Notes

Enantio- and Diastereoselective Aldol-Addition of Chiral Boron Enolates of Carboxylic Acids to Benzaldehyde

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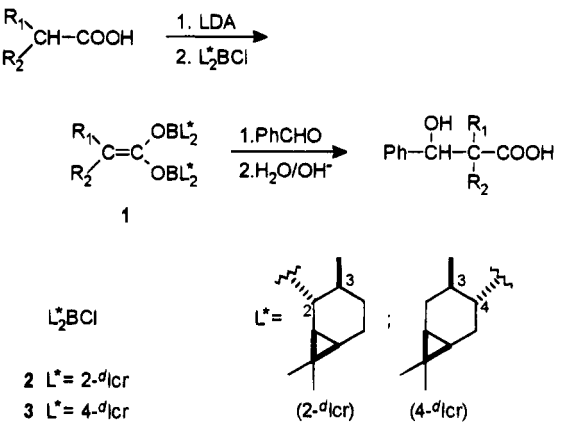
The addition of enolates of carboxylic acids to carbonyl compounds has been widely explored[1] since it is an efficient route to β-hydroxy carboxylic acids, a class of compounds of pharmacological[2] and biosynthetic interest.[3]

In principle, enolates of carboxylic acids are synthetic intermediates which are more advantageous than the analogous enolates of esters[4] and amides[5] because the self-condensation reaction is prevented, the hydrolysis of the addition product to β-hydroxy acid is not necessary and, owing to the lack of *E* and *Z* isomerism, a stereoselective synthesis of *E* and *Z* enols is not required.

Lithium, sodium, and potassium enolates produced by the lithium dialkylamide method or by the alkali metal–arene system, have been widely employed.[1a,b,e] Magnesium and zinc enolates of phenylacetic acid have been prepared with sodium naphthalenide and $MgBr_2$ and $ZnBr_2$ to study the metal chelation effect on the diastereofacial selectivity of the addition reaction to aldehydes.[1c]

Enolboration[6] of propionic acid was achieved with alkylboron triflates (R_2BOTf; R = C_4H_9, c-C_5H_9) in the presence of diisopropylethylamine[1d] and with dicyclohexylchloroborane–triethylamine reagent.[1f] This latter reagent was also successfully employed in the enolization of caproic and phenylacetic acid.[1f]

Scheme 1



The asymmetric aldol–addition of chiral enolates of carboxylic acids has recently been explored in our laboratories.[1g] Chiral boron and titanium enolates of acetic acid were prepared by the transmetalation of dilithiated acid with chiral diisocaranylchloroboranes and chiral diisocaranoxy(chloro)cyclopentadienyltitanates[7] and the enantioselectivity of their addition reaction to benzaldehyde was investigated.[1g]

Since the enantio- and diastereoselection of the addition reaction of prochiral faces of chiral enolates of carboxylic acids to prochiral faces of carbonyl compounds have not been explored, a study of the reaction using representative acids was considered desirable.

In this paper we report the results regarding the aldol-addition of chiral enolborinates of mono- and disubstituted acetic acids to benzaldehyde.

Results and Discussion

The boron enolates **1** of a number of mono- and disubstituted acetic acids were prepared by the transmetalation reaction of dilithiated acids both with (−)-di-2- and (−)-di-4-isocaranylchloroborane (**2** and **3**) in THF at −78 °C.[1g] The addition reactions to benzaldehyde give 2-substituted 3-hydroxy-3-phenylpropionic acids in good yields (Scheme 1). The results are reported in Tables 1 and 2.

The stereoselectivity of the addition of boron enolates of acetic acid and its monosubstituted derivatives to enantiotopic faces of benzaldehyde depends strongly on the type of chiral ligands (Table 1). The enolates with L* = 2-^{d}Icr add, in the main, to the *re* face of the aldehyde and those with L* = 4-^{d}Icr to the *si* face. The presence of a substituent generally increases the diastereofacial selectivity (Scheme 2).

(1) (a) Moersch, G. W.; Burkett, A. R. *J. Org. Chem.* **1971**, *36*, 1149. (b) Mulzer, J.; Segner, J.; Brüntrup, G. *Tetrahedron Lett.* **1977**, 4651. (c) Mulzer, J.; Brüntrup, G.; Finke, J.; Zippel, M. *J. Am. Chem. Soc.* **1979**, *101*, 7723. (d) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099. (e) Petragnani, N.; Yonashiro, M. *Synthesis* **1982**, 523. (f) Brown, H. C.; Dhar, R. K.; Ganesan, K.; Singaram, B. *J. Org. Chem.* **1992**, *57*, 499. (g) Fringuelli, F.; Martinetti, E.; Piermatti, O.; Pizzo, F. *Gazz. Chim. Ital.* **1993**, *123*, 637.

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(7) The transmetalation reaction is also done[1g] to generate enolborinates from esters which fail[1d,f] to undergo enolization with R_2BOTf/R_3N and Chx_2BCl/Et_3N. Recently enolboration of butyl acetates and butyl propionates were achieved with a chiral diazoborolidine in the presence of Et_3N,[4g] and highly stereoselective synthesis of either *Z* or *E* boron enolates from representative esters was achieved with dicyclohexyliodoborane in the presence of suitable tertiary amines.[6f]

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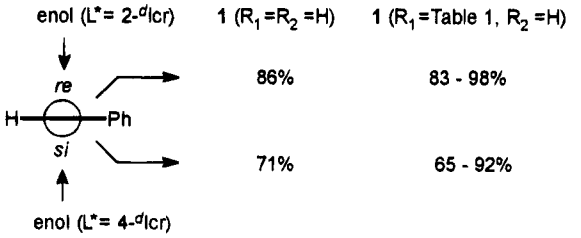
Table 1. Enantio- and Diastereoselectivity of Addition of Boron enolates of Monosubstituted Acetic Acids [$R_1CH{=}C(OBL^*_2)_2$] to Benzaldehyde

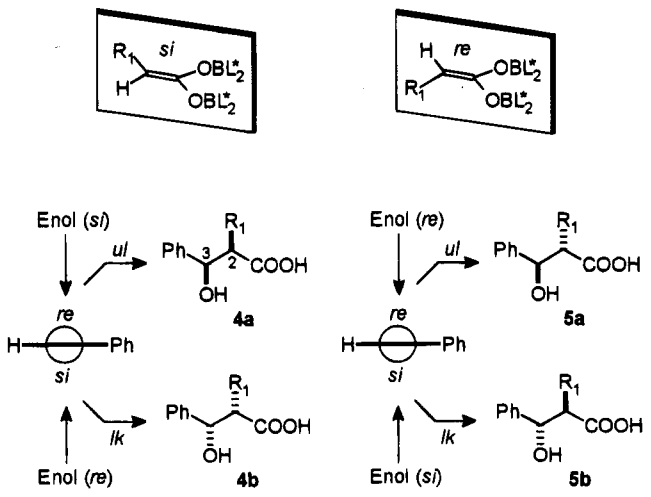
				syn		anti		
entry	R_1	L*[a]	*syn/anti*	product	ee (%)	product	ee (%)	yield (%)[b]
1	H	2-[d]Icr		(+)-**4a**	72[c]			53
2	H	4-[d]Icr		(−)-**5b**	42[c]			50
3	Me	2-[d]Icr	90/10	(+)-**4a**	90	(+)-**5a**	20	90
4	Me	4-[d]Icr	13/87	(−)-**4b**	92	(−)-**5b**	22	90
5	Ph	2-[d]Icr	95/5	(+)-**4a**	>99			68[d]
6	Ph	4-[d]Icr	43/57	(−)-**4b**	>99	(−)-**5a**	52	65[e]
7	SMe	2-[d]Icr	90/10	(+)-**4a**	>99			85
8	SMe	4-[d]Icr	8/92			(+)-**5b**	61	82
9	OPh	2-[d]Icr	80/20	(+)-**4a**	98	(+)-**5a**	50	68
10	OPh	4-[d]Icr	20/80	(−)-**4b**	96	(−)-**5b**	80	70

[a] The symbols 2-[d]Icr and 4-[d]Icr signify that the isocaranyl moiety comes from (+) isomer of 2- and 4-carene, respectively (ref 8a). [b] Yield of isolated products. [c] Reference 1g. [d] Yield by ^{1}H-NMR is 83%. [e] Yield by ^{1}H-NMR is 90%.

Scheme 2. Facial Selectivity of Addition of Boron Enolates of Acetic Acid (1, $R_1 = R_2 = H$) and Its Monosubstituted Derivatives (1, R_1 = Table 1, R_2 = H) to Benzaldehyde)



Scheme 3. Topicity of Approach of Boron Enolates of Monosubstituted Acetic Acids 1 (R_1 = Table 1, R_2 = H) to Benzaldehyde[a]



[a] The same face of enolborinate is designed *si* or *re* according to the nature of the R1 group (Me, Ph, SMe, OPh). In order to simplify the discussion of enolate reactions we adopted the simplified rule proposed by Evans[8b] to define the *E* and *Z* enolate geometry. For the C-2 enolate substituents $C(OBL^*_2)_2$ and R1, the highest priority designation is always assigend to the $C(OBL^*_2)_2$ group.

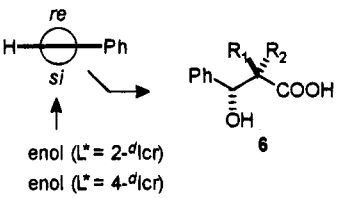
The topicity of the approach of the reactants is unlike (*ul*) prevalent when L* = 2-[d]Icr and like (*lk*) when L* = 4-[d]Icr, producing the *syn* and *anti* β-hydroxy acids, respectively (Scheme 3). With L* = 2-[d]Icr, the *si* (enol)-*re* (aldehyde) approach is always either more prevalent or the only approach and the *syn* enantiomer **4a** is obtained with high ee. With L* = 4-[d]Icr, the *si-si lk* approach is prevalent and the *anti* enantiomer **5b** is more abundant with the exception of the addition of the enol of phenylacetic acid which gives predominately the *anti* enantiomer **5a**. The asymmetric induction of ligand 4-[d]-Icr is less than that of its 2-[d]Icr isomer.

Table 2. Enantioselectivity of Addition of Boron Enolates of Disubstituted Acetic Acids [$R_1R_2CH{=}C(OBL^*_2)_2$] to Benzaldehyde

entry	R_1	R_2	L*[a]	product	ee (%)	yield (%)[b]
1	Me	Me	2-[d]Icr	(−)-**6**	>99	90
2	Me	Me	4-[d]Icr	(−)-**6**	94	90
3	Et	Et	2-[d]Icr	(−)-**6**	>99	60
4	Et	Et	4-[d]Icr	(−)-**6**	>99	56

[a,b] See footnotes of Table 1.

Scheme 4. Facial Selectivity of Addition of Boron Enolates of Disubstituted Acetic Acids (1, $R_1 = R_2$, Table 2) to Benzaldehyde



In brief, the two regioisomer chiral ligands, 2-[d]Icr and 4-[d]Icr, control both the diastereoselectivity and the enantioselectivity of the aldol-addition of monosubstituted acetic acids: the ligand 2-[d]Icr allows *syn* 2-substituted-3-hydroxy-3-phenylpropionic acids to be synthesized with high enantiomeric purity while the 4-[d]Icr ligand gives predominantly the *anti* adducts.

The facial selectivity of the addition of enolborinates of disubstituted acetic acids to benzaldehyde is quite different. Both the enolates **1** which have L* = 2-[d]Icr and those which have L* = 4-[d]Icr add exclusively to the *si* face of the aldehyde (Table 2, Scheme 4) producing the enantiomerically pure β-hydroxy acids **6**. The reaction yield seems to be related to both the size and the electronic nature of the substituents. The boron enolate of diphenylacetic acid, like the lithium enolate,[1a] does not give aldol-addition.

On the basis of the well-established Zimmerman–Traxler chairlike transition-state model,[9] it can be envisaged that the main factors that affect the stability of the transition state of the addition reaction (Scheme 5) are

(8) (a) Brown, H. C.; Vara Prasad, J. V. N.; Zaidlewicz, M. *J. Org. Chem.* **1988**, *53*, 2911. (b) Evans, D. A. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, **1984**; Vol. *3B*, p 11.

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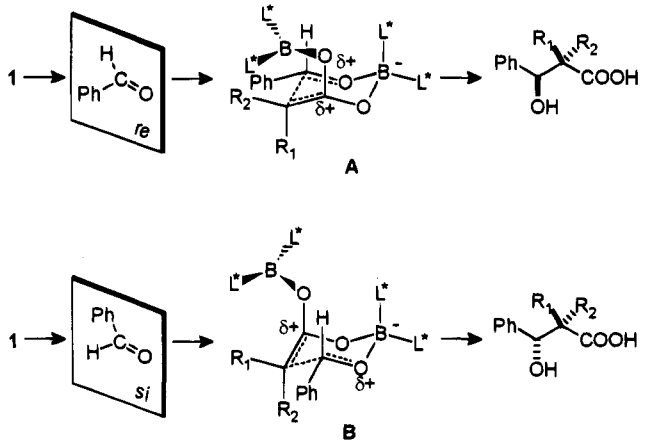
Scheme 5



(i) the methyl group at C-3 of the two ligands, 2-^{d}Icr and 4-^{d}Icr, which has a different influence on the interaction between the axial ligand on the boron atom and one of the ligands of the OBL*$_2$ group; and (ii) the substituents R_1 and R_2.

The prevalence of *syn* enantiomers **4a** can be justified by the idealized transition state **A** (R_1 in Table 1, R_2 = H, L* = 2-^{d}Icr) which accounts for the smaller interactions between the axial groups 2-^{d}Icr and R_1 and one of the ligands of the pseudoaxial OBL*$_2$ group. The transition state **B** (R_1 in Table 1, R_2 = H, L* = 4-^{d}Icr) with the substituent R_1 in the equatorial position is, on the contrary, the one energetically favored to give *anti* enantiomers **5b**.

The different behavior of the addition of the di-4-isocaranyl enolborinate of phenylacetic acid can be justified on the basis of a stabilizing secondary interaction between the boron atom of the OBL*$_2$ group and the pseudoequatorial R_2 phenyl ring which makes the transition state **A** (R_1 = H, R_2 = Ph, L* = 4-^{d}Icr) more stable than **B** (R_1 = Ph, R_2 = H, L* = 4-^{d}Icr).

Computational analysis with the ALCHEMY III program, assuming the Zimmerman–Traxler chairlike transition states **A** and **B** with $R_1 = R_2$ = H and R_1 = Me, R_2 = H, L* = 2-^{d}Icr and 4-^{d}Icr, supports the explanation of the experimental data deduced from the inspection of molecular models.

The preferred transition state for the addition of boron enolates of disubstituted acetic acids is **B** ($R_1 = R_2$ in Table 1, L* = 2-^{d}Icr or 4-^{d}Icr) independent of the type of the ligands because the approach of enolborinates to the *re* face of benzaldehyde is prevented by steric interaction between the substituent in the equatorial position and one of the ligands of the OBL*$_2$ group.

Conclusion

The enantio- and diastereoselection of the aldol-addition of chiral enolborinates of carboxylic acids to benzaldehyde has been investigated for the first time.

The enolboration of mono- and disubstituted acetic acids was easily achieved by transmetalation reaction of lithium enolates with dialkylchloroboranes and highly diastereo- and enantioselective addition to benzaldehyde were carried out using derivatives of (+)-2- and (+)-3-carene as chiral auxiliaries.

The topicity of the approach of boron enolates of monosubstituted acetic acids to benzaldehyde depends on the type of chiral ligand. The 2-isocaranyl ligand allows *syn* 2-substituted-3-hydroxy-3-phenylpropionic acids to be synthesized with high ee, while the 4-isocaranyl ligand gives the *anti* adduct but with less enantioselectivity.

The aldol-addition of isocaranyl enolborinates of disubstituted acetic acids is highly enantioselective and occurs with the same topicity independent of the type of the ligand.

Experimental Section

THF was distilled from sodium/benzophenone. Diisopropylamine was dried by distillation from lithium aluminum hydride. Benzaldehyde was freshly distilled prior to use. All reactions were performed in flame-dried glassware under an atmosphere of extra-dry nitrogen. Reagents were purchased from the Aldrich Chemical Co. and were used without further purification. ^{1}H-NMR spectra were run at 200 MHz in a $CDCl_3$ solution. Optical rotations were run in a $CHCl_3$ solution, if not otherwise specified. Melting points are uncorrected. Elemental analyses to check the purity of the compounds were satisfactory.

For analytical purposes the *syn* and *anti* β-hydroxy acids, obtained by the hydrolysis of pure *syn* and *anti* β-hydroxy esters (see below), were purified by column chromatography (silica gel 230–400 mesh eluting with *n*-hexane–ethyl acetate 6:4) and when the ee is higher than 99% they were recrystallized from *n*-hexane–ethyl acetate.

The *syn* and *anti* configurations were assigned on the basis that the coupling constants J_{H2-H3} and J_{H2-OH} of the methyl esters have greater values for *anti* than for *syn* adducts and observing that the chemical shift of the proton at C-3 of *syn* compounds is down-shifted with respect to that of the *anti* derivative.[10] This is also true for the acids with the exception of J_{H2-OH}, which is not detectable.

General Procedure for Aldol-Addition. A solution of carboxylic acid (10 mmol) in dry THF (5 mL) was added dropwise to a stirred solution of LDA cooled at −78 °C and prepared by treating, at −25 °C for 30 min, a solution of diisopropylamine (22 mmol) in dry THF (40 mL) with 1.6 M solution of butyllithium (22 mmol) in hexane.

After stirring for 2 h at −78 °C a solution of diisocaranylchloroborane **2** or **3** (24 mmol) in dry THF (40 mL) was added to the mixture *via* a syringe in 40 min. After 1 h at −78 °C and 1 h at 0 °C the mixture was cooled again to −78 °C and a solution of benzaldehyde (12 mmol) in dry THF (5 mL) was added dropwise. After 1 h at −78 °C and 15 h at 0 °C a saturated solution of $NaHCO_3$ (25 mL) was added and the mixture stirred for 1 h at room temperature. The organic phase was separated and extracted with a solution of $NaHCO_3$. The combined aqueous phases were acidified with HCl, saturated with NaCl, and extracted with Et_2O. The ether extract was dried and evaporated under reduced pressure.

Enantiomeric Excess and Absolute Configuration. The crude mixture of β-hydroxy acids resulting from the addition reaction was converted into the corresponding methyl esters by CH_2N_2, and *syn* and *anti* adducts were separated by column chromatography (silica gel 230–400 mesh) eluting with *n*-hexane–ethyl acetate 9:1. The ee were then determined on methyl esters by ^{1}H-NMR chiral shift experiments using Eu(hfc)$_3$.[11]

The absolute configurations were assigned from the known sign of the specific rotations reported in the literature and by observing the proton shifts of the OMe group after complexation with Eu(hfc)$_3$ in the ^{1}H-NMR spectrum of methyl ester.[11,12]

Methyl esters of **4a** and **5a** with R_1 = H, Me, Ph have the protons of the OMe group low-field shifted with respect to those of the corresponding esters of **4b** and **5b** of opposite absolute configuration. The methyl esters of enantiomers **5a** and **5b** with R_1 = SMe, OPh behave similarly but in the esters of enantiomers **4a** and **4b** (R_1 = SMe, OPh) the protons shift of the OMe groups are reversed, in conflict with the literature data reported for **4a**

(10) Evans, D. A.; Nelson, J. V., Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1.
(11) Meyers, A. I.; Yamamoto, Y. *Tetrahedron* **1984**, *40*, 2309.
(12) Rinaldi, P. L. *Prog. NMR Spectrosc.* **1982**, *15*, 291.

(R_1 = SMe).[13] To support the spectroscopic data the following experiments were carried out:

(a) The methyl ester of (+)-**4a** (R_1 = SMe) was desulfurized with Raney-nickel (acetone, 60 °C, 20 min) to give the known[1g] methyl ester of (+)-**4a** (R_1 = H) in a good yield.

(b) The enolborinate of phenylthioacetic acid **1** (R_1 = SPh, R_2 = H, L* = 2-^{d}Icr) was added to benzaldehyde to give a mixture of *syn* and *anti* adducts (+)-**4a** and (+)-**5a** (R_1= SPh) in the ratio 80/20. The ^{1}H-NMR chiral shift experiments carried out on the methyl ester of the major reaction product [(+)-**4a**, ee = 84%] show that, as for methyl ester of the phenoxy derivative (+)-**4a** (R_1 = OPh), the protons of the OMe group are high-field shifted with respect to those of corresponding enantiomer.

(c) Desulfurization of methyl ester of (+)-**4a** (R_1 = SPh) with Raney-nickel (acetone, 60 °C, 20 min) gives the known methyl ester of (+)-**4a** (R_1 = H) in a good yield.

(+)-(2*R*,3*R*)-3-Hydroxy-2-methyl-3-phenylpropionic acid (4a, R_1 = Me): mp 74−76 °C; $[\alpha]_D$ + 26.6 (ee 90%) (*c* = 2.2) [lit.[14] $[\alpha]_D$ + 29.5]; ^{1}H-NMR δ 1.16 (d, 3H, *J* = 7.6 Hz), 2.85 (dq, 1H, *J* = 7.6, 4.0 Hz), 5.19 (d, 1H, *J* = 4.0 Hz), 7.35 (m, 5H). *Methyl ester*: $[\alpha]_D$ +20.8 (ee 90%) (*c* = 1.5) [lit.[9d] $[\alpha]_D$ +23.2]; ^{1}H-NMR δ 1.13 (d,3H, *J* = 7.2 Hz), 2.81 (dq, 1H, *J* = 7.2, 4.0 Hz), 2.92 (d, 1H, *J* = 3.1 Hz), 3.70 (s, 3H), 5.12 (dd, 1H, *J* = 4.0, 3.1 Hz), 7.34 (m, 5H).

(−)-(2*R*,3*S*)-3-Hydroxy-2-methyl-3-phenylpropionic acid (5b, R_1 = Me): mp 96−98 °C (lit.[15] 97−98 °C racemate); $[\alpha]_D$ −4.3 (ee 22%) (*c* = 2.0, EtOH) (lit.[15] $[\alpha]_D$ −19.7); ^{1}H-NMR δ 1.02 (d, 3H, *J* = 7.1 Hz), 2.86 (dq, 1H, *J* = 8.8, 7.1 Hz), 4.77 (d, 1H, *J* = 8.8 Hz), 7.35 (m, 5H). *Methyl ester*: $[\alpha]_D$ −12.9 (ee 22%) (*c* =1.4) (lit.[15] $[\alpha]_D$ −57.1); ^{1}H-NMR δ 1.01 (d, 3H, *J* = 7.3 Hz), 2.83 (dq, 1H, *J* = 8.6, 7.3 Hz), 2.91 (d, 1H, *J* = 4.3 Hz), 3.73 (s, 3H), 4.76 (dd, 1H, *J* = 8.6, 4.3 Hz), 7.35 (m, 5H).

(+)-(2*R*,3*R*)-3-Hydroxy-2,3-diphenylpropionic acid (4a, R_1 = Ph): mp 148−150 °C (lit.[16] 142−143 °C racemate); $[\alpha]_D$ +69.2 (ee > 99%) (*c* = 1.6 EtOH); ^{1}H-NMR δ 3.90 (d, 1H, *J* = 7.4 Hz), 5.30 (d, 1H, *J* = 7.4 Hz), 7.29 (s, 5H), 7.33 (s, 5H). *Methyl ester*: mp 105−106 °C (lit.[16] 77−79 °C racemate); $[\alpha]_D$ +141.5 (ee > 99%) (*c* = 1.8); ^{1}H-NMR δ: 2.59 (d, 1H, *J* = 2.5 Hz), 3.55 (s, 3H), 3.89 (d, 1H, *J* = 7.5 Hz), 5.32 (dd, 1H, *J* = 7.5, 2.5 Hz), 7.31 (s, 5H), 7.34 (s, 5H).

(−)-(2*S*,3*R*)-3-Hydroxy-2,3-diphenylpropionic acid (5a, R_1 = Ph): mp 184−185 °C (lit.[16] 176−177 °C racemate), $[\alpha]_D$ −71.4 (ee 52%) (*c* = 1.0 EtOH); ^{1}H-NMR δ 3.92 (d, 1H, *J* = 9.3 Hz), 5.19 (d, 1H, *J* = 9.3 Hz), 7.05−7.25 (m, 10H). *Methyl ester*: mp 100−102 °C (lit.[16] 99−100 °C racemate); $[\alpha]_D$ −79.8 (ee 52%) (*c* = 1.05, EtOH) (lit.[17] $[\alpha]_D$ −13.9, ee 9%); ^{1}H-NMR δ 3.12 (d, 1H, *J* = 4.1 Hz), 3.74 (s, 3H), 3.89 (d, 1H, *J* = 9.3 Hz), 5.19 (dd, 1H, *J* = 9.3, 4.1 Hz), 7.05−7.25 (m, 10H).

(+)-(2*R*,3*S*)-3-Hydroxy-2-(methylthio)-3-phenylpropionic acid (4a, R_1 = SMe): mp 126−128 °C, $[\alpha]_D$ + 46.8 (ee > 99%) (*c* = 1.1); ^{1}H-NMR δ 2.22 (s, 3H, SMe), 3.47 (d, 1H, *J* = 8.2 Hz), 4.98 (d, 1H, *J* = 8.2 Hz), 7.3−7.5 (m, 5H). Anal. Calcd for $C_{10}H_{12}O_3S$: C, 56.59; H, 5.70. Found: C, 56.48; H, 5.72. *Methyl ester*: $[\alpha]_D$ + 40.6 (ee > 99%) (*c* = 2.2); ^{1}H-NMR δ 2.21 (s, 3H), 3.31 (d, 1H, *J* = 1.8 Hz), 3.45 (d, 1H, *J* = 8.3 Hz), 3.61 (s, 3H), 4.97 (dd, 1H, *J* = 8.3, 1.8 Hz), 7.3−7.5 (m, 5H). Anal. Calcd for $C_{11}H_{14}O_3S$: C, 58.39; H, 6.24. Found: C, 58.45; H, 6.27.

(+)-(2*R*,3*R*)-3-Hydroxy-2-(methylthio)-3-phenylpropionic acid (5b, R_1 = SMe): mp 110.112 °C; $[\alpha]_D$ + 5.2 (ee 61%) (*c* = 1.4); ^{1}H-NMR δ 2.05 (s, 3H), 3.51 (d, 1H, *J* = 8.8 Hz), 4.98 (d, 1H, *J* = 8.8 Hz), 7.40 (s, 5H). Anal. Calcd for $C_{10}H_{12}O_3S$: C, 56.59; H, 5.70. Found: C, 56.67; H, 5.73. *Methyl ester*: $[\alpha]_D$ + 6.0 (ee 61%) (*c* = 1.4) (lit.[13] $[\alpha]_D$ + 8.7, ee 88%) ; ^{1}H-NMR δ 2.03 (s, 3H), 2.98 (d, 1H, *J* = 5.2 Hz), 3.51 (d, 1H, *J* = 8.5 Hz), 3.79 (s, 3H), 5.00 (dd, 1H, *J* = 8.5, 5.2 Hz), 7.3−7.5 (m, 5H).

(+)-(2*R*,3*S*)-3-Hydroxy-2-phenoxy-3-phenylpropionic acid (4a, R_1 = OPh): ^{1}H-NMR δ 4.80 (d, 1H, *J* = 3.9 Hz), 5.27 (d, 1H, *J* = 3.9 Hz), 6.8−7.5 (m, 10H). *Methyl ester*: mp 104−106 °C; $[\alpha]_D$ + 44.3 (ee 98%) (*c* = 2.1); ^{1}H-NMR δ 3.03 (d, 1H, *J* = 5.3 Hz), 3.64 (s, 3H), 4.77 (d, 1H, *J* = 5.3 Hz), 5.20 (t, 1H, *J* = 5.3 Hz), 6.8−7.5 (m, 10H). Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.71; H, 5.95.

(−)-(2*R*,3*R*)-3-Hydroxy-2-phenoxy-3-phenylpropionic acid (5b, R_1 = OPh): ^{1}H-NMR δ 4.81 (d, 1H, *J* = 5.9 Hz), 5.21 (d, 1H, *J* = 5.9 Hz), 6.8−7.5 (m, 10H). *Methyl ester*: mp 86−88 °C; $[\alpha]_D$ −8.5 (ee 80%) (*c* = 2.04); ^{1}H-NMR δ 2.88 (d, 1H, *J* = 4.4 Hz), 3.70 (s, 3H), 4.81 (d, 1H, *J* = 6.0 Hz), 5.23 (dd, 1H, *J* = 6.0, 4.4 Hz), 6.8−7.5 (m, 10H). Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.41; H, 5.88.

(+)-(2*R*,3*S*)-3-Hydroxy-3-phenyl-2-(phenylthio)propionic acid (4a, R_1 = SPh): $[\alpha]_D$ +80.4 (ee 84%) (*c* = 1.87); ^{1}H-NMR δ 3.80 (d, 1H, *J* = 7.1 Hz), 5.01 (d, 1H, *J* = 7.1 Hz), 7.2−7.5 (m, 10H). Anal. Calcd for $C_{15}H_{14}O_3S$: C, 65.67; H, 5.14. Found: C, 65.41; H, 5.17. *Methyl ester*: $[\alpha]_D$ + 109.0 (ee 84%) (*c* = 1.63); ^{1}H-NMR δ 3.41 (d, 1H, *J* = 2.1 Hz), 3.56 (s, 3H), 3.84 (d, 1H, *J* = 7.5 Hz), 5.02 (dd, 1H, *J* = 7.5, 2.1 Hz), 7.25−7.45 (m, 10H). Anal. Calcd for $C_{16}H_{16}O_3S$: C, 66.64; H, 5.59. Found: C, 66.48; H, 5.63.

(−)-(*R*)-3-Hydroxy-2,2-dimethyl-3-phenylpropionic acid (6, R_1 = R_2 = Me): mp 160−161 °C from water (lit.[18] mp 141−142 °C); $[\alpha]_D$ −5.2 (ee > 99%) (*c* = 1.0 MeOH) (lit.[18] $[\alpha]_D$ −5.2); ^{1}H-NMR δ 1.15 (s, 3H), 1.17 (s, 3H), 4.95 (s, 1H), 7.34 (s, 5H). *Methyl ester*: mp 71−72 °C; $[\alpha]_D$ - 30.6 (ee > 99%) (*c* = 1.05), (lit.[19] $[\alpha]_D$ −30.8); ^{1}H-NMR δ 1.11 (s,3H), 1.15 (s, 3H), 3.05 (d, 1H, *J* = 4.7 Hz), 3.62 (s, 3H), 4.90 (d, 1H, *J* = 4.7 Hz), 7.33 (s, 5H).

(−)-(*R*)-2-Ethyl-2-(hydroxyphenylmethyl)butyric acid (6, R_1 = R_2 = Et): mp 64−66 °C; $[\alpha]_D$ −51.3 (ee > 99%) (*c* = 2.4); ^{1}H-NMR δ 0.94 (t, 3H, *J* = 7.4 Hz), 0.97 (t, 3H, *J* = 7.4 Hz), 1.41 (dq, 1H, *J* = 14.6, 7.4 Hz), 1.73 (dq, 1H, *J* = 14.6, 7.4 Hz), 1.80 (q, 2H, *J* = 7.4 Hz), 4.98 (s, 1H), 7.33 (s, 5H). Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 69.97; H, 8.10. *Methyl ester*: $[\alpha]_D$ −59.6 (ee > 99%) (*c* = 1.1); ^{1}H-NMR δ 0.92 (t, 6H, *J* = 7.4 Hz), 1.43 (dq, 1H, *J* = 14.8, 7.4 Hz), 1.70 (dq, 1H, *J* = 14.8, 7.4 Hz), 1.78 (q, 2H, *J* = 7.4 Hz), 3.64 (d, 1H, *J* = 6.2 Hz), 3.70 (s, 3H), 4.87 (d, 1H, *J* = 6.2 Hz), 7.29 (s, 5H). Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.28; H, 8.49.

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