Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 2043–2064

TETRAHEDRON: *ASYMMETRY*

Enantiomeric impurities in chiral catalysts, auxiliaries and synthons used in enantioselective synthesis

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Received 24 March 1998; accepted 7 May 1998

Abstract

Eighty three popular chiral reagents that are used to synthesize a wide variety of compounds of high enantiomeric purity were analyzed in order to determine their enantiomeric composition. Included in the study are chiral catalysts for stereoselective reductions, epoxidations and hydrocarboxylations; chiral auxiliaries including a variety of oxazolidinones; a wide variety of chiral synthons and chiral resolving agents. Enantiomeric impurities were found in all reagents. The reagents were categorized by the level of their enantiomeric contaminants. The four level ranges were: 0.01% to 0.1%, 0.1% to 1%, 1% to 10% and >10%. Over half of the chiral reagents tested had enantiomeric impurities at levels >0.1%. The batch to batch enantiopurity of a reagent from a single source was examined as well as the variation in the enantiopurity of the same reagent from different sources. Possible adverse aspects of having unknown quantities of enantiomeric impurities in stereoselective syntheses are mentioned.

1. Introduction

Studies on enantioselective synthesis have increased tremendously over the last 30 years.[1–7] Among the more useful approaches for obtaining products of high enantiomeric or diastereomeric purity involve the use of chiral catalysts, chiral auxiliaries, and chiral synthons (i.e., building blocks). Alternatively, chiral resolving agents can be used to obtain the desired enantiomer from a racemic mixture. Although each procedure has advantages and disadvantages, all are currently needed since no single approach can provide the variety of chiral products and intermediates needed today.

Traditionally, molecules from natural chiral sources have been used in enantioselective synthesis since they were often readily available at reasonable cost.[4,8–11] These naturally occurring molecules include amino acids,[8,9] carbohydrates,[10] and terpenes.[6,11] They continue to be used in new and imaginative ways for enantioselective synthesis. More recently, an increasing number and variety of new chiral reagents

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0957-4166/98/$19.00
PII: S0957-4166(98)00201-8

have become available. Many of these are not obtained from natural products.[3,12] Today, reports involving new chiral agents for stereoselective synthesis are frequently followed by commercialization of the more widely useful agents. Consequently, an ever increasing number and variety of chiral reagents are available for enantioselective syntheses.

One important criterion when considering an asymmetric synthesis is the degree of enantioselectivity of a reaction. The pharmaceutical industry, for example, requires chiral products of greater than 99% enantiomeric excess (e.e.).[13] In general, they would prefer to have <0.1% of the unwanted enantiomer in any product. Enantiomeric or diastereomeric impurities in any asymmetric synthesis product can be: (a) produced in any reaction that is not stereospecific (i.e., most reactions are stereoselective); (b) produced via isomerization during workup (isolation and purification); and (c) present as the result of enantiomeric impurities in the chiral catalysts, auxiliaries and synthons used. As asymmetric synthetic reactions become more stereoselective, factors such as (b) and (c) above may limit the enantiomeric purity of the product. These factors also can obscure the true enantioselectivity of a reaction.

Previously, it was shown that enantiomerically pure amino acids and amino acid derivatives (e.g., t-BOC, FMOC, etc.) are not available commercially, although a few are highly enantioenriched.[14–18] Likewise, most monoterpenes are not enantiomerically pure.[19] Three conclusions can be drawn from early work.[14–19] First, enantiomeric impurities in the range of 0.01% to 1% are usually present and levels in the low percent range (i.e., ~1–10%) are not uncommon. Second, the enantiomeric purity of a specific amino acid or monoterpene varies tremendously with both the source and time of purchase of those compounds. Third, in most cases neither the supplier nor the consumer had any idea as to the enantiomeric purity of these compounds. Typically, the only impurities noted as being present are other nonisomeric substances. These results,[14–19] as well as a recent report on the enantiomeric purity of Jacobsen's catalyst[20] prompted the present work. Here we report on the enantiomeric purity of many of the most common, commercial, chiral reagents for enantioselective synthesis. We do not include amino acids, their derivatives and the most common monoterpenes since they were considered previously.[14–19] In many cases the presence of an enantiomeric impurity in a reagent will result in a comparable level of impurity in the product. However, when using a chiral catalyst or auxiliary to generate an additional stereogenic center in a chiral substrate, the level of stereoisomeric impurity can be substantially different (greater or less) than that present in the chiral reagent (because of kinetic effects).

2. Experimental section

2.1. Materials

All HPLC columns (25 cm×4.6 mm, i.d.) and GC columns (30 m×0.25 mm) were obtained from Advanced Separation Technologies, Inc. (Whippany, NJ). The LC columns used were Cyclobond I 2000 (native β-cyclodextrin), Cyclobond I 2000 RSP (2-hydroxypropyl-β-cyclodextrin), Cyclobond I 2000 Ac (acetylated β-cyclodextrin), Cyclobond I 2000 RN ((R)-naphthylethyl carbamated-β-cyclodextrin), Cyclobond I 2000 SN ((S)-naphthylethyl carbamated-β-cyclodextrin), and Chirobiotic T (teicoplanin). Chiraldex G-TA (2,6-di-*O*-pentyl-3-trifluoroacetyl-γ-cyclodextrin), Chiraldex B-DM (di-*O*-methyl-β-cyclodextrin), Chiraldex B-DA (2,6-di-*O*-pentyl-β-cyclodextrin, and Chiral G-PN (2,6-di-*O*-pentyl-3-propionyl-γ-cyclodextrin) were used for GC analysis. The chiral selectors for capillary electrophoresis (CE) analysis were DM-β-CD (heptakis 2,6-di-*O*-methyl-β-cyclodextrin), S-β-CD (sulfated-β-cyclodextrin) and HP-β-CD (2-hydroxypropyl-β-cyclodextrin). Sodium hydrogenphosphate, phosphoric acid and 18-crown-6 were from Aldrich (Milwaukee, WI). All solvents [methylene chloride, methanol

and acetonitrile, glacial acetic acid and triethylamine (99+% pure)] were purchased from Fisher Scientific (St. Louis, MO). Disposable filters (0.45 μm) used on the buffer and the analytes solution were purchased from Alltech (Deerfield, IL). The sources for all chiral compounds used in this study are given in the appropriate Tables.

2.2. Apparatus and methods

The LC enantioseparations were performed using the following Shimadzu (Columbia, MD) equipment: two LC-10AT pumps, a SPD-10A UV-vis detector, a SIL-10A auto injector, a SCL-10A system controller and a CR 501 Chromatopac integrator. The detection wavelength was set at 254 nm. All chromatograms were run at ambient temperature (22°C). The capillary electrophoresis (CE) were performed at 25°C on a P/ACE 5000 Beckman instrument (Palo Alto, CA). It was equipped with a 75 μm i.d.×57 cm (50 cm to detector) fused silica capillary and monitored at 254 nm. The capillary was conditioned daily with 0.1 N potassium hydroxide for 10 minutes, followed by deionized water for 10 minutes. Between runs, the capillary was rinsed with 0.1 N potassium hydroxide, water and buffer for 2 minutes each. All the samples were dissolved in methanol. Data collection and acquisition were done with System Gold™ software. A Hewlett Packard (Corvallis, OR) model 5890 series II Gas Chromatograph equipped with a flame ionization detector and HP 3396 series II integrator were used for all the GC analyses. Helium was used as the carrier gas. The temperatures for both injector and detector was set at 220°C. A split ratio of about 100/1 was used for all the analyses. All of the compounds with amino and/or hydroxyl functionalities were derivatized with trifluoroacetic anhydride prior to injection. Typical enantioselective HPLC and GC analyses for chiral reagents are shown in Fig. 1. All experimental conditions for resolving over 80 commercially available chiral reagents are given in Table 1. A method number from Table 1 is listed for each compound and the result is in Table 2. Note, that when quantifying peak areas for very low levels of enantiomeric impurities (esp. <0.1%) one cannot always rely on instrumental integration devices. The large peak for the dominant enantiomer is usually off scale. Often the concentration of the compound that the large peak represents is outside the linear dynamic range of the detector. This results in an underestimation of its peak area. To avoid this problem the small peak (representing the enantiomeric impurity) must be first quantified. The area of the large peak is measured subsequently after serial dilution to an appropriate concentration.

3. Results and discussion

Table 2 gives the enantiomeric composition for 83 chiral reagents that are widely used in enantioselective synthesis. They are grouped according to their function as: chiral catalysts and catalyst ligands, chiral auxiliaries, chiral synthons, and chiral resolving agents. Also included in Table 2 are the synthetic use(s), representative reference(s), the commercial source and a referral number for the experimental method used to determine the enantiomeric purity (see Table 1). As can be seen in Table 2, enantiomeric impurities were detected in all samples. Of the samples evaluated (Tables 2 and 3) 51 had levels of enantiomeric impurities between ~0.01% and 0.1%. Another 48 samples had enantiomeric impurities between 0.1% and 1%. The levels of enantiomeric impurity for 12 samples were between 1.0% and 10%. Two samples (both practical grade) had enantiomeric contaminants at levels >10%.

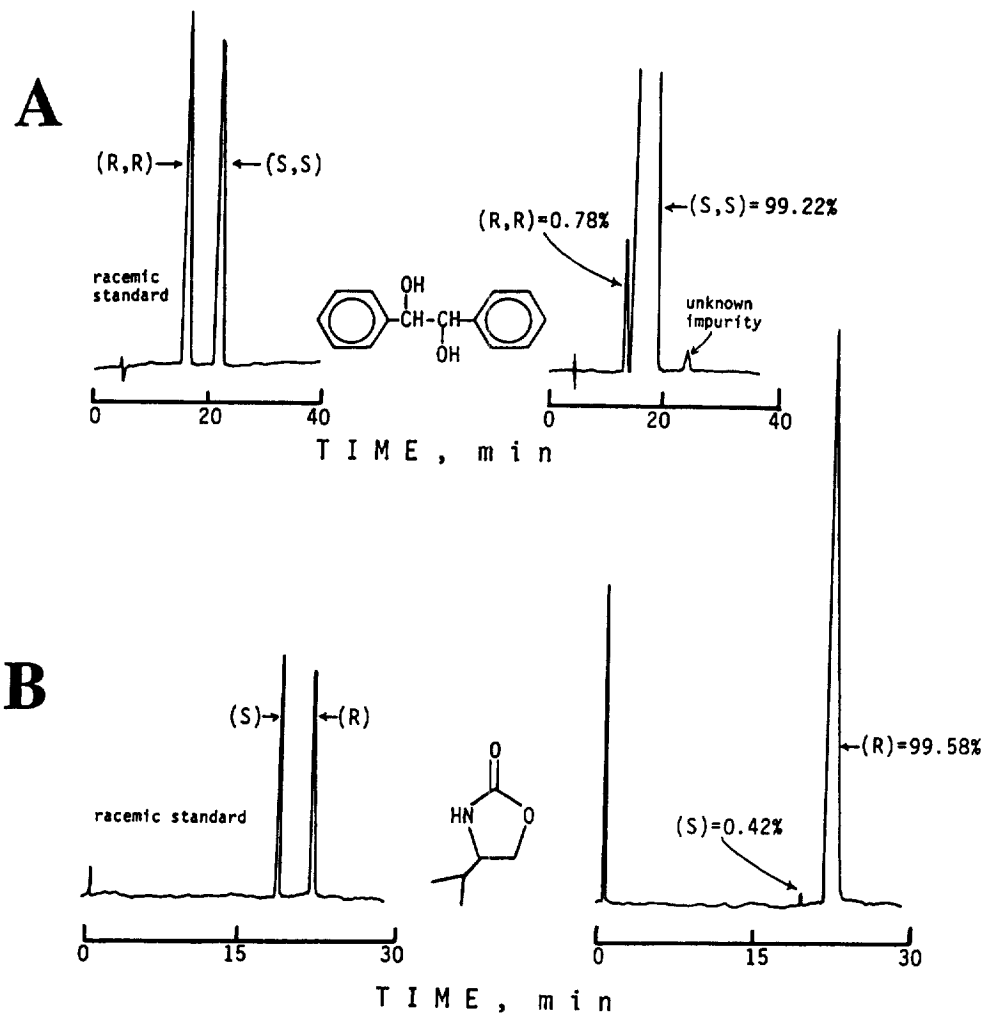


Fig. 1. The chromatograms designated 'A' show the HPLC enantioseparations (from left to right) of racemic hydrobenzoin and a commercial sample (Acros) of (S,S)-hydrobenzoin. The experimental conditions for this reversed phase separation are given in Table 2 as method 'LC-6'. The chromatograms designated 'B' show the GC enantioseparations (from left to right) of racemic 4-isopropyl-2-oxazolidinone and a commercial sample (Aldrich) of (R)-4-isopropyl-2-oxazolidinone. The experimental conditions for this GC separation are given in Table 2 as method 'GC-3'. Note the enantiomeric impurities in both of the above commercial reagents

Table 1
Enantioseparation methods by gas chromatography (GC), high performance liquid chromatography (HPLC), and capillary electrophoresis (CE)

GC Method Number[a]	Column[b]	Length (m)	Temperature (°C)	Pressure (psi)
GC-1	Chiraldex B-DA	20	100-140@2/min	20
GC-2	Chiraldex B-DM	30	75-90@1/min	15
GC-3	Chiraldex G-TA	30	140-160@1/min	20
GC-4	Chiraldex G-PN	20	80-100@1/min	20
GC-5	Chiraldex G-PN	20	50-70@1/min	20
GC-6	Chiraldex G-PN	20	70-100@1/min	20
GC-7	Chiraldex B-DA	20	180-190@1/min	20
GC-8	Chiraldex G-TA	30	175	20
GC-9	Chiraldex B-DM	30	160-180@1/min	20
GC-10	Chiraldex B-DM	30	195	20
GC-11	Chiraldex G-TA	30	90	20
GC-12	Chiraldex B-DM	30	100-120@1/min	20
GC-13	Chiraldex G-TA	20	70-90@1/min	20
GC-14	Chiraldex G-TA	30	100	20
GC-15	Chiraldex G-TA	30	120	20
GC-16	Chiraldex G-TA	30	80	20
GC-17	Chiraldex G-TA	30	110	20
GC-18	Chiraldex G-PN	20	110-140@1/min	20
GC-19	Chiraldex G-TA	20	100-120@1/min	20
GC-20	Chiraldex G-PN	20	65-90@1/min	20
GC-21	Chiraldex B-DM	30	100-130@1/min	20

HPLC Method Number[a]	Column[c]	Mobile Phase[d] (%, v/v)	Flow Rate (ml/min)
LC-1	Cyclobond I 2000	MeOH: 1% TEAA = 20: 80, pH 7.1	1
LC-2	Cyclobond I 2000 SN	ACN: 1% TEAA = 15: 85, pH 4.1	1
LC-3	Cyclobond I 2000 Ac	MeOH: 1% TEAA = 5: 95, pH 4.1	1
LC-4	Cyclobond I 2000 RSP	ACN: HOAc:TEA = 100: 0.25: 0.05	1
LC-5	Cyclobond I 2000 RN	MeOH: 1% TEAA = 20: 80, pH 7.1	1
LC-6	Cyclobond I 2000 RSP	MeOH: 1% TEAA = 10: 90, pH 4.1	0.8
LC-7	Cyclobond I 2000 Ac	MeOH: 1% TEAA = 5: 95, pH 4.1	1
LC-8	Cyclobond I 2000 SN	ACN: 1% TEAA = 10: 90, pH 4.1	1
LC-9	Chirobiotic T	MeOH: 1% TEAA = 10: 90, pH 4.1	1
LC-10	Cyclobond I 2000 RSP x2[g]	MeOH: 1% TEAA = 10: 90, pH 4.1	0.5
LC-11	Cyclobond I 2000	MeOH: 1% TEAA = 10: 90, pH 4.1	1
LC-12	Cyclobond I 2000 RSP x2[g]	MeOH: 1% TEAA = 30: 70, pH 4.1	0.5
LC-13	Cyclobond I 2000 x2[g]	ACN:MeOH:HOAc:TEA = 95:5:0.3:0.2	1
LC-14	Cyclobond I 2000 RSP	MeOH: 1% TEAA = 20: 80, pH4.1	1
LC-15	Cyclobond I 2000 x2[g]	MeOH: 1% TEAA = 30: 70, pH 4.1	0.5

CE Method Number[a]	Chiral Selector Added to Run Buffer[e]	Additive	Run Buffer[f]	Applied Voltage (kV)
CE-1	30 mM DM-β-CD	18 crown 6	50 mM phosphate, pH 2.11	20
CE-2	2% S-β-CD		50 mM phosphate, pH 3.60	-15
CE-3	30 mM HP-β-CD		50 mM phosphate, pH 2.50	20
CE-4	30 mM HP-β-CD		50 mM phosphate, pH 2.20	15

[a] This notation is used to identify the separation techniques in Table 2.

[b] The abbreviation for the GC columns from Astec (Whippany, NJ) are as follows: G-TA is 2,6-di-*O*-pentyl-3-trifluoroacetyl-γ-CD; B-DM is di-*O*-methyl-β-CD; B-DA is 2,6 di-*O*-pentyl-β-CD; G-PN is 2,6 di-*O*-pentyl-3-propionyl-γ-CD.

[c] The abbreviation for the HPLC columns (25 cm x 4.6 mm, i.d.) from Astec (Whippany, NJ) are as follows:2 Cyclobond I 2000 RSP is 2-Hydroxypropyl-β-CD; Cyclobond 2000 I is β-CD; Cyclobond I 2000 Ac is Acetylated-β-CD; Cyclobond 2000 I SN is S-naphthylethyl carbamated-β-CD; Cyclobond I 2000 RN is R-naphthylethyl carbamated-β-CD; Chirobiotic T is Teicoplanin.

[d] Mobile phase: ACN = acetonitrile; TEA = triethylamine; HOAc = glacial acetic acid; MeOH = methanol; 1% TEAA = 1% v/v triethylammonium acetate buffer, pH adjusted by HOAc.

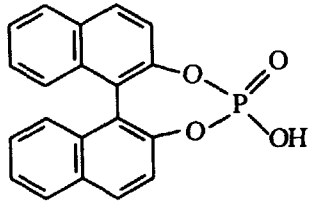
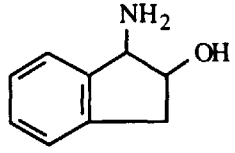
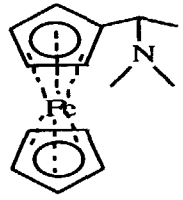
[e] Chiral selector: DM-β-CD = Heptakis 2,6-di-*O*-methyl-β-CD; HP-β-CD = 2-Hydroxypropyl-β-CD; S-β-CD = Sulfated β-CD.

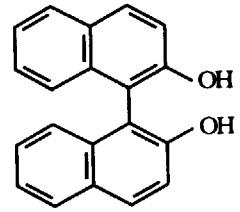
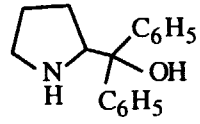
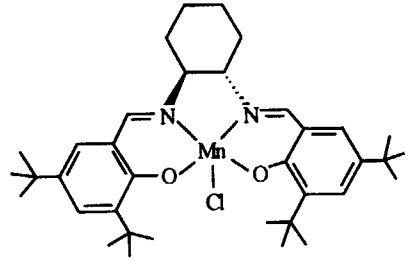
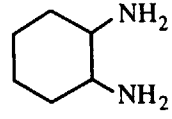
[f] Run Buffer: phosphate buffer is adjusted to an appropriate pH by diluted phosphoric acid.

[g] Two 25 cm Cyclobond columns were used in series.

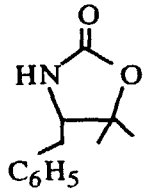
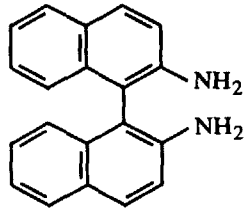
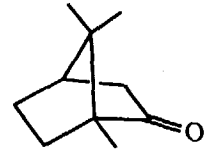
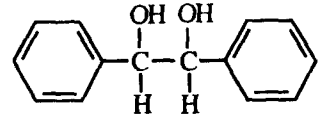
One cannot automatically assume that the enantiomeric purity of a chiral reagent found in this study will be exactly comparable to that of the same compound obtained from the same source at a later date. Nor can one assume that chiral reagents obtained from different sources will be of comparable composition. As can be seen in Table 3, the batch to batch variation of a chiral compound from the same source (in regard to the level of an enantiomeric impurity) can vary as much as the enantiopurity of a chiral compound obtained from different sources. The variation in the concentration of an enantiomeric contaminant can be as much as two orders of magnitude, as seen from the limited number of comparisons done in this and previous studies.[14–19] It appears that most commercially available compounds having a single stereogenic center (or stereogenic axis) contain enantiomeric impurities. It also appears that the level of enantiomeric impurity for any given compound is not controlled and usually not known by the manufacturer(s)/distributor(s).

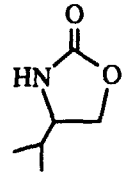
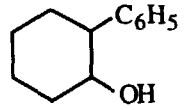
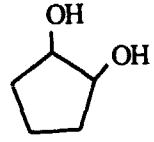
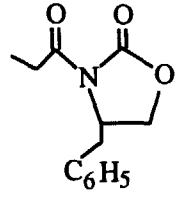
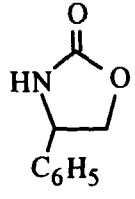
Table 2
The enantiomeric composition of chiral catalysts, auxiliaries, synthons and resolving agents used in asymmetric synthesis

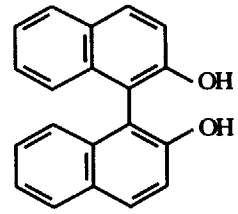
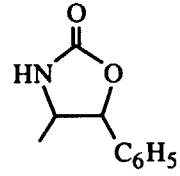
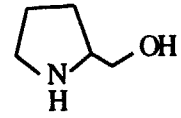
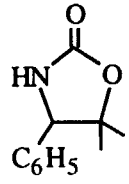
Use in Synthesis	Ref.	Name and Structure of Chiral Reagent	Commercial Source	Enantiomeric Composition		Method Number[b]
				% enantiomeric contaminant	enantiomeric excess[a] (e.e.)	
Catalyst/Catalyst Ligands						
Hydrocarboxylation of olefins	21	1,1'-Binaphthalene-2,2-diyl hydrogen phosphate 	Aldrich	S = 1.85 R = 0.02	96.30 (R) 99.96 (S)	LC-1
a) Oxazaborolidine-catalyzed asymmetric reduction of ketones b) Applications of asymmetric synthesis	22,23	(1S,2R;1R,2S)-cis-1-Amino-2-indanol 	Aldrich	(1R,2S) = 0.52 (1S,2R) = 1.43	98.96 (1S,2R) 97.14 (1R,2S)	CE-1
a) Synthesis of ferrocenyl phosphine ligands for Rh(I) b) Synthesis of chiral sulfides and selenides	24-26	N, N-Dimethyl-1-ferrocenyl-ethylamine 	Aldrich	S = 0.12 R = 0.93	99.76 (R) 98.14 (S)	LC-2

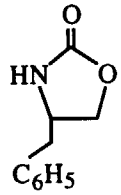
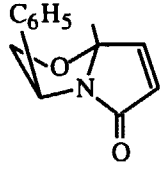
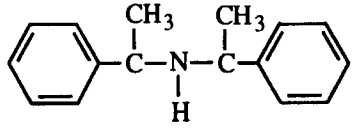
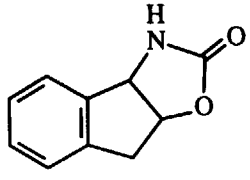
a) Ene reactions b) Diels-Alder reactions	27,28	1,1'-Bi-(2-naphthol) 	Sigma	R = 0.15 S = 0.05	99.70 (S) 99.90 (R)	CE-2
Used as cyclic borane adduct for enantioselective reduction of ketones	29,30	α,α-Diphenyl-2-pyrrolidine methanol 	Aldrich	R = 0.02 S = 0.09	99.96 (S) 99.82 (R)	LC-3
Asymmetric epoxydation of unfunctionalized olefins	12,31	Jacobsen's Catalyst 	Aldrich	(R,R) = 0.01[c] (S,S) = 0.07[c]	99.98[c] (S,S) 99.86[c] (R,R)	LC-4
a) Precursor for epoxidation catalyst b) Chiral reagent	32,33	(1R,2R;1S,2S)-(+)-1,2-Diaminocyclohexane 	Fluka	(1S,2S) = 0.01 (1R,2R) = 0.02	99.98 (1R,2R) 99.96 (1S,2S)	GC-1

Chiral auxiliaries

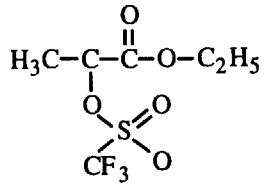
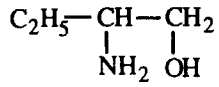
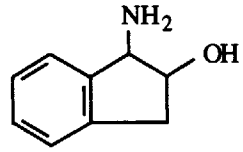
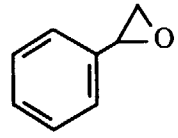
Synthesis of pyrrolinone-based HIV protease inhibitors	9,34	4-Benzyl-5, 5'-dimethyl-2-oxazolidinone 	Aldrich	S = 1.13 R = 0.85	97.74 (R) 98.30 (S)	LC-5
a) Asymmetric synthesis of 5-and 6- membered lactons b) Synthesis of a hydrogenation catalyst by N-phosphinylation c) Reduction of phenyl alkyl ketones	35-37	2,2'-Diamino-1,1'-bi naphthalene 	Fluka	S = 0.28 R =1.14	99.44 (R) 97.72 (S)	CE-3
a) Auxiliary in Wittig rearrangement b) Auxiliary in aldol condensation	38,39	(+,-) Camphor 	Aldrich[d]	(+) = 0.70 (–) = 0.47	98.60 (–) 99.06 (+)	GC-2
Chiral auxiliary for chiral acetals	40	Hydrobenzoin 	(R,R): Fluka (S,S): Acros	(S,S) = 0.26 (R,R) = 0.78	99.48 (R,R) 98.44 (S,S)	LC-6

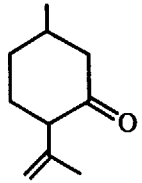
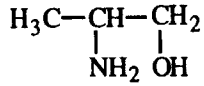
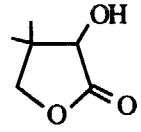
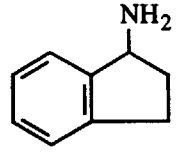
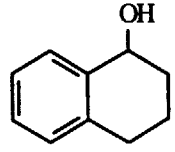
Aldol reaction	9,34	4-Isopropyl-2-oxazolidinone 	Aldrich	R = 0.59 S = 0.42	98.82 (S) 99.16 (R)	GC-3
a) Ene reactions b) Enol ether ketene cycloaddition c) Darzen reaction of chloroacetate	41-43	trans-2-Phenyl-1- cyclohexanol 	Aldrich	(1S,2R) = 0.01 (1R,2S) = 0.65	99.98 (1R,2S) 98.70 (1S,2R)	GC-4
Asymmetric hydrogenation with Rh(I).	44	(1R,2R;1S,2S)-trans-1,2-Cyclopentanediol 	Fluka	(1S,2S) = 0.48 (1R,2R) = 0.02	99.04 (1R,2R) 99.96 (1S,2S)	GC-5
For chain elongation of antibiotic, Nargenicin	9,34	4-Benzyl-3-propionyl-2-oxazolidinone 	Aldrich	S = 0.30 R = 0.14	99.40 (R) 99.72 (S)	LC-2
Aldol reaction	9,34	4-Phenyl-2-oxazolidinone 	Aldrich	S = 0.05 R = 0.20	99.90 (R) 99.60 (S)	LC-7

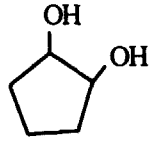
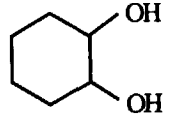
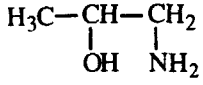
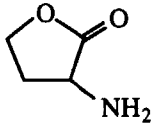
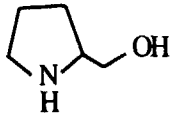
a) Enantioselective reduction of ketones b) Asymmetric oxidation of sulfide to sulfoxide	45,46	1,1'-Bi-(2-naphthol) 	Sigma	R = 0.15 S = 0.05	99.70 (S) 99.90 (R)	CE-2
Aldol reaction	9,34	(4S,5R;4R,5S)-4-Methyl-5-phenyl-2-oxazolidinone 	Aldrich	(4S,5R) = 0.02 (4R,5S) = 0.10	99.96 (4R,5S) 99.80 (4S,5R)	LC-8
a) N-acyl derivatives for enantioselective alkylation b) Asymmetric reduction with borane	47-49	D,L-Prolinol 	L: Sigma D: Fluka	D = 0.02 L = 0.10	99.96 (L) 99.80 (D)	GC-6
Diastereoselective Michael additions	9,34	5,5'-Dimethyl-4-phenyl-2-oxazolidinone 	Aldrich	R = 0.03[e] S = 0.08[e]	99.94[e] (S) 99.84[e] (R)	GC-7 GC-8

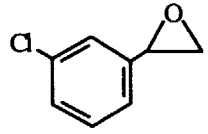
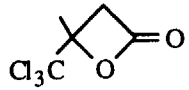
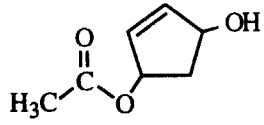
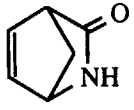
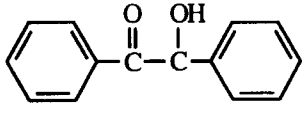
Synthesis of pyrrolinone-based HIV protease inhibitors	9,34	4-Benzyl-2-oxazolidinone 	Aldrich	S = 0.06 R = 0.03	99.88 (R) 99.94 (S)	LC-9
a) Asymmetric conjugate additions b) Asymmetric Lewis Acid catalyzed cycloadditions	50-52	2,3-Dihydro-7a-methyl-3-phenyl-pyrrolo[2,1-b] oxazol-5-(7aH)-on 	Aldrich	S = 0.03 R = 0.01	99.94 (R) 99.98 (S)	GC-9
Used as lithium amide base to stereoselectively remove protons from ketones, epoxides, etc.	53,54	Bis-(1-phenylethyl)-amine HCl 	Aldrich	(S,S) = 0.01 (R,R) = 0.01	99.98 (R,R) 99.98 (S,S)	GC-1
a) Diels-Alder reactions b) Aldol reactions c) Allylations	55-57	(3aR,S-cis)3,3a,8,8a-Tetrahydro-2H-indeno[1,2-d] oxazol-2-one 	Aldrich	R = 0.01 S = 0.01	99.98 (S) 99.98 (R)	GC-10

Synthons or Chiral Building blocks

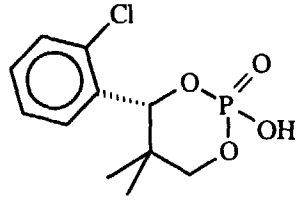
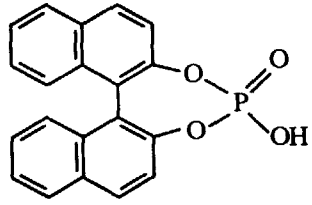
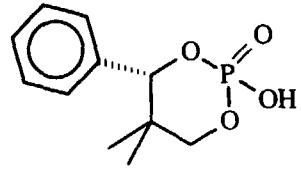
a) Synthesis of N-substituted D-Alanines b) Muramic acid derivative	58,59	Ethyl O-trifluoromethane-sulfonyl-D,L-lactate 	Fluka	L = 7.32 D = 4.36	85.36 (D) 91.28 (L)	GC-11
a) Enantioselective synthesis of 2-aminobutane via N-protection and O- tosyl-ation b) Preparation of thiazo-idine-2-thions and oxazolidine-2-thions	60-62	2-Amino-1-butanol 	R: Aldrich S: Fluka	S = 1.35 R = 1.84	97.30 (R) 96.32 (S)	GC-11
Preparation of HIV protease inhibitor	63	(1S,2R;1R,2S)-cis-1-Amino-2-indanol 	Aldrich	(1R,2S) = 0.52 (1S,2R) = 1.43	98.96 (1S,2R) 97.14 (1R,2S)	CE-1
React to chiral α-substituted benzyl alcohols	64	Styrene oxide 	Fluka	S = 1.61 R = 0.30	96.78 (R) 99.40 (S)	GC-12

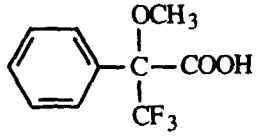
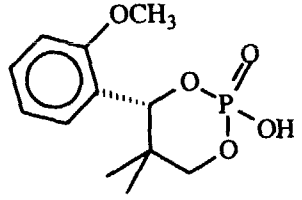
a) Synthesis of antibiotic aplasmomycin b) Asymmetric synthesis of 8-Arylmenthols c) Addition of allyic Grignard reagent d) Synthesis of (-)-α-acorediene	65-68	(+,–)-Pulgone 	Aldrich	(–) = 0.02 (+) = 1.54	99.96 (+) 96.92 (–)	GC-13
a) Synthesis of 2-methyl-aziridine b) N-protection c) Oxidation of the N-protected derivatives to the aldehyde	69-71	2-Amino-1-propanol 	Aldrich	S = 0.07 R = 1.35	99.86 (R) 97.30 (S)	GC-14
a) Preparation of acrylates used in diastereoselective cycloadditions b) Reduction to the triol	72-75	2-Hydroxy-3,3-dimethyl-γ-butyrolactone 	Aldrich Fluka	R = 0.28 S = 0.77	99.44 (S) 98.46 (R)	GC-15
Synthetic intermediate	76	1-Aminoindan 	Aldrich	S = 0.74 R = 0.35	98.52 (R) 99.30 (S)	CE-4
Synthetic intermediate	77	1,2,3,4-Tetrahydro-1-naphthol 	Aldrich	R: 0.32 S: 0.64	99.36 (S) 98.72 (R)	LC-10

Synthesis of chiral phosphine ligands	78	(1R,2R;1S,2S)-trans-1,2-Cyclopentanediol 	Fluka	(1S,2S) = 0.48 (1R,2R) = 0.02	99.04 (1R,2R) 99.96 (1S,2S)	GC-5
a) Conjugate addition reactions b) Asymmetric alkylations	79-81	(1R,2R;1S,2S)-trans-1,2-Cyclohexanediol 	Aldrich	(1S,2S) = 0.05 (1R,2R) = 0.25	99.90 (1R,2R) 99.50 (1S,2S)	GC-16
a) Preparation of chiral enamines b) Synthesis of 2 methyl-aziridine	82,83	1-Amino-2-propanol 	Aldrich	S = 0.13 R = 0.14	99.74 (R) 99.72 (S)	GC-17
a) Synthesis of biologically active peptides b) Preparation of Se- and Te-analogues of methionine	84-86	2-Amino-γ-butyrolactone HBr 	Fluka	R = 0.11	99.78 (S)	GC-18
N-protection and oxidation to the aldehydes	87	L,D-Prolinol 	L: Fluka D: Sigma	L: 0.02 D: 0.10	99.96 (D) 99.80 (L)	GC-6

Asymmetric synthesis of β_3-adrenergic agonist	88,89	3-Chlorostyrene oxide 	Aldrich	S = 0.07	99.86 (R)	GC-12
Synthesis of (S)-citramalic acid	90	3-Hydroxy-3-methyl-4,4,4-trichlorobutyric β-lactone 	Aldrich	S = 0.02 R = 0.06	99.96 (R) 99.88 (S)	GC-19
a) Preparation for both enantiomers of cyclopentanoids b) Use of derivatives in prostaglandins synthesis c) Anti-selective cis hydroxylation of the double bond	91-93	(1S,4R;1R,4S)-cis-4-Acetoxy-2-cyclopenten-1-ol 	Fluka	(1R,4S) = 0.01 (1S,4R) = 0.05	99.98 (1S,4R) 99.90 (1R,4S)	GC-20
Precurors to carbocyclic nucleoside (-) carbovir, a potent inhibitor of HIV-1	94-97	2-Azabicyclo[2,2,1]hept-5-en-3-one 	Aldrich	S = 0.01 R = 0.01	99.98 (R) 99.98 (S)	GC-21
Chiral starting material	98	Benzoin 	Aldrich	R = 0.01	99.98 (S)	LC-11

Chiral resolving agents

Resolution of amines, amino acids and amino alcohols	99,100	4-(2-Chlorophenyl)-2-hydroxy-5,5-dimethyl-1,3,2- dioxaphosphorinane 2-oxide 	Aldrich	S = 0.60[e] R = 3.39[e]	98.80[e] (R) 93.22[e] (S)	LC-12 LC-13
Forms salts to resolve organic bases especially amines	101	1,1'-Binaphthalene-2,2-diyl hydrogen phosphate 	Aldrich	S = 1.85 R = 0.02	96.30 (R) 99.96 (S)	LC-1
Resolution of amines, amino acids and amino alcohols	99,100	2-Hydroxy-5, 5-dimethyl-4-phenyl-1,3,2-dioxaphosphorinane 2-oxide 	Aldrich	S = 0.03 R = 0.41	99.94 (R) 99.18 (S)	LC-14

Determination of enantiomeric purity and absolute configuration of alcohols and amines by NMR	102,103	α-Methoxy-α-(trifluoromethyl) phenylacetic acid 	Aldrich	R = 0.06 S = 0.04	99.88 (S) 99.92 (R)	LC-15
Resolution of amines, amino acids and amino alcohols	99,100	2-Hydroxy-4-(2-methoxyphenyl)-5,5-dimethyl-1,3,2-dioxaphosphorinane 2-oxide 	Aldrich	S = 0.02 R = 0.01	99.96 (R) 99.98 (S)	LC-15

[a] ee: Enantiomeric excess, specifies the excess of the predominant enantiomer over the racemic part in a mixture as a percentage. ee = (A–B)/(A+B)x100, A: predominant enantiomer; B: its antipode. The first eluting one is shown on the top. Note that the enantiomeric impurity is given in the previous column.

[b] This notation is taken from Table 1 which lists the analytical conditions for evaluating the enantiomeric composition of every compound in this study. The intial letters are abbreviation for the analytical method used, i.e., GC = gas chromatography, LC = liquid chromatography (specifically HPLC), and CE = capillary electrophoresis.

[c] From reference 20.

[d] A technical grade of (–)-camphor from Aldrich contained 11.59% of the (+)-enantiomer.

[e] Different chiral stationary phases (CSPs) were used for the R and S enantiomers. This was done because these two CSPs have the opposite elution order for these enantiomers, thereby, allowing the minor antipode to be easily quantitated in these cases.

Table 3
Comparisons of enantiomeric excess[a] for compounds purchased at different times and from different sources

2-Amino-1-butanol	R enantiomer (e.e.)	S enantiomer (e.e.)
Aldrich (8/97)	N/A	98.41 ± 0.05
Aldrich (12/97)	97.30 ± 0.40	98.47 ± 0.07
Sigma (8/97)	98.83 ± 0.04	N/A
Sigma (12/97)	98.72 ± 0.28	N/A
Fluka (12/97)	73.07 ± 0.04 (Pract. grade[b])	96.31 ± 0.08
1,1'-Binaphthalene-2,2-diyl hydrogen phosphate	**R enantiomer (e.e.)**	**S enantiomer (e.e.)**
Aldrich (8/97)	96.29 ± 0.01	99.93 ± 0.10
Aldrich (12/97)	99.97 ± 0.01	99.99 ± 0.01
Sigma (old)	99.99 ± 0.01	99.89 ± 0.02
Sigma (12/97)	99.98 ± 0.02	99.96 ± 0.03
Fluka (12/97)	99.99 ± 0.01	99.96 ± 0.01
Hydrobenzoin	**R enantiomer (e.e.)**	**S enantiomer (e.e.)**
Aldrich (8/97)	99.95 ± 0.01	98.93 ± 0.06
Aldrich (12/97)	99.97 ± 0.01	98.70 ± 0.02
Fluka (1/98)	99.47 ± 0.05	99.61 ± 0.11
Acros (2/98)	99.88 ± 0.01	98.45 ± 0.08

a. The confidence limit is based on 95% confidence interval for the mean.
b. Labelled 90% (Sum of enantiomers).

4. Conclusions

All of the chiral reagents evaluated in this study contained detectable levels of enantiomeric impurities. Over half of the compounds evaluated contained >0.1% of the undesired enantiomer and a significant number had >1% contamination. The contaminant level of compounds having the highest enantiopurities ranged from ~0.01% to 0.1% (of the unwanted enantiomer). The batch to batch enantiomeric purity of a chiral compound from the same source can vary considerably as can the purity of the same compound from different sources. The results found in this study are somewhat analogous to those previously reported for amino acids and monoterpenes in that there are few, if any, enantiomerically pure compounds available (for those reagents that contain one or possibly two stereogenic centers). In general, it would be beneficial for those involved in enantioselective synthesis to have some idea as to the enantiopurity of the catalysts, auxiliaries and synthons used in their work. This information is essential for the accurate evaluation of the enantioselectivity of specific reactions, particularly at the

higher e.e. levels. Chiral catalysts and auxiliaries may produce significantly higher (or lower) levels of stereochemical impurities, when used in conjunction with chiral substrates, than might be indicated from their enantiomeric composition. In a worst-case scenario, a low level enantiomeric impurity in a catalyst could produce an unwanted stereoisomer at a much faster rate than the dominant reagent enantiomer produces the desired product. The methodologies for evaluating the enantiomeric purities of chiral reagents (even at very low or very high levels) are now available.

Acknowledgements

Support of this work by the National Institute of Health (GM53825-02) is gratefully acknowledged.

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