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Enantioselective Conjugate Reduction of α,β-Unsaturated Carboxamides with Semicorrin Cobalt Catalysts

Peter von Matt and Andreas Pfaltz*

Institut für Organische Chemie, Universität Basel, St. Johanns-Ring 19, CH-4056 Basel, Switzerland

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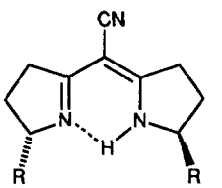
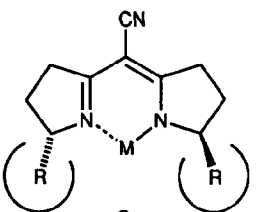
Abstract: Chiral semicorrin cobalt complexes, prepared *in situ* from cobalt(II) chloride and the free ligands, are efficient, highly enantioselective catalysts for the conjugate reduction of α,β-unsaturated carboxamides with sodium borohydride. Enantiomeric excesses of up to 99 %, essentially quantitative yields, and high substrate/catalyst ratios (1000 - 10 000 : 1) are attractive attributes of this catalytic process.

The semicorrins **1** belong to a class of chiral bidentate nitrogen ligands that we specifically designed for enantioselective control of metal-catalyzed reactions.[1] Both enantiomers are readily prepared starting either from D- or L-pyroglutamic acid.[1,2] The easy and flexible synthesis which allows for a wide range of structural variations, the conformationally rigid ligand framework, and the C_2-symmetric arrangement of the two substituents at the stereogenic centers in close proximity to the coordination sphere are essential features of the semicorrins **1** that led us to explore their potential as controller ligands in asymmetric catalysis.[3,4] The high enantiomeric excesses which we obtained in the cyclopropanation of olefins with diazo compounds using semicorrin copper complexes as catalysts[1a,5] demonstrate that the stereochemical course of a metal-mediated process can be effectively controlled by these ligands.



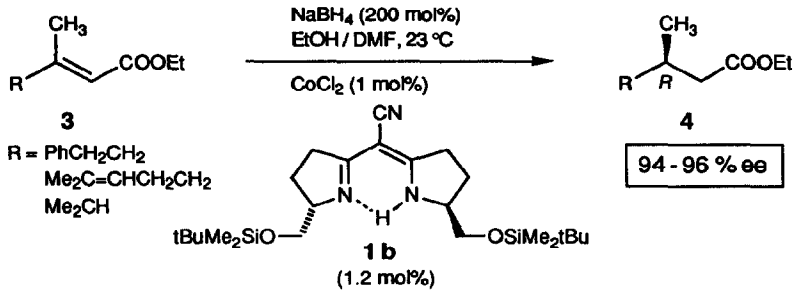
1

a R = COOMe
b R = CH_2OSiMe_2tBu



2

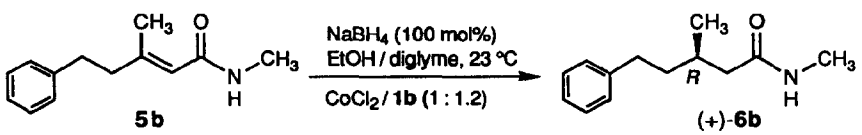
We have recently found that semicorrin cobalt complexes are efficient, highly enantioselective catalysts for the conjugate reduction of α,β-unsaturated carboxylic esters with sodium borohydride (Scheme 1).[6] Among the various semicorrins tested, the silyloxymethyl-substituted derivative **1b** afforded the best selectivity. Here we report the extension of our studies to α,β-unsaturated carboxamides.



Scheme 1

Under the conditions previously used for the reduction of α,β-unsaturated esters (1-2 mol% of catalyst in EtOH/DMF, 23°C),[6] the reaction of the corresponding amides was rather sluggish, and even at elevated temperature, did not go to completion. However, we found that replacement of DMF by diglyme (di-(2-methoxyethyl) ether), which is known to be a good solvent for sodium borohydride,[7] led to a substantial rate enhancement. Using 1 molar equivalent of sodium borohydride and 0.1-2 mol% of catalyst in a mixture of ethanol/diglyme (~1:1), the α,β-unsaturated carboxamide **5b** was quantitatively converted to the saturated amide **6b** within 2-3 days at room temperature (Table 1).[8] The chemical yields and the enantioselectivities obtained under these conditions were excellent. Surprisingly, when the amount of catalyst was reduced from 2 mol% to 0.1 mol% at constant substrate and borohydride concentration, the reaction rate remained essentially

Table 1. Enantioselective Reduction of Carboxamide **5b**: Variation of the Substrate/Catalyst Ratio



[Substrate]/[Catalyst][a]	Reaction Time[8]	Conversion (Yield)[b]	Enantioselectivity[c]
50 : 1	62 h	>99.9 % (95 %)	96.5 %ee
100 : 1	68 h	>99.9 % (96 %)	98.1 %ee
200 : 1	68 h	>99.9 % (92 %)	98.1 %ee
1 000 : 1	68 h	>99.9 % (97 %)	98.7 %ee
10 000 : 1	360 h	90 % (88 %)	95.3 %ee

[a] Molar ratio based on [Co]; $[CoCl_2]/[1b] = 1:1.2$; initial concentration of **5b** and $NaBH_4$: 1.6 M in ethanol/diglyme 1.2:1.

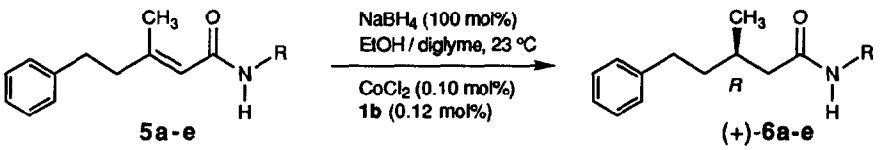
[b] Conversion determined by GC; yield of analytically pure product after column chromatography.

[c] Determined by HPLC analysis of the corresponding (*R*)-1-(1-naphthyl)-ethylamine; estimated error ± 0.2 %. The (*R*)-configuration of (+)-**6b** was assigned on the basis of its optical rotation.[9]

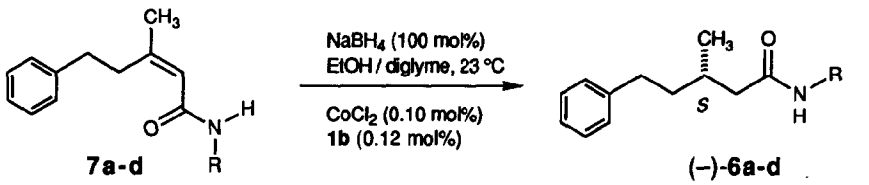
the same, whereas the enantiomeric excess increased from 96.5 to 98.7 %ee. Only at substrate/catalyst ratios as high as 10 000 : 1 did the reaction rate drop substantially. The enantioselectivity also decreased somewhat, but stayed above 95 %. Use of larger excesses of sodium borohydride resulted in higher reaction rates, although at the expense of selectivity (with 200 mol% of $NaBH_4$ (1.6 M solution of **5b**, 0.5 mol% of catalyst, 23 °C): quantitative conversion within 45 h, 96.5 %ee).

Under optimum conditions (0.1 mol% of catalyst), reduction of substrate **5b** afforded analytically pure saturated amide **6b** in 97 % yield and 98.7 %ee after purification by column chromatography. The product could be easily obtained in enantiomerically pure form (>99.9 %ee) by recrystallization from ether/hexane.

Table 2. Enantioselective Reduction of Carboxamides **5a-e** and **7a-d**[a]



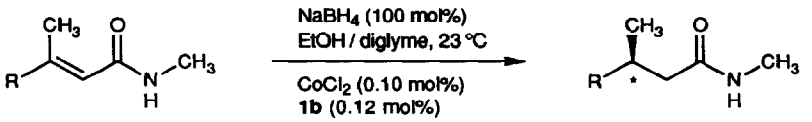
Substrate	R	Reaction Time[8]	Conversion (Yield)[b]	Enantioselectivity[c]
5a	H	68 h	92 % (91 %)	96.6 %ee
5b	Me	72 h	>99.9 % (97 %)	98.7 %ee
5c	Et	68 h	>99.9 % (92 %)	97.7 %ee
5d	$CHMe_2$	68 h	92 % (90 %)	95.4 %ee
5e	CMe_3	118 h	>99.9 % (87 %)	95.7 %ee



Substrate	R	Reaction Time[8]	Conversion (Yield)[b]	Enantioselectivity[c]
7a	H	118 h	99 % (98 %)	95.0 %ee
7b	Me	68 h	>99.9 % (96 %)	97.2 %ee
7c	Et	68 h	>99.9 % (99 %)	95.3 %ee
7d	$CHMe_2$	68 h	>99.9 % (99 %)	92.8 %ee

[a] 0.1 mol% of catalyst; initial concentration of **5** and $NaBH_4$: 1.6 M in ethanol/diglyme 1.2 : 1.
[b,c] See footnotes Table 1.

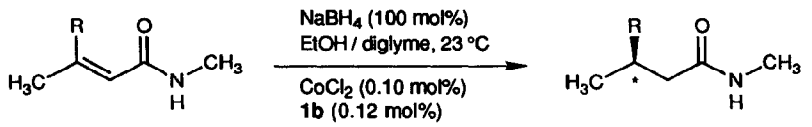
Table 3. Enantioselective Reduction of Carboxamides **5b**, **8ab**, **7b**, and **10a**[a]



5b (R = CH_2CH_2Ph)
8a (R = cyclohexyl)
8b (R = phenyl)

(+)-**6b** (R = CH_2CH_2Ph)[c]
(–)-**9a** (R = cyclohexyl)[d]
(+)-**9b** (R = phenyl)[e]

Substrate	Reaction Time[g]	Conversion (Yield)[b]	Enantioselectivity[c]
5b	72 h	99 % (98 %)	98.7 %ee
8a	118 h	>99.9 % (99 %)	98.9 %ee
8b	277 h	>99.9 % (96 %)	92.4 %ee



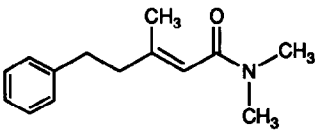
7b (R = CH_2CH_2Ph)
10a (R = cyclohexyl)

(–)-**6b** (R = CH_2CH_2Ph)[c]
(+)-**9a** (R = cyclohexyl)[d]

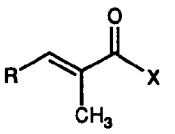
Substrate	Reaction Time[g]	Conversion (Yield)[b]	Enantioselectivity[c]
7b	68 h	99 % (96 %)	97.2 %ee
10a	118 h	>99.9 % (95 %)	97.2 %ee

[a] 0.1 mol% of catalyst; initial concentration of substrate and $NaBH_4$: 1.6 M in ethanol/diglyme 1.2:1.
[b,c] See footnotes Table 1.
[d] The assignment of absolute configuration is tentative.
[e] The (*S*)-configuration of (+)-**9b** was assigned based on the optical rotation of the corresponding acid.[10]

Among the various primary and secondary amides **5a-e** and the corresponding (*Z*)-isomers **7a-d** that were examined, all reacted with remarkable enantioselectivity (Table 2). Consistent with the results obtained for the corresponding esters[6], the (*E*)- and the (*Z*)-isomers are converted to products of opposite configuration.[11] Therefore, it is essential to use only olefins of high isomeric purity as substrates. The highest enantiomeric excesses were obtained with N-methyl amides **5b** and **7b**, although the selectivity differences between the individual derivatives **5a-e** and **7a-d** were rather small. Tertiary amides do not seem to be suitable substrates. Under the conditions given in Table 2, reduction of the N,N-dimethylamide **11** was quite slow and unselective (40 % conversion after 3 days, 40 %ee).



11



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Further examples of α,β-unsaturated amides which can be reduced with high enantioselectivity are shown in Table 3. The selectivity differences between β-phenyl- and β-alkyl-substituted substrates parallel those observed in the ester series[6] (for **3**: 94 %ee for R = CH_2CH_2Ph *vs.* 81 %ee for R = Ph; see Scheme 1). In general, primary amides and secondary *n*-alkylamides afford higher enantiomeric excesses than the corresponding ethyl esters. This method is not suited for substrates with an α-substituent, such as **12**. Previous studies in the ester series[12] using $NaBD_4$ in EtOH/DMF and $NaBH_4$ in EtOD/DMF have shown that formation of the α-(C-H) bond occurs by a non-stereoselective proton transfer from ethanol (in contrast to the the enantioselective introduction of the borohydride-derived β-H-atom). Accordingly, (semicorrinato)cobalt-catalyzed reduction of ester **12** (R = CH_2CH_2Ph, X = OEt) leads to racemic product.

The enantiomeric excesses listed in the Tables were determined by HPLC analysis of the corresponding diastereoisomeric naphthylethyl-amides obtained by hydrolysis of the reaction products, subsequent conversion to the acid chlorides, and reaction with (*R*)- or (*S*)-1-(1-naphthyl)ethylamine. This method has been previously used[6,12b] and was found to give very accurate and reliable results.

In summary, semicorrin cobalt catalysts have proven to be very efficient, highly enantioselective catalysts for the conjugate reduction of β-disubstituted α,β-unsaturated carboxamides. The enantiomeric excesses in the reactions of primary amides and secondary *n*-alkylamides are even better than those obtained with the corresponding esters using the same catalyst system, or with α,β-unsaturated carboxylic acids and ruthenium BINAP catalysts.[13] The simplicity of the experimental procedure and the high substrate/catalyst ratios are further attractive attributes of this method.

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Experimental

General. Solvents: Ethanol (*Fluka puriss.*); diglyme (*Fluka puriss.*, freshly distilled from NaH); benzene (*Fluka puriss.*, stored over 4 Å mol. sieves); Et_2O and THF (*Fluka purum*, distilled from Na/benzophenone). $CoCl_2$ hexahydrate (*Fluka purum p.a.*). Unless otherwise stated, reactions were carried out under N_2 using dried glassware. Flash column chromatography: *Chemische Fabrik Uetikon* silica gel C 560, 0.035-0.070 mm. TLC: *Merck* silica gel 60, 0.25 mm, without fluorescence inidicator; staining with basic $KMnO_4$. Specific rotation: *Perkin-Elmer-241* polarimeter, d = 10 cm, c = 1 g/100 ml, $CHCl_3$, room temperature, estimated error: ± 5 %. IR ($CHCl_3$): selected bands in cm^{-1}, *br* = broad. NMR ($CDCl_3$): δ in ppm *vs.* TMS, *J* in Hz; ^1H: 300 MHz; ^{13}C: 75 MHz, assignments based on DEPT or APT spectra. MS: selected peaks; m/z (%). GC system A: OV 1701 vi, 0.3 mm x 53 m; GC system B: OV 1701 vi, 0.3 mm x 30 m; injector 225 °C, detector 250 °C.

Synthesis of α,β-Unsaturated Carboxamides. General Procedure. Following the procedure of *Coutrot et al.*[14], a solution of 23.5 g (0.16 mol) benzylacetone in 200 ml of THF was slowly added at -70 °C to a solution of the dianion of diethyl carboxymethanephosphonate[15] (31.2 g, 0.16 mol) in 150 ml of THF. After aqueous work-up, the crude product was chromatographed (12 cm x 32 cm column) with hexane/EtOAc 4:1 to give 29.0 g (96 %) of (*E*/*Z*)-3-methyl-5-phenylpent-2-enoic acid **13** (*E* / *Z* = 2.9 : 1) as white crystals. Analytical data: m.p. 55-56 °C. IR: 3600-2400*m(br)*, 3085*m*, 3060*m*, 3025*m*, 2940*m*, 2860*m*, 1690*s*, 1640*s*, 1600*w*, 1495*m*, 1455*m*, 1420*m*, 1290*m*, 1250*s*. ^{1}H-NMR (200 MHz): 1.92 (*d*, *J* = 1.4, 0.77 H, CH_3 of *Z*-isomer); 2.22 (*d*, *J* = 1.2, 2.23 H, CH_3 of *E*-isomer); 2.44-2.94 (*m*, 4 H, CH_2CH_2); 5.72/5.74 (2 *s*, 1 H, CH=C of *E*- and *Z*-isomer); 7.16-7.35 (m, 5 H, Ar-H). TLC: R_f = 0.29 (hexane/EtOAc 4:1).

A solution of 7.5 g (0.04 mol) of (*E*/*Z*)-**13** in 100 ml of CH_2Cl_2 was treated with 10.2 ml (0.12 mol) of oxalyl cloride (*cf.* ref. 16). The resulting acid chloride was taken up in 20 ml of THF and slowly added to an ice-cooled aqueous solution of methyl amine (6.2 g, 0.2 mol).[17] Usual work-up yielded 8.0 g (100 %) of crude (*E*/*Z*)-N,3-dimethyl-5-phenylpent-2-enamide **5b**/**7b** (*E* / *Z* = 2.2 : 1) as orange crystals. The crude product was chromatographed on a silica gel column (7 cm x 42 cm, EtOAc/hexane 5:1; fractions 1-10 : 150 ml each, fract. 11-90 : 30 ml each, fract. 91-110 : 150 ml each). Fractions 25-42 afforded 1.8 g of pure **7b** (> 99.9 % *Z* by GC). Fractions 50-100 contained enriched (*E*)-isomer **5b** (*E* / *Z* > 9 : 1) which was rechromatographed to give 4.1 g of pure **5b** (> 99.9 % *E* by GC). Recrystallization from diethyl ether/hexane (-20 °C) provided 3.5 g (43 %) of **5b** and 1.3 g (16 %) of **7b** as white crystals.

(E)-N,3-Dimethyl-5-phenylpent-2-enamide **5b**: m.p. 84 °C. IR: 3460*m*, 2995*m*, 2940*m*, 2860*m*, 1660*s*, 1645*s*, 1510*s*, 1495*m*, 1450*m*, 1410*m*. ^{1}H-NMR: 2.19 (*d*, *J* = 1.26, 3 H, C(3)-CH_3); 2.36-2.41/2.74-2.79 (2*m*, 4 H, CH_2CH_2); 2.82 (*d*, *J* = 4.92, 3 H, N-CH_3); 5.2-5.5 (*br s*, 1 H, NH); 5.50 (broadened *s*, 1H, HC=C); 7.15-7.31 (*m*, 5 H, Ar-H). ^{13}C-NMR: 18.3 (C(3)-*C*H_3); 26.0 (N-CH_3); 34.0/42.5 (H_2C(4) and H_2C(5)); 118.5 (HC(2)); 126.0/128.3/128.4 (aromat. CH); 141.3 (aromat. C); 152.8 (C(3)); 167.8 (C=O). MS: 203(30, M^+), 173(11), 145(10), 131(13), 112(11), 91(100), 82(5), 77(5), 73(6), 65(15). TLC: R_f = 0.27 (EtOAc/hexane 5:1). GC (system A, 210 °C isotherm.): t_R = 15.9 min. Anal. calc. for $C_{13}H_{17}NO$: C = 76.81, H = 8.43, N = 6.89; found: C = 76.63, H = 8.32, N = 6.90.

(Z)-N,3-Dimethyl-5-phenylpent-2-enamide **7b**: m.p. 93 °C. IR: 3460*m*, 3005*m*, 2940*m*, 2860*m*, 1665*s*, 1640*s*, 1515*s*, 1495*m*, 1455*m*, 1415*m*, 1375*w*. ^{1}H-NMR: 1.83 (*d*, *J* = 1.5, 3 H, C(3)-CH_3); 2.74 (*d*, *J* = 5.1, 3 H, N-CH_3); 2.77-2.90 (*m*, 4 H, CH_2CH_2); 5.0-5.4 (*br s*, 1 H, NH); 5.56 (*s*, 1 H, HC=C); 7.16-7.31 (*m*, 5 H, Ar-H). ^{13}C-NMR: 24.7 (C(3)-*C*H_3); 26.0 (N-CH_3); 34.4/35.3 (H_2C(4) and H_2C(5)); 119.6 (HC(2)); 125.9/128.3/128.6 (aromat. CH); 141.9 (aromat. C); 152.1 (C(3)); 167.4 (C=O). MS: 203(M^+, 69), 188(6), 173(16), 145(14), 131(28), 112(17), 104(7), 91(100), 84(10), 73(9), 65(16), 58(18), 51(6). TLC: R_f = 0.36 (EtOAc/hexane 5:1). GC (system A, 210 °C isotherm.): t_R = 13.1 min. Anal. calc. for $C_{13}H_{17}NO$: C = 76.81, H = 8.43, N = 6.89; found: C = 76.95, H = 8.56, N = 6.94.

(E)-3-Methyl-5-phenylpent-2-enamide **5a**: m.p.: 89 °C. IR: 3530*m*, 3415*m*, 3005*m*, 2950*w*, 2860*w*, 1675*s*, 1640*s*, 1590*s*, 1495*w*, 1455*m*, 1405*m*, 1370*m*, 1305*m*. ^{1}H-NMR: 2.20 (*d*, *J* = 1.26, 3 H, C(3)-CH_3); 2.38-2.43 (*m*, 2 H, CH_2); 2.75-2.81 (*m*, 2 H, CH_2); ca. 5.35/5.45 (2 *br s*, 2 H, NH_2); 5.57-5.58 (*m*, 1 H, HC=C); 7.15-7.32 (*m*, 5 H, Ar-H). ^{13}C-NMR: 18.5 (C(3)-*C*H_3); 34.0/42.6 (H_2C(4) and H_2C(5)); 117.5 (HC(2)); 126.1/128.3/128.4 (aromat. CH); 141.2 (aromat. C); 155.0 (C(3)); 168.9 (C=O). MS: 189(75, M^+), 173(34), 157(6), 145(62), 131(65), 117(12), 98(55), 91(100), 82(37), 65(58), 51(24). TLC: R_f = 0.31 (EtOAc/hexane 5:1). GC (system A, 210 °C isotherm.): t_R = 15.6 min.

(Z)-3-Methyl-5-phenylpent-2-enamide **7a**: m.p. 71 °C. IR: 3530*m*, 3415*m*, 3005*m*, 2940*m*, 2860*w*, 1670*s*, 1640*s*, 1590*s*, 1495*m*, 1455*m*, 1390*m*, 1305*m*, 845*m*. ^{1}H-NMR: 1.84 (*d*, *J* = 1.2, 3 H, C(3)-CH_3); 2.76-2.83 (*m*, 2 H, CH_2); 2.87-2.94 (*m*, 2 H, CH_2); 5.2/5.5 (2 *br s*, 2 H, NH_2); 5.63 (*d*, *J* = 1.2, 1 H, HC=C); 7.15-7.31 (*m*, 5 H, Ar-H). ^{13}C-NMR: 25.0 (C(3)-*C*H_3); 34.4/35.1 (H_2C(4) and H_2C(5)); 118.3 (HC(2)); 125.9/128.3/128.5 (aromat. CH); 141.8 (aromat. C); 155.1 (C(3)); 168.5 (C=O). MS: 189(39, M^+), 145(13), 131(21), 98(8), 91(100), 65(14), 51(6). TLC: R_f = 0.38 (EtOAc/hexane 5:1). GC (system A, 210 °C isotherm.): t_R = 13.3 min.

(E)-N-Ethyl-3-methyl-5-phenylpent-2-enamide **5c**: m.p. 42 °C. IR: 3450*m*, 3005*s*, 2935*m*, 1665*s*, 1635*s*, 1510*s*, 1455*m*, 1380*w*, 1180*m*. ^{1}H-NMR: 1.14 (*t*, *J* = 7.50, 3 H, NCH_2CH_3); 2.20 (*d*, *J* = 1.2, 3 H, C(3)-CH_3); 2.35-2.40 (*m*, 2 H, CH_2); 2.74-2.79 (*m*, 2 H, CH_2); 3.27-3.36 (*m*, 2 H, NCH_2CH_3); 5.2-5.5 (*br s*, 1 H, NH) 5.50-5.52 (*m*, 1 H, HC=C); 7.15-7.31 (*m*, 5 H, Ar-H). ^{13}C-NMR: 14.9 (NCH_2CH_3); 18.3 (C(3)-CH_3); 34.0/42.5 ($H_2C(4)$, $H_2C(5)$, and NCH_2CH_3); 118.7 (HC(2)); 126.0/128.3/128.4 (aromat. CH); 141.4 (aromat. C); 152.7 (C(3)); 166.9 (C=O). MS: 217(M^+, 51), 173(17), 145(10), 131(19), 91(100), 72(9), 65(11). TLC: R_f = 0.24 (EtOAc/hexane 1:1). GC (system A, 205-215 °C, 2 °C/min): t_R = 16.5 min. Anal. calc. for $C_{14}H_{19}NO$: C = 77.38, H = 8.81, N = 6.45; found: C = 77.21, H = 8.89, N = 6.47.

(Z)-N-Ethyl-3-methyl-5-phenylpent-2-enamide **7c**: m.p. 69 °C. IR: 3450*m*, 3410*m*, 3005*s*, 2935*m*, 1660*s*, 1635*s*, 1505*s*, 1455*s*, 1380*m*, 1135*w*. ^{1}H-NMR: 1.09 (*t*, *J* = 7.2, 3 H, NCH_2CH_3); 1.83 (*d*, *J* = 1.2, 3 H, C(3)-CH_3); 2.77-2.90 (*m*, 4 H, CH_2CH_2); 3.25 (*dq*, *J* = 5.7/7.2, 2 H, NCH_2CH_3); 5.0-5.3 (*br s*, 1 H, NH); 5.55 (*d*, *J* =1.2, 1 H, HC=C); 7.16-7.31 (*m*, 5 H, Ar-H). ^{13}C-NMR: 14.9 (NCH_2CH_3); 24.7 (C(3)-CH_3); 34.0/34.4/35.2 (NCH_2CH_3, $H_2C(4)$, and $H_2C(5)$); 119.9 (HC(2)); 125.9/128.3/128.6 (aromat. CH); 141.9 (aromat. C); 152.0 (C(3)); 166.5 (C=O). MS: 217(M^+, 100), 202(6), 188(8) 173(22), 145(15), 131(37), 104(7), 98(13), 91(97), 72(15), 65(12). TLC: R_f = 0.33 (EtOAc/hexane 1:1). GC (system A, 205-215 °C, 2 °C/min): t_R = 13.6 min.

(E)-N-Isopropyl-3-methyl-5-phenylpent-2-enamide **5d**: m.p. 82 °C. IR: 3435*m*, 3005*s*, 2975*s*, 2930*m*, 2870*m*, 1665*s*, 1635*s*, 1500*s*, 1455*s*, 1385*m*, 1365*m*, 1175*m*. ^{1}H-NMR: 1.15 (*d*, *J* = 6.6, 6 H, $NCH(CH_3)_2$); 2.19 (*d*, *J* = 1.2, 3 H, C(3)-CH_3); 2.34-2.39 (*m*, 2 H, CH_2); 2.73-2.79 (*m*, 2 H, CH_2); 4.05-4.17 (*m*, 1 H, $NCH(CH_3)_2$); 5.1-5.3 (*br s*, 1 H, NH); 5.49-5.50 (*m*, 1 H, HC=C); 7.14-7.31 (*m*, 5 H, Ar-H). ^{13}C-NMR : 18.3 (C(3)-CH_3); 22.9 ($NCH(CH_3)_2$); 34.1/42.5 ($H_2C(4)$ and $H_2C(5)$); 40.9 ($NCH(CH_3)_2$); 118.9 (HC(2)); 126.0/128.3/128.4 (aromat. CH); 141.4 (aromat. C); 152.5 (C(3)); 166.2 (C=O). MS: 231(95, M^+), 216(6), 188(9), 173(74), 146(19), 140(33), 131(45), 117(7), 98(9), 91(100), 83(20), 65(16), 58(25). TLC: R_f = 0.28 (hexane/EtOAc 2:1). GC (system A, 195-215 °C, 2 °C/min): t_R = 17.5 min. Anal. calc. for $C_{15}H_{21}NO$: C = 77.88, H = 9.15, N = 6.05; found: C = 77.95, H = 9.23, N = 6.00.

(Z)-N-Isopropyl-3-methyl-5-phenylpent-2-enamide **7d**: m.p. 96 °C. IR: 3435*m*, 3005*m*, 2975*m*, 2935*m*, 2870*m*, 1660*s*, 1635*s*, 1500*s*, 1455*m*, 1385*m*, 1365*m*, 1190*m*. ^{1}H-NMR: 1.11 (*d*, *J* = 6.6, 6 H, $NCH(CH_3)_2$); 1.83 (*d*, *J* = 1.5, 3 H, C(3)-CH_3); 2.77-2.91 (*m*, 4 H, CH_2CH_2); 4.03-4.14 (*m*, 1 H, $NCH(CH_3)_2$); 4.8-5.2 (*br s*, 1 H, NH); 5.54 (*d*, *J* = 0.9, 1 H, HC=C)); 7.15-7.31 (*m*, 5 H, Ar-H). ^{13}C-NMR: 22.9 ($NCH(CH_3)_2$); 24.7 (C(3)-CH_3); 34.4/35.0 ($H_2C(4)$ and $H_2C(5)$); 40.8 ($NCH(CH_3)_2$); 120.1 (HC(2)); 125.9/128.3/128.6 (aromat. CH); 141.8 (aromat. C); 151.9 (C=O); 165.8 (C(1)). MS: 231(98, M^+), 188(13) 173(32), 145(17), 131(36), 112(9), 104(7), 98(6), 91(100), 65(11), 58(18). TLC: R_f = 0.34 (hexane/EtOAc 2:1). GC (system A, 195-215 °C, 2 °C/min): t_R = 14.9 min.

(E)-N-tert-Butyl-3-methyl-5-phenylpent-2-enamide **5e**: m.p. 80 °C. IR: 3435*m*, 3000*m*, 2965*m*, 2860*w*, 1665*s*, 1635*s*, 1500*s*, 1455*s*, 1390*m*, 1365*m*, 1265*m*. ^{1}H-NMR: 1.37 (*s*, 9 H, $NC(CH_3)_3$); 2.17 (*d*, *J* = 1.5, 3 H, C(3)-CH_3); 2.32-2.38 (*m*, 2 H, CH_2); 2.73-2.78 (*m*, 2 H, CH_2); 5.1-5.3 (*br s*, 1 H, NH); 5.47-5.48 (*m*, 1 H, HC=C); 7.15-7.32 (*m*, 5 H, Ar-H). ^{13}C-NMR: 18.1 (C(3)-CH_3); 28.9 ($NC(CH_3)_3$); 34.1/42.5 ($H_2C(4)$ and $H_2C(5)$); 51.0 ($NHC(CH_3)_3$); 119.8 (HC(2)); 126.0/128.3/128.4 (aromat. CH); 141.5 (aromat C); 151.7 (C(3)); 166.7 (C=O). MS: 245(M^+, 39), 173(43), 145(15), 131(16), 98(10), 91(100), 82(6), 65(10), 57(19). TLC (hexane/EtOAc 4:1): R_f = 0.28 (*Z*-isomer: 0.30). GC (system A, 195-215 °C, 2 °C/min): t_R = 16.8 min (*Z*-isomer: 14.4 min). Anal. calc. for $C_{16}H_{23}NO$: C = 78.32, H = 9.45, N = 5.71; found: C = 78.21, H = 9.43, N = 5.46.

(E)-3-Cyclohexyl-N-methyl-but-2-enamide **8a**: m.p. 112 °C. IR: 3460*m*, 3000*s*, 2930*s*, 2850*s*, 1660*s*, 1630*s*, 1510*s*, 1450*m*, 1410*m*, 1370*w*, 1240*m*, 1180*m*. ^{1}H-NMR: 1.13-1.30/1.70-1.80 (2 *m*, 10 H, cyclohexyl-CH_2); 1.88-1.91 (*m*, 1 H, HC(1')); 2.12 (*s*, 3 H, C(3)-CH_3); 2.83 (*d*, *J* = 4.80, 3 H, N-CH_3); 5.54 (*s*, 1 H, HC=C); 5.5-5.6 (*br s*, 1 H, NH). ^{13}C-NMR: 16.6 (C(3)-CH_3); 26.1/26.4/31.4 (cyclohexyl-CH_2); 25.9 (N-CH_3); 48.3 (HC(1')); 116.3 (HC(2)); 158.6 (C(3)); 168.3 (C=O). MS: 181(M^+, 48), 166(23), 151(53), 140(15), 133(7), 126(29), 113(17), 100(10), 95(16), 81(47), 77(14), 73(63), 69(74), 58(75),

53(23), 41(100). TLC: R_f = 0.30 (EtOAc/hexane 2:1). GC (system B, 150-230 °C, 2 °C/min): t_R = 16.08 min. Anal. calc. for $C_{11}H_{19}NO$: C = 72.88, H = 10.56, N = 7.73; found: C = 72.61, H = 10.72, N = 7.63.

(Z)-3-Cyclohexyl-N-methyl-but-2-enamide **10a**: m.p. 72 °C. IR: 3460*m*, 3000*s*, 2930*s*, 2850*s*, 1655*s*, 1630*s*, 1510*s*, 1445*m*, 1410*m*, 1250*m*, 1175*m*, 1020*w*. ^{1}H-NMR: 1.13-1.74 (*m*, 10 H, cyclohexyl-CH_2); 1.75 (*s*, 3 H, C(3)-CH_3); 2.82 (*d*, *J* = 4.8, 3 H, N-CH_3); 3.62-3.70 (*m*, 1 H, HC(1')); 5.3-5.5 (*br s*, 1 H, NH); 5.45 (*s*, 1 H, HC=C). ^{13}C-NMR: 20.4 (C(3)-CH_3); 26.2/26.2/31.0 (cyclohexyl-CH_2); 25.9 (N-CH_3); 39.8 (HC(1')); 117.7 (HC(2)); 159.1 (C(3)); 167.4 (C=O). MS: 181 (M^+, 39), 166(15), 151(22), 138(7), 123(11), 109(12), 95(13), 91(7), 81(38), 77(11), 73(100), 67(38), 58(43), 53(16), 41(64). TLC: R_f = 0.35 (EtOAc/hexane 2:1). GC (system B, 150-230 °C, 2 °C/min): t_R = 12.02 min.

(E)-3-Phenyl-N-methyl-but-2-enamide **8b**: m.p. 113 °C. IR: 3470*m*, 3010*m*, 2950*w*, 1665*s*, 1630*s*, 1580*w*, 1520*s*, 1450*m*, 1430*m*, 1385*w*, 1365*w*, 1280*w*. ^{1}H-NMR: 2.56 (*s*, 3 H, C(3)-CH_3); 2.90 (*d*, *J* = 5.1, 3 H, N-CH_3); 5.5-5.8 (*br s*, 1 H, NH); 6.00 (*d*, *J* = 1.2, 1 H, HC=C); 7.33-7.45 (*m*, 5 H, Ar-H). ^{13}C-NMR: 17.6 (C(3)-CH_3); 26.2 (N-CH_3); 119.8 (HC(2)); 126.1/128.4 (aromat. CH); 142.7 (aromat. C); 150.5 (C(3)); 167.6 (C=O). MS: 175 (M^+, 54), 160(8), 145(100), 117(49), 115(58), 91(32), 77(9), 63(8), 58(13), 51(16). TLC (EtOAc/hexane 3:1): R_f = 0.34 (Z-isomer: 0.18). GC (system B, 175-225 °C, 2 °C/min): t_R = 17.76 min (Z-isomer: 11.60 min).

Enantioselective Reduction of α,β-Unsaturated Carboxamides. General Procedure. To 1.2 g (5.95 mmol) of carboxamide **5b** (>99.9 % *E*) was added a solution of $CoCl_2 \cdot 6H_2O$ (1.42 mg, 5.95 μmol) in 0.61 ml of ethanol, followed by a solution (1*S*, 9*S*)-1,9-bis{[(*tert*-butyl)dimethylsilyloxy]methyl}-5-cyano-semicorrin **1b**[1b] (3.31 mg, 714 μmol) in 1.39 ml of ethanol. After dilution with 1.69 ml of diglyme, the clear, dark blue solution was degassed at 0.01 Torr by three freeze-thaw cycles. The solution, which was kept under nitrogen, was then transferred by syringe into an ampoule containing 225 mg (5.95 mmol) of $NaBH_4$ and a magnetic stirring bar under nitrogen. Rapid addition to the solid sodium borohydride resulted in an instantaneous color change to yellow. The slightly foaming solution was immediately degassed by three freeze-thaw cycles. The evacuated ampoule (0.01 Torr) was sealed with a vacuum-tight Teflon stopper and the yellow, slightly turbid solution stirred at room temperature. In the beginning, slow H_2-evolution was observed which gradually ceased after 2 h. Towards the end of the reaction, a solid precipitate and brown-yellow foam began to form. After 68 h, conversion was quantitative according to GC analysis (OV 1701, 210 °C, t_R(**5b**) = 16.0 min, t_R(**6b**) = 13.9 min). The reaction mixture was transferred to a separatory funnel with 50 ml of dichloromethane and 50 ml of water, diluted with 150 ml of ice water and extracted with dichloromethane. The organic layer was washed four times with sat. aqueous NaCl solution, dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (silica gel, 3 cm x 20 cm, EtOAc/hexane 5:1) afforded 1.18 g (97 %) of (+)-**6b** as a white, crystalline solid (98.7 %ee, m.p. 72-73 °C). Recrystallization from ether/hexane provided (+)-**6b** (85%, m.p. 73-74 °C) in 99.6 %ee; after a second recrystallization (78%, m.p. 74 °C), the minor enantiomer (–)-**6b** could not be detected any more by HPLC analysis (see below).

Determination of Enantiomeric Excesses.[12b,18] To 50 mg (0.24 mmol) of N-methylamide (+)-**6b** in a 7 ml ampoule were added 2 ml of 25 % aqueous sulfuric acid. The mixture was degassed at 0.01 Torr by three freeze-thaw cycles. The evacuated ampoule was sealed with a Teflon stopper and heated to 140 °C for 36 h. The cooled reaction mixture was diluted with base (→ pH = 13-14), washed with ether (3 x 50 ml), acidified, and extracted with ether (3 x 100 ml). The organic extracts were washed with brine (2 x 50 ml), dried with $MgSO_4$ and concentrated *in vacuo*. The resulting colorless 3-methyl-5-phenylpentanoic acid **14** (43.4 mg, 94 %) was dissolved in 1 ml of benzene, treated with 0.06 ml (0.73 mmol) of oxalyl chloride and heated to reflux for 2 h. The acid chloride was concentrated *in vacuo*, taken up in 2 ml of ether and treated with 0.12 ml (0.73 mmol) of (*R*)-1-(1-naphthyl)ethyl-amine (*Fluka* purum, recrystallized twice as the L-tartrate salt[12b,18]). After stirring for 2 h, the mixture was diluted with 100 ml of ether, washed with diluted hydrochloric acid (3 x 100 ml), dried with $MgSO_4$ and concentrated *in vacuo* to yield 77.9 mg of (*R*)-1-(1-naphthyl)ethylamide (*ca.* 100 % from **14**). As reference samples, the racemic amides (±)-**6a-e** and (±)-**9a,b** were prepared by catalytic hydrogenation (Pd/C, H_2, MeOH) and converted to the corresponding (*R*)-1-(1-naphthyl)ethylamides. HPLC analysis (Techsil silica gel 5 μ, 9 mm x 23 cm, hexane/EtOAc 6:1, 27 kg/cm^2, 2.3 ml/min; peak detection:

Kratos Spectroflow 757, 254 nm): retention times of (*R*)-1-(1-naphthyl)ethylamides from **6a-e**: t_R = 24.4 min (3*R*), 28.9 min (3*S*); from **9a**: t_R = 28.3 min, 33.6 min; from **9b**: t_R = 17.8 min (3*S*), 25.7 min (3*R*).

(R)-N,3-Dimethyl-5-phenylpentanamide (+)-**6b**: $[\alpha]_D$ = +18.4; 98.7 %ee (HPLC). M.p. 72-73 °C. IR: 3460*m*, 3005*s*, 2960*m*, 2930*m*, 2870*w*, 1665*s*, 1600*w*, 1520*s*, 1495*m*, 1450*m*, 1415*m*, 1380*w*. ^{1}H-NMR: 0.99 (*d*, *J* = 6.39, 3 H, C(3)-*CH*$_3$); 1.44-1.54 (*m*, 1 H, H*H*C(4)); 1.62-1.74 (*m*, 1 H, *H*HC(4)); 1.94-2.07 (*m*, 2 H, H*H*C(2) and HC(3)); 2.18-2.24 (*m*, 1 H, *H*HC(2)); 2.79 (*d*, *J* = 4.83, 3 H, N-CH$_3$); 2.53-2.74 (*m*, 2 H, H$_2$C(5)); 5.3-5.5 (*br s*, 1 H, NH); 7.14-7.30 (*m*, 5 H, Ar-H). ^{13}C-NMR: 19.6 (C(3)-*C*H$_3$); 26.2 (N-CH$_3$); 30.6 (HC(3)); 33.4/38.7 (H$_2$C(4) and H$_2$C(5)); 44.4 (H$_2$C(2)); 125.7/128.3 (aromat. CH); 142.5 (aromat. C); 173.0 (C=O). MS: 205(M$^+$, 10), 174(5), 131(7), 117(7), 104(10), 100(39), 91(64), 86(32), 77(10), 73(100), 65(17), 58(46), 51(9). GC (system A, 210 °C isotherm.): t_R = 13.9 min. Anal. calc. for $C_{13}H_{19}NO$: C = 76.06, H = 9.33, N = 6.82; found: C = 75.86, H = 9.37, N = 6.78.

(R)-3-Methyl-5-phenylpentanamide (+)**6a**: $[\alpha]_D$ = +17.6; 95.1 %ee (HPLC). IR: 3530*m*, 3410*m*, 3005*m*, 2960*m*, 2930*m*, 2870*w*, 1680*s*, 1590*m*, 1495*w*, 1455*w*, 1380*w*. ^{1}H-NMR: 1.03 (*d*, *J* = 6.3, 3 H, C(3)-CH$_3$); 1.45-1.57 (*m*, 1 H, H*H*C(4)); 1.64-1.76 (*m*, 1 H, *H*HC(4)); 1.95-2.07 (*m*, 2 H, H*H*C(2) and HC(3)); 2.21-2.30 (*m*, 1 H, *H*HC(2)); 2.54-2.74 (*m*, 2 H, H$_2$C(5)); 5.3-5.6/5.7-6.0 (2 *br s*, 2 H, NH$_2$); 7.15-7.30 (*m*, 5 H, Ar-H). ^{13}C-NMR: 19.6 (C(3)-*C*H$_3$); 30.5 (C(3)-H); 33.4/38.6 (H$_2$C(4) and H$_2$C(5)); 43.6 (H$_2$C(2)); 125.8/128.4 (aromat. CH); 142.4 (aromat. C); 175.0 (C=O). MS: 191(M$^+$, 19), 174(11), 117(7), 105(6), 100(10), 91(53), 86(40), 77(8), 72(26), 65(12), 59(100), 51(6). GC (system A, 210 °C isotherm.): t_R = 14.6 min.

(R)-N-Ethyl-3-methyl-5-phenylpentanamide (+)-**6c**: $[\alpha]_D$ = +14.7; 94.8 %ee (HPLC). IR: 3450*m*, 3005*s*, 2970*m*, 2935*m*, 2875*w*, 1660*s*, 1600*w*, 1515*s*, 1455*m*, 1380*m*, 1305*w*. ^{1}H-NMR: 0.99 (*d*, *J* = 6.6, 3 H, C(3)-CH$_3$); 1.12 (*t*, *J* = 7.2, 3 H, NCH$_2$*CH*$_3$); 1.42-1.55 (*m*, 1 H, H*H*C(4)); 1.62-1.74 (*m*, 1 H, *H*HC(4)); 1.92-2.06 (*m*, 2 H, H*H*C(2) und HC(3)); 2.17-2.23 (*m*, 1 H, *H*HC(2)); 2.53-2.73 (*m*, 2 H, H$_2$C(5)); 3.23-3.32 (*m*, 2 H, N*CH*$_2$CH$_3$); 5.3-5.6 (*br s*, 1 H, NH); 7.14-7.30 (*m*, 5 H, Ar-H). ^{13}C-NMR: 15.0 (NCH$_2$*CH*$_3$); 19.6 (C(3)-*C*H$_3$); 30.6 (C(3)-H); 33.4/38.7 (H$_2$C(4) and H$_2$C(5)); 34.3 (N*CH*$_2$CH$_3$); 44.5 (H$_2$C(2)); 125.7/128.4 (aromat. CH); 142.5 (aromat. C); 172.1 (C=O). MS: 219(M$^+$, 24), 131(6), 114(42), 100(27), 91(61), 87(100), 72(34), 65(11). GC (system A, 205-215 °C, 2 °C/min): t_R = 14.4 min.

(R)-N-Isopropyl-3-methyl-5-phenylpentanamide (+)-**6d**: $[\alpha]_D$ = +9.6; 93.5 %ee (HPLC). IR: 3440*m*, 3005*m*, 2960*s*, 2930*s*, 2870*m*, 1660*s*, 1600*w*, 1510*s*, 1455*m*, 1365*m*, 1170*m*, 1110*m*. ^{1}H-NMR: 0.99 (*d*, *J* = 6.3, 3 H, C(3)-*CH*$_3$); 1.126/1.132 (2 *d*, *J* = 6.6, 6 H, NCH(*CH*$_3$)$_2$); 1.42-1.54 (*m*, 1 H, H*H*C(4)); 1.62-1.73 (*m*, 1 H, *H*HC(4)); 1.86-2.21 (*m*, 2 H, H*H*C(2) and HC(3)); 2.18 (*dd*, J = 5.4/12.6, 1 H, *H*HC(2)); 2.53-2.73 (*m*, 2 H, H$_2$C(5)); 4.09 (*oct*, J = 6.6, 1 H, N*CH*(CH$_3$)$_2$); 5.2-5.4 (*br s*, 1 H, NH); 7.14-7.29 (*m*, 5 H, Ar-H). ^{13}C-NMR: 19.6 (C(3)-*C*H$_3$); 22.8 (NCH(*CH*$_3$)$_2$); 30.6 (HC(3)); 33.4/38.7 (H$_2$C(4) and H$_2$C(5)); 41.2 (N*CH*(CH$_3$)$_2$); 44.6 (H$_2$C(2)); 125.7/128.3 (aromat. CH); 142.5 (aromat. C); 171.3 (C=O). MS: 233 (M$^+$, 36), 128(52), 114(30), 101(100), 91(83), 77(8), 69(10), 58(14). GC (system A, 195-215 °C, 2 °C/min): t_R = 15.8 min.

(R)-N-tert-Butyl-3-methyl-5-phenylpentanamide (+)-**6e**: $[\alpha]_D$ = +8.9; 92.0 %ee (HPLC). IR: 3440*m*, 3005*m*, 2960*s*, 2930*m*, 2870*m*, 1665*s*, 1600*w*, 1510*s*, 1455*s*, 1395*m*, 1380*w*, 1365*m*. ^{1}H-NMR: 0.99 (*d*, *J* = 6.3, 3 H, C(3)-CH$_3$); 1.34 (*s*, 9 H, NC(*CH*$_3$)$_3$); 1.44-1.54 (*m*, 1 H, H*H*C(4)); 1.60-1.72 (*m*, 1 H, *H*HC(4)); 1.81-1.91 (*m*, 1 H, H*H*C(2)); 1.95-2.04 (*m*, 1 H, HC(3)); 2.14 (*dd*, J = 5.7/12.9, 1 H, *H*HC(2)); 2.53-2.72 (*m*, 2 H, H$_2$C(5)); 5.1-5.4 (*br s*, 1 H, NH); 7.14-7.29 (*m*, 5 H, Ar-H). ^{13}C-NMR: 19.5 (C(3)-*C*H$_3$); 28.8 (NC(*CH*$_3$)$_3$); 30.7 (HC(3)); 33.4/38.7 (H$_2$C(4) and H$_2$C(5)); 45.4 (H$_2$C(2)); 51.1 (N*C*(CH$_3$)$_3$); 125.7/128.3 (aromat. CH); 142.6 (aromat. C); 171.7 (C=O). MS: 247(M$^+$, 50), 142(32), 131(17), 115(88), 100(13), 91(100), 86(35), 72(24), 65(13), 58(95). GC (system A, 195-215 °C, 2 °C/min): t_R = 14.5 min.

3-Cyclohexyl-N-methyl-butanamide (-)-**9a**: $[\alpha]_D$ = -8.9; 98.9 %ee (HPLC). M.p. 54 °C. IR: 3460*m*, 3000*s*, 2920*s*, 2850*m*, 1665*s*, 1520*s*, 1450*m*, 1410*m*, 1380*w*, 1310*w*, 1280*w*. ^{1}H-NMR: 0.87 (*d*, *J* = 6.0, 3 H, C(3)-CH$_3$); 0.90-1.09 (*m*, 1 H, HC(1')); 1.11-1.28 (*m*, 5 H, H$_{ax}$); 1.61-1.76 (*m*, 5 H, H$_{eq}$); 1.83-1.92 (*m*, 2 H, H*H*C(2) and HC(3)); 2.23-2.32 (*m*, 1 H, *H*HC(2)); 2.81 (*d*, *J* = 4.5, 3 H, N-CH$_3$); 5.5-5.8 (*br s*, 1 H,

NH). ^{13}C-NMR: 16.2 (C(3)-CH_3); 26.1 (N-CH_3); 26.6/28.8/30.4 (cyclohexyl-CH_2); 35.6 (HC(3)); 41.5 (H_2C(2)); 42.6 (HC(1')); 173.8 (C=O). MS: 183(M^+, 1), 100(31), 86(10), 73(100), 69(10), 58(39), 55(27), 53(7), 41(44). GC (system B, 150-230 °C, 2 °C/min): t_R = 14.03 min.

(S)-3-Phenyl-N-Methyl-butanamide (+)-**9b**: $[\alpha]_D$ = +38.2; 92.3 %ee (HPLC). IR: 3460*m*, 3000*m*, 2960*m*, 2910*s*, 2850*m*, 1665*s*, 1600*w*, 1520*m*, 1490*m*, 1410*m*. ^{1}H-NMR: 1.31 (*d*, *J* = 6.9, 3 H, C(3)-CH_3); 2.38/2.44 (AB part of ABX system, J_{AB} = 13.8, $J_{AX} = J_{BX}$ = 7.2, 2 H, H_2C(2)); 2.70 (*d*, *J* = 4.8, 3 H, N-CH_3); 3.30 (*tq*, $J_t \approx J_q \approx 7$, 1 H, HC(3)); 5.2-5.5 (*br s*, 1 H, NH); 7.17-7.32 (*m*, 5 H, Ar-H). ^{13}C-NMR: 21.5 (C(3)-CH_3); 26.2 (N-CH_3); 36.9 (HC(3)); 45.7 (H_2C(2)); 126.3/126.7/128.5 (aromat. CH); 145.9 (aromat. C); 172.3 (C=O). MS: 177(M^+, 46), 162(16), 131(9), 119(13), 118(17), 105(100), 91(30), 77(25), 73(92), 58(44), 51(13), 41(16). GC (system B, 175-225 °C, 2 °C/min): t_R = 12.70 min.

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