Highly Chemoselective Hydrogenation with Retention of the Epoxide Function Using a Heterogeneous Pd/C – Ethylenediamine Catalyst and THF

Hironao Sajiki,* Kazuyuki Hattori, and Kosaku Hirota*[a]

Abstract: In general, palladium – carbon (Pd/C) catalyzed hydrogenation of epoxides affords the corresponding primary and secondary alcohols as a mixture. It has been found that the catalytic activity of a Pd/C – ethylenediamine complex catalyst [Pd/C(en)] in the hydrogenolysis of epoxide functions is drastically reduced. Herein we describe a mild and chemoselective method for the hydrogenation of olefin, nitro, and azide functions with retention of the epoxide function. The chemoselectivity was accomplished by using a combination of 5% Pd/C(en) and THF as solvent. A significant drop in the chemoselectivity of the hydrogenation is observed with 5% Pd/C(en) in MeOH. These results reinforce the utility of epoxides as important precursors of alcohols in synthetic chemistry.

Keywords: chemoselectivity · epoxides · heterogeneous catalysis · hydrogenations

Introduction

Manipulation of functional groups is a fundamental process in synthetic organic chemistry and, hence, the development of new chemoselective transformations remains of great interest.[1] The highly strained epoxy function is easily ring-opened under reductive conditions.[2] Consequently, it is extremely difficult to keep the epoxide function intact during synthetic processes involving reduction steps, such as hydrogenation, and hydride reduction, though epoxides are important and widely used intermediates in organic synthesis as precursors of alcohols. Among the very few examples of chemoselective catalytic hydrogenations that distinguish the epoxide function, their functionality is intrinsically specific and applicable to only the following functions: acetylene (Lindlar catalyst),[3] olefin with sterically hindered epoxide (Pt),[4] epoxy conjugated olefin ($[\{(t\mathrm{Bu}_2\mathrm{Ph})\mathrm{PdP}t\mathrm{Bu}_2\}_2]$ or $[\mathrm{Ir(COD)(PPh_3)(PhCN)}]\mathrm{BF}_4$)[5], and α,β-unsaturated ester (Mg/MeOH).[6]

We recently found that a system comprising palladium/carbon (Pd/C) and added amine is an excellent catalyst for the chemoselective hydrogenation of many reducible functionalities in the presence of an O-benzyl protective group.[7] In addition, Pd/C formed an isolable complex with ethylenediamine, and its complex catalyst [Pd/C(en)] chemoselectively hydrogenated a variety of reducible functionalities with retention of O-benzyl and N-Cbz protective groups and benzyl alcohol grous under mild conditions.[8]

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Results and Discussion

During our efforts to extend the applicability of Pd/C(en), we observed that Pd/C(en) shows very low catalytic activity towards the hydrogenolysis of epoxides, compared with Pd/C. The hydrogenation of epoxydecane (**2b**) catalyzed by 5% Pd/C(en) resulted in very poor conversion to the alcohol (**3b**, 19%),[9] and 81% of the unchanged epoxide (**2b**) remained even after hydrogenation in MeOH for 48 h at ordinary pressure (balloon)(Table 1). On the other hand, the use of 5% Pd/C as catalyst resulted in the hydrogenation of **2b** to give the corresponding alcohols (**3b** and **4b**) within only 6 h. Further fine-tuning of reaction conditions indicated that THF is a highly effective solvent for 5% Pd/C(en)-catalyzed chemoselective hydrogenation in the presence of an epoxy function.

To explore the scope of this method, the hydrogenation of a number of substrates (**1**) was investigated (Table 2). The results shown in entries 1 – 9 demonstrated that the chemoselective hydrogenation could be accomplished by employing epoxy compounds with terminal and internal C–C double bonds. The hydrogenation almost entirely tolerates epoxides. Although the resulting products were contaminated by trace amounts of over-reduction products (**3** and **4**) in some cases (entries 1, 2, 3, and 8), the alcoholic contaminants (**3** and **4**) could be removed easily by simple flash column chromatography.[10] Nitro and azide moieties were also successfully

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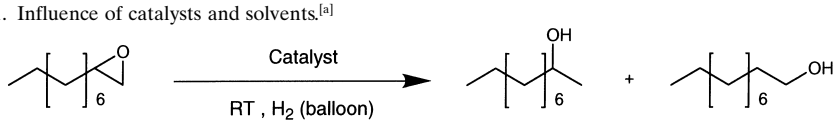
Table 1. Influence of catalysts and solvents.[a]



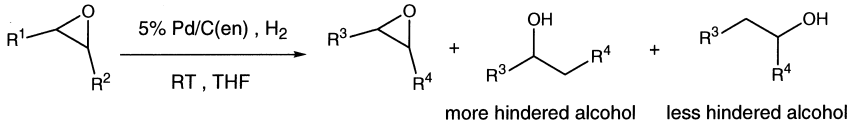
2b **3b** **4b**

Catalyst	Solvent	t [h]	Relative yield [%][b] **2b**	**3b**	**4b**
5% Pd/C	MeOH	6	0	82	18
5% Pd/C(en)	MeOH	48	81	19	0
5% Pd/C(en)	THF	48	100	0	0

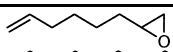
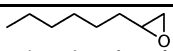
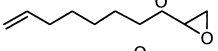
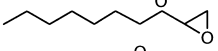
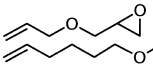
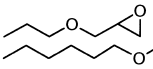
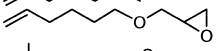
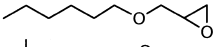
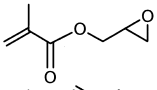
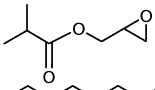
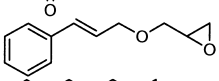
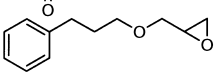
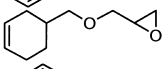
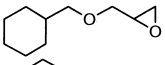
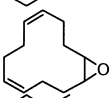
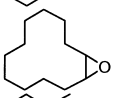
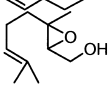
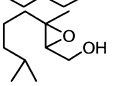
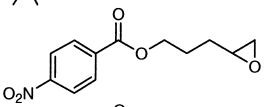
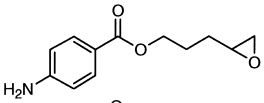
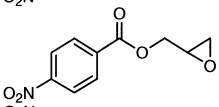
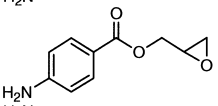
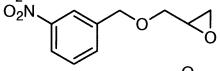
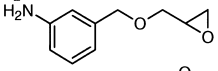
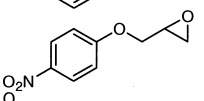
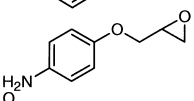
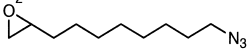
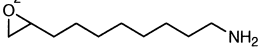
[a] The hydrogenation was carried out using 1 mmol of the substrate in MeOH (1 mL) or THF (1 mL) with catalyst (10% of the weight of the substrate). [b] Determined by ^{1}H NMR spectroscopy.

transformed into an amino group without ring cleavage of the epoxy function under these conditions (entries 10–14). Although purification of glycidyl 4-aminobenzoate (**2k**), 3-aminobenzyl glycidyl ether (**2l**), and 4-aminophenyl glycidyl ether (**2m**) from the reaction mixture has proved to be difficult by column chromatography because of their lability on silica gel (entries 11–13), the selectivity (93–95%) of the formation of the desired amino epoxides (**2k**–**m**) is sufficiently high for the direct use of the crude products in the following reactions. The catalyst could be recovered almost quantitatively after simple filtration and it could be reused.

Table 2. 5% Pd/C(en)-THF catalyzed hydrogenation.[a]



1 **2** **3** **4**

Entry		Substrate **1**	t [h]	Major product **2**	Yield of **2** [%]	Product ratio **2**	**3**	**4**
1	**1a**		3		[b]	96	0	4
2	**1b**		3		85	97	0	3
3	**1c**		2.5		[b]	98	2	0
4	**1d**		3		92	100	0	0
5	**1e**		3		94	100	0	0
6	**1f**		3		98	100	0	0
7	**1g**		9		87	100	0	0
8	**1h**		24[c]		93	97	(3)	
9	**1i**		12[c]		86	100	0	0
10	**1j**		18		100	100	0	0
11	**1k**		8		99[d]	96	4	0
12	**1l**		14		100[d]	93	7	0
13	**1m**		3		94[d]	95	5	0
14	**1n**		19		97	100	0	0

[a] Unless otherwise specified, the reaction was carried out using 0.5 mmol of the substrate in THF (1 mL) with 5% Pd/C(en) (10% of the weight of the substrate) under a hydrogen atmosphere (balloon) for the given reaction time. [b] Because of the low boiling point of the products, the quantitative conversion was observed by NMR spectroscopy in [D_8]THF. [c] Reaction was performed under 5 atm of hydrogen using Ishii medium-pressure hydrogenator CHA-E. [d] The yield was indicated as a crude mixture since the isolation of the product (**2k**, **2l**, or **2m**) from the reaction mixture by column chromatography was difficult because of their lability on silica gel.

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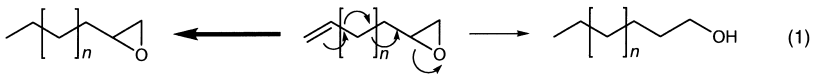
The recovered 5% Pd/C(en) was also effective in the second and third reactions, and the yields and selectivity of the second and third runs were comparable to those of the first run. A limitation of this methodology is that epoxides derived from styrene derivatives would be easily converted into primary alcohols with the ring-cleavage of the epoxide (e. g., phenethyl alcohol).[11]

At present, detailed mechanistic studies have not been undertaken and the exact process that leads to the chemoselectivity is unclear. It is likely that a large excess of THF oxygen atoms occupies the surface of the palladium of 5% Pd/C(en) instead of the epoxide oxygen atoms. This process results in a blocking of the hydrogenolysis of epoxides. It may be noted that the hydrogenation of the unsaturated terminal epoxide **1a** or **1b** gave a small amount of a saturated primary alcohol (**4a** or **4b**) as a by-product together with the desired saturated epoxide (**2a** or **2b**) (Table 1, entries 1 and 2), while the hydrogenolysis of the saturated terminal epoxide **2b** using 5% Pd/C(en) in MeOH only gave the corresponding secondary alcohol (2-decanol, **3b**) together with unchanged **2b** (Table 1).[9] These observations would be explained by the continuous isomerization of the olefin moiety during the catalysis [Eq. (1), see also Supporting Information].[12, 13] The competition between the hydrogenation and the isomerization characterizes the product ratio. In addition, by replacing a methylene moiety between the epoxide and olefin functions of **1a** or **1b** with an oxygen atom to inhibit the isomerization, the formation of the corresponding saturated primary alcohol (**4**) as a by-product was not observed under the same conditions (Table 1, entries 3, 4, 6 and 7).



(1)

2a, **2b** **1a** : $n = 3$ **1b** : $n = 5$ **4a**, **4b**

Conclusion

We have developed a mild and chemoselective hydrogenation method using a 5% Pd/C(en)-THF system, which is widely applicable to the selective hydrogenation of a variety of olefins and nitro and azide groups leaving intact the epoxide functions. These findings reinforce the utility of epoxides as important precursors of alcohols.

Experimental Section

General: ^{1}H NMR and ^{13}C NMR spectroscopy: JEOL JNM GX-270 and JEOL JNM EX-400 (^{1}H NMR: 270 MHz and 400 MHz; ^{13}C NMR: 100 MHz); MS: JMS-SX 102A; TLC (thin-layer chromatography): 0.25 mm silica gel 60 F_{254} plates (Art 5715, Merck) using UV light as a visualizing agent and 7% ethanolic phosphomolybdic acid or *p*-anisaldehyde solution, and heat as developing agent; column chromatography: silica gel 60 (230–400 mesh, Merck). Melting points were determined on a Yanagimoto melting point apparatus and were uncorrected. THF was distilled from sodium benzophenone ketyl immediately prior to use. Medium-pressure (5 atm) hydrogenation was performed using an Ishii hydrogenator CHA-E. 1,2-Epoxy-7-octene (**1a**), 1,2-epoxy-9-decene (**1b**), allyl glycidyl ether (**1c**), glycidyl methacryrate (**1e**), 9,10-epoxy-1,5-cyclododecadiene (**1h**), and 1,2-epoxy-3-(4-nitrophenoxy)propane (**1m**) were purchased from Tokyo Kasei Kogyo Co. (TCI), Kanto Chemical Co., Wako Pure Chemical Industries or Acros Organics and used without further purification. 2,3-Epoxygeraniol (**1i**) was prepared according to the previously outlined procedure.[14]

Glycidyl 5-hexenyl ether (1d): 5-Hexene-1-ol (1.00 g, 10.00 mmol) was added to a solution of epichlorohydrin (5 mL) and tetrabutylammmonium hydrogensulfate (0.34 g, 1.00 mmol) in 50% NaOH aqueous solution (5 mL). The mixture was stirred at room temperature (RT) for 9 h. The reaction mixture was poured into water (15 mL) and extracted with Et_2O (15 mL). The ethereal layer was washed with water (15 mL) and brine (15 mL) and dried over anhydrous magnesium sulfate. The solvent was evaporated to dryness. Flash column chromatography (hexane/ Et_2O 50:1) yielded **1d** (1.18 g, 75%) as a colorless oil. ^{1}H NMR (400 MHz, RT, $CDCl_3$): $\delta = 1.42-1.64$ (m, 4H), 2.07 (q, $J = 7.2$ Hz, 2H), 2.61 (dd, $J = 2.9$ and 4.6 Hz, 1H), 2.79 (t, $J = 4.6$ Hz, 1H), 3.12–3.16 (m, 1H), 3.38 (dd, $J =$ 5.6 and 11.6 Hz, 1H), 3.44–3.55 (m, 2H), 3.70 (dd, $J = 2.9$ and 11.6 Hz, 1H), 4.94–5.03 (m, 1H), 5.76–5.86 (m, 1H); ^{13}C NMR (100 MHz, RT, $CDCl_3$): $\delta = 25.25$, 28.99, 33.35, 44.08, 50.72, 71.28, 71.31, 114.38, 138.50; elemental analysis calcd (%) for $C_9H_{16}O_2 \cdot 1/5\,H_2O$: C 67.63, H 10.34; found: C 67.59, H 10.05. The existence of water in this product was confirmed by ^{1}H NMR analysis.

Cinnamyl glycidyl ether (1f): Preparation of **1f** was performed analogously to the procedure described for **1d** with cinnamyl alcohol (3.83 mL, 29.60 mmol). Yield: 84% (4.75 g); ^{1}H NMR (400 MHz, RT, $CDCl_3$): $\delta =$ 2.64 (dd, $J = 2.7$ and 4.8 Hz, 1H), 2.82 (t, $J = 4.8$ Hz, 1H), 3.18–3.22 (m, 1H), 3.45 (dd, $J = 5.9$ and 11.6 Hz, 1H), 3.78 (dd, $J = 3.2$ and 11.6 Hz, 1H) 4.17–4.27 (m, 2H), 6.26–6.33 (m, 1H), 6.62 (d, $J = 16.1$ Hz, 1H), 7.23–7.41 (m, 5H); ^{13}C NMR (100 MHz, RT, $CDCl_3$): $\delta = 44.23$, 50.74, 70.67, 71.79, 125.54, 126.41, 127.66, 128.46, 132.69, 136.51; HRMS (EI) calcd for $C_{12}H_{14}O_2$ [M^+] 190.0994, found 190.0998.

1-(Glycidoxymethyl)-3-cyclohexene (1g): Preparation of **1g** was performed analogously to the procedure described for **1d** with 3-cyclohexene-1-methanol (2.00 mL, 17.00 mmol). Yield: 53% (1.50 g); ^{1}H NMR (400 MHz, RT, $CDCl_3$): $\delta = 1.23-1.33$ (m, 1H), 1.69–1.84 (m, 2H), 1.88–1.96 (m, 1H), 2.04–2.14 (m, 3H), 2.61 (dd, $J = 2.9$ and 4.4 Hz, 1H), 2.79 (dd, $J = 4.4$ and 5.1 Hz, 1H), 3.13–3.17 (m, 1H), 3.35–3.44 (m, 3H), 3.72 (dd, $J = 1.5$ and 3.2 Hz, 1H), 5.63–5.70 (m, 2H); ^{13}C NMR (100 MHz, RT, $CDCl_3$): $\delta = 24.24$, 25.26, 28.13, 33.64, 43.68, 43.79, 50.50, 50.56, 71.37, 76.07, 76.10, 125.61, 126.69; elemental analysis calcd (%) for $C_{10}H_{16}O_2 \cdot 1/10\,H_2O$: C 70.64, H 9.60; found: C 70.68, H 9.65. The existence of water in this product was confirmed by ^{1}H NMR analysis.

Glycidyl 3-nitrobenzyl ether (1l): Preparation of **1l** was performed analogously to the procedure described for **1d** with 3-nitrobenzyl alcohol (0.77 g, 5.00 mmol). Yield: 90% (0.94 g); ^{1}H NMR (270 MHz, RT, $CDCl_3$): $\delta = 2.65$ (dd, $J = 2.5$ and 4.8 Hz, 1H), 2.84 (t, $J = 4.8$ Hz, 1H), 3.20–3.26 (m, 1H), 3.46 (dd, $J = 6.1$ and 11.5 Hz, 1H), 3.90 (dd, $J = 2.7$ and 11.5 Hz, 1H), 4.65 and 4.72 (d, $J = 12.5$ Hz, each 1H), 7.53 (t, $J = 8.1$ Hz, 1H), 7.69 (d, $J =$ 8.1 Hz, 1H), 8.16 (d, $J = 8.1$ Hz, 1H), 8.23 (s, 1H); ^{13}C NMR (100 MHz, RT, $CDCl_3$): $\delta = 43.31$, 50.10, 70.97, 71.13, 121.37, 121.79, 128.79, 132.80, 139.98, 147.67; MS (FAB: NBA): *m/z* (%): 210 (5) [M^++H].

1,2-Epoxypentyl 4-nitrobenzoate (1j): 4-Nitrobenzoyl chloride (1.85 g, 10.00 mmol) was added to a solution of 4-penten-1-ol (1.03 g, 12.00 mmol), triethylamine (2.09 mL, 15.00 mmol), and 4-(dimethylamino)pyridine (DMAP) (0.12 g, 1.00 mmol) in THF (10 mL). The mixture was stirred at room temperature for 3 h. The reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (50 mL). The organic layer was washed with water (30 mL), saturated aqueous $NaHCO_3$ (30 mL), water (30 mL), 10% $NaHSO_4$ solution (30 mL), water (30 mL), and brine (30 mL), and dried over anhydrous magnesium sulfate. The solvents were evaporated to dryness. Flash column chromatography (hexane/Et_2O 100:1) yielded 4-pentenyl 4-nitrobenzoate (1.09 g, 47%) as a yellow oil. ^{1}H NMR

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(270 MHz, RT, $CDCl_3$): $\delta = 1.91$ (p, $J = 6.2$ Hz, 2H), 2.24 (q, $J = 6.2$ Hz, 2H), 4.40 (t, $J = 6.2$ Hz, 2H), 5.02–5.13 (m, 2H), 5.78–5.93 (m, 1H); ^{13}C NMR (100 MHz, RT, $CDCl_3$): $\delta = 27.70$, 30.00, 65.26, 115.49, 123.45, 130.58, 135.70, 137.09, 150.46, 164.60; HRMS (FAB) calcd for $C_{12}H_{14}O_4N$ [M^++H] 236.0923, found 236.0918.

4-Pentenyl 4-nitrobenzoate (1.00 g, 4.25 mmol) in CH_2Cl_2 (20 mL) was added to a solution of 70% *m*-chloroperbenzoic acid (1.15 g, 4.68 mmol) in CH_2Cl_2 (30 mL) at such a rate as to keep the temperature about 25 °C for 10 min. The mixture was stirred at room temperature for 7 h. The reaction mixture was poured into water (50 mL) and extracted with $CHCl_3$ (100 mL). The organic layer was washed with water (30 mL) and brine (30 mL) and dried over anhydrous magnesium sulfate. The solvents were evaporated to dryness. Flash column chromatography (hexane/Et_2O 2:1) yielded **1j** (0.91 g, 86%) as a yellow oil. ^{1}H NMR (270 MHz, RT, $CDCl_3$): $\delta = 1.62–1.77$ (m, 1H), 1.78–1.86 (m, 1H), 1.86–2.07 (m, 2H), 2.53 (dd, $J = 2.7$ and 4.8 Hz, 1H), 2.80 (t, $J = 4.8$ Hz, 1H), 2.97–3.03 (m, 1H), 4.44 (t, $J = 6.3$ Hz, 2H), 8.21 and 8.30 (each d, $J = 9.3$ Hz, 2H); ^{13}C NMR (100 MHz, RT, $CDCl_3$): $\delta = 24.62$, 28.45, 46.11, 50.94, 64.82, 122.85, 130.00, 135.05, 149.86, 163.81; HRMS (FAB) calcd for $C_{12}H_{14}O_5N$ [M^++H] 252.0872, found 252.0866.

Glycidyl 4-nitrobenzoate (1k): 4-Nitrobenzoyl chloride (1.85 g, 10.00 mmol) was added to a solution of glycidol (0.80 mL, 12.00 mmol), triethylamine (2.09 mL, 15.00 mmol), and 4-(dimethylamino)pyridine (0.12 g, 1.00 mmol) in THF (10 mL). The mixture was stirred at room temperature for 15 h. The reaction mixture was poured into water (50 mL) and extracted with ethyl acetate (50 mL). The organic layer was washed with water (30 mL), saturated aqueous $NaHCO_3$ (30 mL), water (30 mL), 10% $NaHSO_4$ solution (30 mL), water (30 mL), and brine (30 mL) and dried over anhydrous magnesium sulfate. After filtration, the solvents were evaporated to afford **1k** (423 mg, 19%) as a white solid. M. p. 55–56 °C; ^{1}H NMR (400 MHz, RT, $CDCl_3$): $\delta = 2.75$ (dd, $J = 2.4$ and 4.4 Hz, 1H), 2.93 (t, $J = 4.4$ Hz, 1H), 3.36–3.39 (m, 1H), 4.20 (dd, $J = 6.8$ and 12.2 Hz, 1H), 4.74 (dd, $J = 2.9$ and 12.2 Hz, 1H), 8.25 and 8.31 (each d, $J = 9.3$ Hz, 2H); ^{13}C NMR (100 MHz, RT, $CDCl_3$): $\delta = 44.67$, 49.17, 66.43, 123.60, 130.90, 135.03, 150.76, 164.40; MS (FAB: NBA) *m/z* (%) 224 (40) [M^++H]; elemental analysis calcd (%) for $C_{10}H_9O_5N$: C 53.82, H 4.06, N 6.28; found: C 53.72, H 4.03, N 6.36.

1-Azido-9,10-epoxydecane (1n): Methanesulfonyl chloride (0.85 mL, 11.00 mmol) was added dropwise to a cooled (−10 °C) solution of 9-decen-1-ol (1.56 g, 20.00 mmol) and triethylamine (1.50 mL, 11.00 mmol) in CH_2Cl_2 (50 mL) under an Ar atmosphere. The reaction mixture was stirred at room temperature for 12 h and quenched with ice water (30 mL). The organic layer was washed with 5% $KHSO_4$ solution (30 mL), water (30 mL), 5% Na_2CO_3 solution (30 mL), and brine (30 mL), then dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated to afford a pale yellow oil that was used in the next reaction without further purification (1.98 g, 85%). ^{1}H NMR (270 MHz, RT, $CDCl_3$): $\delta = 1.31–1.43$ (m, 10H), 1.75 (pen, $J = 6.6$ Hz, 2H), 2.04 (q, $J = 7.0$ Hz, 2H), 2.96 (s, 3H), 4.22 (t, $J = 6.6$ Hz, 2H), 4.91–5.03 (m, 2H), 5.73–5.88 (m, 1H); MS (FAB: NBA): *m/z* (%): 235 (32%) [M^++H].

To a solution of the above mesylate (2.27 g, 9.70 mmol) in anhydrous DMF (15 mL) was added NaN_3 (0.95 g, 14.55 mmol). The reaction mixture was stirred at 50 °C for 22 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 anhydrous magnesium sulfate. After filtration, the solvent was evaporated to afford 1-azido-9-decene as a colorless oil, which was used in the next reaction without further purification (1.60 g, 91%). ^{1}H NMR (270 MHz, RT, $CDCl_3$): $\delta = 1.31–1.52$ (m, 10H), 1.52–1.65 (m, 2H), 2.04 (q, $J = 7.0$ Hz, 2H), 3.26 (t, $J = 6.8$ Hz, 2H), 4.91–5.04 (m, 2H), 5.74–5.89 (m, 1H).

1-Azido-9-decene (0.91 g, 5.00 mmol) in CH_2Cl_2 (10 mL) was added to a solution of 70% *m*-chloroperbenzoic acid (1.36 g, 5.50 mmol) in CH_2Cl_2 (10 mL) at such a rate as to keep the temperature at about 25 °C for 10 min. The mixture was stirred at RT for 7 h. The reaction mixture was poured into water (20 mL) and extracted with $CHCl_3$ (50 mL). The organic layer was washed with water (20 mL) and brine (20 mL) and dried over anhydrous magnesium sulfate. After filtration, the solvent was evaporated to afford **1n** (0.96 g, 98%) as a pale yellow oil. ^{1}H NMR (270 MHz, RT, $CDCl_3$): $\delta = 1.33–1.63$ (m, 14H), 2.46 (dd, $J = 2.9$ and 4.9 Hz, 1H), 2.74 (dd, $J = 3.9$ and 4.9 Hz, 1H), 2.87–2.94 (m, 1H), 3.26 (t, $J = 6.8$ Hz, 2H); ^{13}C NMR (100 MHz, RT, $CDCl_3$): $\delta = 25.65$, 26.40, 28.56, 28.76, 29.03, 29.09, 32.18, 46.64, 51.16, 51.93; HRMS (FAB) calcd for $C_{10}H_{20}ON_3$ [M^++H] 198.1606, found 198.1611.

General procedure for 5% Pd/C(en)-THF catalyzed hydrogenation (Table 2): Unless otherwise specified, the reaction was carried out as follows. After two vacuum/H_2 cycles to remove air from the reaction tube, the stirred mixture of the substrate **1** (0.5 mmol) and 5% Pd/C(en) (10% of the weight of **1**) in THF (1 mL) was hydrogenated at ambient pressure (balloon) and temperature (ca. 20 °C) for the appropriate time (see Table 2). The reaction mixture was filtered by using a celite cake or a membrane filter (Millipore Dimex-13, 0.22 μm) and the filtrate was concentrated in vacuo. The quantitative conversion of **1** and the product ratio of **2**, **3**, and **4** were confirmed by ^{1}H NMR spectroscopy of the crude mixture in $CDCl_3$. The crude mixture was purified by flash silica gel column chromatography, if necessary.

1,2-Epoxyoctane (2a) and 1-octanol (4a): Because of the low boiling point of the products(**2a** and **4a**), the reaction was carried out using [D_8]THF as a solvent and the quantitative conversion of **1a** and the ratio of **2a** and **4a** (96:4) were confirmed by ^{1}H NMR spectroscopy of the reaction mixture. The products (**2a** and **4a**) were identical with the samples commercially purchased (TCI).

1,2-Epoxydecane (2b) and 1-decanol (4b): The products (**2b** and **4b**) were obtained from **1b** as a crude mixture (**2b**:**4b** = 97:3), which were identical with the samples commercially purchased (TCI). The product **2b** was isolated by flash silica gel column chromatography (hexane/Et_2O 5:1) in 85% yield as a colorless oil.

Glycidyl propyl ether (2c)[15] **and 1-propoxy-2-propanol (3c)**: Because of the low boiling point of the products, the reaction was carried out using [D_8]THF as a solvent, and the quantitative conversion of **1c** was confirmed by ^{1}H NMR spectroscopy of the reaction mixture. The product ratio of **2c** and **3c** (98:2) was determined on the basis of the integration ratio of the epoxide-ring protons of **2c** ($\delta = 2.63$, 2.81 and 3.15–3.19) and the methyl proton (3-position) of **3c** ($\delta = 1.22$, d. $J = 6.4$ Hz). The product **3c** was identical with the sample commercially purchased (Aldrich). **2c**: ^{1}H NMR (400 MHz, RT, [D_8]THF): $\delta = 1.09$ (t, $J = 7.3$ Hz, 3H), 1.73 (m, 2H), 2.63 (dd, $J = 2.4$ and 5.4 Hz, 1H), 2.81 (dd, $J = 3.9$ and 5.4 Hz, 1H), 3.15–3.19 (m, 1H), 3.46 (dd, $J = 5.8$ and 11.6 Hz, 1H), 3.52–3.63 (m, 2H), 3.78 (dd, $J = 3.2$ and 11.6 Hz, 1H); ^{13}C NMR (100 MHz, RT, $CDCl_3$): $\delta = 10.45$, 22.87, 44.32, 50.89, 71.40, 73.27.

Glycidyl hexyl ether (2d): The product **2d** was afforded as the sole product in 92% yield from **1d** as a colorless oil. ^{1}H NMR (400 MHz, RT, $CDCl_3$): $\delta = 0.89$ (t, $J = 6.8$ Hz, 3H), 1.29–1.36 (m, 4H), 1.55–1.60 (m,4H), 2.61 (dd, $J = 2.7$ and 4.8 Hz, 1H), 2.80 (t, $J = 4.8$ Hz, 1H), 3.13–3.17 (m, 1H), 3.38 (dd, $J = 5.9$ and 11.4 Hz, 1H), 3.43–3.54 (m, 2H), 3.70 (dd, $J = 3.2$ and 11.4 Hz, 1H); ^{13}C NMR (100 MHz, RT, $CDCl_3$): $\delta = 14.02$, 22.59, 25.74, 29.65, 31.66, 44.34, 50.90, 71.46, 71.73; elemental analysis calcd (%) for $C_9H_{18}O_2 \cdot 1/4\,H_2O$: C 66.42, H 11.46; found: C 66.30, H 11.23(volatile). The existence of water in this product was confirmed by ^{1}H NMR analysis.

Glycidyl isobutyrate (2e): The product **2e** was afforded as the sole product in 94% yield from **1e** as a colorless oil . ^{1}H NMR (270 MHz, RT, $CDCl_3$): $\delta = 1.19$ (d, $J = 6.8$ Hz, 6H), 2.61 (m, 1H), 2.65 (dd, $J = 2.7$ and 4.8 Hz, 1H), 2.84 (t, $J = 4.8$ Hz, 1H), 3.18–3.24 (m, 1H), 3.93 (dd, $J = 6.3$ and 12.4 Hz, 1H), 4.41 (dd, $J = 3.2$ and 12.4 Hz, 1H); ^{13}C NMR (100 MHz, RT, $CDCl_3$): $\delta = 18.83$, 33.77, 44.45, 49.31, 64.58, 176.69; elemental analysis calcd (%) for $C_7H_{12}O_3 \cdot 1/2\,H_2O$: C 54.89, H 8.55; found: C 55.07, H 8.12(volatile). The existence of water in this product was confirmed by ^{1}H NMR analysis.

1-Glycidoxy-3-phenylpropane (2f): The product **2f** was afforded as the sole product in 98% yield from **1f** as a colorless oil. ^{1}H NMR (400 MHz, RT, $CDCl_3$): $\delta = 1.88–1.95$ (m, 2H), 2.61 (dd, $J = 2.7$ and 5.1 Hz, 1H), 2.70 (t, $J = 7.8$ Hz, 2H), 2.80 (dd, $J = 4.2$ and 5.1 Hz, 1H), 3.13–3.17 (m, 1H), 3.38 (dd, $J = 5.9$ and 11.4 Hz, 1H), 3.45–3.56 (m, 2H), 3.71 (dd, $J = 3.2$ and 11.4 Hz, 1H), 7.16–7.20 (m, 3H), 7.25–7.30 (m, 2H); ^{13}C NMR (100 MHz, RT, $CDCl_3$): $\delta = 31.21$, 32.21, 44.28, 50.83, 70.64, 71.48, 125.76, 128.30, 128.43, 141.83; MS (FAB: NBA): *m/z* (%): 193 (10) [M^++H]; elemental analysis calcd for $C_{12}H_{16}O_2 \cdot 1/12\,H_2O$: C 74.39, H 8.41; found: C 74.38, H 8.45. The existence of water in this product was confirmed by ^{1}H NMR analysis.

Cyclohexylmethyl glycidyl ether (2g): The product **2g** was afforded as the sole product in 87% yield from **1g** as a colorless oil. ^{1}H NMR (400 MHz,

RT, $CDCl_3$): $\delta = 0.89-0.98$ (m, 2H), 1.11–1.29 (m, 2H), 1.55–1.63 (m, 1H), 1.66–1.77 (m, 6H), 2.60 (dd, $J = 2.9$ and 4.6 Hz, 1H), 2.79 (t, $J =$ 4.6 Hz, 1H), 3.12–3.16 (m, 1H), 3.25–3.33 (m, 2H), 3.38 (dd, $J = 5.6$ and 11.5 Hz, 1H), 3.69 (dd, $J = 3.1$ and 11.5 Hz, 1H); ^{13}C NMR (100 MHz, RT, $CDCl_3$): $\delta = 25.81$, 26.58, 29.98, 38.05, 44.26, 50.92, 71.59, 77.46; MS (FAB: NBA) *m/z* (%) 171 (80) $[M^+ + H]$; elemental analysis calcd (%) for $C_{10}H_{18}O_2 \cdot 1/4\,H_2O$: C 68.73, H 10.67; found: C 68.60, H 10.40. The existence of water in this product was confirmed by ^{1}H NMR analysis.

1,2-Epoxycyclododecane (2h): The products (**2h** and **3h** (= **4h**)) were afforded from **1h** as a crude mixture (**2h**:**3h** = 97:3), which were identical with the samples commercially purchased (TCI). The product **2h** was isolated by flash silica gel column chromatography (hexane/ether 5:1) in 93% yield as a colorless oil.

2,3-Epoxy-3,7-dimethyl-1-octanol (2i): The product **2i** was afforded as the sole product in 86% yield from **1i** as a colorless oil. ^{1}H NMR (270 MHz, RT, $CDCl_3$): $\delta = 0.86$ and 0.89 (each s, 3H), 1.16–1.69 (m, 7H), 1.29 (s, 3H) 2.97 (dd, $J = 4.4$ and 6.3 Hz, 1H), 3.69 (dd, $J = 6.3$ and 12.3 Hz, 1H), 3.85 (dd, $J = 4.4$ and 12.3 Hz, 1H); HRMS (FAB) calcd for $C_{10}H_{21}O_2$ $[M^+ + H]$: 173.1541, found: 173.1555.

1,2-Epoxypentyl 4-aminobenzoate (2j): The product **2j** was afforded as the sole product in 100% yield from **1j** as a pale yellow oil. ^{1}H NMR (400 MHz, RT, $CDCl_3$): $\delta = 1.66-1.74$ (m, 2H), 1.87–1.94 (m, 2H), 2.51 (dd, $J = 2.9$ and 4.5 Hz, 1H), 2.77 (t, $J = 4.5$ Hz, 1H), 2.96–2.99 (m, 1H), 4.05 (brs, 2H), 4.30–4.33 (m, 2H), 6.64 and 7.85 (each d, $J = 8.6$ Hz, 2H); ^{13}C NMR (100 MHz, RT, $CDCl_3$): $\delta = 25.36$, 29.20, 47.04, 51.80, 63.76, 113.76, 119.79, 131.57, 150.85, 166.58; HRMS (FAB) calcd. for $C_{12}H_{16}O_3N$ $[M^+ + H]$: 222.1130, found: 222.1120.

Glycidyl 4-aminobenzoate (2k) and 2-hydroxypropyl 4-aminobenzoate (3k): The products (**2k** and **3k**) were otained from **1k** as a crude mixture (a pale yellow oily solid, 99% yield as a mixture), since the isolation of **2k** from the mixture by column chromatography was difficult because of the lability of the components of the mixture on silica gel. The quantitative conversion of **1k** was confirmed by ^{1}H NMR spectroscopy of the crude mixture. The product ratio of **2k** and **3k** (96:4) was determined on the basis of the integration ratio of the epoxide-ring protons of **2k** ($\delta = 2.72$, 2.88, and 3.31–3.33) and the methyl proton of **3k** ($\delta = 1.27$, d, $J = 6.4$ Hz). The mixture was triturated with diethyl ether (5 mL) to give a small amount of the pure **2k** as a pale yellow powder. M. p. 83–84 °C; ^{1}H NMR (400 MHz, RT, $CDCl_3$): $\delta = 2.72$ (dd, $J = 2.4$ and 4.8 Hz, 1H), 2.88 (t, $J = 4.8$ Hz, 1H), 3.31–3.33 (m, 1H), 4.08 (brs, 2H), 4.12 (dd, $J = 6.4$ and 12.3 Hz, 1H), 4.31 (dd, $J = 3.2$ and 12.3 Hz, 1H), 6.64 and 7.88 (each d, $J = 8.8$ Hz, 2H); ^{13}C NMR (100 MHz, RT, $CDCl_3$): $\delta = 44.72$, 49.70, 64.78, 113.76, 119.12, 131.83, 151.09, 166.25; MS (FAB: NBA): *m/z* 194 (%): (40) $[M^+ + H]$; elemental analysis calcd (%) for $C_{10}H_{11}O_3N$: C 62.17, H 5.74, N 7.25; found: C 61.89, H 5.74, N, 7.20.

3-Aminobenzyl glycidyl ether (2l) and 3-aminobenzyl 2-hydroxypropyl ether (3l): The products (**2l** and **3l**) were obtained from **1l** as a crude mixture (a pale yellow oil, 100% yield as a mixture), since the isolation of **2l** from the mixture by column chromatography was difficult because of the lability of the components of the mixture on silica gel. The quantitative conversion of **1l** was confirmed by ^{1}H NMR spectroscopy of the crude mixture. The product ratio of **2l** and **3l** (93:7) was determined on the basis of the integration ratio of the epoxide-ring protons of **2l** ($\delta = 2.62$, 2.80, and 3.16–3.20) and the methyl and methine protons of **3l** ($\delta = 1.13$, d, $J =$ 6.4 Hz and $\delta = 3.96-4.03$, m, respectively). ^{1}H NMR (400 MHz, RT, $CDCl_3$): $\delta = 2.62$ (dd, $J = 2.7$ and 4.8 Hz, 1H), 2.80 (t, $J = 4.8$ Hz, 1H), 3.16–3.20 (m, 1H), 3.43 (dd, $J = 5.9$ and 11.5 Hz, 1H), 3.67 (brs, 2H), 3.75 (dd, $J = 2.9$ and 11.5 Hz, 1H), 4.47 and 4.53 (each d, $J = 12.0$ Hz, 1H), 6.61 (d, $J = 7.8$ Hz, 1H), 6.70 (s, 1H), 6.72 (d, $J = 7.8$ Hz, 1H), 7.12 (t, $J = 7.8$ Hz, 1H); ^{13}C NMR (100 MHz, RT, $CDCl_3$): $\delta = 44.32$, 50.89, 70.73, 73.31, 114.29, 114.51, 117.95, 129.36, 139.14, 146.59; HRMS (FAB) calcd. for $C_{10}H_{14}O_2N$ $[M^+ + H]$: 180.1025, found: 180.1018.

4-Aminophenyl glycidyl ether (2m) and 4-aminophenyl 2-hydroxypropyl ether (3m): The products (**2m** and **3m**) were afforded from **1m** as a crude mixture (a pale yellow oil, 94% yield as a mixture), since the isolation of **2m** from the mixture by column chromatography was difficult because of the lability of the components of the mixture on silica gel. The quantitative conversion of **1m** was confirmed by ^{1}H NMR spectroscopy of the crude mixture. The product ratio of **2m** and **3m** (95:5) was determined on the basis of the integration ratio of the epoxide-ring protons of **2m** ($\delta = 2.72$, 2.87, and 3.29–3.33) and the methyl proton of **3m** ($\delta = 1.25$, d, $J = 6.4$ Hz). ^{1}H NMR (400 MHz, RT, $CDCl_3$): $\delta = 2.72$ (dd, $J = 2.4$ and 4.5 Hz, 1H), 2.87 (t, $J = 4.5$ Hz, 1H), 3.29–3.33 (m, 1H), 3.40 (brs, 2H), 3.88 (dd, $J = 5.9$ and 11.1 Hz, 1H), 4.12 (dd, $J = 3.1$ and 11.1 Hz, 1H), 6.62 and 6.75 (each d, $J =$ 8.8 Hz, 2H); ^{13}C NMR (100 MHz, RT, $CDCl_3$): $\delta = 44.67$, 50.25, 69.58, 115.92, 116.25, 140.53, 151.60; HRMS (FAB) calcd for $C_9H_{12}O_2N$ $[M^+ + H]$: 166.0868, found: 166.0874.

1-Amino-9,10-epoxydecane (2n): The product **2n** was obtained in 97% yield from **1n** as a pale yellow oil. ^{1}H NMR (400 MHz, RT, $CDCl_3$): $\delta =$ 1.23–1.58 (m, 14H), 2.46 (dd, $J = 2.7$ and 4.8 Hz, 1H), 2.68 (t, $J = 7.1$ Hz, 2H), 2.74 (t, $J = 4.8$ Hz, 1H), 2.88–2.95 (m, 1H); ^{13}C NMR (100 MHz, RT, $CDCl_3$): $\delta = 25.90$, 26.80, 29.32, 29.40, 29.45, 32.43, 33.64, 42.13, 47.04, 52.33; HRMS (FAB) calcd. for $C_{10}H_{22}ON$ $[M^+ + H]$: 172.1701, found: 172.1705.

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[9] As shown in Table 1, 1,2-epoxydecane (**2b**) was hydrogenated by using 5% Pd/C(en) in MeOH to afford 2-decanol (**3b**) as a sole product (19%) together with unchanged **2b** (81%), whereas use of 5% Pd/C (Aldrich) resulted in the formation of a mixture of 2-decanol (**3b**) and 1-decanol (**4b**) (82:18). These findings resulted in the development of a new regioselective hydrogenolysis method for terminal epoxides to secondary alcohols. See: H. Sajiki, K. Hattori, K. Hirota, *Chem. Commun.* **1999**, 1041–1042.

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[13] Direct evidence for the continuous isomerization is provided by ^{1}H NMR spectroscopy ($CDCl_3$) during the hydrogenation of **1a** in the presence of 5% Pd/C(en) in THF (see, Supporting Information).

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