3088, 3064, 3031, 2973, 2936, 2877, 2250, 1651, 1496, 1454, 1357, 1273, 1217, 1165, 1112, 1080, 1055, 1029, 960, 919, 809, 732, 699, 617 cm^{-1}.

Eneamino amide 18 was prepared according to the procedure described for **8**. In this way, 2 g (6.47 mmol) of the crude 2-bromobutyramide **17** was converted to 1.1 g (80% from 3-(benzylamino)propionitrile) of **18** after flash chromatography on silica (3:2 hexane–ethyl acetate): mp 144.5–146 °C; FTIR (neat) 3471, 3346, 3222, 3087, 3067, 3025, 2963, 2932, 2870, 1642, 1590, 1477, 1404, 1336, 1247, 1171, 1064, 750, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.92 (t, 3 H, J = 7.3 Hz), 2.21 (m, 4 H), 3.09 (t, 1 H, J = 6.7 Hz), 4.08 (br s, 2 H), 4.51 (s, 2 H), 7.51 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.1, 16.9, 20.7, 40.0, 46.4, 48.1, 56.0, 59.1, 74.1, 109.3, 111.9, 118.7, 120.6, 123.0, 126.3, 131.9, 138.4, 168.3, 203.4.

Keto amide 19 was prepared according to the procedure described for **9**. In this way, 1.0 g (4.34 mmol) of eneamino amide **18** was converted to 0.95 g (95%) of pure **19** as a clear, colorless oil after flash chromatography on silica (3:1 hexanes–ethyl acetate): FTIR (neat) 3050, 3031, 3015, 2966, 2893, 1728, 1668, 1652, 1495, 1454, 1438, 1360, 1275, 1222, 1111, 1080, 736, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.98 (t, 3 H, J = 7.3 Hz), 1.98 (m, 2 H), 2.50 (m, 2 H), 3.17 (t, 1 H, J = 5.8 Hz), 3.45 (m, 2 H), 4.69 (AB q, 2 H), 7.25 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.5, 18.75, 37.9, 41.3, 50.0, 127.4, 127.7 (2 C), 128.5 (2 C), 136.3, 168.2, 204.9; judged to be >96% pure by GC (method C, General Procedures); retention time 22.23. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.68; H, 7.41; N, 6.06. Found: C, 71.95; H, 7.42; N, 6.11. Repeated combustion analyses failed to give satisfactory results due to the apparent hygroscopic nature of **19**.

2-Bromobutyramide 20. (*S*)-1-(Cyanomethyl)-1,2,3,4-tetrahydroisoquinoline (100 mg, 0.581 mmol) (vide infra) was acylated according to the procedure described for **7** to produce 2-bromobutyramide **20** (170 mg, 91.4%) as a 1:1 mixture of diastereomers that was used in the next step without further purification: ^1H NMR ($CDCl_3$, 270 MHz) δ 1.03 (2 t, 3 H), 2.07–2.23 (2 m, 2 H), 2.84–3.07 (several m, 4 H), 3.72–4.50 (several m, 2 H), 4.30 (t, 0.5 H, J = 6.9 Hz), 4.47 (t, 0.5 H, J = 6.7 Hz), 5.59 (t, 0.5 H, J = 5.4 Hz), 5.74 (t, 0.5 H, J = 5.6 Hz), 7.23 (m, 4 H).

Benzoquinolizidinone 21 was prepared by the cyclization procedure described for **8**. In this way, 2-bromobutyramide **20** (170 mg) was converted to benzoquinolizidinone **21** (102 mg, 79.7% for two steps) as a white solid after flash chromatography (SiO_2, 5:3:1 hexanes–ethyl acetate–methanol): mp 191–192 °C; $[\alpha]_D$ –410° (c 1.20, THF); IR (paste) 3342, 3212, 2924, 1644, 1622, 1574, 1455, 1418, 1360, 1328, 1270, 1150, 1118, 1065, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (t, 3 H, J = 7.3 Hz), 2.35 (m, 2 H), 2.39 (m, 2 H), 2.54 (m, 3 H), 4.13 (br s, 2 H), 4.67 (dd, 1 H, J = 11.7 Hz, J = 12.4 Hz), 4.74 (dd, 1 H, J = 4.62 Hz, J = 12.4 Hz), 7.18 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.8, 17.5, 29.8, 37.4, 38.0, 53.4, 103.5, 125.4, 126.3, 126.6, 129.0, 135.4, 136.1, 148.0, 168.2.

Keto amide 22 was prepared according to the procedure given for **9**. In this way, 100 mg of (–)-**21** was converted to 87 mg (87%) of keto amide **22** as an inseparable 3:1 mixture of diastereomers. Data for the major diastereomer: IR (paste) 2932, 2874, 1728, 1651, 1455, 1416, 1362, 1289, 1243, 1116, 1064, 974, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.03 (t, 3 H, J = 7.0 Hz), 2.03 (m, 2 H), 2.43 (dd, 1 H, J = 11.5 Hz, J = 17.9 Hz), 2.85–3.15 (several m, 4 H), 3.32 (t, 1 H, J = 5.6 Hz), 4.69 (dt, 1 H, J = 3.8 Hz, J = 12.7 Hz), 5.14 (dd, 1 H, J = 3.6 Hz, J = 11.5 Hz), 7.24 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.0, 17.4, 29.1, 39.3, 47.7, 51.7, 58.9, 125.8, 127.0, 127.3, 129.0, 134.0, 134.7, 167.9, 203.9; judged to be >98% pure by GC (method B, General Procedures); retention time 4.89; exact mass for $C_{15}H_{18}NO_2$ (MH^+), calcd 244.1260, found 244.1260.

(*S*)-(–)-1-(Cyanomethyl)-1,2,3,4-tetrahydroisoquinoline, used to prepare **20**, was prepared by alkylation of the lithium salt of the valinol-derived tetrahydroisoquinoline[7] with chloroacetonitrile in the same manner as described for β-carboline **6**. In this way, the valinol-derived tetrahydroisoquinoline formamidine (720 mg, 2.38 mmol) was converted to 0.573 g (69.9%) of the cyanomethyl-substituted formamidine after flash chromatography on silica (8:1:1 hexanes–ethyl acetate–triethylamine): IR (paste) 3090, 3023, 2971, 2940, 2871, 2246, 1645, 1456, 1422, 1387, 1362, 1232, 1197, 1080, 1020, 745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (d, 3 H, J = 6.5 Hz), 0.92 (d, 3 H, J = 5.8 Hz), 1.12 (s, 9 H), 1.86 (m, 1 H), 2.83 (m, 2 H), 2.95 (m, 2 H), 3.14 (dd, 1 H, J = 7.6 Hz, J = 8.8 Hz), 3.33 (m, 1 H), 3.48 (dd, 1 H, J = 5.15 Hz, J = 8.9 Hz), 3.55 (m, 1 H), 3.62 (m, 1 H), 5.27 (m, 1 H), 7.24 (m, 4 H), 7.45 (s, 1 H). Hydrazinolysis[3,4] gave (*S*)-1-(cyanomethyl)-1,2,3,4-tetrahydroisoquinoline: $[\alpha]_D$ –51° (c 0.60, $CHCl_3$); IR (paste) 3332, 3062, 3021, 2936, 2832, 2247, 1668, 1602, 1494, 1455, 1428, 1379, 1316, 1129, 960, 745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.25 (br s, 1 H), 2.81 (dd, 2 H, J = 2.5 Hz, J = 7.8 Hz), 2.82 (m, 2 H), 3.10 (m, 1 H), 3.20 (m, 1 H), 4.38 (t, 1 H, J = 6.4 Hz), 7.13 (m, 4 H).

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Registry No. (–)-**1a**, 483-27-2; (–)-**1b**, 2270-72-6; (–)-**3**, 131897-80-8; (–)-**4**, 112459-14-0; (–)-**5**, 114926-74-8; **6**, 131831-92-0; **6** (formamidine derivative), 131793-08-3; **7** (isomer 1), 131792-89-7; **7** (isomer 2), 131831-93-1; **8**, 131792-90-0; **9**, 131792-91-1; 3-*epi*-**9**, 131899-62-2; **10** (isomer 1), 131792-92-2; **10** (isomer 2), 131897-81-9; **11**, 131792-93-3; (*E*)-**12a**, 131792-94-4; (*Z*)-**12a**, 131793-06-1; (*E*)-**12b**, 131899-63-3; (*Z*)-**12b**, 132014-10-9; **13a**, 131792-95-5; 15α-**13a**, 131897-82-0; **13b**, 131897-83-1; **14a**, 131792-96-6; (±)-**15**, 131792-97-7; **16**, 131792-98-8; (±)-**17**, 131792-99-9; **18**, 131793-00-5; (±)-**19**, 131793-01-6; **20** (isomer 1), 131793-02-7; **20** (isomer 2), 131793-09-4; **21**, 131793-03-8; *cis*-**22**, 131897-84-2; *trans*-**22**, 131793-04-9; $ClCH_2CN$, 107-14-2; $BrCOCHBrCH_2CH_3$, 26074-52-2; $NC(CH_2)_2OH$, 109-78-4; $NC(CH_2)_2NHCH_2Ph$, 706-03-6; (*E*)-*O*-*tert*-butyl-*N*-[(1,2,3,4-tetrahydroisoquinolin-2-yl)methylene]-(*S*)-valinol, 99395-58-1; (*S*)-(–)-1-(cyanomethyl)-1,2,3,4-tetrahydroisoquinoline, 131793-05-0; (*E*)-*O*-*tert*-butyl-*N*-[[1*S*-(cyanomethyl)-1,2,3,4-tetrahydroisoquinolin-2-yl]methylene]-(*S*)-valinol, 131793-07-2.

Supplementary Material Available: Proton and carbon NMR spectra for **3**, **4**, **8–15**, and **17–22** (33 pages). Ordering information is given on any current masthead page.

Spontaneous Resolution of 2,2′-Dimethoxy-1,1′-binaphthalene

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The dimethyl ether of 1,1′-bi-2-naphthol crystallizes as a conglomerate and can be resolved without chiral auxiliaries by entrainment. The direct crystallization of a supersaturated solution of the title compound partially enriched by one enantiomer (ee ≈ 2%) is conducted in anisole at 40 °C and gives, after one crystallization, a compound with ee >98%. Demethylation under nonracemizing conditions gives the enantiomeric 1,1′-bi-2-naphthol.

1,1′-Bi-2-naphthol (**1**) and its derivatives are interesting chiral auxiliaries used for many purposes.[1] Several preparative methods for enantiomerically pure **1** are reported in the literature, ranging from the crystallization

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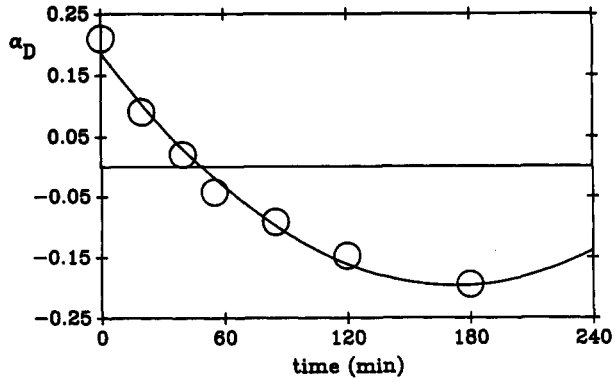
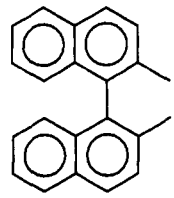


Figure 1. Variation with time of the optical rotation of the solution during the resolution at 40 °C. Initial conditions: 6.14 g of 2/100 mL of anisole, op = 2.3% (see the Experimental Section).

of the cinconine salt of its cyclic acid phosphate[2] to the hydrolysis of its diesters catalyzed by cholesterol esterase.[1]

In the course of our research on chiral biaryl derivatives,[3] we noticed that the melting point of enantiomerically pure 2,2′-dimethoxy-1,1′-binaphthalene (2) was ca. 30 °C higher than that of the racemic derivative. IR spectra of the racemic and resolved bis ethers 2 in the crystalline phase were superimposable. These facts indicate that 2 crystallizes as a conglomerate.[4] This was subsequently confirmed by an X-ray diffraction analysis.[5]



R = H (1)

R = CH_3 (2)

A racemic conglomerate is composed of a mixture of crystals each of which contains only single enantiomers; in principle, one can separate the two enantiomers mechanically, but this procedure is generally only of historical interest. Of more significance is resolution by entrainment,[6] which is easy to perform and, in the case of compound 2, gives a satisfactory overall yield after several cycles. The entrainment procedure involves the direct preferential crystallization of one enantiomer from a supersaturated solution. In the present case we have followed the classical procedure described in ref 4. The crystallization is carried out at 40 °C from a highly supersaturated solution of 2 (61.4 g L^{-1}) enriched with a slight excess of one enantiomer (2.3% ee). This temperature was chosen because of the low solubility of 2 at ambient temperature; operating at higher temperature, it is difficult to prevent undesired crystallization in the subsequent operations (filtrations and polarimetric measurements). Although highly supersaturated (the saturated solution at this temperature has a concentration of 45 g L^{-1}), this solution is stable for several hours. The solution is seeded with crystals of the enantiomer, and the development of the crystallization is followed by measuring the rotatory power of the solution. At the beginning this has the sign of the enantiomer in excess; then it goes to zero and to the opposite sign as crystallization proceeds (see Figure 1). When the optical rotation is equal and opposite to the starting value, the solution is filtered and an amount of the enantiomer twice the initial excess is collected (the time of crystallization depends critically on the excess of the pure enantiomer added at the beginning). At this point the solution is enriched with the opposite enantiomer; racemate is added to restore the initial supersaturation, and the procedure is repeated for the opposite enantiomer. For each crystallization, twice the amount of the initial excess of the enantiomerically pure compound is obtained: after five cycles, for both enantiomers one obtains an amount about 10 times that of the initial investment in the single starting enantiomer (see Table I).

Table I. Resolution of (±)-2 by Entrainment

	2 added (g)		seeds added (g)		recovery of resolved 2	
cycle no.	(±)	(+)	(+)	(-)	(+)[a]	(-)[a]
1	6.00	0.14	0.015		0.29	
	0.29			0.015		0.28
2	0.28		0.016		0.28	
	0.28			0.014		0.26
3	0.26		0.015		0.27	
	0.27			0.017		0.25
4	0.25		0.014		0.26	
	0.26			0.015		0.23
5	0.23		0.015		0.25	
	0.25			0.014		0.23
total	8.37	0.14	0.075	0.075	1.35	1.25

[a] Crystals having ca. 90% optical purity.

Demethylation of the dimethyl ether 2 with BBr_3 gives the binaphthol 1 in a quantitative yield with no evidence of racemization.[7]

Experimental Section

Synthesis of 2,2′-Dimethoxy-1,1′-binaphthalene (2). Racemic (±)-2 and optically pure (+)-2 and (−)-2 were prepared from commercial 1,1′-bi-2-naphthols (±)-1, (+)-1, and (−)-1, respectively (Aldrich). In a typical procedure, to 1 (10 g, 35 mmol) dissolved in aqueous sodium hydroxide (3 g in 31 mL of water) was added dimethyl sulfate (9.7 g, 77 mmol) dropwise while the flask was cooled with a water bath. Then the reaction mixture was heated at ca. 70–80 °C for 1 h. The suspension was filtered; the crystals were washed with aqueous sodium hydroxide and with water and crystallized from toluene to give 2 (7.8 g, 70%): ^1H NMR ($CDCl_3$) δ 3.77 (6 H, s), 7.0–8.0 (12 H, m).

The racemic derivative (±)-2 has mp 198–202 °C. The optically active derivatives (+)-2 and (−)-2 have mp 230–232 °C and $[\alpha]_D$ = +151 and −151 (c 1, anisole); these compounds were crystallized three times to obtain a constant value of optical rotation (in the case of a conglomerate, when a derivative is crystallized until a constant value of the optical rotation is reached, this value represents 100% optical purity). The enantiomeric excess was independently determined by ^1H NMR (200 MHz) in the presence of the chiral alcohol (+)-2,2,2-trifluoro-1-(9-anthryl)ethanol ((+)-TFAE from Aldrich): the methyl hydrogen signal of partially enriched 2, $[\alpha]_D$ = +87.7 (op = 58%), at −55 °C, is split (9.6 Hz) due to the diastereoisomer interaction with a large excess of (+)-TFAE. From the peak areas, 58 ± 1% ee was measured in agreement with the value obtained from the optical rotation.

Typical Entrainment Procedure. The operation was carried out in a three-necked round-bottom flask equipped with a mechanical stirrer and inserted in a Heto 03DT/Hetofrig CB7 thermostat. Optical rotations were measured with a polarimeter,

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Jasco DIP 370, using a water-jacketed cell connected to the thermostat.

Racemic 2 (6.00 g, 19.1 mmol) was suspended in 100 mL of anisole (from Aldrich, used without further purification) together with 0.14 g (0.45 mmol) of (+)-2. The suspension was heated at ca. 90 °C to complete dissolution of the solid (possible undissolved particles were filtered away on fluted filter paper) and then slowly cooled in the thermostat at 40 °C. The solution showed an optical rotation α_D = +0.21 (l = 10 cm). Seeds of (+)-2 (15 mg) were added under constant stirring (100 rpm). The solution became opalescent, and crystallization of the (+)-enantiomer proceeded slowly. The optical rotation of the solution varied with time as shown in the figure. After 3 h, when α_D = −0.18/−0.20, the suspension was rapidly filtered by suction in a preheated Buchner funnel with filter paper (general-purpose filter paper with medium filtration speed; the use of fritted disks, 16–40 μm, did not allow the complete recovery of the crystals) to give, after the residue was dried under vacuum, 0.27 g of the dimethyl ether 2 with $[\alpha]_D$ = +135 (89% optical purity based on the rotation of the (+)-2 obtained from commercial (+)-1).

Racemic (±)-2 (0.27 g, 0.86 mmol) was then added to the remaining solution, which was heated at ca. 90 °C to complete dissolution of the solid (possible undissolved particles were filtered away). The solution was again thermostated at 40 °C and seeded with 15 mg of (−)-2. After 3 h, filtration and drying as above gave the (−) enantiomer. The same cycle of operation was carried out five times, yielding a total of 1.35 g of (+)-2 and 1.25 g of (−)-2 having optical purity of ca. 90% (see Table I).

A single crystallization from toluene gave 1.05 g of (+)-2 and 0.98 g of (−)-2 with optical purity >98%.

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Simple Diastereoselectivity of the Aldol Reaction of Persubstituted Enolates. Stereoselective Construction of Quaternary Centers

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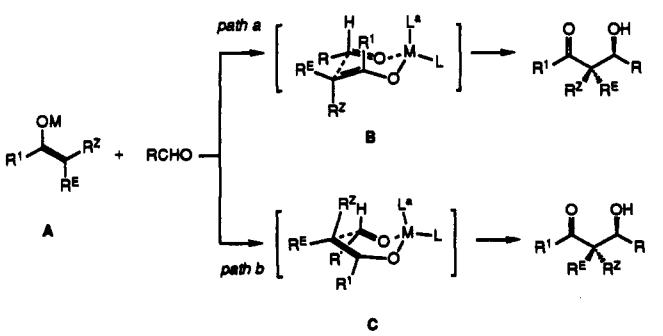
Simple diastereoselectivity of several important categories of aldol reactions of persubstituted enolates has been investigated for sterically least biased cyclic and acyclic ketone and aldehyde enolates, 1–4, and has been found to be useful for the stereoselective construction of quaternary carbon centers. The types of reactions examined involve the reaction of lithium, borinate, borate, trialkoxytitanium, trichlorotitanium, and zirconium (Cp_2ZrCl) enolates, and the reactions of enol silyl ethers under high pressure, fluoride catalysis, and Lewis acid catalysis. In contrast to the less substituted metal enolates, uncatalyzed reactions of persubstituted metal enolates proceeded in a sense anticipated from the conventional Zimmerman–Traxler chair transition state (TS) model. The fluoride-catalyzed reaction of the cyclic enolate **1a** showed stereoselectivity consistent with the open extended TS, while enolates **2a–4a** showed anomalous behavior. The selectivity of the Lewis acid mediated aldol reaction of enol silyl ethers was found to be dependent on the Lewis acid used, and the BF_3·Et_2O-mediated reaction of **2a** and **3a** showed maximum selectivity in a sense predicted by the chair TS. The stereostructures of the aldols have been determined by single-crystal X-ray analysis or by chemical correlations.

In the past decade, aldol reaction of substituted enolates with aldehydes has emerged as an extremely useful method for the stereocontrolled construction of chiral centers.[1] Through accumulated knowledge of numerous varieties of stereochemical observations, some useful inferences as to transition-state (TS) geometries[2] have been drawn on the basis of the data obtained for the reactions of trisubstituted enolates (i.e., either one of R^Z and R^E in A is hydrogen: Scheme I). The aldol reaction of persubstituted enolates (i.e., R^Z, $R^E \neq$ H) creates a quaternary carbon next to the carbonyl group and is expected to provide a powerful method for stereocontrolled construction of quaternary centers,[3,4] especially on an acyclic carbon chain. However, the potential of this promising strategy has rarely been

Scheme I



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