82. Enantioselective Reduction of Electrophilic C=C Bonds with Sodium Tetrahydroborate and 'Semicorrin' Cobalt Catalysts

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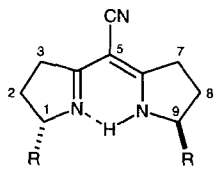
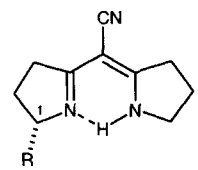
'Semicorrin' cobalt complexes, prepared *in situ* from cobalt(II) chloride and the corresponding ligands, are efficient catalysts for the enantioselective reduction of electrophilic C=C bonds with $NaBH_4$. The best selectivities (> 90% ee) are achieved with α,β-unsaturated carboxamides and carboxylates. Analogous α,β-unsaturated nitriles, sulfones, and phosphonates afford enantiomeric excesses of 50–70%. Interestingly, in the reduction of α,β-unsaturated sulfones, the highest enantioselectivities were obtained with unsymmetrical 'semicorrins', whereas in all other cases C_2-symmetric 'semicorrins' proved to be superior.

1. Introduction. – We have recently shown that cobalt complexes of chiral 'semicorrin' ligands **1**[2]) [1] are highly effective catalysts for the enantioselective conjugate reduction of α,β-unsaturated carboxylic esters [2] and amides [3] with $NaBH_4$. Simple alkenes are not reduced by this catalyst system, indicating that an electron-acceptor group at the C=C bond is essential for this process. To evaluate the scope and limitations of 'semicorrin' cobalt catalysts, we have examined other classes of substrates containing an electrophilic C=C bond. Herein, we report the results obtained with α,β-unsaturated nitriles, sulfones, and phosphonates. We also describe the synthesis of unsymmetrical 'semicorrins' **2** and a comparison of these ligands with analogous C_2-symmetric 'semicorrins' **1**.



1 corrin numbering

a R = COOMe
b R = CH_2OH
c R = $CH_2OSiMe_2(t\text{-Bu})$
d R = $CH_2OSiPh_2(t\text{-Bu})$



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2. Synthesis of Unsymmetrical 'Semicorrins'. – Ligands **2** were readily prepared from pyroglutamic acid (5-oxo-L-proline) and butyrolactam (**3**) by the route previously used for the synthesis of C_2-symmetrical 'semicorrins' **1** [4]. As described by *Wild* and *Eschenmoser* [5], *O*-alkylation of pyrrolidinone (**3**) with triethyloxonium tetrafluoroborate and

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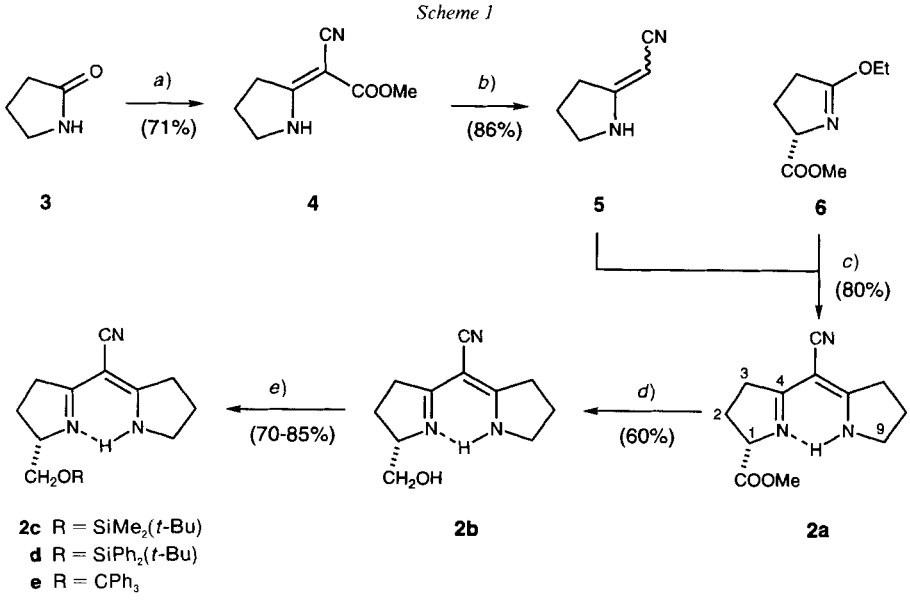
[2]) Systematic name of the parent ligand system: 3,4-dihydro-5-[(pyrrolidin-2-ylidene)methyl]-2*H*-pyrrole.

Scheme 1



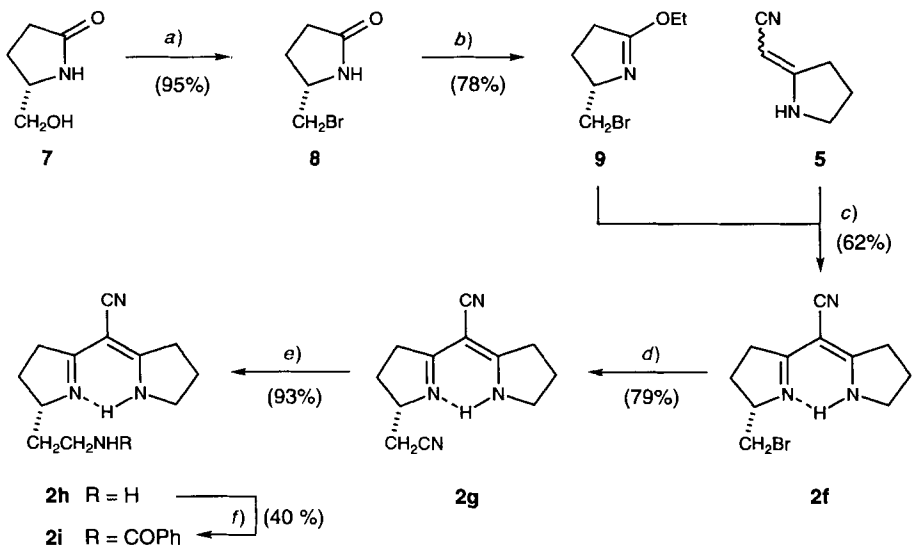
a) $(Et_3O)BF_4$, CH_2Cl_2, r.t.; $NCCH_2COOMe$, 100°. *b*) 1N NaOH, 100°; HCl, 0°. *c*) CF_3COOH, $ClCH_2CH_2Cl$, 60°. *d*) $NaBH_4$, THF/H_2O 4:1, 80°. *e*) **2c**: (*t*-Bu)Me_2SiCl, 1*H*-imidazole, 40°; **2d**: (*t*-Bu)Ph_2SiCl, 1*H*-imidazole, 40°; **2e**: Ph_3CCl, Et_3N, 4-(dimethylamino)pyridine, CH_2Cl_2, 25°.

condensation of the resulting imidic ester with methyl cyanoacetate afforded the methyl ester **4**, which was hydrolyzed with concomitant decarboxylation to give a 3:1 mixture of (*E*)- and (*Z*)-cyano-enamines **5** (*Scheme 1*). Subsequent condensation with imidic ester **6** [4b] afforded the 'semicorrin' **2a** in high yield. After reduction of the methoxycarbonyl group, the resulting hydroxymethyl derivative **2b** was converted to the silyl and trityl ethers **2c–e**.

Other unsymmetrical 'semicorrins' were prepared starting from commercially available (*S*)-5-(hydroxymethyl)pyrrolidin-2-one (**7**; *Scheme 2*). Reaction with tetrabromomethane/triphenylphosphine gave the (bromomethyl)pyrrolidinone **8** [6] in essentially quantitative yield. The standard sequence, *O*-alkylation of the lactam function and subsequent condensation with the (*E*/*Z*)-cyano-enamine **5**, led to the 'semicorrin' **2f**. Nucleophilic substitution with cyanide, using NaCN on Al_2O_3 [7] in toluene, afforded the '1-(cyanomethyl)semicorrin' **2g** which was converted to the aminoethyl derivative **2h** and the corresponding benzamide **2i**. Compounds of this type are of interest as potential tridentate ligands and as precursors for the synthesis of metal catalysts containing a reactive side chain capable of interacting with the substrate.

3. Enantioselective Reduction of Electrophilic C=C Bonds. – To evaluate the scope of 'semicorrin' cobalt catalysts for enantioselective reduction of C=C bonds, we prepared a series of substrates **13a–f** and **15a–f** with different electron-withdrawing groups (*Table*). Substrates **13a–d** and **15a–d** were synthesized by standard procedures from benzylacetone (**10**) and the corresponding phosphonates [3]. The alkenyl sulfones **13e**/**15e** and

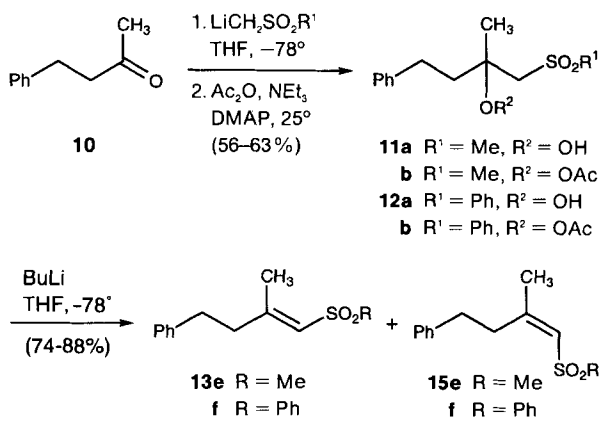
Scheme 2



a) CBr_4, PPh_3, MeCN, 25°. *b*) $(Et_3O)BF_4$, CH_2Cl_2, r.t. *c*) CF_3COOH, $ClCH_2CH_2Cl$, 60°. *d*) $NaCN/Al_2O_3$, toluene, 90°. *e*) Ni, H_2, EtOH. *f*) PhCOCl, pyridine, 25°.

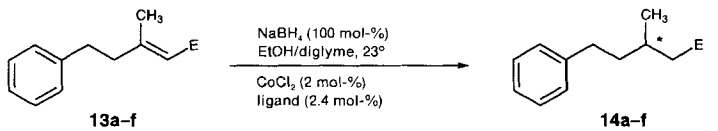
13f/15f were prepared as (*E*/*Z*)-mixtures in three steps from **10**, as shown in *Scheme 3*. Addition of lithiated dimethyl sulfone or methyl phenyl sulfone to **10** afforded hydroxy sulfones **11a** and **12a** in 80 and 85% yield, respectively. Acetylation and subsequent treatment of the resulting β-acetoxy sulfones **11b** and **12b** with BuLi in THF at −78° led exclusively to the desired α,β-unsaturated sulfones (ratio of α,β- to β,γ-unsaturated sulfones > 99:1), whereas other methods afforded mixtures of C=C bond isomers (**11b**, NaOH powder, dioxane, 23°: α,β-/β,γ-isomers 1:7; TsOH, toluene, reflux: 1:7; lithium diisopropylamide, THF, −78°: 8:1). The (*E*/*Z*)-mixtures **13e/15e** and **13f/15f** ((*E*)/(*Z*) *ca.* 2:1) were separated by column chromatography on silica gel.

Scheme 3



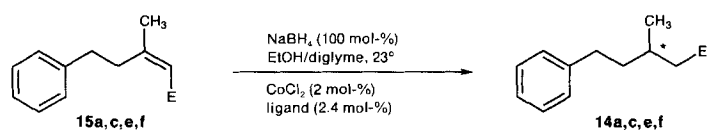
All substrates except the phosphonate **13d** were cleanly reduced in high yield in the presence of catalytic quantities of 'semicorrin' complexes, formed *in situ* from $CoCl_2$ and the corresponding ligand (*Table*). Among the various 'semicorrins' tested, the silyloxymethyl-substituted derivatives **1c** and **2c** afforded the best enantioselectivities. α,β-Unsaturated ethyl carboxylates, carboxamides, and nitriles **13a–c** and **15a, c** were converted to the corresponding saturated derivatives **14a–c** with 53–96.5% ee using 2 mol-% of catalyst derived from the C_2-symmetric semicorrin **1c**. The distinctly lower enantioselectivity in the reduction of nitriles **13c** and **15c** compared to analogous esters and amides is consistent with our mechanistic model[3]), according to which the ee depends on the difference in steric size between the electron-acceptor group E and $H-C(\alpha)$. For α,β-unsaturated carboxamides, we had found that the enantioselectivity increases when the

Table. *Enantioselective Reduction of* **13** *and* **15** *with* $NaBH_4$ *and 'Semicorrin' Cobalt Catalysts*



13a–f **14a–f**

	E	Reaction time [h]	Product	Yield[a]) [%]	Enantioselectivity[b]) [% ee]	
					ligand **1c**	ligand **2c**
13a	COOEt	17 h	**14a**	90–95	93.1 (*R*)	80 (*R*)
13b	CONH(Me)	60 h	**14b**	90–95	96.5 (*R*)	15 (*R*)
13c	CN	47 h	**14c**	75	68.8 (*R*)	–
13d	$PO(OEt)_2$	13 h	**14d**	40[c])	55 (–)	4 (–)[d])
13e	SO_2Me	15 h	**14e**	90–95	12 (–)	66 (–)
13f	SO_2Ph	15 h	**14f**	90–95	1 (–)	40 (–)



15a,c,e,f **14a,c,e,f**

	E	Reaction time [h]	Product	Yield[a]) [%]	Enantioselectivity[b]) [% ee]	
					ligand **1c**	ligand **2c**
15a	COOEt	17	**14a**	95	93 (*S*)	–
15c	CN	60	**14c**	76	53 (*S*)	–
15e	SO_2Me	15	**14e**	91	–	54 (+)
15f	SO_2Ph	24	**14f**	94	–	35 (+)

[a]) Yield of analytically pure product after column chromatography.

[b]) Determined by HPLC (see *Exper. Part*); in brackets: absolute configuration or sign of optical rotation.

[c]) Conversion (determined by GC). The enantioselectivity and the yield with this substrate were not reproducible.

[d]) 20% conversion after 60 h.

[3]) For a mechanistic discussion of this catalyst system and a model rationalizing the observed enantioselectivities, see [1].

amount of catalyst is reduced to 0.1 mol-% [3]. However, this was not observed with other substrates. Compared to the carboxylic-acid derivatives **13a–c**, analogous α,β-unsaturated phosphonates reacted more sluggishly giving lower and less reproducible enantioselectivities. Consistent with previous results [2] [3], (*E*)- and (*Z*)-isomers were converted to products of opposite configuration[3]).

In contrast to all other substrates, α,β-unsaturated sulfones gave better results with the unsymmetrical 'semicorrin' **2c**. Using 2 mol-% of catalyst derived from ligand **2c**, the saturated alkyl methyl sulfone **14e** was obtained in high yield with 66% ee, whereas the corresponding C_2-symmetric 'semicorrin' **1c** afforded only 12% ee. Unfortunately, screening of additional differently substituted 'semicorrins' did not lead to higher ee's. The enantioselectivities observed with other ligands decreased in the order **2d** (53% ee), **2f** (51% ee), and **2e** (39% ee). Surprisingly, the cyanomethyl-substituted ligand **2g** produced the (+)-enantiomer of **14e** in 27% ee starting from the (*E*)-alkenyl methyl sulfone **13e**, whereas with all other ligands, the (−)-enantiomer was formed preferentially. At present, we are unable to explain the better performance of unsymmetrical 'semicorrins' in the reduction of α,β-unsaturated sulfones. However, our results clearly demonstrate that C_2 symmetry is not always beneficial to the enantioselectivity of a catalyst, and that the generally accepted rule according to which C_2-symmetric ligands are superior to unsymmetric analogues [8] should be applied with caution.

α,β-Unsaturated ketones, oxime ethers, and hydrazones were also tested as substrates. In all cases, the observed enantioselectivities were low (< 20%) because the uncatalyzed reduction with $NaBH_4$ proceeds at a similar rate as the cobalt-catalyzed process. Somewhat higher ee's could be obtained in the reaction of 3-methylcyclohex-2-enone using $NaBH_3CN$ (up to 30% ee compared to 4–7% ee with $NaBH_4$). However, further variation of the reducing agent and other reaction parameters did not lead to better enantioselectivities.

In summary, we have shown that α,β-unsaturated carboxylic esters, carboxamides, nitriles, and sulfones can be selectively reduced at the C=C bond in high yield, with moderate to very high enantioselectivity. By far the best ee's are obtained with carboxylic esters and amides, while for nitriles and sulfones further improvement of the catalyst will be necessary.

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Experimental Part

1. *General.* EtOH, 1,2-dichloroethane, $CHCl_3$, and DMF: *Fluka puriss.*; diglyme: *Fluka puriss.*, freshly distilled from NaH; Et_2O and THF: *Fluka purum*, distilled from Na/benzophenone; CH_2Cl_2, AcOEt, and hexane: technical grade, distilled before use; CF_3COOH: *Fluka purum*; $CoCl_2 \cdot 6\ H_2O$: *Fluka purum p.a.*; methyl cyanoacetate, 1*H*-imidazole: *Fluka puriss.* $(Et_3O)BF_4$: *Fluka purum* washed with anh. Et_2O under N_2 and dried at 25°/0.05 Torr before use. Unless otherwise stated, reactions were carried out under N_2 using dried glassware. Flash column chromatography (FC): *Chemische Fabrik Uetikon* silica gel *C 560*, 0.035–0.070 mm. TLC: *Merck* silica gel *60*, 0.25 mm, without fluorescence indicator; staining with basic $KMnO_4$. GC: *OV 1701 vi*, 0.3 mm × 53 m; injector 225°, detector 250°; t_R in min. HPLC: *Merck-Hitachi-L-6200* gradient pump, *Merck-Hitachi-L-4200* UV/VIS detector, *Merck-Hitachi-D-2500* integrator; chiral columns: *Daicel Chemical Industries Ltd.*, 0.46 cm

× 25 cm; system *A*: *Chiralcel OB*, hexane/i-PrOH 97:3, 0.3 ml/min; system *B*: *Chiralcel OJ*, hexane/i-PrOH 99:1, 0.7 ml/min; system *C*: *Daicel Chiralcel OJ*, hexane/i-PrOH 50:50, flow 0.75 ml/min; system *D*: *Chiralcel OJ*, hexane/i-PrOH 80:20, 0.8 ml/min; t_R in min. Specific rotation: *Perkin-Elmer-141* polarimeter, $d = 10$ cm, c in g/100 ml, $CHCl_3$, r.t.; estimated error ± 5%. UV/VIS (EtOH): λ in nm (ε). IR ($CHCl_3$): selected bands in cm^{-1}, br. = broad. NMR ($CDCl_3$): δ in ppm *vs.* $SiMe_4$, J in Hz; ^1H: 300 MHz; ^{13}C: 75 MHz, assignments based on DEPT or APT spectra. MS: selected peaks; *m/z* (%).

2. '*Semicorrins*'. *Methyl 2-Cyano-2-(pyrrolidin-2-ylidene)acetate* (**4**) [5]. Pyrrolidin-2-one (**3**; 40.0 g, 0.47 mol) in anh. CH_2Cl_2 (75 ml) was slowly added to an ice-cooled soln. of $(Et_3O)BF_4$ (119.9 g, 0.63 mol) in anh. CH_2Cl_2 (600 ml). The soln. was stirred at 25° for 4 h until the reaction was complete (TLC). After cooling to 0° in an ice bath, 5M aq. K_2CO_3 (270 ml) was slowly added. The mixture was shaken and the resulting emulsion filtered through *Celite* to separate the two phases. The aq. layer was extracted with CH_2Cl_2 (3 × 200 ml), the combined org. extracts washed with ice water (250 ml), dried (anh. K_2CO_3), evaporated, and distilled: 40.4 g (76%; b.p. 44°/26 Torr) of colorless **6**. A mixture of **6** (40.4 g, 0.36 mol) and methyl cyanoacetate (144 g, 1.5 mol) was stirred under N_2 at 100° for 21 h. Upon cooling to 25°, the product crystallized. The white crystals were washed with hexane and recrystallized from CH_2Cl_2/hexane: 52.1 g of **4** (m.p. 136°). Excess methyl cyanoacetate was recovered by distillation. From the residue, additional 3.1 g of **4** (m.p. 136°) were obtained by recrystallization from CH_2Cl_2/hexane. Combined yield: 55.2 g (93%). TLC (AcOEt): R_f 0.48. Spectroscopic data: see [5].

(E/Z)-(Pyrrolidin-2-ylidene)acetonitrile (**5**) [5]. A suspension of **4** (12 g, 72 mmol) in 1M aq. NaOH (200 ml) was stirred at 100° until **4** had completely dissolved. After cooling to 0° in an ice bath, conc. HCl soln. (75 ml) was slowly added. The clear soln. was neutralized by addition of K_2CO_3, saturated with NaCl, and extracted with CH_2Cl_2 (5 × 250 ml). The combined org. extracts were dried ($MgSO_4$) and evaporated. The residue was sublimed at 70°/0.03 Torr: colorless **5** (6.7 g, 86%; (*E*)/(*Z*) *ca.* 3:1). M.p. 73°. Spectroscopic data: see [5].

(2S)-Methyl 5-[Cyano(pyrrolidin-2-ylidene)methyl]-3,4-dihydro-2H-pyrrole-2-carboxylate (**2a**). CF_3COOH (36.2 ml, 377 mmol) was added to a soln. of **5** (10.2 g, 94 mmol) and **6** (64.6 g, 377 mmol) [4b] in anh. 1,2-dichloroethane (90 ml) at 25°. The soln. was stirred under N_2 at 60° for 6 h until **5** was completely consumed (TLC (AcOEt/hexane 2:1): R_f (**5**) 0.38, R_f (**6**) 0.27, R_f (**2a**) 0.33). The mixture was cooled to 25°, diluted with CH_2Cl_2 (90 ml), and washed with sat. aq. $NaHCO_3$ soln. The aq. layer was extracted with CH_2Cl_2 and the combined org. phase washed with sat. NaCl soln., dried (Na_2SO_4), and evaporated. FC (11 × 35-cm column, AcOEt/hexane 2:1) of the crude product in two batches gave 19 g of crystalline solid, which was recrystallized from AcOEt: 17.6 g (80% based on **5**) of anal. pure, white **2a**. M.p. 150–151°, $[\alpha]_D = -38.6$ ($c = 1.0$, $CHCl_3$). UV: 296 (16170). IR: 3010*m*, 3005*m*, 2950*w*, 2190*s*, 1735*s*, 1610*s*, 1560*s*, 1555*s*, 1435*m*, 1430*m*, 1310*m*. ^{1}H-NMR[4]): 2.01–2.30 (*m*, CH_2(2), CH_2(8)); 2.75–3.01 (*m*, CH_2(3), CH_2(7)); 3.74 (*m*, CH_2(9)); 4.72 (*t*, $J = 7.5$, H–C(1)); 10–11 (br. *s*, NH). ^{13}C-NMR[4]): 21.6 (C(8)); 26.3 (C(2)); 33.0 (C(7)); 36.6 (C(3)); 49.7 (C(9)); 52.1 (MeO); 69.9 (C(5)); 72.6 (C(1)); 121.5 (CN); 170.6 (C(6)); 174.0 (C(4)); 174.3 (COO). MS: 233 (7, M^+), 174 (100), 145 (22), 132 (17), 119 (18), 105 (31), 92 (13), 78 (23), 67 (26), 59 (87). Anal. calc. for $C_{12}H_{15}N_3O_2$: C 61.79, H 6.48, N 18.01; found: C 61.57, H 6.52, N 18.14.

[(2S)-3,4-Dihydro-2-(hydroxymethyl)-2H-pyrrol-5-yl](pyrrolidin-2-ylidene)acetonitrile (**2b**). To an ice-cooled soln. of **2a** (2 g, 8.57 mmol) in THF (65 ml) and H_2O (16.4 ml) was slowly added $NaBH_4$ (1.62 g, 42.9 mmol) [9]. The soln. was heated to reflux for 80 min, then cooled in an ice bath and neutralized by addition of 1N HCl. The aq. layer was saturated with NaCl, separated, and extracted with THF (8 × 10 ml). The combined org. phase was dried ($MgSO_4$) and evaporated and the residue dried at 50°/0.05 Torr for 10 h to give 1.71 g of crude **2b**, which was converted to the ligands **2c**, **2d**, and **2e** without further purification. Crystallization from CH_2Cl_2/hexane gave 1.06 g (60%) of anal. pure **2b**. M.p. 96–97°. $[\alpha]_D = +26.2$ ($c = 1.0$, $CHCl_3$). UV: (14600). IR: 3010*m*, 2955*m*, 2930*w*, 2190*s*, 1610*s*, 1560*s*, 1480*w*, 1460*w*, 1430*w*, 1310*m*. ^{1}H-NMR[4]): 1.64–1.76 (*m*, 1 H–C(2)); 1.99–2.08 (*m*, 1 H–C(2), CH_2(8)); 2.74–2.97 (*m*, CH_2(3), CH_2(7)); 3.52–3.58 (*m*, CH_2OH); 4.15–4.23 (*m*, H–C(1)); 5.3–6.5 (br. *s*, OH, NH). ^{13}C-NMR[4]): 21.8 (C(8)); 24.0 (C(2)); 33.9 (C(7)); 35.7 (C(3)); 52.3 (C(9)); 66.1 (CH_2OH); 69.9 (C(5)); 70.6 (C(1)); 121.8 (CN); 170.7 (C(6)); 172.0 (C(4)). MS: 205 (10, M^+), 174 (100), 145 (6), 107 (11), 70 (5), 57 (12). Anal. calc. for $C_{11}H_{15}N_3O$: C 64.37, H 7.37, N 20.47; found: C 64.09, H 7.43, N 20.21.

{(2S)-2-{[(tert-Butyl)dimethylsilyloxy]methyl}-3,4-dihydro-2H-pyrrol-5-yl}(pyrrolidin-2-ylidene)acetonitrile (**2c**). A soln. of crude **2b** (800 mg, 3.90 mmol) and 1*H*-imidazole (2.12 g, 31.2 mmol) in anh. DMF (6.5 ml) was treated with (*tert*-butyl)(chloro)dimethylsilane (2.35 g, 15.6 mmol) [10]. After stirring for 24 h at 40°, the mixture was diluted with H_2O (15 ml) and extracted with Et_2O (3 × 10 ml). The combined org. phase was washed with brine, dried (Na_2SO_4), and evaporated. The crude product was chromatographed (4 × 30-cm column, hexane/

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[4]) Corrin numbering is used in the NMR spectra, see **1**.

AcOEt 5:1) and the product (1.2 g) crystallized from MeOH at −20°: 693 mg (56% based on **2a**) of anal. pure **2c**. M.p. 103°. $[\alpha]_D = -25.2$ ($c = 1.0$, $CHCl_3$). UV: 295 (15250). IR: 3010*m*, 2950*s*, 2925*s*, 2865*m*, 2195*s*, 1610*s*, 1560*s*, 1470*m*, 1460*m*, 1305*s*, 1255*s*, 1115*s*, 840*s*. ^{1}H-NMR[4]): 0.02 (*s*, MeSi); 0.05 (*s*, MeSi); 0.88 (*s*, *t*-Bu); 1.68–1.79 (*m*, 1 H–C(2)); 1.91–2.03 (*m*, CH_2(8)); 2.04–2.13 (*m*, 1 H–C(2)); 2.75–2.96 (*m*, CH_2(3), CH_2(7)); 3.55–3.65 (*m*, CH_2OSi); 3.75–3.80 (*t*, CH_2(9)); 4.06–4.14 (*m*, H–C(1)); 9.5–11.5 (br. *s*, NH). ^{13}C-NMR[4]): −5.4 (MeSi); 18.2 (Me_3C); 22.0 (C(8)); 24.2 (C(2)); 25.8 (Me_3C); 34.0 (C(7)); 34.9 (C(3)); 55.4 (C(9)); 66.5 (CH_2OSi); 67.5 (C(1)); 69.7 (C(5)); 122.0 (CN); 170.5 (C(4)); 171.0 (C(6)). MS: 319 (2, M^+), 304 (2), 262 (24), 174 (100), 73 (7), 59 (4). Anal. calc. for $C_{17}H_{29}N_3OSi$: C 63.90, H 9.15, N 13.15; found: C 63.66, H 9.19, N 13.26.

*{(2S)-2-{[(*tert*-Butyl)diphenylsilyloxy]methyl}-3,4-dihydro-2*H*-pyrrol-5-yl}(pyrrolidin-2-ylidene)acetonitrile* (**2d**). As described for **2c**, with **2b** (116 mg, 0.57 mmol), 1*H*-imidazole (115 mg, 1.70 mmol), DMF (0.45 ml), and (*tert*-butyl)(chloro)diphenylsilane (217 µl, 0.85 mmol) [11] (23 h at 40°). Workup with H_2O (30 ml) and Et_2O (3 × 20 ml) and chromatography (silica gel, 1.7 × 17-cm column, hexane /AcOEt 5:1) and crystallization of the product (236 mg) from MeOH at −20° afforded 181 mg (72%) of anal. pure **2d**. M.p. 97–98°. $[\alpha]_D = -49.7$ ($c = 0.66$, $CHCl_3$). UV: 220 (25600), 296 (15720). IR: 3420*m* (br.), 3080*m* (br.), 3060*m*, 3005*m*, 2950*m*, 2190*s*, 1610*s*, 1565*s*, 1430*m*, 1265*m*. H-NMR[4]): 1.05 (*s*, *t*-Bu); 1.73–1.84 (*m*, 1 H–C(2)); 1.93–2.14 (*m*, 1 H–C(2), CH_2(8)); 2.77–2.91 (*m*, CH_2(3), CH_2(7)); 3.60–3.78 (*m*, CH_2(9), CH_2OSi); 4.13–4.19 (*m*, H–C(1)); 7.34–7.45, 7.62–7.66 (2*m*, 2 Ph). ^{13}C-NMR[4]): 19.2 (Me_3C); 22.0 (C(8)); 24.1 (C(2)); 26.7 (Me_3C)); 34.1 (C(7)); 34.8 (C(3)); 55.2 (C(9)); 67.0 (CH_2OSi); 67.4 (C(1)); 69.7 (C(5)); 121.9 (CN); 127.6, 129.7 (arom. CH); 133.3 (arom. C); 135.5 (arom. CH); 170.5, 170.9 (C(4), C(6)). MS: 387 (21), 386 (69), 308 (20), 175 (12), 174 (100). Anal. calc. for $C_{27}H_{33}N_3OSi$: C 73.09, H 7.50, N 9.47; found: C 73.01, H 7.61, N 9.44.

*{(2S)-3,4-Dihydro-2-[(triphenylmethoxy)methyl]-2*H*-pyrrol-5-yl}(pyrrolidin-2-ylidene)acetonitrile* (**2e**). Et_3N (86 mg, 0.85 mmol) was added to a mixture of **2b** (114 mg, 0.56 mmol), 4-(dimethylamino)pyridine (5.5 mg, 0.05 mmol), and (chloro)triphenylmethane (186 mg, 0.67 mmol) in anh. CH_2Cl_2 (1 ml) [12]. The suspension was stirred for 40 h at 25°, until no more **2b** was detectable (TLC (hexane/EtOH 1:1): R_f (**2b**) 0.49, R_f (**2e**) 0.72). The mixture was diluted with H_2O (10 ml) and extracted with CH_2Cl_2 (3 × 5 ml). The combined org. extracts were washed with H_2O, dried (MgSO), and evaporated. FC (2 × 23-cm column, AcOEt/hexane 2:5) of the crude product gave 205 mg (82%) of anal. pure **2e**. Colorless solid. M.p. 58–60°. $[\alpha]_D = -75.8$ ($c = 1.0$, $CHCl_3$). IR: 3680*w*, 3070*w*, 2960*w*, 2190*m*, 1610*s*, 1560*s*, 1490*w*, 1440*m*, 1340*w*, 1290*w*, 1080*w*. ^{1}H-NMR[4]): 1.67–1.78 (*m*, 1 H–C(2)); 1.95–2.15 (*m*, 1 H–C(2), CH_2(8)); 2.76–2.97 (*m*, CH_2(3), CH_2(7)); 3.10–3.18 (*m*, CH_2O); 3.81 (*t*, $J = 7.1$, CH_2(9)); 4.16–4.25 (*m*, H–C(1)); 7.19–7.34, 7.39–7.44 (2*m*, 3 Ph). ^{13}C-NMR[4]): 22.0 (C(8)); 24.9 (C(2)); 34.2 (C(7)); 34.7 (C(3)); 54.8 (C(9)); 66.2 (C(1)); 66.7 (CH_2O); 69.9 (C(5)); 86.5 (Ph_3C); 121.8 (CN); 127.0, 127.8, 128.7 (arom. CH); 143.9 (arom. C); 170.6, 171.0 (C(4), C(6)). CI-MS (NH_3): 450 (7), 449 (37), 448 (100, M^+), 244 (13), 243 (58), 206 (23), 174 (15). Anal. calc. for $C_{30}H_{29}N_3O$: C 80.51, H 6.53, N 9.33; found: C 80.36, H 6.76, N 9.10.

(5S)-5-(Bromomethyl)pyrrolidin-2-one (**8**) [6]. To an ice-cooled suspension of (5*S*)-5-(hydroxymethyl)pyrrolidin-2-one (**7**) [6] (5.0 g, 43 mmol) and Ph_3P (11.6 g, 44 mmol) in anh. MeCN (100 ml) was added within 30 min a soln. of CBr_4 (14.5 g, 44 mmol) in anh. MeCN (40 ml). The resulting soln. was stirred for 70 h at 25°, until no more 7 was detectable (TLC (CH_2Cl_2/MeOH 5:1): R_f (**7**) 0.35, R_f (**8**) 0.67). Hexane/H_2O 1:1 (300 ml) was quickly added to the stirred mixture, whereupon Ph_3PO precipitated. After filtration, the org. phase was discarded, the aq. phase extracted with CH_2Cl_2 (8 × 100 ml) and Et_2O (2 × 100 ml), the combined org. extract dried ($MgSO_4$) and evaporated, and the residue dried at 25°/0.05 Torr for 5 h: 7.6 g (98%) of colorless crystals, which contained only traces of Ph_3PO and were used in the next step without purification. Anal. pure **8** was obtained by bulb-to-bulb distillation (116–125°/0.04 mbar). M.p. 77–80°. $[\alpha]_D = -27.4$ ($c = 5$, EtOH). IR: 3410*m*, 3190*w*, 2960*m*, 1685*s*, 1410*m*, 1380*m*, 1330*m*, 1280*m*, 1265*m*, 1080*w*, 1050*w*. ^{1}H-NMR: 1.86–1.98 (*m*, 1 H–C(4)); 2.29–2.57 (*m*, CH_2(3), 1 H–C(4)); 3.37–3.51 (*m*, CH_2Br); 4.00–4.08 (*m*, H–C(5)); 7.12 (br. *s*, NH). ^{13}C-NMR: 25.5, 29.9 (C(3), C(4)); 36.6 (CH_2Br); 55.0 (C(5)); 178.3 (C=O). CI-MS (NH_3): 197 (96), 195 (98, $[M + NH_4]^+$), 180 (33), 178 (34), 117 (100), 115 (40), 100 (59), 98 (55), 84 (17).

*(2S)-2-(Bromomethyl)-5-ethoxy-3,4-dihydro-2*H*-pyrrole* (**9**). A soln. of $(Et_3O)BF_4$ (7.6 g, 40 mmol) in anh. CH_2Cl_2 (30 ml) was added within 15 min to a soln. of **8** (5.48 g, 31 mmol) in anh. CH_2Cl_2 (30 ml), and the mixture was stirred under reflux for 22 h. After cooling to 0°, K_2CO_3 (7.3 g in 10 ml of H_2O) was added and stirring continued for 10 min. Then H_2O (100 ml) was added, the aq. phase extracted with CH_2Cl_2 (4 × 80 ml), the combined org. phase dried ($MgSO_4$) and evaporated, and the remaining oil distilled: colorless **9** (4.95g, 78%). B.p. 52–55°/0.09 Torr. TLC (AcOEt): R_f 0.59 $[\alpha]_D = -36.5$ ($c = 1$, EtOH). IR: 2960*s*, 2895*m*, 1630*s*, 1470*w*, 1450*m*, 1425*w*, 1400*m*, 1380*s*, 1340*s*, 1280*m*, 1120*w*, 1090*w*, 1025*s*, 915*s*, 870*m*, 650*m*. ^{1}H-NMR: 1.32 (*t*, $J = 7.1$, Me-CH_2O); 1.82–1.94 (*m*, 1 H–C(4)); 2.14–2.27 (*m*, 1 H–C(4)); 2.41–2.63 (*m*, CH_2(3)); 3.46 (*dd*, $J = 10.0$, 6.5, 1 H, CH_2Br); 3.61 (*dd*, $J = 10.0$, 3.8, 1 H, CH_2Br); 4.13–4.27 (*m*, H–C(5), MeCH_2O). ^{13}C-NMR: 14.3 ($MeCH_2O$); 27.4,

31.6 (C(3), C(4)); 39.4 (CH_2Br); 64.2 (MeCH_2O); 66.9 (C(5)); 173.8 (C(2)). MS: 207 (4, M^+), 205 (4), 112 (42), 84 (100), 82 (17), 70 (5), 56 (16), 41 (15).

*[(2S)-2-(Bromomethyl)-3,4-dihydro-2*H*-pyrrol-5-yl](pyrrolidin-2-ylidene)acetonitrile* (**2f**). CF_3COOH (2 ml) was added within 10 min to a soln. of **9** (4.34 g, 21 mmol) and **5** (0.65 g, 6 mmol) in anh. 1,2-dichloroethane (4.3 ml) at 25°. The soln. was stirred for 6 h at 60°, until no more **5** was detectable (TLC (AcOEt/hexane 2:1): R_f (**9**) 0.52, R_f (**5**) 0.44, R_f (**2f**) 0.37). The mixture was cooled to 25°, diluted with CH_2Cl_2 (10 ml) and washed with sat. aq. $NaHCO_3$ soln. (3 × 20 ml). The aq. layer was extracted with CH_2Cl_2 (6 × 20 ml) and the combined org. phase dried ($MgSO_4$) and evaporated. FC (7 × 42-cm column, hexane/AcOEt 2:1) gave colorless **2f**, which was recrystallized from CH_2Cl_2/hexane: 921 mg (57% based on **5**) of anal. pure, white **2f**. Recrystallization of the mother liquor afforded further 80 mg of **2f** with the same m.p. Combined yield 62%. M.p. 147–148°. $[\alpha]_D = -72.5$ ($c = 1$, $CHCl_3$). IR: 2960*m*, 2880*w*, 2200*s*, 1610*s*, 1560*s*, 1480*w*, 1450*w*, 1420*w*, 1310*m*, 1290*m*, 1030*w*. ^{1}H-NMR[4]): 1.67–1.80 (*m*, 1 H–C(2)); 2.05–2.20 (*m*, 1 H–C(2), CH_2(8)); 2.73–2.99 (*m*, CH_2(3), CH_2(7)); 3.48 (*dd*, $J = 10.0, 6.1$, 1 H, CH_2Br); 3.55 (*dd*, $J = 10.0, 5.1$, 1 H, CH_2Br); 3.69–3.77 (*m*, CH_2(9)); 4.35–4.40 (*m*, H–C(1)). ^{13}C-NMR[4]): 21.6 (C(8)); 26.8 (C(2)); 33.1 (C(7)); 36.4 (C(3)); 38.1 (CH_2Br); 50.2 (C(9)); 69.7 C(C(5)); 71.1 (C(1)); 121.4 (CN); 170.4 (C(4)); 172.3 (C(6)). MS: 269 (11), 268 (5, M^+), 267 (11), 188 (8), 175 (13), 174 (100), 86 (9), 84 (15), 41 (8). Anal. calc. for $C_{11}H_{14}BrN_3$: C 49.27, H 5.26, N 15.67; found: C 49.14, H 5.37, N 15.51.

*[(2S)-2-(Cyanomethyl)-3,4-dihydro-2*H*-pyrrol-5-yl](pyrrolidin-2-ylidene)acetonitrile* (**2g**). A suspension of **2f** (1.8 g, 7 mmol) and NaCN on Al_2O_3 [7] (11.5 g) in toluene (25 ml) was stirred under N_2 for 50 h at 90°. The suspension was diluted with CH_2Cl_2 (30 ml), the solid filtered off and washed with CH_2Cl_2 (3 × 50 ml), and the filtrate evaporated. The crude, colorless product (1.79 g) was chromatographed (5 × 30-cm column, AcOEt/hexane 2:1), then recrystallized (CH_2Cl_3/hexane) at 0°. Drying at 25°/0.05 Torr afforded 1.14 g (79%) of anal. pure **2g**. Colorless needles. M.p. 163–164°. TLC (AcOEt/hexane 2:1): R_f 0.24. $[\alpha]_D = +10.2$ ($c = 1$, $CHCl_3$). IR: 3150*w*, 2860*w*, 2250*m*, 2190*m*, 1610*s*, 1550*s*, 1460*w*, 1370*w*, 1340*w*, 1290*m*, 1100*m*, 990*w*, 900*s*, 640*m*. ^{1}H-NMR[4]): 1.54–1.67 (*m*, 1 H–C(2)); 2.07–2.26 (*m*, 1 H–C(2), CH_2(8)); 2.59 (*AB* of *ABX*, $J_{AB} = 16.5$, $J_{AX} = 6.6$, $J_{BX} = 5.8$, CH_2(CN)); 2.73–3.01 (*m*, CH_2(3), CH_2(7)); 3.64–3.77 (*m*, CH_2(9)); 4.26–4.35 (*m*, H–C(1)); 10.50 (br. *s*, NH). ^{13}C-NMR[4]): 21.5 (C(8)); 25.1 (C(2)); 27.7 (C(7)); 32.7 (CH_2CN); 37.0 (C(3)); 49.1 (C(9)); 67.4 (C(1)); 69.5 (C(5)); 118.2 (CH_2CN); 121.3 (CN–C(5)); 170.5 (C(4)); 172.9 (C(6)). MS: 214 (9, M^+), 175 (11), 174 (100), 146 (4), 145 (5), 132 (4), 105 (6), 41 (17), 39 (9). Anal. calc. for $C_{12}H_{14}N_4$: C 67.27, H 6.59, N 26.15; found: C 67.24, H 6.57, N 26.02.

*[(2S)-2-(Aminoethyl)-3,4-dihydro-2*H*-pyrrol-5-yl](pyrrolidin-2-ylidene)acetonitrile* (**2h**). To a suspension of **2g** (96 mg, 0.5 mmol) and NaOH (0.6 g, 15 mmol) in EtOH (3 ml) and H_2O (0.5 ml) was added activated *Raney*-Ni (0.5 g). The total volume of the suspension was adjusted to 10 ml by addition of EtOH, and after degassing the suspension by three freeze-pump-thaw cycles, it was set under 3 bar of H_2. After stirring for 21 h at 25°, no more **2g** was detectable (TLC (AcOEt/hexane 2:1): R_f (**2g**) 0.24, R_f (**2h**) 0). The catalyst was filtered off over *Celite*, the soln. evaporated to 2 ml and transferred to a separatory funnel with H_2O (3 ml). The pH of the soln. was adjusted to 10–11 with aq. sat. NaOH soln. Extraction with CH_2Cl_2 (6 × 3 ml), drying (Na_2SO_4), and evaporation afforded, after drying at 25°/0.05 Torr for 7 h, 91 mg (93%) of **2h** as a greenish oil, which was used in the next step without further purification. IR (neat): 3500–3100*w*, 2940*m*, 2880*m*, 2200*m*, 1660*w*, 1610*s*, 1560*s*, 1450*m*, 1430*m*, 1370*w*, 1340*w*, 1300*m*, 1250*w*, 1130*w*, 1080*w*, 980*w*. ^{1}H-NMR[4]): 1.00–3.00 (br. *s*, NH_2); 1.51–1.86 (*m*, 1 H–C(2), $CH_2CH_2NH_2$); 1.96–2.05 (*m*, CH_2(8)); 2.11–2.22 (*m*, 1 H–C(2)); 2.72–2.95 (*m*, $CH_2CH_2NH_2$, CH_2(3), CH_2(7)); 3.77 (*t*, $J = 7.1$, CH_2(9)); 4.00–4.10 (*m*, H–C(1)); 5.30 (*s*, NH). ^{13}C-NMR[4]): 21.8 (C(8)); 28.3 (C(2)); 34.3 (C(3), C(7)); 39.7, 40.1 ($CH_2CH_2NH_2$); 54.0 (C(9)); 65.1 (C(1)); 69.4 (C(5)); 121.8 (CN); 169.7, 170.6 (C(4), C(6)). MS: 218 (13, M^+), 189 (16), 188 (100), 175 (29), 174 (41), 160 (7), 147 (8), 134 (8), 42 (9), 41 (17).

*{(2S)-[2-(Benzoylamino)ethyl]-3,4-dihydro-2*H*-pyrrol-5-yl}(pyrrolidin-2-ylidene)acetonitrile* (**2i**). Benzoyl chloride (0.2 ml, 1.7 mmol) was added dropwise to an ice-cooled soln. of crude **2h** (231 mg, 1.1 mmol) in anh. pyridine (0.7 ml). After stirring for 12 h at 25°, the mixture was diluted with CH_2Cl_2 (10 ml) and washed with H_2O. The aq. phase was reextracted with CH_2Cl_2 and the combined org. phase washed with 1M HCl, 1M NaOH, and H_2O, dried ($NaSO_4$), and evaporated. The crude product was chromatographed (2 × 10-cm column, CH_2Cl_2/MeOH 25:1) to give a yellow oil. Crystallization from $CHCl_3$/hexane gave 100 mg (29%) of anal. pure **2i** (m.p. 131–132°). From the mother liquor, additional 38 mg of **2i** (m.p. 131–132°) were obtained. Combined yield: 138 mg (40%). TLC (AcOEt/hexane 3:1): R_f 0.14. $[\alpha]_D = +10.4$ ($c = 0.63$, $CHCl_3$). IR: 3550–3200*m*, 3020*w*, 2980*m*, 2200*m*, 1650*s*, 1610*s*, 1560*s*, 1520*s*, 1490*m*, 1400*m*, 1340*m*, 1290*m*, 1200*m*, 1080*w*, 900*w*. ^{1}H-NMR[4]): 1.52–1.65 (*m*, 1 H–C(2)); 1.75–2.05 (*m*, CH_2CH_2NH, CH_2(8)); 2.12–2.24 (*m*, 1 H–C(2)); 2.71–2.96 (*m*, CH_2(3), CH_2(7)); 3.48–3.72 (*m*, CH_2CH_2NH, CH_2(9)); 3.80 (br. *s*, NH); 4.07–4.14 (*m*, H–C(1)); 6.46 (br. *s*, CH_2CH_2NH); 7.37–7.53, 7.70–7.76 (2*m*, arom. H). ^{13}C-NMR[4]): 21.8 (C(8)); 28.4 (C(2)); 33.6, 35.6, 36.4, 38.2 (C(3), (C(7), CH_2CH_2NH); 51.5 (C(9)); 67.9 (C(1)); 69.9 (C(5)); 121.7 (CN); 126.8, 128.5, 131.3 (arom. CH); 134.6 (arom. C); 167.4 (C=O);

170.3, 170.8 (C(4), C(6)). MS: 322 (4, M^+), 189 (14), 188 (100), 175 (7), 174 (23), 105 (36), 77 (40), 51 (9), 41 (9). Anal. calc. for $C_{19}H_{22}N_4O$: C 70.78, H 6.88, N 17.38; found: C 70.68, H 6.70, N 17.41.

3. *Substrates.* (E/Z)*-3-Methyl-5-phenylpent-2-enenitrile* (**13c**/**15c**). Diethyl cyanomethylphosphonate (11.3 g, 63.8 mmol) was slowly added to an ice-cooled suspension of NaH (1.44 g, 60 mmol) in anh. diglyme (60 ml). After stirring at 25° for 30 min, the resulting clear soln. was cooled to 0°. Benzylacetone (= 4-phenylbutan-2-one; **10**; 8.89 g, 60 mmol) was then added within 30 min. The reaction was allowed to warm to 25°, and stirring was continued for 5 h [13]. The mixture was transferred to a separatory funnel with Et_2O (120 ml) and H_2O (120 ml) and extracted with Et_2O (3 × 40 ml). The combined org. layers were dried ($MgSO_4$) and evaporated. FC (7 × 32-cm column, hexane/Et_2O 20:3) afforded 7.24 g (70%) of **13c**/**15c** 2.2:1 as a colorless oil. A 4-g portion was rechromatographed, affording 550 mg of enriched **13c** (> 93.6% (*E*) by GC) and 110 mg of enriched **15c** (> 90.0% (*Z*) by GC).

(E)*-Isomer* **13c**: TLC (hexane/Et_2O 10:2): R_f 0.27. GC (155–190°, 1°/min): t_R 10.2. IR: 3060*w*, 3020*w*, 2950*w*, 2220*s*, 1630*m*, 1605*w*, 1495*m*, 1455*m*, 1430*m*, 1385*m*, 1030*w*, 910*w*, 700*s*. ^{1}H-NMR: 2.09 (*s*, Me); 2.50, 2.80 (2*t*, J = 8.5, CH_2(4), CH_2(5)); 5.09 (*s*, H–C(2)); 7.15–7.34 (*m*, arom. H). ^{13}C-NMR: 21.1 (Me); 33.4, 40.1 (C(4), C(5)); 95.7 (C(2)); 117.0 (CN); 126.4, 128.1, 128.5 (arom. CH); 140.0 (arom. C); 164.1 (C(3)). MS: 171 (7, M^+), 92 (7), 91 (100), 65 (10), 51 (4), 39 (5).

(Z)*-Isomer* **15c**: TLC (hexane/Et_2O 10:2): R_f 0.26. GC (155–190°, 1°/min): t_R 8.5. IR: 3090*w*, 3060*w*, 3020*w*, 2950*w*, 2220*s*, 1640*m*, 1610*w*, 1495*m*, 1450*m*, 1445*m*, 1030*w*, 700*s*. ^{1}H-NMR: 1.88 (*d*, J = 1.5, Me); 2.66–2.84 (*m*, CH_2(4), CH_2(5)); 5.06 (*d*, J = 1.1, H–C(2)); 7.12–7.31 (*m*, arom. H). ^{13}C-NMR: 22.9 (Me); 33.7, 37.7 (C(4), C(5)); 96.2 (C(2)); 116.6 (CN); 126.2, 128.2, 128.4 (arom. CH); 139.9 (arom. C); 164.2 (C(3)). MS: 171 (19, M^+), 92 (8), 91 (100), 77 (2), 65 (9), 51 (3), 39 (4).

(E/Z)*-Diethyl (2-Methyl-4-phenylbut-1-enyl)phosphonate* (**13d**/**15d**). At –78°, 1.7M BuLi in hexane (22.6 ml, 38.4 mmol) was slowly added to a soln. of tetraethyl methylenebisphosphonate (10.5 g, 36.6 mmol) in THF (19 ml). The clear soln. was allowed to warm to 25°. Then, **10** (5.9 ml, 40.3 mmol) was added and the mixture stirred at 25° for 3 h [14]. The mixture was then diluted with H_2O (200 ml) and Et_2O (200 ml), and extracted with Et_2O (3 × 100 ml), the combined org. phase dried ($MgSO_4$) and evaporated, and the resulting colorless oil chromatographed (7 × 45-cm column, hexane/AcOEt 1:3) to afford 2.67 g of enriched **13d** (> 94% (*E*) by GC), 0.75 g of enriched **15d** (> 92% (*Z*) by GC), and 4.12 g of **13d**/**15d** (combined yield 73%). Further purification of the enriched isomers was achieved by bulb-to-bulb distillation (130–160°/0.03 mbar): 2.11 g of **13d** (> 98% (*E*) by GC) and 0.62 g of **15d** (> 98% (*Z*) by GC).

(E)*-Isomer* **13d**: TLC (hexane/AcOEt 1:3): R_f 0.23. GC (180° isotherm): t_R 28.4. HPLC (system *B*): t_R 35.4. IR: 2980*m*, 1630*m*, 1490*w*, 1435*w*, 1380*w*, 1200*m*, 1150*w*, 1090*w*, 1050*s*, 1020*s*, 960*s*. ^{1}H-NMR: 1.29 (*t*, J = 7.1, *Me*CH_2O); 2.12 (*d*, J = 2.5, Me–C(2)); 2.44–2.50, 2.77–2.82 (2*m*, CH_2(3), CH_2(4)); 3.99 (*quint.*, J(H,H) = J(P,H) = 7.1, CH_3CH_2O); 5.37 (*d*, J(P,H) = 18.3, H–C(1)); 7.14–7.30 (*m*, arom. H). ^{13}C-NMR: 16.1 (*d*, J(C,P) = 6.6, *Me*CH_2O); 19.8 (*d*, J(C,P) = 7.0, *Me*–C(2)); 33.4 (CH_2(4)); 42.8 (*d*, J(C,P) = 22.7, CH_2(3)); 60.9 (*d*, J(C,P) = 5.5, Me*C*H_2O); 112.0 (*d*, J(C,P) = 187.7, C(1)); 125.9, 128.1, 128.2 (arom. CH); 140.5 (arom. C); 161.5 (*d*, J(C,P) = 5.9, C(2)). MS: 283 (10), 282 (60, M^+), 145 (9), 144 (50), 143 (23), 129 (51), 128 (17), 91 (100), 65 (19).

(Z)*-Isomer* **15d**: TLC (hexane/AcOEt 1:3): R_f 0.30. GC (180° isotherm): t_R 19.6. HPLC (system *B*): t_R 16.8. IR: 2990*s*, 1630*m*, 1490*w*, 1440*m*, 1390*w*, 1290*w*, 1200*m*, 1150*m*, 1090*m*, 1050*s*, 1020*s*, 960*s*, 880*w*. H-NMR: 1.31 (*t*, J = 7.1, *Me*CH_2O); 1.94 (*d*, J = 1.0, Me–C(2)); 2.78–2.85 (*m*, CH_2CH_2); 3.98–4.08 (*m*, MeCH_2O); 5.41 (*ABX*, J_{AB} = J(P,H) = 18.4, J_{AX} = 1.3, H–C(1)); 7.16–7.20, 7.21–7.28 (2*m*, arom. H). ^{13}C-NMR: 16.3 (*d*, J(C,P) = 6.8, *Me*CH_2O); 25.8 (*d*, J(C,P) = 24.8, *Me*–C(2)); 34.5 (CH_2(4)); 36.7 (*d*, J(C,P) = 6.7, CH_2(3)); 61.0 (*d*, J(C,P) = 5.7, MeCH_2O); 112.9 (*d*, J(C,P) = 188.9, H–C(1)); 125.8, 128.2, 128.3 (arom. CH); 141.2 (arom. C); 162.3 (*d*, J(C,P) = 7.5, C(2)). MS: 282 (36, M^+), 144 (34), 143 (13), 129 (29), 91 (100), 65 (13).

2-Methyl-1-(methylsulfonyl)-4-phenylbutan-2-ol (**11a**). At –78°, 1.7M BuLi in hexane (200 ml, 0.34 mol) was slowly added over 2 h to dimethyl sulfone (31.9 g, 0.34 mol) [15] in anh. THF (480 ml). The resulting white suspension was allowed to warm to 10°, cooled again to –78°, and after addition of **10** (60 ml, 0.41 mol) allowed to warm to 25° in the cooling bath within 17 h. The mixture was washed with sat. NH_4Cl soln. (3 × 300 ml) and brine (1 × 300 ml), the org. phase dried ($MgSO_4$) and evaporated, and the colorless crude product recrystallized from AcOEt/hexane. The crystals were washed with hexane and Et_2O: 61.0 g of **11a** (m.p. 96–97°). From the mother liquor, additional 5.1 g of **11a** (m.p. 96–97°) were obtained by recrystallization. Combined yield: 66.1 g (80%). TLC (AcOEt): R_f 0.39. IR: 3600*w*, 3530*m*, 3080*w*, 3060*w*, 3020*s*, 2980*m*, 2930*m*, 2860*w*, 1600*w*, 1490*m*, 1450*m*, 1410*m*, 1380*m*, 1310*s*, 1130*s*, 1060*m*, 960*s*, 850*m*, 700*s*. ^{1}H-NMR: 1.54 (*s*, Me); 2.01 (*m*, CH_2(3)); 2.74 (*m*, CH_2(4)); 3.03 (*s*, $MeSO_2$); 3.18 (*s*, overlapping *d*, OH); 3.21 (*d*, J = 15.0, H–C(1)); 3.33 (*d*, J = 14.4, H–C(1)); 7.20–7.33 (*m*, arom. H). ^{13}C-NMR: 27.0 (Me); 30.0 (CH_2); 44.2 (CH_2); 44.3 ($MeSO_2$); 63.3 (CH_2(1)); 71.5 (C(2)); 126.0, 128.3,

128.5 (arom. CH); 141.3 (arom. C). MS: 243 (0.01, $[M + H]^+$), 146 (11), 145 (100), 144 (58), 137 (17), 129 (38), 117 (11), 105 (20), 104 (10), 91 (73), 81 (14), 77 (12), 43 (22).

1-Methyl-1-[(methylsulfonyl)methyl]-3-phenylpropyl Acetate (**11b**). A mixture of **11a** (61 g, 0.25 mol), Ac_2O (35.7 ml, 0.38 mol), Et_3N (52.7 ml, 0.38 mol), and 4-(dimethylamino)pyridine (DMAP; 2.45 g, 0.02 mol) [16] was stirred for 40 h at 25° until no more **11a** was detectable (TLC (hexane/AcOEt 1:1): R_f (**11a**) 0.14, R_f (**11b**) 0.29). The mixture was dissolved in Et_2O (3 l) and extracted with 1M aq. HCl (2 × 500 ml). The aq. extracts were reextracted with Et_2O and the combined org. phases washed with sat. $NaHCO_3$ soln. (1 × 500 ml) and H_2O (1 × 500 ml), dried ($MgSO_4$), and evaporated. The crude product was chromatographed (11 × 26-cm column, hexane/AcOEt 2:1): 56.0 g (78%) of **11b**. Colorless crystals. M.p. 102–103°. IR: 3060*w*, 3020*s*, 2930*m*, 1730*s*, 1495*m*, 1450*m*, 1395*m*, 1370*s*, 1315*s*, 1290*m*, 1240*s*, 1160*m*, 1135*s*, 1125*s*, 1080*m*, 1060*m*, 1020*m*, 960*m*, 940*m*. ^{1}H-NMR: 1.77 (*s*, Me); 2.05 (*s*, MeCO); 2.19–2.30 (*m*, 1 H–C(2)); 2.42–2.52 (*m*, 1 H–C(2)); 2.65–2.73 (*m*, CH_2(3)); 2.95 (*s*, $MeSO_2$); 3.60 (*d*, J = 14.3, 1 H, $MeSO_2CH_2$); 3.90 (*d*, J = 14.3, 1 H, $MeSO_2CH_2$); 7.18–7.32 (*m*, arom. H). ^{13}C-NMR: 22.1 (*Me*CO); 24.2 (*Me*–C(1)); 29.7, 40.6 (CH_2(2), CH_2(3)); 43.6 ($MeSO_2$); 59.6 ($MeSO_2CH_2$); 80.8 (C(1)); 126.1, 128.4, 128.5 (arom. CH); 140.8 (arom. C); 170.6 (CO). CI-MS (NH_3): 302 (16, $[M + NH_4]^+$), 243 (14), 242 (100), 145 (11).

Methyl (E/Z)-2-Methyl-4-phenylbut-1-enyl Sulfone (**13e**/**15e**). Within 2 h, 1.7M BuLi in hexane (127 ml, 0.22 mol) was slowly added to a soln. of **11b** (56 g, 0.20 mol) in anh. THF (680 ml) keeping the internal temp. below −73° to prevent formation of allyl sulfones. After additional 2 h, sat. NH_4Cl soln. (100 ml) was added to the cold mixture, and the resulting suspension allowed to warm to −20°. Additional sat. NH_4Cl soln. (300 ml) and Et_2O (500 ml) were added, and the aq. phase was extracted with Et_2O (3 × 100 ml). The combined org. extracts were dried ($MgSO_4$) and evaporated. FC (11 × 26-cm column, hexane/AcOEt 10:4) afforded 32.6 g (74%) of **13e**/**15e** 1.8:1 as a colorless oil. This oil (10 g) was rechromatographed twice (7 × 41-cm column, hexane/AcOEt 10:3) to give 3.1 g of pure **13e** (> 99.9% (*E*) by GC) and 400 mg of enriched **15e** (> 90.0% (*Z*) by GC).

(E)-Isomer **13e**: TLC (hexane/AcOEt 1:1): R_f 0.30. GC (185–210°, 1°/min): t_R 21.8. IR: 3090*w*, 3060*w*, 3020*m*, 2940*w*, 2860*w*, 1630*m*, 1600*w*, 1495*w*, 1455*m*, 1300*s*, 1130*s*, 1080*w*, 960*m*, 700*m*. ^{1}H-NMR: 2.20 (*s*, Me–C(2)); 2.48, 2.82 (2*t*, J = 8, CH_2(3), CH_2(4)); 2.84 (*s*, overlapping *t*, $MeSO_2$); 6.03 (*s*, H–C(1)); 7.14–7.33 (*m*, arom. H). ^{13}C-NMR: 17.7 (*Me*–C(2)); 33.3, 41.8 (CH_2(3), CH_2(4)); 43.6 ($MeSO_2$); 125.8, 126.3, 128.2, 128.5 (CH(1), arom. CH); 139.9 (arom. C); 156.9 (C(2)). CI-MS (NH_3): 243 (14), 242 (100, $[M + NH_4]^+$), 145 (6), 108 (6), 91 (9).

(Z)-Isomer **15e**: TLC (hexane/AcOEt 1:1): R_f 0.29. GC (185–210°, 1°/min): t_R 18.6. IR: 3090*w*, 3060*w*, 3020*m*, 2935*m*, 2860*w*, 1630*m*, 1605*w*, 1500*m*, 1455*m*, 1440*s*, 1410*w*, 1300*s*, 1230*m*, 1135*s*, 760*m*, 830*m*, 700*m*. ^{1}H-NMR: 1.98 (*d*, *J*(allyl.) = 1.3, Me–C(2)); 2.74 (*s*, $MeSO_2$); 2.80–2.96 (*m*, CH_2CH_2); 6.12 (*s*, H–C(1)); 7.16–7.32 (*m*, arom. H). ^{13}C-NMR: 24.6 (*Me*–C(2)); 34.3, 34.4 (CH_2(3), CH_2(4)); 43.8 ($MeSO_2$); 125.9, 126.3 128.3, 128.5 (CH(1), arom. CH); 140.7 (arom. C); 157.5 (C(2)). CI-MS (NH_3): 243 (14), 242 (100, $[M + NH_4]^+$), 145 (4), 91 (6).

2-Methyl-4-phenyl-1-(phenylsulfonyl)butan-2-ol (**12a**). At −78°, 1.6M BuLi in hexane (120 ml, 0.19 mol) was slowly added to a suspension of methyl phenyl sulfone (30 g, 0.19 mmol) in anh. THF (500 ml). The suspension was stirred at 25° for 14 h, cooled again to −78°, and **10** (33 ml, 0.22 mol) was added over 30 min. The mixture was allowed to warm to 25° in the cooling bath overnight, washed with sat. NH_4Cl soln. (3 × 200 ml) and brine (1 × 200 ml), dried ($MgSO_4$), and evaporated. The crude product was chromatographed (11 × 35-cm column, hexane/AcOEt 2:1): 50 g (85%) of **12a**. Colorless oil. TLC (hexane/AcOEt 5:1): R_f 0.18. IR: 3535*w*, 3075*w*, 3020*m*, 2940*w*, 1495*w*, 1450*m*, 1315*s*, 1310*s*, 1150*s*, 1075*m*, 955*w*, 700*m*, 685*m*. ^{1}H-NMR: 1.50 (*s*, Me); 1.97 (*dd*, *AB* of *ABXX'*, J_{AB} = 11.0, J_{AX} = 6.3, J_{BX} = 5.7, CH_2(3)); 2.70 (*m*, *XX'* of *ABXX'*, CH_2(4)); 3.30 (*d*, J = 14.1, 1 H–C(1)); 3.38 (*d*, J = 14.1, 1 H–C(1)); 7.13–7.28 (*m*, Ph–C(4)); 7.52–7.68, 7.91–7.94 (2*m*, $PhSO_2$). ^{13}C-NMR: 27.0 (Me); 30.0, 44.2 (C(3), C(4)); 64.9 (C(1)); 72.1 (C(2)); 125.8, 127.4, 128.2, 128.3, 129.3, 133.8 (arom. CH); 141.0, 141.5 (arom. C). MS: 304 (3, M^+), 175 (9), 174 (100), 166 (61).

1-Methyl-3-phenyl-1-[(phenylsulfonyl)methyl]propyl Acetate (**12b**). As described for **11b**, with **12a** (37.7 g, 0.17 mol). The crude product was chromatographed (11 × 23-cm column, hexane/AcOEt 3:1): 38.2 g (66%) of **12b**. Colorless crystals. M.p. 61–62°. TLC (hexane/AcOEt 3:1): R_f 0.27. IR: 3020*m*, 2935*m*, 2860*w*, 1730*s*, 1670*m*, 1500*w*, 1450*m*, 1370*m*, 1320*s*, 1310*s*, 1240*s*, 1150*s*, 1085*s*, 1060*m*, 1020*m*, 960*w*, 700*s*, 685*s*, 660*m*. ^{1}H-NMR: 1.73 (*s*, Me); 1.83 (*s*, Me); 2.15–2.25 (*m*, 1 H–C(2)); 2.41–2.52 (*m*, 1 H–C(2)); 2.58–2.74 (*m*, CH_2(3)); 3.72 (*d*, J = 14.5, 1 H, $PhSO_2CH_2$); 3.91 (*d*, J = 14.5, 1 H, $PhSO_2CH_2$); 7.16–7.30 (*m*, Ph–C(3)); 7.52–7.66, 7.90–7.93 (2*m*, $PhSO_2$). ^{13}C-NMR: 21.9 (Me); 24.4 (Me); 29.7, 40.9, 60.6 (CH_2(1), CH_2(3), CH_2(4)); 80.8 (C(2)); 126.0, 127.9, 128.4, 129.2, 133.6 (arom. CH); 140.9, 141.0 (arom. C); 170.7 (CO). CI-MS (NH_3): 366 (6), 365 (20), 364 (92, $[M + NH_4]^+$), 305 (19), 304 (100), 52 (9).

(E/Z)-2-Methyl-4-phenylbut-1-enyl Phenyl Sulfone **13f**/**15f**. Within 90 min, 1.7M BuLi in hexane (73 ml, 0.13 mol) was slowly added to a soln. of **12b** (39.5 g, 0.11 mol) in anh. THF (450 ml) keeping the internal temp.

below −73° to prevent formation of allyl sulfones. After additional 90 min, the reaction was quenched and worked up as described for **13e**/**15e**: 28.8 g (88%) of **13f**/**15f** 1.9:1 as a yellowish oil. FC (7 × 36-cm column, hexane/AcOEt 3:1) afforded 14.5 g of enriched **13f** (> 72% (*E*) by GC) and 13.3 g of **13f**/**15f** 1:1 (combined yield 85%). A portion of each fraction (6 and 8 g, resp.) was rechromatographed twice to give 2.5 g of pure **13f** (> 99% (*E*) by GC) and 1.1 g of enriched **15f** (> 96% (*Z*) by GC).

(E)-Isomer **13f**: TLC (hexane/AcOEt 2:1): R_f 0.44. GC (230° isotherm): t_R 19.7. IR: 3060*w*, 3020*m*, 2940*w*, 1630*m*, 1600*w*, 1490*w*, 1445*w*, 1310*m*, 1300*s*, 1235*w*, 1145*s*, 1080*s*, 695*m*, 680*m*. ^{1}H-NMR: 2.15 (*s*, Me); 2.43 (2*t*, *J* = 8, CH_2(3), CH_2(4)); 6.11 (*s*, H–C(1)); 7.05 (*d*, *J* = 6.3, 2 H, Ph–C(4)); 7.14–7.26 (*m*, 3 H, Ph–C(4)); 7.48–7.63 (*m*, 2 H, $PhSO_2$); 7.80–7.83 (*dd*, *J* = 6.9, 1.5, 3 H, $PhSO_2$). ^{13}C-NMR: 17.9 (Me); 33.3, 42.1 (C(3), C(4)); 126.3, 126.6, 127.0, 128.2, 128.5, 129.0, 132.9 (C(1), arom. CH); 140.0, 142.3 (arom. C); 156.4 (C(2)). CI-MS (NH_3): 305 (20), 304 (100, $[M + NH_4]^+$), 287 (7), 145 (10), 46 (10).

(Z)-Isomer **15f**: TLC (hexane/AcOEt 2:1): R_f 0.45. GC (230° isotherm): t_R 16.8. IR: 3090*m*, 3060*m*, 3020*s*, 2940*m*, 2860*m*, 1630*s*, 1605*m*, 1590*m*, 1500*m*, 1450*s*, 1300*s*, 1145*s*, 1085*s*, 1025*w*, 830*m*, 700*s*, 680*s*. ^{1}H-NMR: 1.88 (*d*, *J* = 1.3, Me); 2.87–2.93 (*m*, CH_2(3), CH_2(4)); 6.17 (*s*, H–C(1)); 7.04 (*d*, *J* = 7.8, 2 H, Ph–C(4)); 7.15–7.31 (*m*, 3 H, Ph–C(4)); 7.46–7.60, 7.80–7.89 (2*m*, $PhSO_2$). ^{13}C-NMR: 24.8 (Me); 34.3, 34.5 (C(3), C(4)); 126.1, 126.4, 127.0, 128.1, 128.3, 129.1, 132.9 (CH(1), arom. CH); 140.7, 142.2 (arom. C); 156.8 (C(2)). CI-MS (NH_3): 306 (7), 305 (20), 304 (100, $[M + NH_4]^+$), 145 (4).

4. *Enantioselective Reduction of* **13a–f** *and* **15a,c,e,f**. *General Procedure*. To the substrate (0.47 mmol) was added a soln. of $CoCl_2 \cdot 6\ H_2O$ (0.94 μmol, 2 mol-%) and 'semicorrin' ligand (1.12 μmol, 2.4 mol-%) in EtOH (0.25 ml) and diglyme (0.21 ml). The clear, dark blue soln. was degassed at 0.01 Torr by three freeze-thaw cycles. The soln. was then transferred under N_2 by syringe into an ampoule containing $NaBH_4$ (17.8 mg, 0.47 mmol) and a magnetic stirring bar. The foaming soln. was immediately degassed by three freeze-pump-thaw cycles. The evacuated ampoule (0.01 Torr) was sealed with a vacuum-tight *Teflon* stopper (*Young* valve) and the soln. stirred at r.t. Towards the end of the reaction, a solid precipitate began to form. After 15–60 h, conversion was quantitative according to GC (*OV 1701*). The mixture was transferred to CH_2Cl_2/H_2O 1:1 (40 ml) and extracted with CH_2Cl_2. The org. phase was washed with H_2O (3 ×), dried ($MgSO_4$), and evaporated. FC afforded the product in 75–96% yield.

5. *Determination of Enantiomeric Excesses*. The enantiomeric excesses of **14b** and **14c** were determined by HPLC of the corresponding (*R*)-1-(1-naphthyl)-ethylamide following the procedures in [17] and [3]. As reference samples, the racemic amide (±)-**14b** and nitrile (±)-**14c** were prepared by catalytic hydrogenation of the α,β-unsaturated precursors (Pd/C, H_2, MeOH) and converted to the (*R*)-1-(1-naphthyl)-ethylamides. HPLC (*Techsil* silica gel 5 μ, 9 mm × 23 cm, hexane/AcOEt 6:1, 27 kg/cm^2, 2.3 ml/min; peak detection with *Kratos Spectroflow 757*, 254 nm): t_R 24.4 (*R*) and 28.9 (*S*) for (*R*)-1-(1-naphthyl)-ethylamide from **14b** and **14c**. For anal. data of **14a** and **14b**: see [3] [17b].

(R)-3-Methyl-5-phenylpentanenitrile ((+)-**14c**). GC (155–190°, 1°/min): t_R 8.8. IR: 3065*w*, 3035*w*, 3005*m*, 2960*s*, 2935*s*, 2880*m*, 2860*m*, 2225*m*, 1605*s*, 1500*s*, 1455*s*, 1425*s*, 1385*m*, 1350*w*, 910*w*, 700*s*. ^{1}H-NMR: 1.14 (*d*, *J* = 6.6, Me); 1.61–1.93 (*m*, H–C(3), CH_2); 2.25–2.40 (*m*, CH_2); 2.60–2.70 (*m*, CH_2); 7.18–7.33 (*m*, arom. H). ^{13}C-NMR: 19.3 (Me); 24.4 (CH_2); 29.8 (CH(3)); 33.0 (CH_2); 37.4 (CH_2); 118.6 (CN); 126.0, 128.2, 128.4 (arom. CH); 141.3 (arom. C). MS: 173 (10, M^+), 158 (20), 105 (8), 92 (27), 91 (100), 77 (6), 65 (10), 51 (5).

The enantiomeric excesses of **14a,d–f** were determined by HPLC with chiral columns. As reference samples, the racemic ester (±)-**14a**, phosphonate (±)-**14d**, and sulfones (±)-**14e** and (±)-**14f** were prepared by catalytic hydrogenation of the α,β-unsaturated precursors (Pd/C, H_2, EtOH).

(+)-(R)-Ethyl 3-Methyl-5-phenylpentanoate (**14a**) [2] [17a]. HPLC (system *A*): t_R 48.5 (*S*), 53.0 (*R*).

(−)-Diethyl (2-Methyl-4-phenylbutyl)phosphonate ((−)-**14d**). TLC (hexane/AcOEt 1:3): R_f 0.19. GC (180° isotherm): t_R 21.4. HPLC (system *B*): t_R 24.6 ((−)-**14d**), 28.2 ((+)-**14d**). IR: 2980*s*, 2920*m*, 1600*w*, 1490*w*, 1450*m*, 1380*w*, 1200*m*, 1150*m*, 1090*m*, 1050*s*, 1020*s*, 960*s*, 820*m*. ^{1}H-NMR: 1.11 (*d*, *J* = 6.6, Me–C(2)); 1.30 (*t*, *J* = 7.1, 2 *Me*CH_2O); 1.51–1.85 (*m*, CH_2CH_2); 1.88–2.00 (*m*, H–C(2)); 2.54–2.69 (*m*, CH_2(1)); 4.01–4.13 (*m*, 2 MeCH_2O); 7.14–7.29 (*m*, arom. H). ^{13}C-NMR: 16.4 (*d*, *J*(C,P) = 5.8, 2 *Me*CH_2O); 20.8 (*d*, *J*(C,P) = 7.7, *Me*–C(2)); 27.9 (*d*, *J*(C,P) = 4.1, C(2)); 32.7 (*d*, *J*(C,P) = 139.1, C(1)); 33.0 (CH_2(4)); 39.9 (*d*, *J*(C,P) = 13.7, CH_2(3)); 61.2 (*d*, *J*(C,P) = 4.3, 2 Me*C*H_2O); 125.7, 128.2 (arom. CH); 142.1 (arom. C). MS: 285 (6), 284 (31, M^+), 180 (73), 179 (18), 152 (25), 138 (100), 125 (15), 111 (29), 110 (12), 91 (52), 82 (11), 65 (12).

(−)-2-Methyl-4-phenylbutyl Methyl Sulfone ((−)-**14e**). TLC (hexane/AcOEt 1:1): R_f 0.46. GC (185–210°, 1°/min): t_R 20.1. HPLC (system *C*): t_R 29.6 ((−)-**14e**), 40.0 ((+)-**14e**); 66% ee. $[\alpha]_D = -14.1$ (*c* = 0.50, $CHCl_3$). IR: 3065*w*, 3020*m*, 2970*w*, 2930*w*, 2860*w*, 1605*w*, 1510*m*, 1440*w*, 1310*s*, 1215*s*, 1140*m*, 960*m*, 930*w*, 700*m*, 680*m*, 660*m*. ^{1}H-NMR: 1.22 (*d*, *J* = 6.8, Me); 1.59–1.72 (*m*, H–C(3)); 1.80–1.92 (*m*, H–C(3)); 2.20–2.28 (*m*, *X* of *ABX*,

H–C(2)); 2.57–2.76 (*m*, CH_2(4)); 2.86 (*s*, overlapping *AB*, $MeSO_2$); 2.97 (*AB* of *ABX*, J_{AB} = 14.0, J_{AX} = 7.7, J_{BX} = 4.9, CH_2(1)); 7.17–7.31 (*m*, Ph). ^{13}C-NMR: 19.9 (*Me*–C(2)); 28.2 (C(2)); 32.8 (CH_2); 38.3 (CH_2); 41.8 ($MeSO_2$); 60.9 (CH_2); 126.0, 128.3, 128.5 (arom. CH); 141.4 (arom. C). CI-MS (NH_3): 246 (5), 245 (14), 244 (100, $[M + NH_4]^+$), 242 (4), 104 (5), 91 (4).

(–)-2-Methyl-4-phenylbutyl Phenyl Sulfone ((–)-**14f**). TLC (hexane/AcOEt 2:1): R_f 0.44. GC (120° isotherm): t_R 15.6. HPLC (system *D*): t_R 37.8 ((–)-**14f**), 42.6 ((+)-**14f**); 40% ee. $[\alpha]_D$ = –8.1 (*c* = 0.48, $CHCl_3$). IR: 3060*m*, 3020*m*, 2960*m*, 2860*m*, 2030*m*, 1605*m*, 1500*m*, 1450*s*, 1305*s*, 1225*m*, 1145*s*, 1085*s*, 700*s*, 680*s*. ^{1}H-NMR: 1.13 (*d*, *J* = 6.8, Me–C(2)); 1.51–1.61 (*m*, H–C(3)); 1.73–1.83 (*m*, H–C(3)); 2.08–2.14 (*m*, *X* of *ABX*, H–C(2)); 2.47–2.66 (*m*, CH_2(4)); 3.01 (*AB* of *ABX*, J_{AB} = 14.2, J_{AX} = 7.4, J_{BX} = 5.1, CH_2(1)); 7.09–7.28 (*m*, Ph–C(4)); 7.51–7.66 (*m*, 3 H, $PhSO_2$); 7.85–7.88 (*m*, 2 H, $PhSO_2$). ^{13}C-NMR: 19.8 (Me); 28.2 (C(2)); 32.6, 38.2, 62.4 (3 CH_2); 125.8, 127.8, 128.2, 128.3, 129.2, 133.5 (arom. CH); 139.9, 141.4 (arom. C). CI-MS (NH_3): 307 (20), 306 (100, $[M + NH_4]^+$).

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