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Enantiomeric impurities in chiral catalysts, auxiliaries, synthons and resolving agents. Part 2

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Abstract

The enantiomeric purity of reagents used in asymmetric synthesis is of fundamental importance when evaluating the selectivity of a reaction and the product purity. In this work, 109 chiral reagents (many recently introduced) are assayed. Approximately 64% of these reagents had moderate to high levels of enantiomeric impurities (i.e. from >0.1% to <16%). The type of chiral reagents assayed and used in enantioselective synthesis Include: (a) metal–ligand catalysts for allylic substitutions, catalysts for addition of Grignard reagents and other additions, epoxidations and reduction of ketones and aldehydes; (b) Ru-complex auxiliaries for asymmetric cyclopropanation, as well as amine, diamine, alcohol, diol, aminoalcohol, carboxylic acid and oxazolidione auxiliaries; (c) epoxide, lactone, furanone, pyrrolidinone, nitrile, sulfoximine and carboxylic acid synthons (including malic acid, mandelic acid, lactic acid and tartaric acid); and (d) a variety of chiral resolving agents. Accurate, efficient assays for all compounds are given.

1. Introduction

A recently published study indicated that many chiral catalysts and other reagents used in enantioselective synthesis contained widely varying levels of enantiomeric impurities.[1] This followed earlier studies which indicated that many naturally occurring molecules (i.e. amino acids, monoterpenes, etc.) used in asymmetric synthesis also contained significant levels of enantiomeric impurities.[2–10] The results of all of these studies can be summarized as follows: (a) commercially available compounds (whether natural or synthetic) with one stereogenic center or a stereogenic axis almost always contains some level of enantiomeric impurity; (b) the level of enantiomeric impurities ranges from slightly less than 0.01% to more than 40%; (c) over half of the compounds analyzed had enantiomeric impurity levels >0.1%; (d) the enantiomeric purity of chiral reagents can vary tremendously from different sources and with the

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time of procurement from the same source; and (e) usually neither the supplier nor the consumer has any idea as to the enantiomeric purity of chiral reagents.

As the stereoselectivity of synthetic reactions continues to improve, factors such as the stereochemical purity of the catalysts, auxiliaries and synthons used limit product ees (not to mention the accurate calculation of these ees). In the last year a large number of new chiral reagents have become available.[11] In addition, new synthetic approaches that make use of naturally occurring chiral molecules, that have not been assayed, have been reported.[12–23] In this work we report on the enantiomeric purity of 109 commercial reagents that have not been assayed previously. Methods were developed that the allow detection of enantiomeric impurities in these reagents to ~0.01%.

2. Experimental section

2.1. Materials

All HPLC columns (25 cm×4.6 mm i.d.) and GC columns (20 m×0.25 mm, 30 m×0.25 mm, 40 m×0.25 mm) were obtained from Advanced Separation Technologies, Inc. (Whippany, NJ). The LC columns used were 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), Chirobiotic T (teicoplanin), Chirobiotic V (vancomycin) and Astec CLC-D (chiral ligand column). Chiradex G-TA (2,6-di-*O*-pentyl-3-trifluoroacetyl-γ-cyclodextrin), Chiraldex B-DM (di-*O*-methyl-β-cyclodextrin), Chiradex B-DA (2,6-di-*O*-pentyl-β-cyclodextrin), Chiradex G-PN (2,6-di-*O*-pentyl-3-propionyl-γ-cyclodextrin), and Chiradex A-TA (2,6-di-*O*-pentyl-3-trifluoroacetyl-α-cyclodextrin) columns were used for GC analysis. The solvents [methylene chloride, methanol, acetonitrile, glacial acetic acid and triethylamine (99+% pure)] were purchased from Fisher Scientific (St. Louis, MO); isopropyl alcohol was from EM Science (Gibbstown, NJ); tetrahydrofuran was from Aldrich (Milwaukee, WI). Chemicals (cupric sulfate and ammonium nitrate) were purchased from Fisher Scientific (St. Louis, MO). The derivatizing agents, trifluoroacetic anhydride (99+%) and chloroacetic anhydride (97%), were from Aldrich (Milwaukee, WI). The sources for all chiral compounds used in this study were purchased from Aldrich (Milwaukee, WI).

2.2. Apparatus and methods

The LC enantioseparations were performed using the following Shimadzu (Columbia, MD) equipment: 2 LC-6A and 2 LC-10AT pumps, an SPD-2AM and an SPD-10A US–vis detector, an SCL-6A and an SCL-10A system controller, a CR601 and a CR501 chromatopac integrator, and a SIL-10A auto injector. The detection wavelength was set at 254 nm. All chromatograms were run at ambient temperature (22°C). All samples were dissolved in methanol. 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 GC analysis. With the exception of 2-(dibutylamine)-1-phenyl-1-propanol and *N*-methylephedrine which were derivatized with chloroacetic anhydride, 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 all commercially available chiral reagents are given in Table 1. A method number from Table 1 is listed for each compound (along with the result of the analysis) in Table 2. Note that, when quantifying peak areas for very low levels of enantiomeric impurities (esp. <0.1%), one cannot

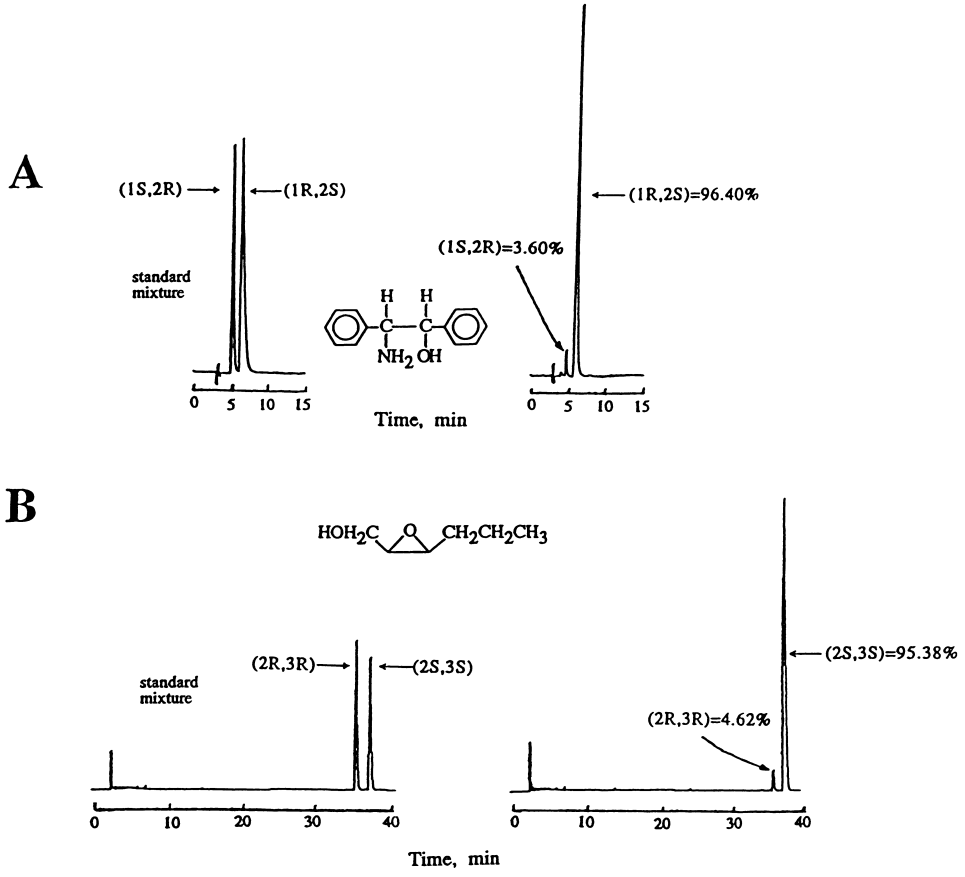


Figure 1. The chromatograms designated 'A' show the HPLC enantioseparations (from left to right) of a mixture of two enantiomers of 2-amino-1,2-diphenylmethanol and a commercial sample (Aldrich) of (1*R*,2*S*)-(−)-2-amino-1,2-diphenylmethanol. The experimental conditions for this reversed phase separation are given in Table 2 as method 'LC-2'. The chromatograms designated 'B' show the GC enantioseparations (from left to right) of a mixture of two enantiomers of 3-propyloxiranemethanol and a commercial sample (Aldrich) of (2*S*,3*S*)-(−)-3-propyloxiranemethanol. The experimental conditions for this GC separation are given in Table 2 as method 'GC-27'. Note the enantiomeric impurities in both of the above commercial reagents.

always rely on instrumental integration devices. The large peak for the dominant enantiomer is usually off scale. Often the absorbance 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 first be quantified. The area of the large peak is measured subsequently after serial dilution to an appropriate concentration. The purities given in Table 2 are the average of at least three determinations. In addition to more common experimental variations, the error in each determination is dependent on the enantiomeric resolution, peak shape and baseline noise inherent for each separation. Typical standard deviations (s) for three reagents containing different levels of enantiomeric purities are as follows: (*R*)-3-propyloxiranemethanol, ee=90.76, s=0.02, n=3; (L)-(+)-lactic acid, ee=98.85, s=0.08, n=5; (L)-dimethyl-2,3-*O*-isopropylidene tartrate, ee=99.97, s=0.008, n=4.

Table 1
Enantioselective methods by gas chromatography (GC) and high performance liquid chromatography (HPLC)

GC Method Number [a]	Column [b]	Length (m)	Temperature (°C)	Pressure(psi)
GC-1	Chiraldex G-PN	30	135	20
GC-2	Chiraldex A-TA	30	40	20
GC-3	Chiraldex G-TA	30	100	20
GC-4	Chiraldex B-DM	40	182	20
GC-5	Chiraldex B-DM	40	170	20
GC-6	Chiraldex B-DM	40	140	20
GC-7	Chiraldex B-DM	40	110	20
GC-8	Chiraldex G-TA	20	140	20
GC-9	Chiraldex G-TA	30	105	20
GC-10	Chiraldex B-DM	30	160	20
GC-11	Chiraldex B-DM	30	210	20
GC-12	Chiraldex G-TA	30	120	20
GC-13	Chiraldex B-DM	40	130	20
GC-14	Chiraldex B-DM	40	90	20
GC-15	Chiraldex G-PN	20	110	18
GC-16	Chiraldex G-TA	30	130	20
GC-17	Chiraldex G-TA	30	45	15
GC-18	Chiraldex G-TA	40	150	20
GC-19	Chiraldex G-TA	30	50	20
GC-20	Chiraldex G-PN	30	100	20
GC-21	Chiraldex G-TA	30	60	20
GC-22	Chiraldex B-DM	30	90	20
GC-23	Chiraldex G-TA	30	140	20
GC-24	Chiraldex B-DM	30	110	20
GC-25	Chiraldex B-DA	20	100	20
GC-26	Chiraldex G-TA	20	85	18
GC-27	Chiraldex G-TA	30	40	20
GC-28	Chiraldex A-TA	30	60	20

HPLC Method Number [a]	Column [c]	Mobile Phase [d] (%, v/v)	Flow Rate (ml/min)
LC-1	Cyclobond I 2000 SN	ACN:MeOH:HOAc:TEA = 95:5:0.3:0.2	1
LC-2	Cyclobond I 2000 Ac	ACN:1% TEAA = 5:95, pH 4.1	1
LC-3	Cyclobond I 2000 SN	ACN:1% TEAA = 15:85, pH 4.1	1
LC-4	Chirobiotic V	MeOH:HOAc:TEA = 100:0.1:0.4	1
LC-5	Chirobiotic V	MeOH:HOAc:TEA = 100:0.02:0.01	1
LC-6	Chirobiotic V	THF:20 mM NH_4NO_3 = 10:90	0.6
LC-7	Cyclobond I 2000 RSP x 2 [e]	MeOH:1% TEAA = 30:70, pH 5.0	0.6
LC-8	Cyclobond I 2000 Ac	ACN:1%TEAA = 20:80, pH 4.1	1
LC-9	Astec CLC-D	1 mM $CuSO_4$	1
LC-10	Chirobiotic T	MeOH:1% TEAA = 5:95, pH 4.1	1
LC-11	Cyclobond I 2000 SN	ACN:1% TEAA = 20:80, pH 7.1	1
LC-12	Chirobiotic T	MeOH:1% TEAA =15:85, pH 4.1	1
LC-13	Astec CLC-D	5 mM $CuSO_4$, pH 3.0	1.5
LC-14	Cyclobond I 2000 RSP	MeOH:1% TEAA = 30:70, pH 4.1	1
LC-15	Chirobiotic V	MeOH:1% TEAA = 10:90, pH 4.1	0.5
LC-16	Astec CLC-D	5 mM $CuSO_4$:MeOH:IPA = 100:15:7.5	1.5
LC-17	Cyclobond I 2000 RSP x 2 [e]	MeOH:1% TEAA = 30:70, pH 4.1	0.7

[a] This notation is used to identify the separation techniques in Table 2. Also all analytes containing amine and/or hydroxy functionalities were derivatized with trifluoroacetic anhydride, except for 2-(Dibutylamine)-1-phenyl-1-propanol and N-Methylephedrine which were derivatized with chloroacetic anhydride (see Experimental section).

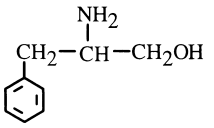
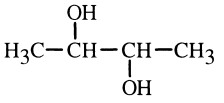
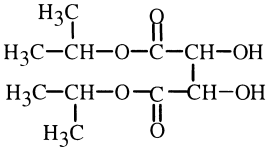
[b] The abbreviation for the GC columns from Astec (Whippany, NJ) are as follows: G-TA is 2,6-di-O-pentyl-3-trifluoroacetyl-γ-CD; B-DM is di-O-methyl-β-CD; B-DA is 2,6-di-O-pentyl-β-CD; G-PN is 2,6-di-O-penty-3-propionyl-γ-CD; A-TA is 2,6-di-O-pentyl-3-trifluoroacetyl-α-CD.

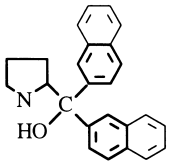
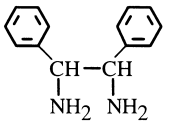
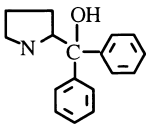
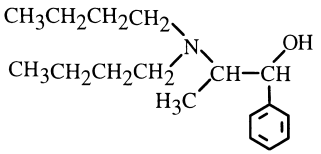
[c] The abbreviation for the HPLC columns (25 x 4.6 mm, i.d.) from Astec (Whippany, NJ) are as follows: Cyclobond I 2000 RSP is 2-Hydroxypropyl-β-CD; Cyclobond I 2000 Ac is Acetylated-β-CD; Cyclobond I 2000 SN is S-Naphthylethyl carbamated-β-CD; Chirobiotic T is Teicoplanin; Chirobiotic V is Vancomycin.

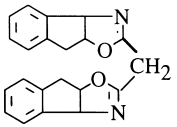
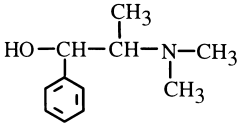
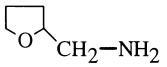
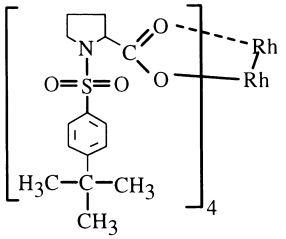
[d] Mobile phase: ACN=acetonitrile; TEA=triethylamine; HOAc=glacial acetic acid; MeOH = methanol; 1% TEAA =1% v/v triethylammonium acetate buffer, pH adjusted by HOAc

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

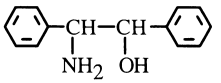
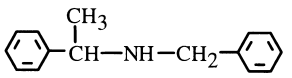
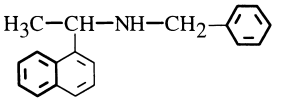
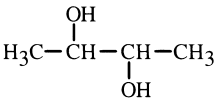
Table 2
The enantiomeric composition of chiral catalysts, auxiliaries, synthons and resolving agents used in asymmetric synthesis[24–121]

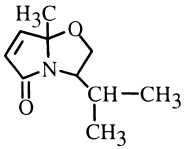
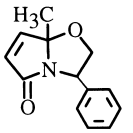
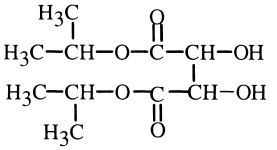
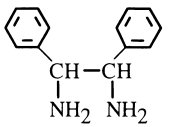
Synthetic use	Ref.	Name and Structure of Chiral Compound	Chemical Source	Enantiomeric composition enantiomeric contaminant (%)	enantiomeric excess [a] (e.e.)	Method Number [b]
Catalyst/Catalyst Ligands						
a)Pd-catalyzed allylic substitution b)Cu-catalyzed 1,4 addition of Grinard reagent to α, β unsaturated ketones	24,25	2-Amino-3-phenyl-1-propanol 	Aldrich	S=0.01 R=0.01	99.98(R) 99.97(S)	GC-1
Used in enantioselective capture and retroracemization of (1-bromoalkyl) boronic esters	26	2,3-Butanediol 	Aldrich	2S,3S=0.11 2R,3R=0.17	99.77(2R,3R) 99.65(2S,3S)	GC-2
Enantioselective epoxidation of racemic allylic alcohols	27,28	Diisopropyl tartrate 	Aldrich	L=0.29 D=0.01	99.43(D) 99.98(L)	GC-3

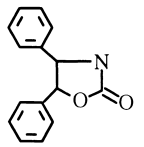
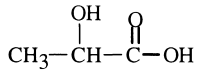
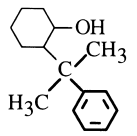
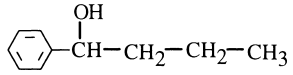
The oxazaborolidine prepared from this compound was used as a reagent for enantioselective reduction of prochiral ketones	29,30	α, α-Di(2-naphthyl)-2-pyrrolidinemethanol 	Aldrich	R=0.10 S=0.07	99.80(S) 99.87(R)	LC-1
Versatile ligand for the formation of metal complexes	31	1,2-Diphenylethylene-diamine 	Aldrich	1S,2S=0.50 1R,2R=0.07	99.00(1R,2R) 99.87(1S,2S)	GC-4
Used to prepare the corresponding oxazaborolidines for the borane-mediated asymmetric reduction of ketones	32,33	α, α-Diphenyl-2-pyrrolidine 	Aldrich	R=0.01 S=0.08	99.98(S) 99.83(R)	LC-2
Ligand for enantioselective addition of dialkylzinc to carbonyls and imines	34,35	2-(Dibutylamine)-1-phenyl-1-propanol 	Aldrich	1S,2R=0.32[c] 1R,2S=0.14[c]	99.36(1R,2S)[c] 99.72(1S,2R)[c]	GC-5

C_2 symmetric chiral ligand for enantioselective catalysis	36,37	[3aR-[2(3'**a**R*,8'**a**S*), 3'**a**β,8'a β]]-2,2'-methyl-ene-bis[3a,8a-dihydro-8H -indeno[1,2-d]]oxazole 	Aldrich	S=0.03 R=0.05	99.94(R) 99.89(S)	LC-3
Employed as bifuctional chiral base catalyst in enantioselective synthesis of 2,3-dihydroindole	38	N-Methylephedrine 	Aldrich	1S,2R=0.03[c] 1R,2S=0.03[c]	99.94(1R,2S)[c] 99.94(1S,2R)[c]	GC-6
Chiral ligand for lithium in the reduction of aldehydes and ketones	39	Tetrahydrofurfurylamine 	Aldrich	S=0.90 R=0.44	98.21(R) 99.13(S)	GC-7
Used for asymmetric cyclopropanation	40,41	Tetrakis[1-[(4-tert-butyl-phenyl)sulfonyl]-pyrro-lidine-carboxylate] dirhodium(II) 	Aldrich	R=0.03 S=0.38	99.95(S) 99.25(R)	LC-4

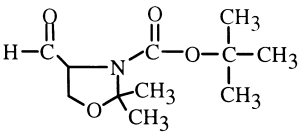
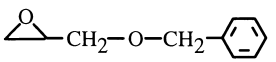
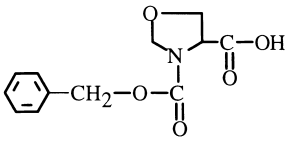
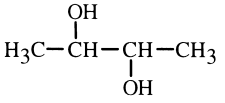
Chiral Auxiliaries

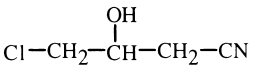
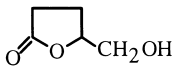
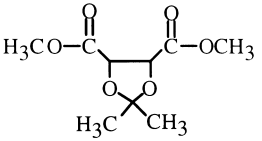
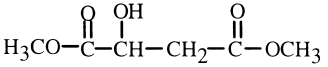
Chiral auxiliary used for Pd(II)-assisted chiral tandem alkylation/ carbonylative coupling reactions	42,43	2-amino-1,2-diphenyl-ethanol 	Aldrich	1R,2S=0.10 1S,2R=3.60 1S,2R=3.68 1R,2S=0.10	99.79(1S,2R) 92.79(1R,2S) 92.64(1R,2S) 99.80(1S,2R)	LC-2 GC-8
a)Asymmetric enolisation reaction b)Asymmetric metallation of ferrocenes c)Enantioselective deprotonation/ silylation	44-47	N-Benzyl- α-methyl-benzylamine 	Aldrich	S=1.08 R=0.86	97.85(R) 98.27(S)	LC-5
Chiral amine used for enantioselective deprotonations	44-47	N-Benzyl-1-(1-naphthyl)-ethylamine hydrochloride 	Aldrich	R=0.04 S=0.40	99.92(S) 99.20(R)	LC-6
Synthesis of C_{20}-C_{34} subunit of the immunosupprassant FK-506	48	2,3-Butanediol 	Aldrich	2S,3S=0.11 2R,3R=0.17	99.77(2R,3R) 99.65(2S,3S)	GC-2

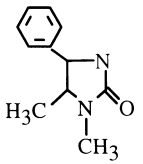
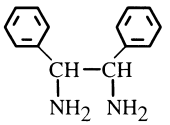
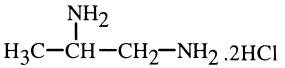
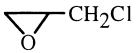
a)Single and double diastereoselection in azomethine ylide cycloaddition b)Annulation to electron deficient olefine	49,50	cis-2,3-Dihydro-3-isopropyl -7a-methylpyrrolo[2,1-b] oxazol-5(7aH)-one 	Aldrich	R=0.05 S=0.01	99.90(S) 99.98(R)	GC-9
a)Single and double diastereoselection in azomethine ylide cycloaddition b)Annulation to electron deficient olefine	49,50	cis-2,3-Dihydro-7a-methyl-3-phenylpyrrolo[2,1-b] oxazol-5(7aH)-one 	Aldrich	S=0.01 R=0.01 S=0.01 R=0.01	99.98(R) 99.98(S) 99.98(R) 99.98(S)	GC-10 LC-7
Used in chiral allylic boronates and catalytic trimethylsilyl-cyanation of aldehydes	12,13	Diisopropyl tartrate 	Aldrich	L=0.29 D=0.01	99.43(D) 99.98(L)	GC-3
Used in various catalyst systems for asymmetric reaction and the bis(sulfonamide) is a powerful chiral auxiliary: cyclic Lewis acid complexes catalyze enantioselective aldol, allylation , propargylation and similar reactions	51-53	1,2-Diphenylethylenedi-amine 	Aldrich	1S,2S=0.50 1R,2R=0.07	99.00(1R,2R) 99.87(1S,2S)	GC-4

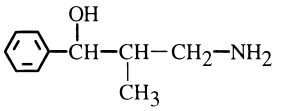
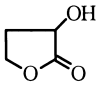
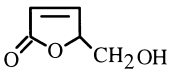
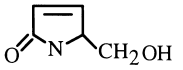
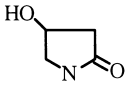
Versatile chiral auxiliary used in asymmetric synthesis in a)Michael additions b)Allylations c)Diels-Alder reactions	54-57	cis-4,5-Diphenyl-2-oxazolidinone 	Aldrich	4R,5S=0.01 4S,5R=0.01 4R,5S=0.02 4S,5R=0.01	99.98(4S,5R) 99.98(4R,5S) 99.95(4S,5R) 99.98(4R,5S)	LC-8 GC-11
Reduction of ketones	14	Lactic acid 	Aldrich	D(-)=0.58 L(+)=0.14	98.85(L(+)) 99.71(D(-))	LC-9
New cyclohexyl-based chiral auxiliary that provides greater level of asymmetric induction	58,59	trans-2-(1-Methyl-1-phenyl-ethyl)-cyclohexanol 	Aldrich	1S,2R=0.49 1R,2S=0.49	99.01(1R,2S) 99.02(1S,2R)	GC-12
Asymmetric reduction of prochiral aromatic ketones	60	1-Phenyl-1-butanol [d] 	Aldrich	R=0.01[d] S=0.02[d]	99.97(S)[d] 99.95(R)[d]	LC-7

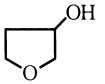
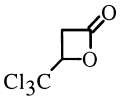
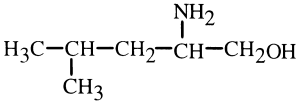
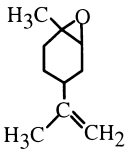
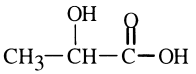
Synthons or Chiral Building blocks

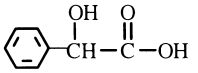
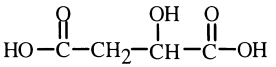
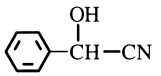
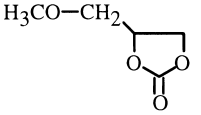
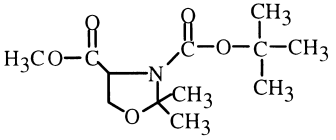
Widely utilized in the asymmetric synthesis of natural products	61,62	tert-Butyl-4-formyl-2,2-dimethyl-3-oxazolidine 	Aldrich	R=15.11 S=4.50	69.79(S) 90.99(R)	GC-3
Used in the preparation of dideoxynucleosides and spirolacetal cyanohydrin	63,64	Benzyl-glycidyl ether 	Aldrich	R=1.80 S=1.73	96.40(S) 96.54(R)	GC-13
Chiral synthon for N-containing targets	65	3-(Benzyloxycarbonyl)-4-oxazolidine carboxylic acid 	Aldrich	R=0.05 S=0.42	99.90(S) 99.17(R)	LC-10
Synthesis of 2,5-Disubstituted pyrrolidines	66	2,3-Butanediol 	Aldrich	2S,3S=0.11 2R,3R=0.17	99.77(2R,3R) 99.65(2S,3S)	GC-2

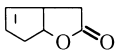
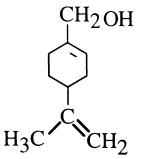
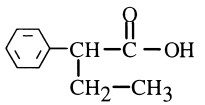
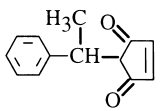
(-)-Carnitine and (-)-γ-amino-β-hydroxybutyric acid have been prepared using this synthon	67	4-Chloro-3-hydroxy-butyronitrile 	Aldrich	S=0.76 R=1.14	98.47(R) 97.73(S)	GC-14
a)Chiral synthon used in synthesis of natural and unnatural products b)Chiral synthon for merinic acid	68-70	Dihydro-5-(hydroxy-methyl)-2(3H)-furanone 	Aldrich	R=0.29 S=0.30	99.43(S) 99.41(R)	GC-15
Valuable building block for TADDOL chiral auxiliaries and dipyridine	71,72	Dimethyl-2,3-O-iso-propylidene tartrate 	Aldrich	D=0.02 L=0.22	99.97(L) 99.56(D)	GC-12
Used to prepare cytochrome P450 metabolites of arachidonic acid and cyclic sulfolanes with HIV-1 protease inhibition potential	15,16	Dimethyl malate 	Aldrich	S=2.04 R=1.07	95.92(R) 97.87(S)	GC-3

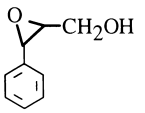
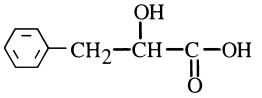
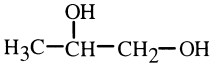
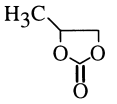
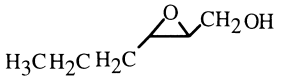
Employed in the synthesis of optically active mono-, di- and trihydroxy compounds	73	1,5-Dimethyl-4-phenyl-2-imidazolidinone 	Aldrich	4S,5R=0.05 4R,5S=0.17	99.90(4R,5S) 99.66(4S,5R)	GC-11
Used in the synthesis of chiral tropocoronands	74	1,2-Diphenylethylenediamine 	Aldrich	1S,2S=0.50 1R,2R=0.07	99.00(1R,2R) 99.87(1S,2S)	GC-4
Synthesis of chiral imidazolines	75,76	1,2-Diaminopropane dihydrochloride 	Aldrich	R=1.26 S=3.90	97.47(S) 92.20(R)	GC-16
Chiral synthon employed in the preparation of glycidyl ethers	77	Epichlorohydrin 	Aldrich	R=1.58 S=1.27	96.83(S) 97.45(R)	GC-17

Versatile chiral synthon employed in catalyst and in the preparation of optically pure sulfoxides and oxazolidines	78-80	Ephedrine 	Aldrich	1S,2R=0.02 1R,2S=0.05	99.95(1R,2S) 99.90(1S,2R)	GC-7
Used to prepare functionalized D-ring side chains of Vitamin D analogs and pesticides	81,82	α-Hydroxy-γ-butyro-lactone 	Aldrich	R=0.32 S=0.59	99.35(S) 98.82(R)	GC-16
Used in preparation of partially saturated heterocycles via diastereoselective ring chain formation	83	5-(Hydroxymethyl)-2-2(5H)-furanone 	Aldrich	R=0.59 S=0.77	98.82(S) 98.46(R)	GC-12
Building block in the synthesis of R-, S-diaminovaleric acids and of 5-azasemicorrins for enantioselective catalyst	84,85	5-(Hydroxymethyl)-2-pyrrolidinone 	Aldrich	S=0.23 R=0.02	98.53(R) 99.95(S)	GC-18
Synthesis of (-)-γ-amino-β-hydroxybutyric acid	86	4-Hydroxy-2-pyrro-lidinone 	Aldrich	S=0.02 R=0.02	99.95(R) 99.95(S)	GC-16

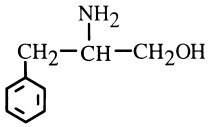
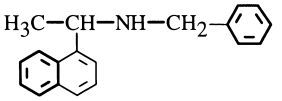
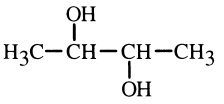
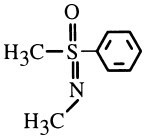
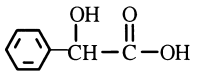
Used in synthesis of chiral atrolactic acid	87	3-Hydroxytetrahydrofuran 	Aldrich	R=0.09 S=1.28	99.83(S) 97.43(R)	GC-19
Used in the preparation of (R) - carnitine	88	3-Hydroxy-4,4,4,-tri-chloro-butyric β-lactone 	Aldrich	S=0.05 R=0.02	99.90(R) 99.95(S)	GC-20
Starting material for the synthesis of aminopeptides N and phospholipase A_2 inhibitors	89,90	Leucinol 	Aldrich	R=1.38 S=0.10	97.23(S) 99.80(R)	GC-12
Involved in the stereospecific synthesis of cis- and trans- Δ-p-methene 1,2-epoxides	91	Limonene oxide 	Aldrich	(+)=0.52 (-)=1.23	98.96(-) 97.54(+)	GC-21
Chiral synthon in preparation of benproperinium dihydrogen phosphate	17	Lactic acid 	Aldrich	D(-)=0.58 L(+)=0.14	98.85(L(+)) 99.71(D(-))	LC-9

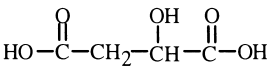
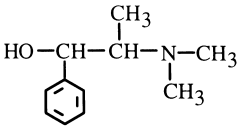
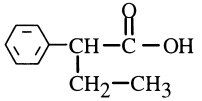
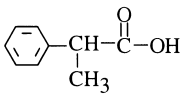
Versatile reagent used in the preparation of amides	18,19	Mandelic acid 	Aldrich	S=0.09 R=14.00	99.82(R) 72.01(S)	LC-12
Versatile synthon for chiral compounds including κ-opioid receptor agonists and a 1α, 25–dihydroxy vitamin D_3 analogue	20,21	Malic acid 	Aldrich	D(+)=0.21 L(-)=1.22	99.59(L(-)) 97.56(D(+))	LC-13
Used in the preparation of optically active α-hydroxy carboxylic acids, α-hydroxy aldehydes, α-hydroxy ketones and 2-amino alcohols	92	Mandelonitrile 	Aldrich	S=10.26	79.47(R)	GC-22
Asymmetric synthesis of chiral 3-aryl-2-oxazolidinones	93	4-(Methoxymethyl)-1,3-dioxolan-2-one 	Aldrich	R=1.10 S=0.74	97.80(S) 98.52(R)	GC-23
This precursor to a configurationally stable serinal derivative had been used to make azasugars, sphingolipids and amino sugars	94,95	Methyl-3-(tert-butoxy carbonyl)-2,2-dimethyl-4-oxazolidinecarboxylate 	Aldrich	R=0.32 S=0.10	99.36(S) 99.80(R)	GC-24

Synthesis of carboxylic nucleosides	96	2-Oxabicyclo[3.3.0]oct-6-en-3-one 	Aldrich	S=0.01 R=0.12	99.98(R) 99.75(S)	GC-18
a)Selective cyclopropanation of exo- or endocyclic double bonds b)Rearrangement of derivatives to isocarvyl compounds	97,98	Perillyl alcohol 	Aldrich	R=3.75 S=4.61	92.50(S) 90.79(R)	GC-25
Synthesis of the corresponding alcohol, amide and olefine	99,100	2-Phenylbutyric acid 	Aldrich	S=1.82 R=2.16	96.35(R) 95.69(S)	LC-14
Used in radical copolymerization for nonlinear materials	101,102	N-(1-Phenylethyl)maleimide 	Aldrich	S=1.11 R=0.07	97.79(R) 99.87(S)	LC-15

a)Stereoselective addition reaction at C-3 b)Use of the phenyl group as a carboxyl synthon	103,104	3-Phenylglycidol 	Aldrich	2R,3R=0.75 2S,3S=0.08	98.49(2S,3S) 99.84(2R,3R)	GC-26
Starting material in the preparation of the hypoglycemic agent enlitazone and of ^{15}N-labelled phenylalanine	105,106	3-Phenyllactic acid 	Aldrich	L=0.33 D=0.26	99.35(D) 99.48(L)	LC-16
Synthesis of the enantiomeric forms of α– and β–alkoxycarbonyl compounds	107	1,2-Propanediol 	Aldrich	S=0.52 R=0.06	98.96(R) 99.88(S)	GC-27
Chiral solvent	108,109	Propylene carbonate 	Aldrich	S=0.33 R=0.46	99.34(R) 99.09(S)	GC-14
Useful building block for stereocontrolled synthesis of complex molecules	110,111	Propyloxiranemethanol 	Aldrich	2S,3S=2.51 2R,3R=4.62	94.98(2R,3R) 90.76(2S,3S)	GC-27

Chiral resolving agents

Employed in amidation for chiral resolution	112	2-Amino-3-phenyl-1-propanol 	Aldrich	S=0.01 R=0.01	99.98(R) 99.98(S)	GC-1
Base for enantioselective ketone enolate formation	113,114	N-Benzyl-1-(1-naphthyl)-ethylamine hydrochloride 	Aldrich	R=0.04 S=0.40	99.92(S) 99.20(R)	LC-6
a)Resolution of esters via ortho esters b)Determination of enantiomeric purity of ketones by acetal formation and ^{13}C-NMR	115,116	2,3-Butanediol 	Aldrich	2S,3S=0.11 2R,3R=0.17	99.77(2R,3R) 99.65(2S,3S)	GC-2
Resolves racemic mixtures of cyclic ketones	117	N,S-Dimethyl-S-phenyl-sulfoximine 	Aldrich	R=0.05 S=0.05	99.90(S) 99.91(R)	GC-16
Versatile reagent used in the resolution of racemates	22	Mandelic acid 	Aldrich	S=0.19 R=14.00	99.82(R) 72.01(S)	LC-12

Stereoselective α- alkylation via dioxolanone	23	Malic acid 	Aldrich	D(+)=0.21 L(-)=1.22	99.59(L(-)) 97.56(D(+))	LC-13
Precursor to chiral supporting electrolytes	118	N-Methylephedrine 	Aldrich	1S,2R=0.03 1R,2S=0.03	99.94(1R,2S) 99.94(1S,2R)	GC-6
Chiral derivatizing agent used in the determination of absolute configuration of secondary alcohols, amines and thiols	119	2-Phenylbutyric acid 	Aldrich	S=1.82 R=2.16	96.35(R) 95.69(S)	LC-14
Chiral derivatizing agent used for the assignment of absolute configuration of alcohols by H-NMR and amines	120,121	2-Phenylpropionic acid 	Aldrich	S=0.24 R=0.34	99.52(R) 99.32(S)	LC-17

[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) x 100, 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 initial letters are abbreviation for the analytical method used, i.e., GC = gas chromatography, LC = liquid chromatography (specifically HPLC).

[c] see Experimental section.

[d] The enantiomers of this compound are easily resolved by GC on a Chiraldex GTA column after trifluoroacelytation with trifluoroacetic anhydride. However, partial racemization takes place during the derivtization giving a lower apparent ee value than that found with LC.

3. Results and discussion

The enantiomeric composition of 109 compounds that are used as catalysts, auxiliaries and synthons in enantioselective synthesis, as well as several chiral resolving agents, are listed in Table 2. The first group of compounds listed in this table are chiral catalysts or ligands for catalysts. The second group of chiral compounds are auxiliaries. These are followed by chiral synthons and resolving agents, respectively (Table 2). The commercial source for each compound is listed and at least one representative publication which utilized this compound is given. In addition, the last column in Table 2 gives an assay method number which refers to the method in Table 1 where the exact experimental details are given. Each of these methods is able to detect ≤0.01% of an enantiomeric impurity for the indicated compound.

Approximately 36% of the reagents analyzed contained low levels of enantiomeric contaminants (i.e. between ~0.01% and 0.1%). Only about 3% of the reagents had high levels of enantiomeric impurities (i.e. >10%). The vast majority of reagents analyzed had moderate levels of enantiomeric impurities, including 43 reagents in the 0.1–1% range and 24 reagents with unwanted enantiomeric impurities in the 1–10% range (Table 2).

If a particular chiral reagent has a high ee, one cannot automatically assume that its enantiomer will have a comparable purity (even if both reagents are obtained from the same source at the same time). Compare, for example, the ees for the enantiomeric reagents of 3-hydroxytetrahydrofuran, leucinol and mandelic acid (Table 2). Perhaps the biggest difference was found for mandelic acid enantiomers in which the *S*-reagent had an ee of 99.8% and the *R*-reagent was 72%. Also, as reported previously, the batch to batch enantiopurity of a chiral reagent can vary tremendously.[1] This is most likely the result of a lack of quality control by the manufacturers. Consequently, the levels of enantiomeric impurities reported in Table 2 are likely to vary widely in the foreseeable future. However, efficient and sensitive methods are now available (Table 2) that allow facile determination of the enantiomeric composition of these increasingly useful reagents.

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