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Pd/C(en)-Catalyzed Chemoselective Hydrogenation with Retention of the *N*-Cbz Protective Group and its Scope and Limitations

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Abstract—A chemoselective method for the hydrogenation of acetylene, olefin, azide, nitro and benzyl ester functionalities with retention of the aliphatic *N*-Cbz group was established. The chemoselectivity was accomplished by using a combination of 5% Pd/C–ethylenediamine [5% Pd/C(en)] and THF (or 1,4-dioxane) as a solvent, and the scope and limitations of this methodology were investigated. These results reinforce the utility of *N*-Cbz protective groups in synthetic chemistry, especially in peptide synthesis.

Protective groups play a central role in modern organic synthesis, and the selective deprotection of one protective group in the presence of others is a key to the success or failure of the synthesis of target compounds. An *N*-benzyloxycarbonyl (*N*-Cbz) group[1,2] is one of the most common amino protective groups used for the syntheses of amino acids, alkaloids, peptides and so on.[3] Although the *N*-Cbz protective group is relatively resistant to a variety of organic reaction conditions, they are easily removed by Pd-catalyzed hydrogenolysis to provide parent amines. Consequently, it is extremely difficult to retain the *N*-Cbz group intact during hydrogenation steps. Ghosh et al. have recently reported a chemoselective hydrogenation of alkenes using Lindlar catalyst ($PbO–Pd/CaCO_3$).[4] In their report, they mentioned that the hydrogenolysis of the *N*-Cbz protective group proceeded smoothly even using the highly-poisoned Lindlar catalyst. Among the very few examples of chemoselective hydrogenation that distinguish an *N*-Cbz group, their functionality is intrinsically specific and applicable to very limited substrates. For example, Zappia et al. have reported selective catalytic hydrogenation of γ-amino α, β-unsaturated esters to the corresponding γ-amino saturated esters in the presence of hydrogenable protective groups such as *O*-benzyl ether, *N*-Cbz and benzyl ester using 3% Pd/C in EtOAc.[5] It was mentioned that the stability of the *N*-Cbz group under their conditions was time-dependent, and the expected selectivity was not obtained. Furthermore, Emoto et al. have reported the chemoselective hydrogenation of an azide group using Raney Ni, which must be added into the reaction mixture in portions with careful monitoring.[6] If a general method for the retention of the *N*-Cbz protective group under hydrogenation can be developed, it would increase the utility of the *N*-Cbz protective group in organic synthesis.

We have recently demonstrated the addition of a catalytic amount of nitrogen containing a base, such as ammonia, pyridine, ammonium acetate and so on, to the reaction system selectively suppressed the Pd/C-catalyzed hydrogenolysis of the *O*-benzyl protective group of alcohols in the coexistence of other reducible functionalities (e.g., olefin, *N*-Cbz, nitro, benzyl ester or azide).[7] On the basis of these results, we succeeded in the development of a novel catalyst, a Pd/C-ethylanediamine (en) complex [Pd/C(en)], that catalyzed chemoselective hydrogenation of a variety of reducible functionalities with retention of the *O*-benzyl protective group of alcohols and phenols,[8] benzyl alcohols[9] and epoxies.[10] While we described, in part, the *N*-Cbz group of some aliphatic amines is inert toward the Pd/C(en) catalyzed hydrogenation in our earlier paper,[8] we have further made quite significant development of this hydrogenation method. Herein we provide a more detailed discussion of the earlier results as well as the scope and limitations of the chemoselective hydrogenation without deprotection of the *N*-Cbz protective groups.

Results and Discussion

To establish the optimal reaction conditions, *N*-(benzyloxycarbonyl)propargylamine (**1a**) was chosen as a model substrate of the chemoselective hydrogenation, and the solvent effect toward the hydrogenolysis of the *N*-Cbz group using 5% Pd/C(en) catalyst was studied (Table 1). Nevertheless, smooth hydrogenation of the acetylene and also hydrogenolysis of the *N*-Cbz group occurred simultaneously in MeOH or CD_3OD to form propylamine (**3a**)

Keywords: chemoselective hydrogenation; *N*-Cbz protective group; Pd/C(en) catalyst.

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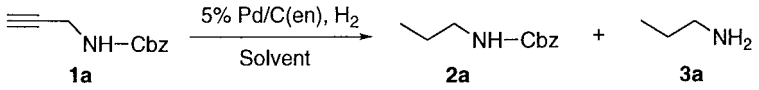
Table 1. Solvent effect toward the hydrogenation of alkynyl group in the presence of *N*-Cbz protective group



1a **2a** **3a**

Entry	Solvent	Time (h)	Yield of **2a** (%)
1	MeOH	0.5	0
2	CD_3OD	1	0[a]
3	THF	2	76
4	1,4-dioxane[b]	4	83

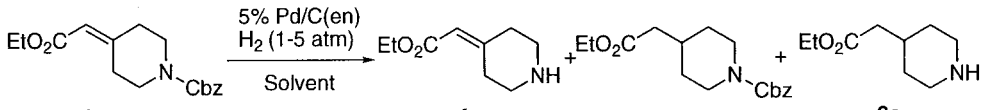
[a] Because of the low boiling point of **3a**, the quantitative formation of **3a** was observed by direct ^{1}H NMR of the reaction mixture in CD_3OD.
[b] When 10% Pd/C was used as a catalyst, **2a** was obtained in 56% yield.

(entries 1 and 2). We recently reported a chemoselective method for the hydrogenation of olefin, nitro and azide functions with retention of an epoxide. The chemoselectivity was accomplished by using a combination of 5% Pd/C(en) catalyst and THF.[10] THF is extremely important as a solvent to achieve dramatic suppressive effect toward the hydrogenolysis of the epoxides. Similarly, the use of THF as a solvent in the hydrogenation of **1a** resulted in chemoselective hydrogenation of the acetylene function to give *N*-(benzyloxycarbonyl)propylamine (**2a**) in 76% isolated yield (entry 3). Moreover, the use of 1,4-dioxane as a solvent gave a more effective result to yield **2a** in 83% yield (entry 4). Probably, a large excess of THF or 1,4-dioxane oxygen atoms would act as a quite gentle catalyst poison against the Pd/C(en) catalyst, resulting in improved chemoselectivity.

Ghosh et al. have reported that chemoselective hydrogenation of the *tri*-substituted olefin function of *N*-benzyloxycarbonyl-4-(ethoxycarbonylmethylidene)piperidine (**1c**) with retention of the *N*-Cbz protective group even using highly poisoned Lindlar catalyst (H_2, 1 atm, MeOH, 45 min) was unsuccessful.[4] Accordingly, these results encouraged us to examine the chemoselective hydrogenation of **1c** as one more substrate (Table 2). In analogy with the case of **1a**, the preferential hydrogenolysis of the *N*-Cbz group of **1c** occurred in MeOH under 1 atm of hydrogen to give **4** and **3c** as a mixture in the ratio 64:36 without formation of the expected product (**2c**) (entry 1). In order to raise the chemoselectivity, we examined the use of THF or 1,4-dioxane as a solvent at ordinary pressure. Unexpectedly, our efforts met with little success. The hydrogenation of the tri-substituted olefin function and the hydrogenolysis of the *N*-Cbz group of **1c** occurred simultaneously to form a mixture containing the deprotected product (**3c**) in 16 or 18% yield, respectively (entries 2 or 3). The problem seems to arise from the slow hydrogenation of the sterically-hindered *tri*-substituted olefin. In order to overcome the problem, the hydrogen pressure was elevated to 5 atm. As a result, the chemoselective hydrogenation of the tri-substituted olefin without hydrogenolysis of the *N*-Cbz group was achieved in 1,4-dioxane to form **2c** in 94% yield (entry 4). However, when the hydrogenation was allowed to continue for 9.5 h, slight but significant hydrogenolysis of the *N*-Cbz group was observed (11%, entry 5).

Next, we decided to explore the generality of the chemoselective hydrogenation using various aliphatic *N*-Cbz compounds possessing other reducible functionalities within the molecule. The chemoselective hydrogenation of acetylene (**1a**), olefin (**1b**–**f**) or azide (**1g**) was achieved by using THF or 1,4-dioxane as a solvent, and the desired products (**2a**–**g**) were obtained in good to excellent yields (Table 3, entries 1–7). The hydrogenation of **1h** possessing a nitro group gave lower yield (60%) of the desired product (**2h**) (entry 8) because of the formation of small amounts of 4-aminophenetylamine and 4,4′-azobis-(*N*-benzyloxycarbonyl)phenetylamine as by-products (see Experimental).

Table 2. Solvent and hydrogen pressure effects toward the hydrogenation of alkenyl group in the presence of *N*-Cbz protective group

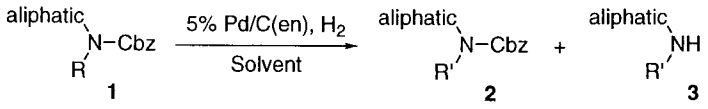


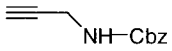
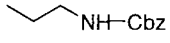
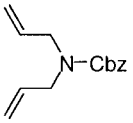
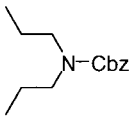
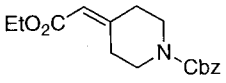
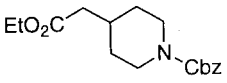
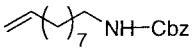
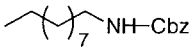
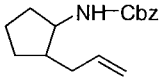
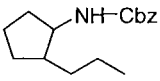
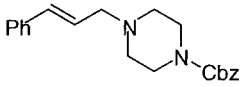
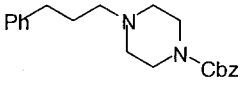
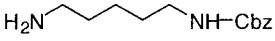
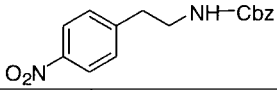
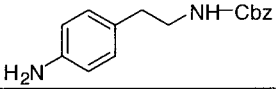
1c **4** **2c** **3c**

Entry	Solvent	H_2 pressure (atm)	Time (h)	**1c**	**4**	**2c**	**3c**[a]
1	MeOH	1	0.75	0	64	0	36
2	THF	1	1	32	32	20	16
3	1,4-dioxane	1	4.5	6	0	76	18
4	1,4-dioxane	5	3	6	0	94	0
5	1,4-dioxane	5	9.5	3	0	86	11

[a] The yields of **1c**, **4**, **2c** and **3c** were determined by ^{1}H NMR.

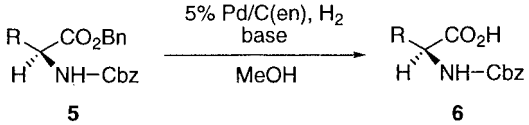
Table 3. Chemoselective hydrogenation of aliphatic *N*-Cbz compounds using a 5% Pd/C(en) catalyst[a]



Entry		Substrate (**1**)	Solvent	Time (h)		Product (**2**)	Yield (%)[b]
1	**1a**		1,4-dioxane	4	**2a**		83
2[c]	**1b**		THF	17	**2b**		92
3	**1c**		1,4-dioxane	3[d]	**2c**		94[e]
4	**1d**		THF	18[d]	**2d**		99
5	**1e**		THF	22[d]	**2e**		96
6	**1f**		THF	24[d]	**2f**		93[e]
7	**1g**		THF	2	**2g**		99
8	**1h**		THF	8	**2h**		60[f]

[a] Unless otherwise specified, the reaction was carried out using 0.2 mmol of the substrate (**1**) with 5%Pd/C(en) (10% of the weight of the substrate) in 1,4-dioxane or THF (1 mL) under hydrogen atmosphere (1–5 atm) at room temperature for the given reaction time.
[b] Isolated yield.
[c] Only this result on Table 3 was described in the earlier paper.[8]
[d] The reaction was performed under 5 atm of hydrogen.
[e] Calculated by ^{1}H NMR.
[f] Small amounts of 4-aminophenetylamine and 4,4′-azobis-(*N*-benzyloxycarbonyl)phenetylamine were generated as by-products (see Experimental).

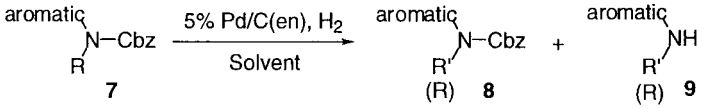
Table 4. Chemoselective hydrogenation of *N*-Cbz and benzyl ester protected amino acid derivatives (the reaction was carried out using 0.2 mmol of the substrate (**5**) with 5% Pd/C(en) (10% of the weight of the substrate) and base (1.4 equiv. vs substrate) in MeOH (1 mL) under hydrogen atmosphere (1 atm) at room temperature for the given reaction time).

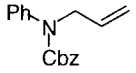
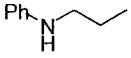
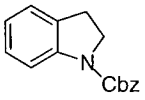
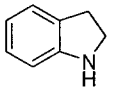
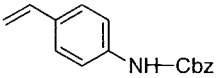
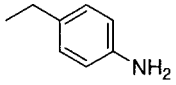
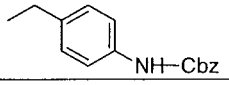


Entry		Substrate (**5**)	Base	Time (h)		Product (**6**)	Yield (%)[a]
1	**5a**	Cbz–Phe–OBn	none	2	**6a**	Cbz–Phe–OH	30[b]
2			Hunig's base	14		Cbz–Phe–OMe	100
3			DMAP	2	**6a**	Cbz–Phe–OH	78
4			Dabco®	2			86
5	**5b**	Cbz–Pro–OBn	Dabco®	6	**6b**	Cbz–Pro–OH	76
6	**5c**	Cbz–Tyr(Bn)–OBn	Dabco®	24[c]	**6c**	Cbz–Tyr(Bn)–OH	72
7	**5d**	Cbz–Trp–OBn	Dabco®	18	**6d**	Cbz–Trp–OH	78

[a] Isolated yield.
[b] A significant amount of the deprotected product, phenylalanine, was detected by TLC analysis visualized using ninhydrin reagent with subsequent heating.
[c] Reaction was performed with MeOH and EtOAc (1:1) as solvents for the solubility of the substrate.

Table 5. Hydrogenation of aromatic *N*-Cbz compounds (the reaction was carried out using 0.2 mmol of the substrate (**7a–c**) with 5%Pd/C(en) (10% of the weight of the substrate) in 1,4-dioxane or THF (1 mL) under hydrogen atmosphere (1 atm) at room temperature for the given reaction time) (limitation of this methodology)



Entry	Substrate (7)	Solvent	Time (h)	Product	Yield (%)
1	**7a** 	1,4-dioxane	5	**9a** 	90
2		THF	4		96
3	**7b** 	THF	1.5	**9b** 	quant.
4	**7c** 	THF	16	**9c** 	89
5		THF	2	**8c** 	95

The present procedure can be applied to the chemoselective hydrogenation of *N*-Cbz protected amino acid benzyl ester derivatives (Cbz-AA-OBn, **5a–d**, Table 4). Benzyl ester is one of the quite common protective groups of carboxylic acid, and is frequently used for peptide syntheses.[3] It is well known that benzyl esters are easily deprotected to carboxylic acid by mild catalytic hydrogenolysis.[12,13] We recently reported the presence of acids such as a carboxylic acid function decreased the chemoselectivity of the Pd/C(en) catalyzed hydrogenation.[8] The problem has been temporarily solved by the addition of DMAP to quench the carboxylic acid moiety. During the course of our further study, we found significant difference in the chemoselective effect on the hydrogenetic and undesirable deprotection of the *N*-Cbz protective group depending upon the amines employed as an additive. After screening some bases and solvents, we found that 1,4-diazabicyclo[2.2.2]octane (Dabco®) in MeOH was the most effective for the chemoselective hydrogenation (Table 4). The use of DMAP as a base resulted in a rather lower yield (compare entries 3 and 4). In the presence of Dabco® (1.4 equiv. vs. substrate), the chemoselective hydrogenation of benzyl esters of **5a–d** proceeded selectively, and *N*-Cbz protected amino acids (**6a–d**) were obtained in good yields. It is noteworthy that the reaction also tolerates the *O*-benzyl ether of **5c**. When THF or 1,4-dioxane was used as a solvent in the presence of Dabco®, the hydrogenolysis of the benzyl ester was incomplete. When Hunig's base was used as a base, ester exchange unexpectedly occurred, and *N*-Cbz-phenylalanine methyl ester was obtained in 100% isolated yield (entry 2). This ester exchange reaction also proceeded easily in the absence of the catalyst and hydrogen. Therefore, it would result from the formation of methoxide anione in the presence of a strong base (basity: Hunig's base> DMAP>Dabco®).[14]

Furthermore, we studied the chemoselective hydrogenation of aromatic *N*-Cbz compounds (**7a–c**) using 5% Pd/C(en) as a catalyst. Hydrogenolysis of the *N*-Cbz groups of **7a** and **7b** smoothly occurred even in 1,4-dioxane or THF to give the corresponding deprotected amines in the quantitative yields (Table 5, entries 1 and 2). As an exceptional case, the chemoselective hydrogenation of the olefin moiety of *N*-benzyloxycarbonyl-4-vinylaniline (**7c**) occurred in 2 h to give **8c** in 95% isolated yield (entry 5). However, when the reaction was continued for longer time (16 h), complete hydrogenolysis of the *N*-Cbz group occurred to give **9c** as the sole product in 89% isolated yield (entry 4). These results indicate that it is extremely difficult to suppress the hydrogenolysis of the aromatic *N*-Cbz group even under the 5% Pd/C(en)-THF (1,4-dioxane) hydrogenation system. We concluded these results to be the limitation of this methodology.

Conclusion

We have described a chemoselective hydrogenation method of acetylene, olefin, azide, nitro and benzyl ester functionalities distinguishing the aliphatic *N*-Cbz group, using a 5% Pd/C(en) catalyst, depending upon the solvent. The chemoselective hydrogenation with retention of the aromatic *N*-Cbz group could not be accomplished. These results made clear the scope and limitations of the chemoselective hydrogenation without the deprotection of the *N*-Cbz protective group. Moreover, this method would increase the utility of the *N*-Cbz protective groups in organic synthesis including liquid and solid-phase peptide synthesis.

Experimental

Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification.

THF was distilled from sodium benzophenone ketyl immediately prior to use. Column chromatography was carried out under air by flash method with silica gel (230–400 mesh, Merck).[11] All reactions were monitored by thin-layer chromatography (TLC) performed on glass-backed silica gel 60 F_{254}, 0.2 mm plates (Merck), and compounds were visualized under UV light (254 nm), *p*-anisaldehyde solution or ninhydrin reagent with subsequent heating. Medium-pressure (5 atm) hydrogenation was performed using Ishii hydrogenator CHA-E. Melting points were determined on a Yanagimoto melting point apparatus and were uncorrected. ^{1}H NMR spectra were recorded on a JEOL GX-270 (270 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 100 MHz. Low- and high-resolution mass spectra were taken on a JMS-SX 102A machine. Microanalyses were accomplished at the Microanalytical Laboratory of Gifu Pharmaceutical University, Japan. *N*-(Benzyloxycarbonyl)-L-phenylalanine benzyl ester (**5a**) and *N*-(benzyloxycarbonyl)-L-tryptophan benzyl ester (**5d**) were purchased from Watanabe Chemical Industries, Japan.

***N*-(Benzyloxycarbonyl)propargylamine (1a).**[8] A solution of propargylamine (1.10 g, 20.00 mmol) and *N*-(benzyloxycarbonyloxy)succinimide (5.48 g, 22.00 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 7 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 (30 mL), saturated aqueous $NaHCO_3$ solution (30 mL), water (30 mL) and brine (30 mL), then dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated to afford **1a** (2.90 g, 77%) as a white needle. Mp 39°C; ^{1}H NMR (400 MHz): δ 2.24 (t, J=2.4 Hz, 1H), 3.98–4.02 (m, 2H), 4.92 (brs, 1H), 5.13 (s, 2H), 7.32–7.36 (m, 5H); ^{13}C NMR: δ 30.8, 67.1, 71.6, 79.6, 128.1, 128.2, 128.5, 136.1, 155.8; MS (EI) *m/z* 189 (M^+), 128 (15), 108 (77), 91 (100); Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.81; H, 5.96; N, 7.40.

***N*-(Benzyloxycarbonyl)diallylamine (1b).**[8] Preparation of **1b** was performed analogously to the procedure described for **1a** with diallylamine (1.94 g, 20.00 mmol). Yield: 55% (2.52 g, as a colorless oil); ^{1}H NMR (400 MHz): δ 3.87–3.90 and 5.05–5.19 (each m, 4H), 5.15 (s, 2H), 5.70–5.83 (m, 2H), 7.30–7.36 (m, 5H); ^{13}C NMR: δ 48.2, 48.8, 66.8, 116.4, 116.8, 127.5, 127.6, 128.1, 133.2, 136.6, 155.7; HRMS (FAB) Calcd for $C_{14}H_{18}NO_2$ (M^++H) 232.1337. Found 232.1346.

1-Benzyloxycarbonyl-4-(ethoxycarbonylmethylidene)piperidine (1c). A solution of 4-hydroxypiperidine (1.00 g, 10.00 mmol) and *N*-(benzyloxycarbonyloxy)succinimide (2.99 g, 12.00 mmol) in dry THF (10 mL) was stirred at room temperature for 20 h. The solvent was evaporated and the residue was partitioned between chloroform (50 mL) and water (50 mL). The organic layer was washed with water (30 mL), saturated aqueous $NaHCO_3$ solution (30 mL), water (30 mL) and brine (30 mL), then dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated to afford 1-benzyloxycarbonyl-4-hydroxypiperidine (235 mg, crude), which was used in the next reaction without further purification. ^{1}H NMR (400 MHz): δ 1.50–1.64 (m, 4H), 1.83–14.95 (m, 2H), 3.11–3.18 (m, 2H), 3.86–3.96 (m, 2H), 3.95 (brs, 1H), 5.13 (s, 2H), 7.30–7.40 (m, 5H); MS (EI) *m/z* 235 (M^+, 15%), 91 (100).

Commercial grade PCC (4.3 g, 20 mmol) was ground with silica gel (1 wt equiv.) in a mortar. To a suspension of the resulting free-running light orange solid of PCC in CH_2Cl_2 (25 mL) was added 1-benzyloxycarbonyl-4-hydroxypiperidine (235 mg, 10 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at room temperature for 4 h. The reaction mixture was filtered by using a celite cake, washed with Et_2O (150 mL) and the filtrate was concentrated in vacuo. Flash column chromatography (chloroform) yielded 1-benzyloxycarbonyl-4-piperidinone (1.53 g, 66%) as a colorless oil. ^{1}H NMR (400 MHz): δ 2.41–2.46 (m, 4H), 3.80 (t, J=6.1 Hz, 4H), 5.18 (s, 2H), 7.33–7.38 (m, 5H); ^{13}C NMR: δ 41.01, 43.09, 67.60, 128.01, 128.23, 128.55, 136.31, 155.09, 207.12; MS (EI) *m/z* 233 (M^+, 20%), 91 (100).

To a solution of (ethoxycarbonylmethyl)triphenylphosphonium bromide (4.29 g, 10 mmol) in water (100 mL) was added sodium hydroxide (1.0 g, 25 mmol) at 0°C. Filtration of the crystalline precipitate afforded (ethoxycarbonylmethylene)triphenylphosphorane. A solution of (ethoxycarbonylmethylene)triphenylphosphorane (2.00 g, 5.7 mmol) and 1-benzyloxycarbonyl-4-piperidinone (1.40 g, 6.0 mmol) in THF (15 mL) was heated under reflux for 43 h. The solvent was removed in vacuo, and flash column chromatography (hexane/ether 50:1) yielded **1c** (1.34 g, 74%) as a white solid. Mp 40°C; ^{1}H NMR (400 MHz): δ 1.28 (t, J=7.1 Hz, 3H), 2.28–2.35 (m, 2H), 2.93–3.02 (m, 2H), 3.53–3.65 (m, 4H), 4.15 (q, J=7.1 Hz, 2H), 5.15 (s, 2H), 5.72 (s, 1H), 7.33–7.37 (m, 5H); ^{13}C NMR: δ 14.24, 29.38, 44.19, 44.94, 59.79, 67.23, 115.57, 127.90, 128.04, 128.50, 136.64, 157.12, 166.23; MS (EI) *m/z* 303 (M^+, 29%), 258 (45), 230 (36), 91 (100); HRMS (EI) Calcd for $C_{17}H_{21}NO_4$ (M^+) 303.1471. Found 303.1461.

***N*-Benzyloxycarbonyl-9-decene-1-amine (1d).** To a solution of triphenylphosphine (2.62 g, 10.00 mmol), phthalimide (1.47 g, 10.00 mmol) and 9-decen-1-ol (1.56 g, 10.00 mmol) in THF (30 mL) was slowly (over 15 min) added diethyl azodicarboxylate (40% in toluene, 4.5 mL, 10 mmol) with stirring. The mixture was stirred at room temperature for 48 h and the solvent was evaporated to dryness. To a suspension of the residue in methanol (30 mL) was added hydrazine (640 mg, 20.00 mmol). The mixture was heated under reflux for 4 h and the solution was cooled to room temperature. A mixture of hydrochloric acid (2 mL) and methanol (10 mL) was added, and the mixture was refluxed overnight. The resulting reaction mixture was filtered to remove the precipitate, and the solvent was evaporated under reduced pressure. The residue was washed with water (20 mL×2) and hydrochloric acid (2 mL). The liquids were combined and washed with chloroform (25 mL×3) and ether (25 mL×2). The aqueous layer was cooled in an ice bath. A saturated aqueous sodium hydroxide solution was used to make the solution basic to approximately pH 14. The basic solution was extracted with ether (25 mL×10) and the combined organic layers were dried

over anhydrous magnesium sulfate. After filtration, the solvent was evaporated to afford 9-decenylamine (371 mg, 24%), which was used in the next reaction without further purification. ^{1}H NMR (400 MHz): δ 1.29–1.47 (m, 12H), 2.04 (q, J=7.2 Hz, 2H), 2.68 (q, J=7.1 Hz, 2H), 4.92–4.97 (m, 2H), 5.01–5.86 (m, 1H); MS (EI) m/z 155 (M^+, 30%), 114 (55), 55 (100), 45 (78).

Preparation of **1d** was performed analogously to the procedure described for **1a** with 9-decenylamine (371 mg, 2.4 mmol). Yield: 82% (567 mg, as a colorless oil); ^{1}H NMR (400 MHz): δ 1.28–1.57 (m, 12H), 2.03 (q, J=7.0 Hz, 2H), 3.18 (q, J=6.4 Hz, 2H), 4.72 (brs, 1H), 4.92–5.01 (m, 2H), 5.09 (s, 2H), 5.76–5.86 (m, 1H), 7.31–7.36 (m, 5H); ^{13}C NMR: δ 26.56, 28.72, 28.87, 29.07, 29.21, 29.78, 33.62, 40.94, 66.32, 114.03, 127.84, 127.90, 128.30, 136.60, 138.92, 156.28; HRMS (EI) Calcd for $C_{18}H_{27}NO_2$ (M^+) 289.2042. Found 289.2045.

***N*-Benzyloxycarbonyl-2-(2-propenyl)cyclopentylamine (1e).** Preparation of **1e** was performed analogously to the procedure described for **1a** with 2-(2-propenyl)cyclopentylamine[15] (693 mg, 5.50 mmol). Yield: 87% (1.25 g, as a pale yellow oil); ^{1}H NMR (400 MHz): δ 1.24–1.31 (m, 1H), 1.49–2.00 (m, 7H), 2.17–2.22 (m, 1H), 4.08–4.16 (m, 1H), 4.66 (brs, 1H), 4.95–5.02 (m, 2H), 5.09 (s, 2H), 5.70–5.83 (m, 1H), 7.30–7.37 (m, 5H); ^{13}C NMR: δ 21.35, 28.98, 32.32, 34.08, 42.42, 54.60, 66.61, 115.41, 128.08, 128.50, 136.58, 137.50, 156.58; HRMS (EI) Calcd for $C_{16}H_{21}NO_2$ (M^+) 259.1572. Found 259.1560.

1-Benzyloxycarbonyl-*trans*-4-cinnamylpiperazine (1f).[8] Preparation of **1f** was performed analogously to the procedure described for **1a** with *trans*-1-cinnamylpiperazine (3.00 g, 14.80 mmol). Yield: 85% (4.24 g, as a pale yellow oil); ^{1}H NMR (400 MHz): δ 2.23–2.50 (m, 4H), 3.16 (d, J=6.6 Hz, 2H), 3.54 (t, J=4.9 Hz, 4H), 5.13 (s, 2H), 6.24 (dt, J=6.6 and 15.9 Hz, 1H), 6.52 (d, J=15.9 Hz, 1H), 7.21–7.38 (m, 10H); ^{13}C NMR: δ 43.8, 52.8, 61.0, 67.1, 126.0, 126.3, 127.6, 127.8, 128.0, 128.4, 133.4, 136.7, 155.2; HRMS (EI) Calcd for $C_{21}H_{24}N_2O_2$ (M^+) 336.1838. Found 336.1844.

1-Azidopentane-5-(*N*-benzyloxycarbonyl)amine (1g). A solution of 5-amino-1-pentanol (1.00 g, 10 mmol) and *N*-(benzyloxycarbonyloxy)succinimide (2.99 g, 12.00 mmol) in THF (10 mL) was stirred at room temperature for 19 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 (30 mL), saturated aqueous $NaHCO_3$ solution (30 mL), water (30 mL) and brine (30 mL), then dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated to afford *N*-benzyloxycarbonyl-1-hydroxypentyl-5-amine (2.77 g, crude), which was used in the next reaction without further purification. ^{1}H NMR (400 MHz): δ 1.39–1.58 (m, 6H), 3.20 (q, J=6.8 Hz, 2H), 3.60–3.68 (m, 2H), 4.79 (brs, 1H), 5.09 (s, 2H), 7.31–7.36 (m, 5H).

Methanesulfonyl chloride (0.93 mL, 12.00 mmol) was added dropwise to a cooled (−10°C) solution of *N*-benzyloxycarbonyl-1-hydroxypentyl-5-amine (2.77 g, 11.70 mmol) and triethylamine (1.70 mL, 12.00 mmol) in CH_2Cl_2 (20 mL) under Ar atmosphere. The reaction mixture was stirred at room temperature for 15 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 (2.70 g, crude). ^{1}H NMR (400 MHz): δ 1.42–1.55 (m, 4H), 1.74–1.78 (m, 2H), 2.99 (s, 3H), 3.20 (q, J=6.4 Hz, 2H), 4.21 (t, J=6.4 Hz, 2H), 4.82 (brs, 1H), 5.09 (s, 2H), 7.31–7.36 (m, 5H).

To a solution of the above mesylate (2.70 g, 8.60 mmol) in anhydrous DMF (10 mL) was added NaN_3 (0.84 g, 12.80 mmol). The reaction mixture was stirred at room temperature for 24 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. The solvent was removed in vacuo, and flash column chromatography (hexane/ether 5:1) yielded **1g** (1.77 g, 79%) as a colorless oil. ^{1}H NMR (400 MHz): δ 1.39–1.62 (m, 6H), 3.19 (q, J=6.6 Hz, 2H), 3.26 (t, J=6.6 Hz, 2H), 4.82 (brs, 1H), 5.09 (s, 2H), 7.31–7.36 (m, 5H); ^{13}C NMR: δ 23.82, 28.45, 29.51, 40.79, 51.21, 66.59, 128.06, 128.46, 136.56, 156.37; HRMS (FAB; NBA) Calcd for $C_{13}H_{19}N_4O_2$ (M^++H) 263.1508. Found 263.1498.

***N*-Benzyloxycarbonyl-4-nitrophenethylamine (1h).** A suspension of 4-nitro phenethylamine hydrochloride (910 mg, 4.50 mmol) and triethylamine (0.60 mL, 4.40 mmol) in THF (10 mL) was stirred at room temperature for 1 h. To this suspension was added a solution of *N*-(benzyloxycarbonyloxy)succinimide (1.40 g, 5.40 mmol) in THF (10 mL). The reaction mixture was stirred at room temperature for 17 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 (30 mL), saturated aqueous $NaHCO_3$ solution (30 mL), water (30 mL) and brine (30 mL), then dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated to dryness. The residue was recrystallized from EtOH to obtain **1h** (1.11 g, 82%) as a white solid. Mp 73°C; ^{1}H NMR (400 MHz): δ 2.94 (t, J=6.6 Hz, 2H), 3.49 (q, J=6.6 Hz, 1H), 4.81 (brs, 1H), 5.09 (s, 2H), 7.32–7.36 (m, 7H), 8.14 (d, J=8.3 Hz, 2H); ^{13}C NMR: δ 36.07, 41.69, 66.81, 123.78, 128.13, 128.24, 128.54, 129.63, 136.31, 146.49, 146.79, 156.19; MS (EI) m/z 300 (M^+, 8%), 176 (85), 164 (82), 120 (70), 108 (80); Anal. Calcd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 63.80; H, 5.41; N, 9.20.

***N*-Benzyloxycarbonyl-L-proline benzyl ester (5b).**[8] A suspension of L-proline benzyl ester hydrochloride (2.42 g, 10.00 mmol) and triethylamine (1.30 mL, 9.30 mmol) in THF (10 mL) was stirred at room temperature for 1 h. To this suspension was added a solution of *N*-(benzyloxycarbonyloxy)succinimide (2.99 g, 12.00 mmol) in THF (10 mL). The reaction mixture was stirred at room temperature for 17 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 (30 mL), saturated aqueous $NaHCO_3$ solution (30 mL),

water (30 mL) and brine (30 mL), then dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and flash column chromatography (hexane/ether 10:1) yielded **5b** (2.75 g, 81%) as a colorless oil. ^{1}H NMR (400 MHz): δ 1.86–2.02 (m, 3H), 2.17–2.26, 3.44–3.56 and 3.58–3.67 (each m, 1H), 4.38 and 4.45 (each dd, J=3.7 and 8.5 Hz, 0.5H), 4.99–5.09 and 5.11–5.23 (each m, 2H), 7.22–7.36 (m, 10H); ^{13}C NMR: δ 23.5, 24.3, 29.9, 30.9, 46.4, 46.9, 58.9, 59.3, 66.7, 66.8, 66.9, 67.0, 85.3, 127.77, 127.84, 127.9, 128.0, 128.1, 128.2, 128.28, 128.37, 128.42, 128.5, 135.5, 135.7, 136.6, 136.7, 154.3, 154.9, 172.4, 172.6; HRMS (EI) Calcd for $C_{20}H_{21}NO_4$ (M^+) 339.1471. Found 339.1456.

***N*-Benzyloxycarbonyl-*O*-benzyl-L-tyrosine benzyl ester (5c).** To a solution of *N*-benzyloxycarbonyl-*O*-benzyl-L-tyrosine (2.00 g, 4.94 mmol) and triethylamine (0.80 mL, 5.92 mmol) in THF (10 mL) was added benzyl bromide (0.70 mL, 5.92 mmol). The reaction mixture was stirred at room temperature for 17 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 (30 mL), saturated aqueous $NaHCO_3$ solution (30 mL), water (30 mL) and brine (30 mL), then dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated to dryness. The residue was recrystallized from MeOH to obtain **5c** (2.39 g, 98%) as a white solid. ^{1}H NMR (400 MHz): δ 3.04 (d, J=4.9 Hz, 2H), 4.65–4.67 (m, 1H), 5.00 (s, 2H), 5.08–5.24 (m, 4H), 6.79 (d, J=8.3 Hz, 2H), 6.90 (d, J=8.3 Hz, 2H), 7.23–7.42 (m, 15H); ^{13}C NMR: δ 37.30, 54.93, 66.92, 67.18, 69.98, 114.91, 127.42, 127.73, 127.95, 128.06, 128.13, 128.48, 128.55, 130.33, 135.08, 136.25, 136.97, 155.60, 157.92, 171.38; MS (EI) m/z 495 (M^+, 2%), 344 (23), 197 (32), 91 (100); Anal. Calcd for $C_{31}H_{29}NO_5$: C, 75.13; H, 5.90; N, 2.83. Found: C, 74.90; H, 5.78; N, 2.86.

***N*-Allyl-*N*-benzyloxycarbonylaniline (7a).** Preparation of **7a** was performed analogously to the procedure described for **1a** with *N*-allylaniline (1.33 g, 10.00 mmol). Yield: 85% (2.28 g, as a yellow oil); ^{1}H NMR (400 MHz); δ 4.26–4.29 (m, 2H), 5.10–5.20 (m, 2H), 5.16 (s, 2H), 5.86–5.98 (m, 1H), 7.19–7.40 (m, 10H); ^{13}C NMR: δ 53.26, 67.22, 117.11, 126.45, 126.73, 127.57, 127.80, 128.33, 128.79, 133.68, 136.55, 142.00, 155.20; HRMS Calcd for $C_{17}H_{17}NO_2$: 267.1259. Found: 267.1250.

***N*-(Benzyloxycarbonyl)indoline (7b).** Preparation of **7b** was performed analogously to the procedure described for **1a** with indoline (1.19 g, 10.00 mmol). Yield: 92% (2.22 g, as a pale yellow oil); ^{1}H NMR (400 MHz): δ 3.12 and 4.05 (t, J=8.7 Hz, each 2H), 5.26 (s, 2H), 6.95 (t, J=7.0 Hz, 1H), 7.15 (d, J=7.0 Hz, 1H), 7.31–7.41 (m, 7H); MS (EI) m/z 253 (M^+, 22%), 91 (100); Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.98; H, 6.04; N, 5.57.

***N*-Benzyloxycarbonyl-4-vinylaniline (7c).** Preparation of **7c** was performed analogously to the procedure described for **1a** with 4-vinylaniline (1.00 g, 8.39 mmol). Yield: 92% (1.96 g, as a pale yellow powder); ^{1}H NMR (270 MHz): δ 520 (s, 2H), 5.66 (d, J=17.6 Hz, 1H), 6.67 (dd, J=10.8 and 17.6 Hz, 2H), 7.35–7.40 (m, 9H); MS (EI) m/z 253 (M^+, 25%), 209 (20), 145 (27), 91 (100); Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.79; H, 5.99; N, 5.54.

Hydrogenation of 1a (Table 1). After two vacuum/H_2 cycles to remove air from the reaction tube, the stirred mixture of the substrate **1a** (94.5 mg, 0.50 mmol), 5% Pd/C(en) (10 mg, 10% of the weight of **1a**) in MeOH, THF or 1,4-dioxane (1 mL) was hydrogenated at ambient pressure (balloon) and temperature (ca. 20°C) for the appropriate time (see Table 1). The reaction mixture was filtered using a membrane filter (Advantec Dismic-13HP, 0.45 μm) and the filtrate was concentrated in vacuo to yield **2a** (0, 76 or 83%, respectively). Because of the low boiling point of **3a**, the quantitative formation of **3a** was observed by direct ^{1}H NMR of the reaction mixture in CD_3OD.

Hydrogenation of 1c (Table 2)

After two vacuum/H_2 cycles to remove air from the reaction tube, the stirred mixture of the substrate **1c** (152 mg, 0.50 mmol), 5% Pd/C(en) (15 mg, 10% of the weight of **1c**) in MeOH, THF or 1,4-dioxane (1 mL) was hydrogenated at 1 or 5 atm and temperature (ca. 20°C) for the appropriate time (see Table 2). The reaction mixture was filtered using a membrane filter (Advantec Dismic-13HP, 0.45 μm) and the filtrate was concentrated in vacuo. The quantitative conversion of **1c** and the products ratio of **2c**, **3c** and **4** were confirmed by ^{1}H NMR of the crude mixture in $CDCl_3$.

General procedure for 5% Pd/C(en) catalyzed chemoselective hydrogenation (Table 3)

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** (0.2 mmol), 5% Pd/C(en) (10% of the weight of **1**) in 1,4-dioxane or THF (1 mL) was hydrogenated at ambient pressure (balloon) and temperature (ca. 20°C) for the appropriate time (see Table 3). The reaction mixture was filtered using a celite cake or a membrane filter (Advantec Dismic-13HP, 0.45 μm) and the filtrate was concentrated in vacuo. The quantitative conversion of **1** and the products ratio of **2** and **3** were confirmed by ^{1}H NMR of the crude mixture in $CDCl_3$. The crude mixture was purified by flash silica gel column chromatography, if necessary.

***N*-(Benzyloxycarbonyl)propylamine (2a).** Yield: 77% as a clear oil; ^{1}H NMR (400 MHz): δ 0.91 (t, J=7.6 Hz, 3H), 1.45–1.56 and 3.10–3.20 (each m, 2H), 4.78 (brs, 1H), 5.09 (s, 2H), 7.31–7.36 (m, 5H); ^{13}C NMR: δ 11.2, 23.2, 42.8, 66.5, 128.0, 128.5, 136.7, 156.4; HRMS (EI) Calcd for $C_{11}H_{15}NO_2$ (M^+) 193.1103. Found 193.1098.

***N*-(Benzyloxycarbonyl)dipropylamine (2b).** Yield: 92% as a clear oil; ^{1}H NMR (400 MHz): δ 0.86–0.89 (m, 6H), 1.49–1.61 and 3.12–3.25 (each m, 4H), 5.12 (s, 2H), 7.28–7.36 (m, 5H); ^{13}C NMR: δ 11.2, 21.3, 21.8, 48.6, 49.2, 66.7, 127.6, 127.7, 128.4, 137.1, 156.2; HRMS (FAB) Calcd for $C_{14}H_{21}NO_2$ (M^++H) 236.1650. Found 236.1648.

***N*-Benzyloxycarbonyl-4-(ethoxycarbonylmethyl)piperidine (2c).** The products (**1c** and **2c**) were obtained from **1c**

as a crude mixture (**1c**:**2c**=6:94). The product **2c** was isolated by flash column chromatography (hexane/ether 30:1) as a clear oil; ^{1}H NMR (400 MHz): δ 1.15–1.21 (m, 2H), 1.25 (t, J=7.0 Hz, 3H), 1.68–1.75 (m, 2H), 1.91–2.02 (m, 1H), 2.23 (d, J=7.3 Hz, 2H) 2.74–2.85 (m, 2H), 4.12 (q, J=7.0 Hz, 2H), 4.13–4.24 (m, 2H), 5.12 (s, 2H), 7.26–7.35 (m, 5H); ^{13}C NMR: δ 14.16, 31.63, 32.85, 40.94, 43.86, 60.23, 66.91, 127.73, 127.82, 128.35, 136.82, 155.15, 172.19; HRMS (EI) Calcd for $C_{17}H_{23}NO_4$ (M^+) 305.1627. Found 305.1632.

***N*-(Benzyloxycarbonyl)decylamine (2d).** Yield 99% as a white solid; Mp 38°C; ^{1}H NMR (400 MHz): δ 0.88 (t, J=6.8 Hz, 3H), 1.25–1.49 (m, 16H), 3.18 (q, J=6.7 Hz, 2H), 4.75 (brs, 1H), 5.09 (s, 2H), 7.31–7.36 (m, 5H); ^{13}C NMR: δ 14.09, 22.65, 26.71, 29.27, 29.51, 29.93, 31.87, 41.10, 66.54, 128.10, 128.48, 136.66, 156.35; HRMS (EI) Calcd for $C_{18}H_{29}NO_2$ (M^+) 291.2198. Found 291.2208.

***N*-Benzyloxycarbonyl-2-propylcyclopentylamine (2e).** Yield 96% as a pale yellow oil; ^{1}H NMR (400 MHz): δ 0.88 (t, J=6.8 Hz, 3H), 1.11–1.89 (m, 11H), 4.03–4.13 (m, 1H), 4.63 (brs, 1H), 5.10 (s, 2H), 7.29–7.37 (m, 5H); ^{13}C NMR: δ 14.22, 21.33, 21.40, 29.23, 31.68, 32.52, 42.67, 54.51, 66.38, 127.90, 128.35, 136.64, 155.91; HRMS (EI) calcd for $C_{16}H_{23}NO_2$ (M^+) 261.1729. Found 261.1737.

1-Benzyloxycarbonyl-4-(3-phenylpropyl)piperazine (2f). The products (**1f** and **2f**) were obtained from **1f** as a crude mixture (**1c**:**2c**=7:93). The product **2f** was isolated by flash column chromatography (chloroform) as a pale yellow oil; ^{1}H NMR (400 MHz): δ 1.81 (p, J=7.6 Hz, 2H), 2.34–2.38 (m, 6H), 2.64 (t, J=7.6 Hz, 2H), 3.52 (t, J=4.9 Hz, 4H), 5.13 (s, 2H), 7.16–7.36 (m, 10H); ^{13}C NMR: δ 28.4, 33.5, 43.8, 52.8, 57.8, 67.0, 125.8, 127.8, 128.0, 128.28, 128.33, 128.4, 136.7, 142.0, 155.2; HRMS (EI) Calcd for $C_{21}H_{26}N_2O_2$ (M^+) 338.1994. Found 338.2009.

5-(Benzyloxycarbonylamino)pentane-1-amine (2g). Yield 99% as a clear oil; ^{1}H NMR (400 MHz): δ 1.35–1.55 (m, 6H), 2.68 (t, J=6.8 Hz, 2H), 3.20 (q, J=6.0 Hz, 2H), 4.80 (brs, 1H), 5.09 (s, 2H), 7.31–7.36 (m, 5H); ^{13}C NMR: δ 23.93, 29.76, 33.24, 40.92, 41.94, 66.48, 128.01, 128.43, 136.62, 156.37; HRMS (FAB; NBA) Calcd for $C_{13}H_{21}N_2O_2$ (M^++H) 237.1603. Found 237.1609.

***N*-Benzyloxycarbonyl-4-aminophenethylamine (2h).** The product **2h** was isolated by flash column chromatography (chloroform) as a yellow solid. Yield 60%; Mp 77°C; ^{1}H NMR (400 MHz); δ 2.69 (t, J=6.6 Hz, 2H), 3.39 (q, J=6.6 Hz, 2H), 3.59 (brs, 2H), 4.75 (brs, 1H), 5.09 (s, 2H), 6.62 and 6.95 (d, J=8.3 Hz, each 2H) 7.27–7.34 (m, 5H); ^{13}C NMR: δ 35.12, 42.42, 66.56, 115.37, 128.06, 128.48, 129.58, 136.60, 144.85, 156.28; HRMS (EI) Calcd for $C_{16}H_{18}N_2O_2$ (M^+) 270.1368. Found 270.1360.

Hydrogenation of 1h (see Scheme in Table 3)

After two vacuum/H_2 cycles to remove air from the reaction tube, the stirred mixture of the substrate **1h** (75 mg, 0.25 mmol), 5% Pd/C(en) (8 mg, 10% of the weight of **1h**) in THF (1 mL) was hydrogenated at ambient pressure (balloon) and temperature (ca. 20°C) for 8 or 24 h. The reaction mixture was filtered using a membrane filter (Advantec Dismic-13HP, 0.45 μm) and the filtrate was concentrated in vacuo. The quantitative conversion of **1h** and the products ratio of **2h**, **3h** and azo compound were confirmed by ^{1}H NMR of the crude mixture in $CDCl_3$ (**2h**:**3h**:azo compound=25:67:8 for 8 h reaction or 30:57:13 for 24 h reaction, respectively).

4,4′-azobis(*N*-benzyloxycarbonyl)phenethylamine. ^{1}H NMR (400 MHz, DMSO): δ 2.77–2.86 (m, 4H), 3.27–3.31 (m, 4H), 4.99 (s, 2H), 5.00 (s, 2H), 7.29–7.34 (m, 12H), 7.42 (d, J=8.3 Hz, 2H), 8.04 and 8.13 (each d, J=7.8 Hz, each 2H); ^{13}C NMR (DMSO-d_6): δ 35.11, 35.40, 41.55, 41.66, 65.25, 122.05, 125.31, 127.78, 127.87, 128.45, 129.35, 139.68, 137.41, 141.75, 141.97, 144.12, 146.17, 156.21; HRMS (EI) Calcd for $C_{32}H_{32}N_4O_4$ (M^+) 536.2423. Found 536.2415.

General procedure for 5% Pd/C(en) catalyzed chemoselective hydrogenation (Table 4)

After two vacuum/H_2 cycles to remove air from the reaction tube, the stirred mixture of the substrate **5** (0.2 mmol), 5% Pd/C(en) (10% of the weight of **5**), and base (1.4 equiv. vs. **5**) in MeOH (1 mL) was hydrogenated at ambient pressure (balloon) and temperature (ca°C) for the appropriate time (see Table 4). The solvent was evaporated and the residue was diluted with water (1 mL). The mixture was adjusted to approximately pH 2.6 by adding 5% citric acid aqueous solution. Chloroform (3 mL) was added to the acidic suspension. The resulting mixture was filtered using a membrane filter (Millipore LCR13-LG, 0.2 μm) and the filtrate was extracted with chloroform (10 mL×3). The chloroform layers were combined, washed with water (5 mL) until the aqueous layer revealed approximately pH 4.0. The chloroform layer was dried over anhydrous sodium sulfate. After filtration, the solvent was evaporated to afford **6**. All products (**6**) are commercially available.

Hydrogenation of aromatic *N*-Cbz compounds (Table 5)

After two vacuum/H_2 cycles to remove air from the reaction tube, the stirred mixture of the substrate **7** (0.2 mmol), 5% Pd/C(en) (10% of the weight of **7**) in 1,4-dioxane or THF (1 mL) was hydrogenated at ambient pressure (balloon) and temperature (ca. 20°C) for the appropriate time (see Table 5). The reaction mixture was filtered using a membrane filter (Advantec Dismic-13HP, 0.45 μm) and the filtrate was concentrated in vacuo.

***N*-Propylaniline (9a).**[16] Yield 90% in 1,4-dioxane and 96% in THF; ^{1}H NMR (400 MHz): δ 1.00 (t, J=7.3 Hz, 3H), 1.64 (hex, J=7.3 Hz, 2H), 3.08 (t, J=7.3 Hz, 2H), 3.61 (brs, 1H), 6.61 (d, J=7.5 Hz, 2H), 6.69 (t, J=7.5 Hz, 1H), 7.17 (t, J=7.5 Hz, 2H).

***N*-Benzyloxycarbonyl-4-ethylaniline (8c).** Yield 95%; ^{1}H NMR (400 MHz): δ 1.21 (t, J=7.5 Hz, 3H), 2.60 (q, J=7.5 Hz, 2H), 5.20 (s, 2H), 6.60 (brs, 1H), 7.13 and 7.28 (d, J=8.5 Hz, each 2H), 7.33–7.41 (m, 5H); HRMS (EI) Calcd for $C_{16}H_{17}NO_2$ (M^+) 255.1259. Found 255.1269.

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