase, H.; Sajiki, H. *Appl. Catal., B* **2008**, *81*, 274–282. (c) Concibido, N. C.; Okuda, T.; NaKano, Y.; Nishijima, W.; Okada, M. *Tetrahedron Lett.* **2005**, *46*, 3613–3617. (d) Nishijima, W.; Ochi, Y.; Tsai, T. Y.; Nakano, Y.; Okada, M. *Appl. Catal., B* **2004**, *51*, 135–140.

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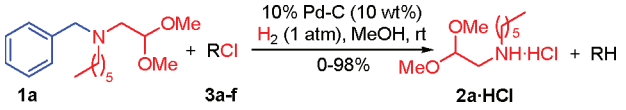
TABLE 1. Chemoselective Hydrodechlorination of 3a−f

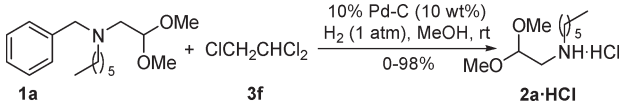


1a 3a-f 2a·HCl

entry	3a−f	1a:3 (equiv)	absorbed H_2 (equiv)[a]	yield of 2a·HCl (%)[c]
1	chlorocyclohexane (**3a**)	1:1.1	1.0 (2 h)	0[d]
2	$CH_3(CH_2)_4CH_2Cl$ (**3b**)	1:1.1	1.0 (2 h)	0[d]
3	$CH_3CH_2CHCl_2$ (**3c**)	1:1.1	2.0 (60 min)[b]	98
4	$^tBuCH_2CHCl_2$ (**3d**)	1:1.1	2.0 (60 min)[b]	98
5	$CH_3CCl_2CH_3$ (**3e**)	1:1.1	2.0 (60 min)[b]	98
6	$CH_2ClCHCl_2$ (**3f**)	1:1.1	2.0 (60 min)[b]	98

[a]Absorption of hydrogen ceased completely. [b]One mole of H_2 was consumed for normal *N*-debenzylation and another 1 mol for hydrodechlorination. [c]Isolated yield was obtained. [d]No **1a** was isolated, and **2a** was obtained as a single product.

TABLE 2. Highly Efficient *N*-Debenzylation of 1a in the Presence of 3f



1a 3f 2a·HCl

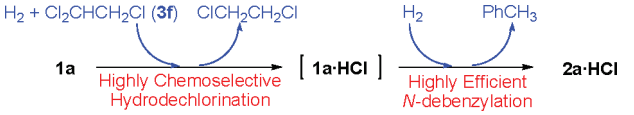
entry	1a:3f (equiv)	absorbed H_2 (equiv)[a]	time (min)	yield of 2a·HCl (%)[b]
1	1:1.1	2.0	60	98
2	0:1	0.0	180	0
3	1:5	2.0	60	98
4	1:0.6	1.6	50	58
5	1:0	1.0	180	0[c]

[a]Absorption of hydrogen ceased completely. [b]Isolated yield was obtained. [c]No **1a** was isolate and **2a** was obtained as a single product.

Thus, when a tertiary benzylamine is used as a HCl acceptor in a hydrodechlorination, it should carry out a catalytic hydrogenolysis to directly yield the corresponding amine hydrochloride. By this strategy, **1q** was converted into **2q·HCl** in 97% yield directly in hydrodechlorination of CH_2Cl_2 (Scheme 1).[4]

However, one drawback of this otherwise efficient *N*-debenzylation is that the hydrogen consumption was unpredictable because the system pressure was increased rather than decreased during the hydrogenolysis. Thus, the reaction time was estimated leading to low efficiency (for example, 48 h for **1q**).[4] The control experiments indicated that the drawback was mainly caused by two factors: (1) the hydrodechlorination of CH_2Cl_2 is a non-chemoselective process, which can occur slowly even without tertiary amine (as a HCl acceptor), and (2) the cleavage of each C−Cl bond absorbed 1 mol of gaseous H_2 and released 2 mol of gaseous products HCl and CH_3Cl.[9] Deductively, the drawback should be overcome by replacement of CH_2Cl_2 with a suitable chloroalkane that can take place a chemoselective hydrodechlorination to release 1 mol of HCl and 1 mol of liquid residue.[10] However, the investigation showed that no such chloroalkanes or such chemoselctive hydrodechlorination were reported in the literature to date.

SCHEME 2



On the basis of the above facts, different chloroalkanes with higher molecular weights were tested for their chemoselective hydrodechlorinations by employing *N*-benzyl-*N*-hexyl-2,2-dimethoxyethylamine (**1a**) as an HCl acceptor. As shown in Table 1, the monochloroalkanes resisted a catalytic hydrodechlorination under the mild conditions. When the mixture of **1a** (1.0 equiv), 10% Pd−C (10 wt%), and chlorocyclohexane (**3a**, 1.1 equiv) or 1-chlorohexane (**3b**, 1.1 equiv) was hydrogenated at room temperature and atmospheric pressure, the normal hydrogenolysis of **1a** occurred quantitatively within 2 h, but no expected product **2a·HCl** was obtained (entries 1 and 2). Luckily, when the geminal dichloroalkanes, such as 1,1-dichloropropane (**3c**), 1,1-dichloro-3,3-dimethylbutane (**3d**), 2,2-dichloropropane (**3e**), or 1,1,2-trichloroethane (**3f**), were tested, a crystal product **2a·HCl** was obtained in 98% yield within 60 min (entry 3−6). In each case of **3c−f**, the theoretical amount of hydrogen was absorbed (2.0 mol of H_2 was consumed, one for the normal hydrogenolysis and the other for the hydrodechlorination), and a very sharp end-point was observed. Since the control experiment[11] proved that **3f** was converted into $ClCH_2CH_2Cl$ after the hydrodechlorination, it was confirmed that the geminal dichloroalkanes underwent a monohydrodechlorination. To the best of our knowledge, this is the first highly chemoselective Pd−C catalyzed monohydrodechlorination of geminal dichloroalkanes.

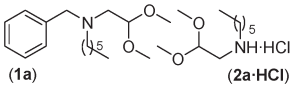
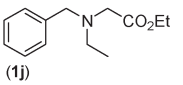
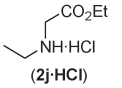
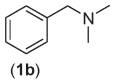
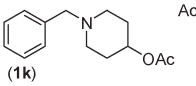
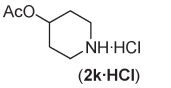
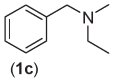
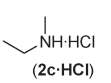
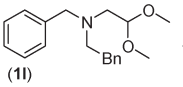
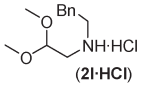
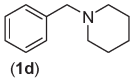
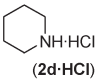
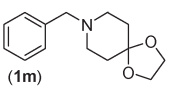
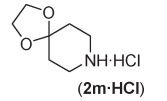
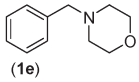
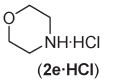
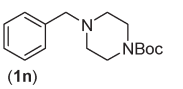
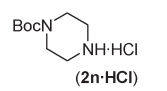
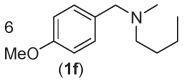
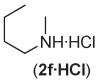
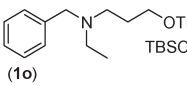
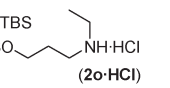
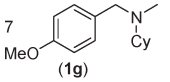
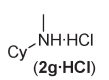
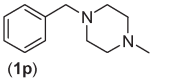
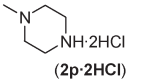
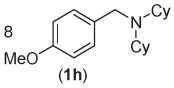
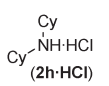
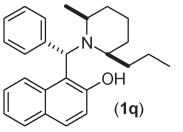
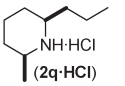
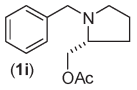
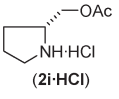
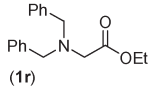
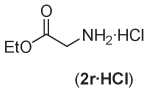
To explore the application of this chemoselective hydrodechlorination to the *N*-debenzylation of benzylamines, 1,1,2-trichloroethane (**3f**) was chosen as a practical HCl donor because it is a very cheap, commercially available geminal dichloroalkane. As shown in Table 2, the experimental results clearly revealed that the chemoselective hydrodechlorination, in fact, was well controlled by the amount of benzylamine **1a**. There was no hydrodechlorination of **3f** in the absence of **1a** (entry 2). When 1:5 (by mole) of **1a**:**3f** was used, no more than 2 mol of hydrogen was absorbed (entry 3). The result in entry 4 proved again that the geminal dichloroalkanes underwent only

(9) Prati, L.; Rossi, M. *Appl. Catal., B* **1999**, *23*, 135–142.

(10) Because HCl molecules occupy the Pd−C catalytic sites unreversably under anhydrous conditions (anhydrous HCl is a strong poison for Pd−C catalyst) and its amount is not easily controllable, anhydrous gaseous HCl could not be used for this purpose. See : Nishimura, S. *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*; John Wiley & Sons, Inc.: New York, 2001; Chapter 2.

(11) Details are described in Supporting Information.

TABLE 3. ***N*-Debenzylation of 1a−r in the Presence of Geminal Dichloroalkane 3f**

Entry	1	2·HCl	Time (min)[a]	Yield (%)[b]	Entry	1	2·HCl	Time (min)[a]	Yield (%)[b]
1	 (1a)	(2a·HCl)	60	98	10	 (1j)	 (2j·HCl)	90	97
2	 (1b)	 (2b·HCl)	40	98	11	 (1k)	 (2k·HCl)	70	94
3	 (1c)	 (2c·HCl)	40	97	12	 (1l)	 (2l·HCl)	60	98
4	 (1d)	 (2d·HCl)	60	98	13	 (1m)	 (2m·HCl)	75	97
5	 (1e)	 (2e·HCl)	60	97	14	 (1n)	 (2n·HCl)	140	98
6	 (1f)	 (2f·HCl)	40	98	15	 (1o)	 (2o·HCl)	70	98
7	 (1g)	 (2g·HCl)	40	98	16	 (1p)	 (2p·2HCl)	60	98
8	 (1h)	 (2h·HCl)	40	97	17	 (1q)	 (2q·HCl)	70	97
9	 (1i)	 (2i·HCl)	90	96	18	 (1r)	 (2r·HCl)	60	99

[a] The absorption of hydrogen ceased completely. [b] The isolated yields were obtained.

a monohydrodechlorination. By using 1:0.6 (by mole) of **1a**:**3f**, the exact 1.6 mol of hydrogen was absorbed. Additionally, we also observed that the hydrogenolysis of **1a** was accelerated remarkably by HCl released *in situ* in the hydrodechlorination of **3f**. For example, the *N*-debenzylation of **1a** took 3 h without **3f** (entry 5), whereas the same reaction was accomplished within 60 min by addition of **3f** (entries 1 and 3).

Thus, a novel procedure for the *N*-debenzylation of benzylamines was established, which exhibited high chemoselectivity and efficiency because it proceeded in a synergistic catalytic system. As shown in Scheme 2, the hydrodechlorination of **3f** initially was promoted by using **1a** as an HCl acceptor. Then, *N*-debenzylation of **1a**·**HCl** was accelerated by HCl to directly give the corresponding **2a**·**HCl**.

As shown in Table 3, the method showed very general scope and chemoselectivity. Different substrates **1a**−**r** were *N*-debenzylated smoothly to give the corresponding amine hydrochlorides **2a**−**r**·***n*HCl** in excellent yields, whether the *N*-debenzyled products are a gaseous amine (entry 2), a low-boiling point amine (entry 3), or highly volatile amines (entries 4, 6, and 7). There was no loss of enantiomeric excess for the chiral amines (entries 9 and 17). The acetate moieties (entries 9, 10, and 11) and the highly acid-sensitive acetal (entries 1 and 12), ketal (entry 13), *N*-Boc (entry 14), and *O*-TBS (entry 15) groups stayed intact to give the corresponding amine hydrochlorides in effectively quantitative yields. When double the amount of **3f** was used, the substrate **1p** was converted automatically into the corresponding dihydrochloride **2p**·**2HCl** (entry 16). However, although two benzyl groups in **1r** were hydrogenolyzed completely to produce **2r**·**HCl** in 99% yield (entry 18), no *N*-debenzylation occurred when the alkyl-substituted secondary benzylamines were used as substrates. Thus, EtNHBn, ^{t}BuNHBn, and $HOCH_2CH_2NHBn$ were quantitatively converted into the corresponding hydrochlorides EtNHBn·HCl, ^{t}BuNHBn·HCl, and $HOCH_2CH_2NHBn$·HCl. This chemoselective hydrogenolysis between tertiary and secondary benzylamines is fully in agreement with those reported in the references.[12] Under our standard conditions, the *N*-benzylanilines could not give the expected *N*-debenzylated products because the aromatic ring hydrogenated products were produced. It is noteworthy that the workup procedure for this method is just

(12) For selected references, see (a) Tircsó, G.; Bényei, A.; Király, R.; Lázár, I.; Pál, R.; Brücher, E. *Eur. J. Inorg. Chem.* **2007**, 701–713. (b) Lee, J.-D.; Lee, Y. J.; Jeong, H.-J.; Lee, J. S.; Lee, C. H.; Ko, J.; Kang, S. O. *Organometallics* **2003**, *22*, 445–449. (c) Kuehne, M. E.; Cowen, S. D.; Xu, F.; Borman, L. S. *J. Org. Chem.* **2001**, *66*, 5303–5316. (d) Studer, M.; Blaser, H.-U. *J. Mol. Catal. A: Chem.* **1996**, *112*, 437–445.

a simple filtration because all substrates gave their products as solid crystal amine hydrochlorides.

In summary, a novel method of Pd−C catalyzed *N*-debenzylation of benzylamine was developed. The method was characterized by simple addition of a geminal dichloroalkane into a conventional hydrogenolysis system and achieved high efficiency and clean products. The benefits of this method are 3-fold. First, the poor yield in the conventional *N*-debenzylation was overcome completely and the volatile amines, even the gaseous amines, can be obtained as their hydrochlorides in practically quantitative yields. Second, the traditional two steps (Pd−C catalytic hydrogenolysis and conversion of amine into its hydrochloride) are combined into a single easy procedure. Third, the new *N*-debenzylation provides a method to prepare amine hydrochlorides bearing functional groups that might be unstable to hydrogenolysis conditions employing acidic media. This method can be expected to replace the conventional catalytic hydrogenolysis to be used widely in asymmetric syntheses and in natural products syntheses.

Experimental Section

Preparation of *N*-Boc-Piperazine Hydrochloride (2n·HCl). A mixture of **1n** (691 mg, 2.5 mmol), $CH_2ClCHCl_2$ (369 mg, 2.75 mmol), and 10% Pd−C (69.1 mg) in MeOH (50 mL) was stirred under hydrogen atmosphere until the absorption of hydrogen ceased (140 min) (the hydrogenation was carried out on an atmospheric pressure hydrogenator). After the Pd−C catalyst was filtered off, the solvent was removed by rotary evaporation. The residue was diluted with dry diethyl ether, and crystalline product **2n·HCl** (545 mg, 98%) was collected by filtration: mp 236−238 °C ($MeOH/Et_2O$). IR (KBr): ν 2967, 2799, 2732, 2619, 2474, 1695 cm^{-1}. ^1H NMR (D_2O): δ 3.68 (t, J = 4.1 Hz, 4H), 3.22 (t, J = 5.5 Hz, 4H), 1.43 (s, 9H). ^{13}C NMR (D_2O): δ 155.8, 82.8, 43.1 (2C), 40.4 (2C), 27.6 (3C). MS *m*/*z* (%): 186 (M-HCl, 15.6), 56 (100). Anal. Calcd for $C_9H_{19}ClN_2O_2$: C, 48.54; H, 8.60; N, 12.58. Found: C, 48.56; H, 8.57; N, 12.62.

Prepation of *N*-Ethyl-(3-*tert*-butyldimethyl-silyloxy)-propylamine Hydrochloride (2o·HCl). A mixture of **1o** (769 mg, 2.5 mmol), $CH_2ClCHCl_2$ (369 mg, 2.75 mmol), and 10% Pd−C (76.9 mg) in MeOH (50 mL) was stirred under hydrogen atmosphere until the absorption of hydrogen ceased (70 min) (the hydrogenation was carried out on an atmospheric pressure hydrogenator). After the Pd−C catalyst was filtered off, the solvent was removed by rotary evaporation. The residue was diluted with dry diethyl ether, and crystalline product **2o·HCl** (622 mg, 98%) was collected by filtration: mp 168−170 °C ($MeOH/Et_2O$). IR (KBr): ν 2956, 1469, 1256 cm^{-1}. ^1H NMR (D_2O): δ 3.77 (t, J = 5.8 Hz, 2H), 3.09−3.01 (m, 4H), 1.92−1.83 (m, 2H), 1.24 (t, J = 7.5 Hz, 3H), 0.86 (s, 9H), 0.09 (s, 6H). ^{13}C NMR (D_2O): δ 60.9, 44.8, 42.9, 28.4, 25.6 (3C), 17.8, 10.7, −5.9 (2C). MS (EI): *m*/*z* (%) 217 (M-HCl, 4.8), 160 (100). Anal. Calcd for $C_{11}H_{28}ClNOSi$: C, 52.04; H, 11.12; N, 5.52. Found: C, 52.02; H, 11.16; N, 5.50.

The same procedure was used to convert the substrates **1a**−**r** efficiently to the corresponding products **2a**−**r·*n*HCl**.

Acknowledgment. This work was supported by the CFKSTIP from Ministry of Education of China (706003) and NNSFC (20672066, 30600779).

Supporting Information Available: Experiments, characterization, and ^1H and ^{13}C NMR spectra for all products **2a**−**r·*n*HCl**. This material is available free of charge via the Internet at http://pubs.acs.org.