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A Novel Type of Pd/C-catalyzed Hydrogenation Using a Catalyst Poison: Chemoselective Inhibition of the Hydrogenolysis for *O*-Benzyl Protective Group by the Addition of a Nitrogen-containing Base

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Abstract: *A mild and chemoselective hydrogenation method for a variety of reducible functional groups distinguishing from aliphatic and aromatic benzyl ethers was accomplished by the addition of an appropriate nitrogen-containing base to the Pd/C-catalyzed hydrogenation system.* © 1998 Elsevier Science Ltd. All rights reserved.

Functional group manipulation is fundamental in synthetic organic chemistry. Hence, the development of new chemoselective transformations continues to be of great importance. While many applications of catalyst poisons to Pd/C-catalyzed hydrogenation have been evaluated to obtain a chemoselective catalyst, only a few studies, the Lindlar catalyst and Rosenmund's reaction, have been accepted as general methodologies.[2] There is currently extensive interest in controlling benzyl ether hydrogenolysis in the transformation of an organic compound containing plural reducible functional groups.[3] Although benzyl ethers are a widely used protective group chiefly because of their stability under a variety of reaction conditions, low cost, ease of formation, and removal by mild catalytic hydrogenolysis, the lack of chemoselectivity between the benzyl groups and other reducible functional groups toward Pd-catalyzed hydrogenolysis has been a serious problem.[4,5,6] As part of our ongoing studies, we anticipated the chemoselective inhibition of Pd/C-catalyzed hydrogenation for aliphatic[7a] and aromatic[7b] benzyl ethers by employing a nitrogen-containing base as a catalyst poison. We now report the full details of these studies, which provide a mild and chemoselective hydrogenation method distinguishing a variety of reducible functionalities from the benzyl protective group.[8]

RESULTS AND DISCUSSION

I. Chemoselective Inhibition of Hydrogenation for Aliphatic Benzyl Ether Derivatives.

Our first attempts to achieve the hydrogenolysis of the *O*-benzyl protective group were made by reacting of 3-

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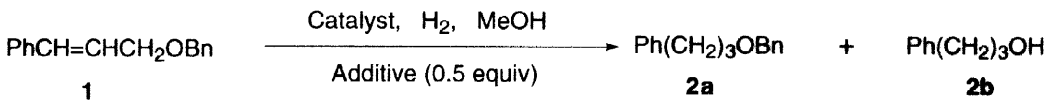
benzyloxy-1-phenyl-1-propene (**1**) in the presence of an additive (0.5 equiv) and a Pd-catalyst (10% of the weight of the substrate) in methanol (Table 1). The 5% Pd/C and Pd-black-catalyzed hydrogenolysis of the *O*-benzyl protective group was entirely blocked by the addition of ammonia, triethylamine, pyridine[9] and ammonium acetate and the corresponding 1-benzyloxy-3-phenylpropane (**2a**) was obtained quantitatively (entries 3–7). Although these hydrogenations of the olefin moiety of **1** were completed within 15 min in each case, the benzyl group was not removed even after 15 h. On the other hand, when ammonium chloride was used as an additive, no inhibition was observed, and debenzylated 3-phenylpropanol (**2b**) was formed (entry 8) in analogy with the case of no additive (entries 1 and 2). Ammonium chloride did not function as a partial catalyst poison.

Table 1. Effect of the Nitrogen-containing Base on Pd Catalyzed Hydrogenolysis of the Aliphatic *O*-Benzyl Ether **1**



Entry	Catalyst	Additive	Yield (%)[a]	
			2a[b]	**2b**
1	5% Pd/C	None	0	100[c]
2	Pd-black	None	0	98
3	5% Pd/C	NH_3	98	0
4	Pd-black	NH_3	99	0
5	5% Pd/C	Et_3N	97	0
6	5% Pd/C	Pyridine	98	0
7	5% Pd/C	NH_4OAc	97	0
8	5% Pd/C	NH_4Cl	0	98

[a]Isolated yield unless otherwise noted. [b]Though Reactions were completed within 15 min, these were allowed to stand for 15 h to prove the selectivity of the inhibition. [c]By ^1H NMR.

The reaction profile on the hydrogenation of **1** using 5% Pd/C (**A**) or 5% Pd/C plus ammonia (**B**) is shown in Figure 1. Under 5% Pd/C catalyzed hydrogenation conditions, the olefin moiety of **1** could be rapidly reduced prior to the hydrogenolysis of the *O*-benzyl group (**A** in Figure 1). Cinnamyl alcohol was never detected in the reaction mixture indicating that the debenzylation was ahead of the hydrogenation of the olefin moiety of **1**,. The ability of the catalyst for the hydrogenation toward the olefin moiety seems to be retained completely in spite of the addition of ammonia, which is seen in the fact that the rates for the hydrogenation of **1**

into **2a** are not affected in the presence of ammonia. The addition of ammonia, however, entirely blocked the reduction of the benzyl group.

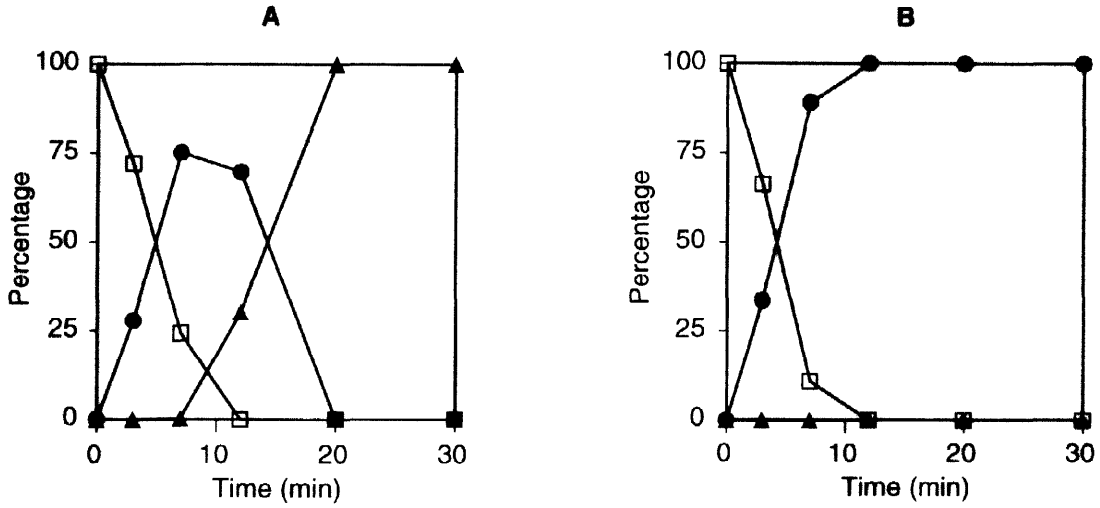
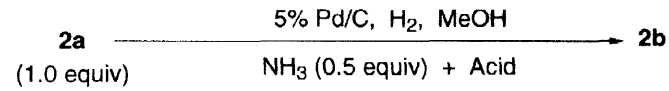


Figure 1. Reaction profile on the hydrogenation of 3-benzyloxy-1-phenyl-1-propene (**1**) using 5% Pd/C (**A**) or 5% Pd/C plus ammonia (**B**); □, 3-benzyloxy-1-phenyl-1-propene (**1**); ●, 1-benzyloxy-3-phenylpropane (**2a**); ▲, 3-phenyl-1-propanol (**2b**).

Table 2. Effect of the Counter Acid of the Ammonium Salt on the Hydrogenolysis of **2a** into **2b**[a]



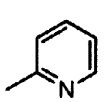
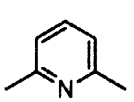
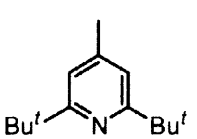
Entry	Acid	pK_a	Amount (equiv)	Yield of **2b** (%) 2.5 h	24 h
1	AcOH	4.76	0.5	0	0
2	$NCCH_2CO_2H$	2.47	0.5	0	0
3			5.0	0	16
4			10.0	0	46
5	H_3PO_4	2.12	0.5	0	16
6	Cl_2CHCO_2H	1.29	0.5	100	100
7	Cl_3CCO_2H	0.65	0.5	100	100

[a]The reaction was carried out using 0.25 mmol of the substrate, 0.25 mmol of ammonia and 0.25 mmol of acid with 5% Pd/C (5 mg) in methanol (2 mL) under hydrogen atmosphere (balloon) for the given reaction time. The reaction progress was monitored by TLC scanner (Shimadzu CS-9000) at 254 nm.

Upon employment of ammonium acetate and ammonium chloride as additives, the antipodal results were obtained (entries 7 and 8 in Table 1). As both additives were completely dissolved in the solvent (methanol), it was presumed that the difference of the inhibitory effect between the two ammonium salts depended on the acidity of each additive's counter acid. In order to confirm the hypothesis, the hydrogenation of **2a** with 5% Pd/C in the presence of ammonia (0.5 equiv) and free acid (0.5 equiv) was carried out in methanol (Table 2). Although the inhibitory effect of ammonia was not influenced by the addition of acetic acid (pK_a 4.76) or cyanoacetic acid (pK_a 2.47), addition of dichloroacetic acid and trichloroacetic acid inhibited the effect to afford the debenzylated product. Therefore, both acids seem to be acidic enough to quench the basicity of ammonia. On the other hand, the inhibitory effect of ammonia was eliminated by the addition of excess equivalents (*vs.* ammonia) of cyanoacetic acid while it was not affected by the equimolar amount of cyanoacetic acid (Table 2). We concluded that the presence of free ammonia could be important to obtain an inhibitory effect.

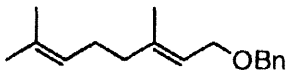
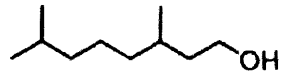
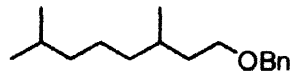
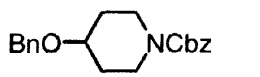
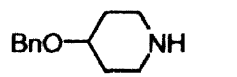
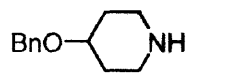
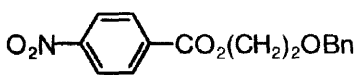
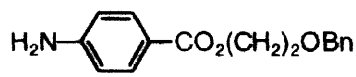
Next, the steric effect of the additive toward the inhibition of hydrogenolysis for the benzyl ether was investigated using *ortho*-substituted pyridine derivatives (Table 3). The inhibitory effect decreased as steric hindrance increased, and the most sterically hindered 2,6-di-*tert*-butyl-4-methylpyridine did not suppress the hydrogenolysis of the *O*-benzyl group of **2a**. Such a steric hindrance around the nitrogen lone pair of pyridine ring may weaken the interaction with Pd metal. These facts suggest that the interaction between the nitrogen-containing base and Pd metal could bring partial loss of the hydrogenation ability from the Pd/C catalyst.

Table 3. Steric Effect of the *o*-Substituent of Pyridine Ring on the Hydrogenolysis of **2a** into **2b**[a]

Base	Yield of **2b** (%)	
	10 h	24 h
	0	0
	0	2.6
	0	6.5
	66	100

[a]The reaction was carried out using 1.00 mmol of the substrate and a pyridine derivative (0.05 mmol) with 5% Pd/C (22 mg) in methanol (2 mL) under hydrogen atmosphere (balloon) for the given reaction time. The reaction progress was monitored by TLC scanner (Shimadzu CS-9000) at 254 nm.

Table 4. Chemoselective Hydrogenation of Aliphatic Benzyl Ether Derivatives[a]

Entry	Substrate	Additive	Product	Yield (%)[b]
1		None		93
2		NH_3		93
3	$BnO(CH_2)_2OH$	NH_3	Recovery	99
4	$BnO(CH_2)_2N_3$	NH_3	$BnO(CH_2)_2NH_2$	95
5	Boc-Ser(Bn)-OH	None	Boc-Ser-OH	94
6		NH_3	Recovery[c]	99
7		NH_4OAc	Recovery	95
8	Cbz-Ser(Bn)-OH	None	H-Ser(Bn)-OH, Ser	40, 60[d]
9		NH_3	H-Ser(Bn)-OH	97
10	Cbz-Thr(Bn)-OH	NH_3	H-Thr(Bn)-OH	93
11		NH_3		97
12		NH_4OAc		95
13		NH_4OAc		90
14	Boc-Ser(Bn)-OBn	NH_4OAc	Boc-Ser(Bn)-OH	96
15	Boc-Tyr(Bn)-OH (**3**)	NH_3	Boc-Tyr-OH (**4**)	89

[a]The reaction was carried out using 1.0 mmol of the substrate with 5% Pd/C (10% of the weight of the substrate) in methanol (2 mL) under hydrogen atmosphere (balloon). Although most of the chemoselective hydrogenations were completed within 3 h,[11] the benzyl group remained intact even after 15–24 h. [b]Isolated yield unless otherwise noted. [c]The optical rotation of *N*-Boc-*O*-benzyl-L-serine did not change before ($[\alpha]^{20}_D$ +22.6, c 2, ethanol) and after (+22.5) the hydrogenation. [d]Partial removal of *O*-benzyl group was carried out and the ratio of *O*-benzylserine and serine was confirmed by ^{1}H-NMR.

To explore the generality of the chemoselective hydrogenation of benzyl ether derivatives a number of substrates was investigated using 5% Pd/C[10] in the presence of 0.5 equiv of ammonia or ammonium acetate. As shown in Table 4, the present techniques selectively inhibited the hydrogenolysis of the aliphatic *O*-benzyl group with smooth hydrogenation of olefin (entry 2), azido (entry 4), *N*-Cbz (entries 9–12), nitro (entry 13) and

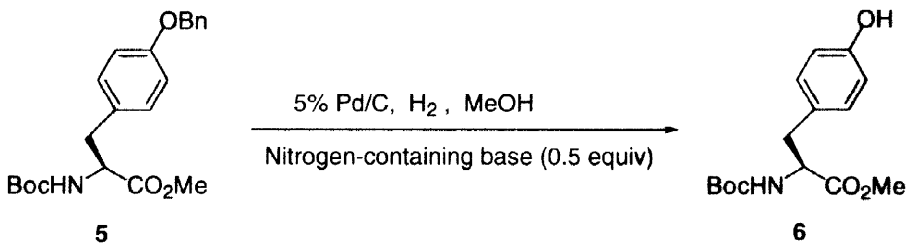
benzyl ester (entry 14) functionalities. The selectively hydrogenated products were obtained in excellent isolated yields in each case. Although most of the chemoselective hydrogenations were completed within 3 h,[11] the benzyl group remained intact even after 15–24 h. The present inhibition of aliphatic benzyl ether hydrogenolysis can be applicable to compounds which possess alcohol (entry 3) and carboxylic acid (entries 6, 7, 9 and 10) functionalities. Control experiments indicated that under 5% Pd/C hydrogenolysis conditions without the additive, the benzyl group was smoothly deprotected to the corresponding alcohol in excellent yields (entries 1 and 5). Although the partial suppression of the hydrogenolysis of the *O*-benzyl group was observed in the reaction without the additive, this is attributable to an effect of the intramolecular amino group being produced by the hydrogenolysis of *N*-Cbz group (entry 8). However, the hydrogenation of a aromatic benzyl ether, *N*-Boc-*O*-benzyltyrosine (**3**), caused the smooth cleavage of the *O*-benzyl protective group within 30 min (entry 15).[12,13]

II. Chemoselective Inhibition of Hydrogenation for Aromatic Benzyl Ether Derivatives.

The chemoselective hydrogenation method for a variety of reducible functionalities distinguishing from the aliphatic benzyl ether was not applicable to the aromatic benzyl ether as noted above. The problem was temporarily solved by employing of a 4-methoxybenzyl (MPM) group instead of the benzyl group as a protective group and using a Pd/C and pyridine combination as a catalyst.[14] During the course of further study, we found large difference in the inhibitory effect on the hydrogenolysis of the aromatic *O*–benzyl ether depending upon the nitrogen-containing bases employed as additive. Various sorts of nitrogen-containing bases were evaluated as catalyst poisons to develop a general procedure for the selective inhibition of the aromatic benzyl ether hydrogenolysis using *N*-Boc-*O*-benzyltyrosine methyl ester (**5**) as a substrate (Table 5). Addition of 0.5 equiv of ammonia at room temperature under hydrogen atmosphere expectedly led to the smooth loss of the *O*-benzyl protective group within 30 min. Even upon using 4 equiv of ammonia, the rate of the hydrogenolysis was not entirely changed. Further, when methylamine, triethylamine and pyridine were used instead of ammonia, the rates of hydrogenolysis did not change significantly to afford the debenzylated product **6** (entries 3–5). However, the employment of a 1,2-ambident amine, ethylenediamine, dramatically suppressed the hydrogenolysis of the *O*-benzyl protective group of **5** (entry 6). Although some conversion into the debenzylated product **6** was apparent after 2 h (28%), the hydrogenolysis was much slower compared with that achieved using non-ambident amines (entries 2–5).

In order to elucidate the effect of the length of the C–C chain between two nitrogen atoms on the catalyst activity, 1,3-propanediamine (C-3), 1,4-butanediamine (C-4), and 1,10-decanediamine (C-10) were also examined under identical reaction conditions (entries 7–9). As shown in Table 5 ethylenediamine (C-2) yielded the best inhibitory effect among the diamines. This fact suggests that the length of the C-C chain between two nitrogen atoms plays a crucial role in these inhibitions. An analogous experiment with diethylenetriamine, which possesses three nitrogen atoms which get in the C-2 unit between the nitrogen atoms, produced better results (entry 10).

Table 5. Conversion (%) of **5** to **6** after Hydrogenolysis for 2 h with 5% Pd/C in the Presence of Nitrogen-containing Base[a]



5 **6**

Entry	Amine or base	Conversion [%]	Entry	Amine or base	Conversion [%]
1	None	100	8	1,4-Butanediamine	95
2	Ammonia	100	9	1,10-Decanediamine	98
3	Methylamine	100	10	Diethylenetriamine	7
4	Triethylamine	100	11	*o*-Phenylenediamine	19
5	Pyridine	100	12	8-Aminoquinoline	11
6	Ethylenediamine	28	13	2,2'-Dipyridyl	0
7	1,3-Propanediamine	41	14	1,10-Phenanthroline	0

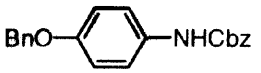
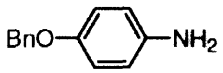
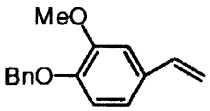
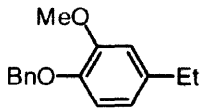
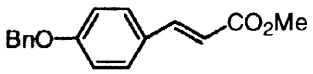
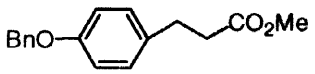
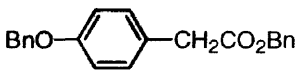
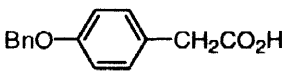
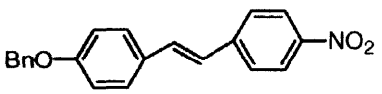
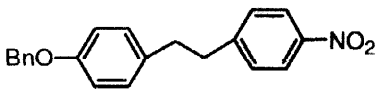
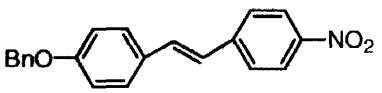
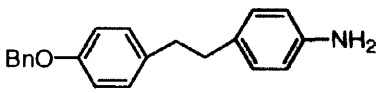
[a]The reaction was carried out using 0.10 mmol of **5** and a nitrogen-containing base or amine (0.05 mmol) with 5% Pd/C (3.9 mg) in methanol (1 mL) under hydrogen atmosphere (balloon) for 2 h. The reaction progress was monitored by TLC scanner (Shimadzu CS-9000) at 275 nm.

Much better results were obtained with the hydrogenolysis in the presence of an aromatic 1,2-ambident nitrogen-containing base, *e.g.*, *o*-phenylenediamine, 8-aminoquinoline, 2,2'-dipyridyl, and 1,10-phenanthroline (entries 11–14). It is noteworthy that the hydrogenolysis of the *O*-benzyl protective group of **5** was completely blocked during at least 2 h by the addition of 2,2'-dipyridyl or 1,10-phenanthroline to the reaction mixture. The critical property of the additives for the successful inhibition procedure of the hydrogenolysis may be their affinity to the palladium metal. Consequently, the structural requisite for the nitrogen-containing base would be 1,2-ambident base moiety which possesses the ability to form a five-membered cyclic-complex chelated with palladium.[13,15]

The present inhibition procedure of the hydrogenolysis of the phenolic benzyl protective group can be applied to several substrates which possess other reducible functionalities (*N*-Cbz, olefin, benzyl ester and nitro) within the molecule. 2,2'-Dipyridyl was chosen[16] as an additive for its high performance and stability under the hydrogenation conditions. As shown in Table 6, a combination of 5% Pd/C and 2,2'-dipyridyl could chemoselectively hydrogenate *N*-Cbz (entries 1 and 2), olefin (entries 3, 4 and 6), benzyl ester (entry 5), and nitro (entry 7) functionalities, while the phenolic benzyl protective group remained unchanged. Careful hydrogenation (2 h) of 4-benzyloxy-4'-nitrostilbene selectively reduced only olefin moiety (84%, entry 6), and

longer treatment (24 h) reduced both olefin and nitro functionalities to provide 4-amino-4'-benzyloxybibenzyl in 86% yield (entry 7). No reduction of an aromatic *O*-benzyl moiety was observed in any cases.

Table 6. Chemoselective Hydrogenation of Aromatic Benzyl Ether Derivatives.

Entry	Substrate	Product	Time (h)	Yield (%)[a]
1	Cbz-Tyr(OBn)-OMe	H-Tyr(OBn)-OMe	24[b]	91
2			22[b]	82
3			3	89
4			15[b]	95
5			24[b]	92
6			2	84
7			24	86

[a]Yields refer to products isolated. [b]Although the reaction was completed within 2–5 h, the benzyl protective group remained intact even after the shown time.

We have described a palladium catalyzed chemoselective hydrogenation method of aliphatic and aromatic benzyl ether derivatives by the addition of a nitrogen-containing base. Although 5% Pd/C can be generally used as a catalyst for hydrogenation with removal of all the *O*-benzyl protective groups,[2,3] the addition of ammonia to the Pd/C-catalyzed hydrogenation inhibits the hydrogenolysis of only the aliphatic *O*-benzyl protective group. By using of Pd/C-2,2'-dipyridyl combination as a catalyst for the hydrogenation, the aliphatic and the phenolic *O*-benzyl protective groups can be retained without any hydrogenolysis. These methods would increase the utility of the *O*-benzyl protective group in organic synthesis. Moreover, the simplicity of this method makes it an attractive new tool to organic chemist.

ACKNOWLEDGMENT

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EXPERIMENTAL

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. THF was distilled from potassium benzophenone ketyl immediately prior to use. Methylene chloride was distilled over calcium hydride. Column chromatography was carried out under nitrogen or air by flash method described by Still[17] with silica gel (230-400 mesh, Merck). All reactions were monitored by thin-layer chromatography (TLC) performed on aluminum or glass-backed silica gel 60 F_{254}, 0.2 mm plates (Merck), and compounds were visualized under UV light (254 nm), phosphomolybdic acid reagent (Aldrich) or ninhydrin reagent with subsequent heating, or Dragendorff's reagent.[18] Medium pressure (5 atm) hydrogenation was performed using Ishii hydrogenator CHA–E. Melting points were determined on a Electrothermal digital melting point apparatus or a Yanagimoto melting point apparatus and were uncorrected. ^{1}H NMR spectra were recorded on a JEOL GX-270 (270 MHz), Varian Unity-300 (300 MHz) or JEOL EX-400 (400 MHz). Chemical shifts are given in parts per million from Me_4Si in $CDCl_3$ and coupling constants (J) were reported in hertz (Hz). ^{13}C NMR spectra were obtained at 75.5 or 100 MHz. Low and high resolution mass spectra were carried out by Mass Spectrometry Lab., University of California, Berkeley, CA, USA or were taken on a JMS-SX 102A machine. Microanalyses were accomplished at Atlantic Microlab, Inc., GA, USA or the Microanalytical Laboratory of Gifu Pharmaceutical University, Japan.

3-Benzyloxy-1-phenyl-1-propene (1): To a stirring mixture of cinnamyl alcohol (4.03 g, 30.0 mmol) and NaH (60% W/W in mineral oil, 1.44 g, 36.0 mmol) in anhydrous DMF (30 mL) was added benzyl bromide (3.93 mL, 33.0 mmol) at room temperature. The mixture was stirred at room temperature for 12 h, after which it was concentrated *in vacuo*. The residue was partitioned between ether (100 mL) and water (100 mL). The ethereal layer was washed with water (100 mL) and brine (100 mL) and dried over $MgSO_4$. Concentration followed by flash column chromatography (hexane : ether = 20 : 1) provided **1** (6.11 g, 91%) as a clear oil: ^{1}H NMR (300 MHz): δ 4.21 (dd, J = 1.5 and 6.3 Hz, 2H), 4.58 (s, 2H), 6.34 (dt, J = 6.1 and 15.9 Hz, 1H), 6.64 (d, J = 15.9 Hz, 1H), 7.19–7.44 (m, 10H); ^{13}C NMR (75 MHz): δ 70.7, 72.1, 126.0, 126.5, 127.6, 127.7, 127.8, 128.4, 128.5, 132.5, 136.7, 138.2; HRMS (EI) calcd for $C_{16}H_{16}O$ (M^+) 224.1201, found 224.1203.

Hydrogenation of 3-Benzyloxy-1-phenyl-1-propene (1) (Table 1): After two vacuum/H_2 cycles to remove air from the reaction tube, a mixture of 3-benzyloxy-1-phenyl-1-propene (**1**) (224 mg, 1.0 mmol), 5% Pd/C or Pd-black (22 mg, 10% of the weight of the substrate) and an additive (0.5 mmol) in methanol (3 mL) was stirred under hydrogen atmosphere (balloon) at room temperature (*ca.* 20 ℃) for 15 h. The reaction mixture was filtered using celite® cake or a membrane filter (Millipore Dimex-13, 0.22 mm), the filtrate was

concentrated, and the residue was partitioned between chloroform or ethyl acetate (20 mL) and water (20 mL). The organic layer was washed with 10% $NaHSO_4$ solution (15 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated to provide 1-benzyloxy-3-phenylpropane (**2a**)[19] or 3-phenylpropane (**2b**) as a colorless oil without any by-product (see Table 1): **2a**: ^{1}H NMR (400 MHz): δ 1.88–2.02 (m, 2H), 2.72 (d, J = 7.7 Hz, 2H), 3.49 (dt, J = 1.4 and 6.5 Hz, 2H), 4.51 (s, 2H), 7.14–7.20 (m, 10H); ^{13}C NMR (100 MHz): δ 31.3, 32.3, 69.4, 72.9, 125.7, 127.5, 127.6, 128.2, 128.3 128.4 141.9; HRMS (EI) calcd for $C_{16}H_{18}O$ (M^+) 226.1358, found 226.1356. **2b** was identical with commercial sample.

Time Course of Hydrogenation of 3-Benzyloxy-1-phenyl-1-propene (1) (Figure 1): A mixture of **1** (224 mg, 1.00 mmol), methanol (5 mL), and 5% Pd/C (22 mg) or 5% Pd/C (22 mg) plus 2 M methanolic ammonia (0.25 mL, 0.50 mmol) was stirred under hydrogen atmosphere (balloon) at room temperature. Reaction progress was monitored at 3, 7, 12, 20, 30, and 60 min and 4 and 20 h by ^{1}H NMR after filtration using a membrane filter (Millipore Dimex-13, 0.22 μm) and evaporation of the solvent.

Hydrogenation of 1-Benzyloxy-3-phenylpropane (2a) in the Presence of Ammonia and Acid (Table 2): A mixture of **2a** (57 mg, 0.25 mmol), 5% Pd/C (5 mg), 0.1 M methanolic ammonia (250 μL, 0.25 mmol) and 0.1 M methanolic acid (250 μL, 0.25 mmol) in methanol (2 mL) was stirred under hydrogen atmosphere (balloon) at room temperature. Acetic acid, cyanoacetic acid, phospholic acid, dichloroacetic acid, and trichloroacetic acid were employed as an acid. Reaction progress was monitored by TLC Scanner (Shimadz CS-9000) at 254 nm (Rf value of **2a**: 0.74, Rf value of **2b**: 0.12, ether : hexane = 1 : 2). The yields were calculated on the integration ratio of each peaks, which were corrected by molar extinction coefficients of **2a** and **2b**.

Hydrogenation of 1-Benzyloxy-3-phenylpropane (2a) in the Presence of Pyridine Derivative (Table 3): A mixture of **2a** (226 mg, 1.00 mmol), 5% Pd/C (22 mg, 0.01 mmol of Pd metal) and a pyridine derivative (0.05 mmol) in methanol (2 mL) was stirred under hydrogen atmosphere (balloon) at room temperature. Pyridine, α-picoline, 2,6-lutidine, and 2,6-di-*tert*-butyl-4-methylpyridine were employed as a pyridine derivative. Reaction progress was monitored by TLC Scanner (Shimadz CS-9000) at 254 nm (Rf value of **2a**: 0.74, Rf value of **2b**: 0.12, ether : hexane = 1 : 2). The yields were calculated on the integration ratio of each peaks, which were corrected by molar extinction coefficients of **2a** and **2b**.

Benzyl Geranyl Ether was prepared from geraniol (5.62 mL, 21.3 mmol), benzyl bromide (2.78 mL, 23.4 mmol) and NaH (60% W/W in mineral oil, 0.94 g, 23.4 mmol) in anhydrous DMF (30 mL) by the procedure described for the preparation of **1** (3.87 g, 49% as a clear oil): ^{1}H NMR (400 MHz): δ 1.60, 1.65 and 1.68 (each s, 3H), 2.01–2.18 (m, 4H), 4.03 (d, J = 6.8 Hz, 2H), 4.50 (s, 2H), 5.10 (br t, J = 6.6 Hz, 1H), 5.40 (br t, J = 6.8 Hz, 1H), 7.22–7.43 (m, 5H); ^{13}C NMR (100 MHz): δ 16.4, 17.6, 25.6, 26.3, 39.5, 66.5, 71.9, 120.8, 123.9, 127.4, 127.8, 128.3, 131.6, 138.5, 140.3; HRMS (FAB) calcd for $C_{17}H_{25}O$ ($M^+ + H$) 245.1905, found 245.1896.

2-Benzyloxyethyl Azide:[20] To a stirring solution of 2-benzyloxyethanol (Aldrich, 3.81 g, 25.0 mmol) and Et_3N (3.90 mL, 28.0 mmol) in methylene chloride (50 mL) was added MsCl (2.17 mL, 28.0 mmol) at room

temperature. The mixture was stirred at room temperature for 15 h, after which it was concentrated *in vacuo*. The residue was partitioned between ethyl acetate (30 mL) and water (30 mL). The organic layer was washed with water (30 mL), saturated $NaHCO_3$ solution (30 mL), water (30 mL), 10% $NaHSO_4$ solution (30 mL), water (30 mL), and brine (30 mL) and dried over $MgSO_4$. The solvent was removed by evaporation *in vacuo* to give 2-benzyloxy-1-(methanesulfonyloxy)ethane, which was used for the next reaction without further purification (5.71 g, 99% crude) as a yellow oil: ^{1}H NMR (300 MHz): δ 3.04 (s, 3H), 3.75 (t, J = 4.7 Hz, 2H), 4.40 (t, J = 4.7 Hz, 2H), 4.58 (s, 2H), 7.27–7.39 (m, 5H); ^{13}C NMR (75 MHz): δ 37.7, 67.8, 69.1, 73.3, 127.8, 128.0, 128.5, 137.3.

To a mixture of the mesylate (5.71 g, crude) in anhydrous DMF (50 mL) was added NaN_3 (1.95 g, 30 mmol). The reaction mixture was stirred at room temperature for 48 h. The solvent was evaporated and the residue was partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was washed with water (50 mL) and brine (50 mL) and dried over $MgSO_4$. Concentration followed by flash column chromatography (hexane : ether = 20 : 1) provided pure 2-benzyloxyethyl azide[20] (4.21 g, 83% for two steps) as a clear oil: ^{1}H NMR (300 MHz): δ 3.41 and 3.66 (each t, J = 5.0 Hz, 2H), 4.58 (s, 2H), 7.23–7.38 (m, 5H); ^{13}C NMR (75 MHz): δ 50.79, 68.83, 73.25, 127.61, 127.76, 128.44, 137.68.

4-Benzyloxy-*N*-(benzyloxycarbonyl)piperidine: A mixture of 4-hydroxypiperidine (Lancaster, 2.53 g, 25.0 mmol) and *N*-(benzyloxycarbonyloxy)succinimide (6.23 g, 25.0 mmol) in methylene chloride (25 mL) was stirred at room temperature for 16 h. The mixture was washed with water (25 mL), 10% $KHSO_4$ solution (25 mL), water (25 mL x 2), and brine (25 mL) and dried over $MgSO_4$. The solvent was removed by evaporation *in vacuo* to give *N*-benzyloxycarbonyl-4-hydroxypiperidine, which was used for the next reaction without further purifications (pale yellow oil, 5.16 g crude, 88%): ^{1}H NMR (300 MHz): δ 1.38–1.55 (m, 2H), 1.80–1.94 (m, 2H), 3.14 (ddd, J = 3.5, 9.7 and 13.3 Hz, 2H), 3.83–4.05 (m, 3H), 5.13 (s, 2H), 7.24–7.46 (m, 5H).

To a mixture of the *N*-Cbz-piperidine (5.16 g, crude) and NaH (60% W/W in mineral oil, 0.96 g, 24.1 mmol) in anhydrous DMF (20 mL) was added benzyl bromide (2.87 mL, 24.1 mmol). The reaction mixture was stirred at room temperature for 24 h. The solvent was removed by evaporation and the residue was partitioned between ethyl acetate (100 mL) and water (100 mL). The organic layer was washed with water (100 mL) and brine (100 mL) and dried over $MgSO_4$. Concentration followed by flash column chromatography (hexane : ether = 4 : 1) provided 4-benzyloxy-*N*-(benzyloxycarbonyl)piperidine (2.77 g, 39% for two steps) as a waxy solid: ^{1}H NMR (300 MHz): δ 1.50–1.73 (m, 2H), 1.76–1.98 (m, 2H), 3.23 (ddd, J = 3.9, 9.1 and 13.1 Hz, 2H), 3.81 (tt, J = 4.8 and 9.6 Hz, 1H), 3.74–3.92 (m, 2H), 4.56 and 5.13 (each s, 2H), 7.23–7.45 (m, 10H); ^{13}C NMR (75 MHz): δ 30.9, 41.3, 67.0, 69.9, 73.5, 127.4, 127.6, 127.8, 127.9, 128.4, 128.5, 136.8, 138.6, 155.3; HRMS (EI) calcd for $C_{20}H_{23}NO_3$ (M^+) 325.1678, found 325.1678.

2-Benzyloxyethyl 4-nitrobenzoate: To a stirring mixture of 2-(benzyloxy)ethanol (3.04 g, 20.0 mmol), Et_3N (3.07 mL, 22.0 mmol) and DMAP (0.24 g, 2.0 mmol) in THF (20 mL) was added 4-nitrobenzoyl chloride (3.90 g, 21.0 mmol) at room temperature. The mixture was stirred at room temperature for 24 h, after

which it was concentrated *in vacuo*. The residue was partitioned between ethyl acetate (100 mL) and water (100 mL). The organic layer was washed with water (100 mL), saturated $NaHCO_3$ solution (100 mL), water (100 mL), 10% $NaHSO_4$ solution (100 mL), water (100 mL), and brine (100 mL) and dried over $MgSO_4$. Concentration followed by flash column chromatography (hexane : ether = 4 : 1) provided 2-benzyloxy-1-(4-nitrobenzoyloxy)ethane (5.18 g, 92%) as a pale yellow oil: ^{1}H NMR (270 MHz): δ 3.83 and 4.55 (each t, J = 4.6 Hz, 2H), 4.61 (s, 2H), 7.22–7.48 (m, 5H), 8.22 and 8.30 (each d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz): δ 65.0, 67.7, 73.2, 123.5, 127.7, 127.9, 128.5, 130.8, 135.5, 137.7, 150.6, 164.7; HRMS (EI) calcd for $C_{16}H_{15}NO_5$ ($M^+ + H$) 301.0950, found 301.0939.

***N*-Boc-*O*-benzyl-L-serine Benzyl Ester:** To a stirring mixture of *N*-Boc-*O*-benzyl-L-serine (2.95 g, 10.0 mmol) in dry DMF (5 mL) was added *N,N*-dimethylformamide dibenzylacetal (purity 90%, 3.47 mL, 12.0 mmol) at room temperature. The mixture was stirred at room temperature for 15 h, after which it was concentrated *in vacuo*. The residue was subjected to a flash column chromatography (hexane : ether = 5 : 1) to obtain *N*-Boc-*O*-benzyl-L-serine benzyl ester (3.43 g, 89%) as a clear oil: ^{1}H NMR (300 MHz): δ 1.44 (s, 9H), 3.60 and 3.91 (each dd, J = 3.0 and 9.2 Hz, 1H), 4.32–4.58 (m, 5H), 5.14 and 5.23 (each d, J = 12.2 Hz, 1H), 5.43 (br d, J = 9.2 Hz, 1H), 7.10–7.43 (m, 10H); ^{13}C NMR (75 MHz): δ 28.3, 54.1, 67.1, 70.1, 73.3, 80.0, 127.5, 127.8, 128.1, 128.3, 128.4, 128.5, 135.4, 137.5, 155.5, 170.6; HRMS (FAB) calcd for $C_{22}H_{28}NO_5$ ($M^+ + H$) 386.1967, found 386.1960.

Chemoselective Hydrogenation of Aliphatic Benzyl Ether Derivatives (Table 4): After two vacuum/H_2 cycles to remove air from the reaction tube, the substrate (1.0 mmol) in methanol (2–5 mL) was hydrogenated (balloon) using 5% Pd/C (10% of the weight of the substrate) in the presence of additive at room temperature (*ca.* 20 °C). Although most of the chemoselective hydrogenations were completed within 3 h,[11] the benzyl group remained intact even after 15–24 h. The reaction mixture was filtered using celite® cake or a membrane filter (Millipore Dimex-13, 0.22 mm) and the filtrate was concentrated *in vacuo*. The residue was partitioned between chloroform or ethyl acetate (30 mL) and water (30 mL). The organic layer was washed with 10% $NaHSO_4$ solution (15 mL) and brine (30 mL), dried ($MgSO_4$) and concentrated mostly to give an analytically pure product. If the product possesses an amino moiety (entries 4 and 8–13 in Table 4), the organic layer was washed with only brine (30 mL). The crude product was purified by flash column chromatography.

Benzyl 3,7-Dimethyl-1-octyl Ether: 91% as a clear oil; ^{1}H NMR (400 MHz): δ 0.86 (d, J = 6.8 Hz, 6H), 0.86 (d, J = 6.4 Hz, 3H), 1.05–1.35 (m, 6H), 1.37–1.74 (m, 4H), 3.45–3.55 (m, 2H), 4.50 (s, 2H), 7.24–7.36 (m, 5H); HRMS (FAB) calcd for $C_{17}H_{29}O$ ($M^+ + H$) 249.2218, found 249.2225.

2-Benzyloxyethylamine:[19] 93% as a pale yellow oil; ^{1}H NMR (270 MHz): δ 1.48 (br, 2H), 2.90 and 3.52 (each t, J = 5.3 Hz, 2H), 4.54 (s, 2H), 7.25–7.43 (m, 5H).

4-Benzyloxy-piperidine:[21] 97% (using NH_3) and 95% (using ammonium acetate) as a colorless needle (recrystallized from ethyl acetate–hexane): mp 61–63 °C; ^{1}H NMR (300 MHz): δ 1.42–1.59 (m, 2H), 1.90–2.05 (m, 2H), 2.61 (ddd, J = 3.0, 10.2 and 12.8 Hz, 2H), 3.10 (dt, J = 4.8 and 12.8 Hz, 2H), 3.40–3.54 (m, 1H),

4.56 (s, 2H), 7.20–7.41 (m, 10H); ^{13}C NMR (75 MHz): δ 32.9, 44.4, 69.4, 74.9, 127.3, 127.4, 128.3, 138.8; HRMS (EI) calcd for $C_{12}H_{18}NO$ (M^++1) 192.1388, found 192.1386.

2-Benzyloxy-1-(4-Aminobenzoyloxy)ethane: 90% as a pale yellow oil; ^{1}H NMR (400 MHz): δ 3.78 (t, J = 4.9 Hz, 2H), 3.97 (br, 2H), 4.44 (t, J = 4.9 Hz, 2H), 4.60 (s, 2H), 6.62 (d, J = 8.8 Hz, 2H), 7.30–7.41 (m, 5H), 7.86 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz): δ 63.5, 68.1, 73.1, 113.7, 119.5, 127.7, 128.4, 131.7, 138.0, 150.9, 166.6; HRMS (EI) calcd for $C_{16}H_{17}NO_3$ (M^+) 271.1208, found 271.1216.

***N*-Boc-*O*-benzyl-L-tyrosine Methyl Ester (5):** To a stirring mixture of *N*-Boc-*O*-benzyl-L-tyrosine (1.71 g, 4.6 mmol) in dry DMF (5 mL) was added *N,N*-dimethylformamide dimethylacetal (3.06 mL, 23.0 mmol) at room temperature. The mixture was stirred at room temperature for 15 h, after which it was concentrated *in vacuo*. The residue was subjected to a flash column chromatography (hexane : ether = 5 : 1) to obtain *N*-Boc-*O*-benzyl-L-tyrosine methyl ester (**5**) (1.30 g, 73%) as a white solid: mp 61–64 ℃; ^{1}H NMR (400 MHz): δ 1.42 (s, 9H), 2.92–3.14 (m, 2H), 3.70 (s, 3H), 4.48–4.62 (m, 1H), 4.97 (br, 1H), 5.03 (s, 2H), 6.90 and 7.04 (each d, J = 8.8 Hz, 2H), 7.27–7.45 (m, 5H); ^{13}C NMR (100 MHz): δ 28.3, 37.5, 52.2, 54.5, 70.0, 79.9, 114.9, 127.4, 128.0, 128.2, 128.6, 130.3, 137.0, 155.1, 157.9, 172.4; LRMS (EI) m/z 385 (M^+), 268, 197, 91 (base peak). Anal. Calcd for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.39; H, 7.17; N, 3.66.

Hydrogenation of *N*-Boc-*O*-benzyl-L-tyrosine Methyl Ester (5) Monitored by a TLC Scanner (Table 5): A mixture of **5** (38.5 mg, 0.10 mmol), nitrogen–containing base or amine (0.05 mmol), 5% Pd/C (3.9 mg) and methanol (1 mL) was stirred under hydrogen atmosphere (balloon) at room temperature. Reaction progress was monitored by TLC Scanner (Shimadz CS-9000) at 275 nm (Rf value of **5**: 0.65, Rf value of **6**: 0.39, ether : hexane = 2 : 1). The yields were calculated on the integration ratio of each peaks, which were corrected by molar extinction coefficients of **5** and **6**.

***N*-Cbz-*O*-benzyl-L-tyrosine Methyl Ester** was prepared by a procedure similar to that described above using *N*-Cbz-*O*-benzyl-L-tyrosine (202 mg, 0.50 mmol) and *N,N*-dimethylformamide dimethylacetal (332 μL, 2.50 mmol) in dry DMF (3 mL) (190 mg, 91% as a waxy solid): ^{1}H NMR (400 MHz): δ 2.92–3.12 (m, 2H), 3.69 (s, 3H), 4.52–4.68 (m, 1H), 5.01 (s, 2H), 5.06 and 5.10 (each d, J = 12.2 Hz, 1H), 5.24 (br d, J = 7.8 Hz, 1H), 6.89 and 6.99 (each d, J = 8.8 Hz, 2H), 7.26–7.45 (m, 10H); ^{13}C NMR (100 MHz): δ 37.3, 52.2, 54.9, 66.9, 69.9, 114.9, 127.4, 127.9, 128.0, 128.1, 128.4, 128.5, 130.2, 136.3, 136.9, 155.6, 157.9, 172.0; HRMS (EI) calcd for $C_{25}H_{25}NO_5$ (M+) 419.1742, found 419.1733.

4-Benzyloxy-*N*-benzyloxycarbonylaniline: To a solution of commercial (Aldrich) 4-benzylaniline hydrochloride (1.00 g, 4.16 mmol) and Et_3N (1.25 mL, 8.97 mmol) in DMF (15 mL) was added benzyl chloroformate (0.61 mL, 4.27 mmol) at room temperature. The mixture was stirred at room temperature for 15 h and concentrated *in vacuo*. The residue was partitioned between chloroform (30 mL) and water (30 mL) and the organic layer was washed with brine (30 mL), dried over $MgSO_4$ and evaporated *in vacuo*. The residue was passed through a flash column chromatography eluted with chloroform to obtain the white solid (1.22 g, 88%): mp 142 ℃; ^{1}H NMR (400 MHz): δ 5.04 and 5.19 (each s, 2H), 6.52 (br, 1H), 6.92 (d, J = 8.8 Hz, 2H),

7.19–7.45 (m, 12H); LRMS (EI) *m/z* = 333 (M^+); HRMS (EI): *m/z* calcd for $C_{21}H_{19}NO_3$ (M^+) 333.1365, found 333.1379; Anal. Calcd For $C_{21}H_{19}NO_3$: C 75.66, H 5.74, N 4.20; found: C 75.47, H 5.72, N 4.19.

4-Benzyloxycinnamic Acid Methyl Ester: To a stirring mixture of commercial (TCI) 4-hydroxycinnamic acid methyl ester (178 mg, 1.00 mmol) and NaH (60% W/W in mineral oil, 48 mg, 2.00 mmol) in DMF (3.5 mL) was added benzyl bromide (0.14 mL, 1.20 mmol) at room temperature. The mixture was stirred at room temperature for 14 h and poured into water (30 mL). The resulting precipitate was collected by filtration and the pale yellow solid was purified through a flash column chromatography eluted with chloroform to obtain a white solid (232 mg, 87%): mp 136 ℃; ^{1}H NMR (270 MHz): δ 3.79 (s, 3H), 5.10 (s, 2H), 6.31 (d, *J* = 16.1 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 7.28–7.53 (m, 7H), 7.65 (d, *J* = 16.1 Hz, 2H); LRMS (EI) *m/z* = 268 (M^+); Anal. Calcd For $C_{17}H_{16}O_3$: C 76.10, H 6.01; found: C 76.03, H 6.08.

4-Benzyloxyphenylacetic Acid Benzyl Ester: To a stirring mixture of commercial (TCI) 4-benzyloxyphenylacetic acid (2.42 g, 10.0 mmol) and Et_3N (1.40 mL, 10.0 mmol) in dry THF (20 mL) was added benzyl bromide (1.19 mL, 10.0 mmol) at room temperature. The mixture was stirred at room temperature for 24 h and concentrated *in vacuo*. The residue was partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was washed with water (50 mL), 10% $NaHSO_4$ solution (25 mL), water (50 mL), saturated $NaHCO_3$ solution (50 mL), water (50 mL) and brine (30 mL) and dried over $MgSO_4$. Concentration followed by recrystallization from 50% EtOH provided a white needle (2.91 g, 88%): mp 69–70 ℃; ^{1}H NMR (400 MHz): δ 3.60, 5.05 and 5.12 (each s, 2H), 6.93 and 7.20 (each d, *J* = 8.8 Hz, 2H), 7.30–7.45 (m, 10H); LRMS (EI) *m/z* = 332 (M^+); Anal. Calcd For $C_{22}H_{20}O_3$: C 79.49, H 6.06; found: C 79.21, H 6.10.

4-Benzyloxy-4'-nitrostilbene: To a stirring mixture of commercial (Lancaster) 4-hydroxy-4'-nitrostilbene (1.00 g, 4.2 mmol) and NaH (60% W/W in mineral oil, 119 mg, 8.3 mmol) in DMF (10 mL) was added benzyl bromide (0.54 mL, 4.6 mmol) at room temperature. The mixture was stirred at room temperature for 27 h and concentrated *in vacuo*. The residue was partitioned between ethyl acetate (50 mL) and water (50 mL) and the organic layer was washed with water (50 mL), 10% $NaHSO_4$ solution (25 mL), water (50 mL), saturated $NaHCO_3$ solution (50 mL), water (50 mL) and brine (30 mL) and dried over $MgSO_4$. Concentration followed by flash column chromatography eluted with ethyl acetate : hexane (1 : 4) provided a light yellow solid (0.97 g, 71%): mp 201.5–202.5 ℃; ^{1}H NMR (400 MHz): δ 5.11 (s, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 7.01 and 7.22 (each d, *J* = 15.6 Hz, 2H), 7.28–7.47 (m, 5H), 7.49, 7.59 and 8.20 (each d, *J* = 8.8 Hz, 2H); LRMS (EI) *m/z* = 331 (M^+); Anal. Calcd For $C_{21}H_{17}NO_3$: C 76.12, H 5.17, N 4.23; found: C 75.90, H 5.05, N 4.11.

Chemoselective Hydrogenation of Aromatic Benzyl Ether Derivatives (Table 6): After two vacuum/H_2 cycles to remove air from the reaction tube, the substrate (0.2 mmol) was hydrogenated (balloon) using 5% Pd/C (10 % of the weight of the substrate) in the presence of 2,2'-dipyridyl (0.1 mmol) in methanol or 1,4-dioxane (1 mL) at room temperature (*ca.* 20 ℃) for the appropriate time (see Table 2). The reaction mixture was filtered (celite® cake), the filtrate was concentrated and the residue was partitioned between chloroform or ethyl acetate (20 mL) and water (20 mL). The organic layer was washed with 10% $NaHSO_4$ solution (10 mL)

and brine (20 mL), dried ($MgSO_4$) and concentrated to provide the product (**6**) without any by-product. If the product possesses an amino moiety (entries 1, 2 or 7 in Table 6), the organic layer was washed only with brine (20 mL). After concentration, the residue was purified by flash column chromatography to remove 2,2'-dipyridyl.

4-Benzyloxyaniline: ^{1}H NMR (400 MHz): δ 3.42 (br, 2H), 4.98 (s, 2H), 6.63 and 6.81 (each d, J = 8.8 Hz, 2H), 7.28-7.42 (m, 5H); LRMS (EI) m/z = 199 (M^+); HRMS (EI) calcd for $C_{13}H_{13}NO$ (M^+) 199.0997, found 199.0995. The product was identical with the sample commercially purchased (Aldrich).

4-Benzyloxy-3-methoxyethylbenzene: ^{1}H NMR (400 MHz): δ 1.21 (t, J = 7.8 Hz, 3H), 2.59 (q, J = 7.8 Hz, 2H), 3.88 (s, 3H), 5.12 (s, 2H), 6.67 (dd, J = 8.1 and 2.0 Hz, 1H), 6.75 (d, J = 2.0 Hz, 1H), 6.80 (d, J = 8.1 Hz, 1H), 7.29 (t, J = 7.3 Hz, 1H), 7.35 (t, J = 7.3 Hz, 2H), 7.44 (d, J = 7.3 Hz, 2H); LRMS (FAB$^+$) m/z = 243 (M^++H); HRMS (FAB$^+$) calcd for $C_{16}H_{18}O_2$ (M^++H) 243.1384, found 243.1385.

4-(Benzyloxy)hydrocinnamic Acid Methyl Ester: ^{1}H NMR (270 MHz): δ 2.60 and 2.89 (each t, J = 7.8 Hz, 2H), 3.67 (s, 3H), 5.04 (s, 2H), 6.90 (d, J = 8.8 Hz, 2H), 7.11 (d, J = 8.8 Hz, 2H), 7.27–7.46 (m, 5H) ; LRMS (EI) m/z = 270 (M^+); HRMS (EI): m/z calcd for $C_{17}H_{18}O_3$ (M^+) 270.1256, found 270.1262.

4-Benzyloxy-4'-nitrobibenzyl: ^{1}H NMR (400 MHz): δ 2.89 and 2.98 (each t, J = 8.1 Hz, 2H), 5.04 (s, 2H), 6.89 and 7.03 (each d, J = 8.3 Hz, 2H), 7.22–7.53 (m, 7H), 8.11 (d, J = 8.8 Hz, 2H); LRMS (EI) m/z = 333 (M^+); HRMS (EI): m/z calcd for $C_{21}H_{19}NO_3$ (M^+) 333.1365, found 333.1375.

4-Amino-4'-benzyloxybibenzyl: ^{1}H NMR (400 MHz): δ 2.72–3.03 (m, 4H), 3.57 (br, 2H), 5.04 (s, 2H), 6.62 (d, J = 8.8 Hz, 2H), 6.89 and 6.96 (each d, J = 8.3 Hz, 2H), 7.08 (d, J = 8.8 Hz, 2H), 7.31–7.46 (m, 5H); LRMS (EI) m/z = 303 (M^+); HRMS (EI): m/z calcd for $C_{21}H_{21}NO$ (M^+) 303.1623, found 303.1616.

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