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Enantiomeric impurities in chiral synthons, catalysts, and auxiliaries. Part 3

Ke Huang, Zachary S. Breitbach, and Daniel W. Armstrong*

Department of Chemistry and Biochemistry, University of Texas at Arlington, Arlington, TX 76019, USA

Abstract

The enantiomeric excess of chiral reagents used in asymmetric syntheses directly affects the reaction selectivity and product purity. In this work, 84 of the more recently available chiral compounds were evaluated to determine their actual enantiomeric composition. These compounds are widely used in asymmetric syntheses as chiral synthons, catalysts, and auxiliaries. These include chiral alcohols, amines, amino alcohols, amides, carboxylic acids, epoxides, esters, ketones, and oxolanes among other classes of compounds. All enantiomeric test results were categorized within five purity levels (i.e. <0.01%, 0.01% to 0.1%, 0.1% to 1%, 1% to 10%, and >10%). The majority of the reagents tested were determined to have enantiomeric impurities over 0.01%, and two of them were found to contain enantiomeric impurities exceeding the 10% level. The most effective enantioselective analysis method was a GC approach using a Chiraldex GTA chiral stationary phase (CSP). This method worked exceedingly well with chiral amines and alcohols.

1. Introduction

Enantioselective reactions are of great importance to chemists involved in asymmetric synthesis. The enantiomeric purity of a product is affected by 3 factors: 1) the enantioselectivity of the reaction; 2) the enantiomeric excess of the starting material and/or the catalyst/auxiliary used; and 3) the susceptibility for the desired product to racemize, especially during work-up or storage. Previously, we found detectable amounts of enantiomeric impurities in 192 commercial chiral compounds.^{1, 2}

These compounds are widely employed in asymmetric syntheses as chiral catalysts/catalyst ligands, synthons/synthetic building blocks, chiral auxiliaries and chiral resolving agents. New chiral compounds, catalysts, auxiliaries and synthons are continually being developed, the most useful of which are made available commercially. Herein, we examine new chiral compounds that have not been assayed previously and/or have been introduced after 1999, when the last comprehensive evaluation of commercial chiral compounds was reported.²

*Corresponding author. addr.: University of Texas at Arlington, Arlington, TX 76019, USA. Tel.: +1 817 272 0632, fax: +1 817 2 72 0619, e-mail: sec4dwa@uta.edu.

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When enantiomerically impure compounds are employed in asymmetric synthesis, especially in the pharmaceutical industry, the underestimated contaminants will introduce various amounts of enantiomeric impurities in the “single-enantiomer” reaction and products. In biological processes, these undesired enantiomeric byproducts usually show different effects and/or different pharmacokinetics/pharmacodynamics and thus have different therapeutic values.³ Although the stereoselectivity of asymmetric synthetic processes continue to improve, an awareness of the enantiomeric composition of chiral reagents being used remains essential.

2. Results and Discussion

Of the 84 chiral compounds tested, 85 % of them were separated via enantioselective GC, and of these, 54 % were best separated on the ChiralDEX GTA column. This is due to the fact that many of the compounds in this study were chiral amines and alcohols which, when trifluoroacetylated, gained distinct enantioselective interactions with the trifluoroacetylated chiral stationary phase of the GTA column.⁴ Also, the GTA chiral stationary phase showed impressive separating capabilities for ketones, epoxides, and halogenated acids. Examples of these include the separations of 3-methylcyclopentanone, epoxybutane, and chloropropionic acid, respectively.

Other effects of the trifluoroacetylation of free alcohols and amines include altered enantioselectivity, increased analyte volatility, faster analysis time, improved peak shape, and increased efficiency. Figure 1 illustrates some of these properties in the GC enantiomeric separations of derivitized (Fig 1A and B) and native (Fig 1C and D) ethyl-4-chloro-3-hydroxybutyrate. Peaks A and D represent the (S)-(-) enantiomer while peaks B and C represent the (R)-(+) enantiomer. Both enantiomeric separations have comparable baseline separations with resolutions greater than two. However, a comparison of the separation of the native analyte versus its trifluoroacetyl derivative (Figure 1) shows that the analysis time for the derivative is shorter and the peaks are sharper (which makes the detection and quantitation of enantiomeric impurities much easier). Furthermore, the reversal of the elution order of the two enantiomers prior to, and after, derivatization indicates that the introduction of the trifluoroacetyl group alters the separation mechanism. It has also been reported that acetic anhydride, chloroacetic anhydride, dichloroacetic anhydride, and trichloroacetic anhydride may be used for this same purpose.⁵

Table 3 lists all chiral compounds examined in this study, as well as, references describing their use in asymmetric syntheses. The separation conditions for each compound assayed are listed in Table 1 and Table 2. Also, Table 3 indicates the actual enantiomeric composition of each compound and the technique used to determine this composition. As shown in Figure 2, 82% of the compounds analyzed were found to contain enantiomeric impurities over 0.01%. Only 8% of the compounds contained enantiomeric impurities between 0.01%–0.1%, whereas, 46% of the samples had enantiomeric impurities in the level 0.1%–1%, and 25% of the samples displayed enantiomeric impurities in the range of 1%–10%. Two compounds were found with enantiomeric contaminants over 10%.

Figure 2 also shows a direct comparison of the level of enantiomeric contaminants found in the chiral compounds assayed in this study with those that were tested in 1998–99. In both studies, 2% of the chiral compounds tested contained enantiomeric impurities greater than 10%. However, the greatest enantiomeric impurity for any chiral compound was found in the 1998 analysis of (*R*)-*tert*-butyl-4-formyl-2, 2-dimethyl-3-oxazolidine, which was determined to contain 15.11% of the (*S*)-enantiomer. This is just slightly higher than the 13.80% maximum enantiomeric impurity found in (*R*)-1-indanol during this study. Figure 2 also shows that within the enantiomeric impurity ranges of 1–10% and 0.1–1%, the results of the two studies are fairly comparable with the abundances in this study being just slightly higher. The major difference in reagent purity in the studies is in the 0.01–1% and <0.01% ranges. The number of very high enantiomeric excess compounds found in this study approached 20%, whereas few, if any, chiral compounds of these purities were available prior to 1998–99. However, there were a higher percentage of compounds in the 0.01–1% range in previous studies.

It was also observed that two enantiomeric compounds will not necessarily contain comparable amounts of enantiomeric impurities. This trend is best observed with the assay of 2, 3-O-benzylidene-D-threitol. The (+)-enantiomer had an enantiomeric excess of 85.16%, while the much more pure (–)-enantiomer had an enantiomeric excess of 99.60%. This determination is consistent with findings in other studies.^{1, 2}

Given the results of this and previous studies, it is apparent that further improvements in the enantiomeric purities of reagents used in asymmetric synthesis would be beneficial. This can be achieved through further refinements in the manufacture and purification of most of these chiral reagents. Since novel chiral compounds are constantly being developed and added to the repertoire of synthetic organic chemists, 6–21 some knowledge as to their enantiomeric composition and the availability of facile methods for their analysis will remain important.

3. Experimental

3.1 Materials

All HPLC columns (25 cm × 4.6 mm i. d.) and GC columns (10 m × 0.25 mm, 20 m × 0.25 mm, 30 m × 0.25 mm) were obtained from Advanced Separation Technologies, Inc. (Whippany, NJ). The LC columns used were Cyclobond I 2000 AC (acetylated-β-cyclodextrin), Cyclobond I 2000 DM (dimethylated-β-cyclodextrin), Chirobiotic T₂ (teicoplanin), and Poly-DPEDA (poly N,N'-[(1*R*, 2*R*)-1,2-diphenyl-1,2-ethanediyl] bis-2-propenamide).²² GC analysis was performed using Chiraldex B-DM (di-O-methyl-β-cyclodextrin), Chiraldex G-PN (2, 6-di-O-pentyl-3-propionyl-γ-cyclodextrin), Chiraldex G-BP (2, 6-di-O-pentyl-3-butyl-γ-cyclodextrin), Chiraldex G-TA (2, 6-di-O-pentyl-3-trifluoroacetyl-γ-cyclodextrin) columns and Chiraldex B-TA (2, 6-di-O-pentyl-3-trifluoroacetyl-β-cyclodextrin).

Trifluoroacetic anhydride (99+ %) was from Aldrich (Milwaukee, WI). Trifluoroacetic acid was obtained from Fisher Scientific (St Louis, MO). The water used, was deionized and purified with a Synergy 185, Millipore filter. All the mobile phases were degassed with a

VWR Model 250HT sonicator before HPLC analyses. All the chiral compounds examined in this paper were obtained from Aldrich.

3.2 Apparatus and methods

All HPLC separations were performed on the following Shimadzu (Columbia, MD) instrumentation: two LC-6A pumps; a SPD-6A UV spectrophotometric detector; a SCL-10A system controller; and a CR 601 Chromatopac integrator. All compounds were dissolved in acetonitrile and the wavelength of detection was 254 nm. Most of the compounds were tested with a flow rate of 1 ml/min at ambient temperature (25°C). Lower flow rate was used for 2-(Anilinomethyl) pyrrolidine, 6-hydroxy-2, 5, 7, 8- tetramethyl-chroman-2-carboxylic acid and 1-(2-methoxybenzoyl)-2-pyrrolidinemethanol to increase peak efficiency through decreasing the band broadening effect of mass transfer of analyte. Also, 2-(anilinomethyl) pyrrolidine was chromatographed at 0°C in order to optimize the selectivity of separation.

The GC equipment used was a Shimadzu (Columbia, MD) model GC-17A gas chromatograph equipped with a flame ionization detector and EZStart 7.2.1 SP1 data acquisition software. All analyses were performed with a helium carrier gas flow rate of 1 ml/min and a split ratio of 100/1. The injector and detector temperature was set at 250°C and 280°C, respectively. In all GC analyses, chiral compounds with amino and/or hydroxyl groups were derivatized with excess trifluoroacetic anhydride, an achiral reagent that does not induce any change of analyte configuration. 23

Typical enantiomeric separations on HPLC and GC are shown in Figure 3. All the results were calculated from at least 3 parallel measurements of sample with different concentrations. Each pair of enantiomers were separated with resolution greater than 1.5, so that when an excessive amount of a single enantiomer was injected, its broadening baseline width would not cause a co-elution of the single enantiomer being tested and the enantiomeric impurity.

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Figure 1. GC enantiomeric separations of derivatized (A and B) and native (C and D) ethyl-4-chloro-3-hydroxybutyrate. Peaks A and D represent the (*S*)-(-)-enantiomer and peaks B and C represent the (*R*)-(+)-enantiomer. Helium carrier gas, G-TA column, 120°C, FID.

Figure 2.
Comparison of results obtained in this study (2006) and results obtained in prior work (1998–99)

Figure 3.

Chromatograms A show the enantiomeric separation of 1-indanol on HPLC and the impurity tested in the (*R*)-enantiomer purchased from Aldrich. Chromatograms B show the enantiomeric separation of 4-(chloromethyl)-2, 2-dimethyl-1, 3-dioxolane on GC and the assay of the (*S*)-enantiomer obtained from Aldrich. The separation methods for A and B are listed in Table 3 as LC-7 and GC-11, respectively.

Table 1

Enantioselective methods by gas chromatography (GC)

GC Method Number ^a	Column ^b	Length (m)	Temperature (°C)	flow rate (ml/min)
GC-1	Chiraldex G-PN	20	110	1
GC-2	Chiraldex G-TA	30	110	1
GC-3	Chiraldex G-PN	20	100	1
GC-4	Chiraldex G-TA	30	115	1
GC-5	Chiraldex G-TA	30	100	1
GC-6	Chiraldex G-TA	30	130	1
GC-7	Chiraldex B-DM	20	130	1
GC-8	Chiraldex G-TA	30	110	1
GC-9	Chiraldex B-DM	20	150	1
GC-10	Chiraldex G-BP	20	135	1
GC-11	Chiraldex B-DM	20	90	1
GC-12	Chiraldex B-DM	20	140	1
GC-13	Chiraldex G-TA	30	60	1
GC-14	Chiraldex G-TA	30	140	1
GC-15	Chiraldex G-TA	30	120	1
GC-16	Chiraldex G-TA	30	65	1
GC-17	Chiraldex G-TA	30	50	1
GC-18	Chiraldex G-TA	30	160	1
GC-19	Chiraldex B-DM	20	80	1
GC-20	Chiraldex G-TA	30	150	1
GC-21	Chiraldex B-TA	20	100	1
GC-22	Chiraldex G-BP	20	140	1
GC-23	Chiraldex G-TA	30	35	1
GC-24	Chiraldex B-DM	20	125	1
GC-25	Chiraldex G-TA	30	80	1

^aIs used to identify the Separation techniques in Table 3. Every analyte with amino or hydroxyl functional groups was derivatized with trifluoroacetic anhydride to help with the selectivity of separation and the volatility of analytes (see experimental section)

^bIs the abbreviation for the GC columns used. All the full names can be looked up in the experimental section.

Table 2

Enantioselective methods by gas chromatography (GC)

HPLC Method Number ^a	Column ^b	Mobile Phase ^c (% v/v)	Flow Rate (ml/min)
LC-1	Chirobiotic T ₂	H ₂ O:TEAA=100:0.1, pH 4.1	0.25
LC-2	Chirobiotic T ₂	ACN: HOAc: TEA=100:0.15:0.15	1
LC-3	Poly-DPEDA	Heptane: IPA: TFA=95:5:0.1	0.25
LC-4	Cyclobond I 2000 AC	H ₂ O:TEAA=100:0.1, pH 4.1	1
LC-5	Cyclobond I 2000 AC	H ₂ O:TEAA=100:0.1, pH 4.1	1
LC-6	Cyclobond I 2000 AC	H ₂ O:TEAA =100:0.3, pH 4.1 (0 °C)	0.25
LC-7	Cyclobond I 2000 DM	H ₂ O:TEAA:CH ₃ OH=97:0.1:3, PH=7.1	1

^a is notation is used to identify the separation techniques in Table 3

^b is the abbreviation for the HPLC columns used. All the full names can be looked up in the experimental section.

^c Mobile phase: ACN=acetonitrile; TEAA=triethylamine acetate; HOAc=acetic acid

Table 3

The enantiomeric excess of the organic synthesis reagents

Use in Asymmetric Synthesis and References	Name and Structure of Chiral Compound	Enantiomeric Composition		Method Number ^b
		%enantiomeric contaminant	enantiomeric excess (e. e.) ^a	
Synthons or Chiral building blocks				
1 Development and synthesis of 2- <i>o</i> -methylcytidine ²⁴ 2 Synthesis of amide analogs of the cannabinoid CB1 receptor antagonist ²⁵		(<i>S</i>)=0.09	*99.83 (<i>R</i>)	GC-1
		(<i>R</i>)=0.35	99.31 (<i>S</i>)	
2-amino-3-thiazolidine derivatives as nitric oxide synthase inhibitors ^{27, 28}		(<i>S</i>)=0.07	*99.87 (<i>R</i>)	GC-2
		(<i>R</i>)=0.09	99.82 (<i>S</i>)	
1 Enantioselective acylation ²⁹ 2 Synthesis of a new class of nitric oxide synthase inhibitor, 4, 5 disubstituted-1,3-oxazolidin-2-imin e derivatives ³⁰		(<i>S</i>)<0.01	*>99.99 (<i>R</i>)	GC-3
		(<i>R</i>)<0.01	>99.99 (<i>S</i>)	
1 Synthesis of crystalline chelates ³¹ 2 Preparation of imidazo[1,2- <i>b</i>]pyridazines under Swern oxidative conditions ³²		(<i>S,S</i>)=0.52	*98.97 (<i>R,R</i>)	GC-4
		(<i>R,R</i>)=0.06	>99.89 (<i>S,S</i>)	
1 Structure –activity relationship study of 1 <i>H</i> -imidazo [4,5- <i>c</i>]quinolines that induce interferon production ³³ 2 Preparation of 2'-aldehyde oligonucleotides for chemoselective ligation study ³⁴		(<i>S</i>)=0.28	99.44 (<i>R</i>)	GC-5
		(<i>R</i>)=0.93	*98.14 (<i>S</i>)	

Use in Asymmetric Synthesis and References	Name and Structure of Chiral Compound	Enantiomeric Composition		Method Number ^b
		%enantiomeric contaminant	enantiomeric excess (e. e.) ^a	
Synthesis of antitumor agent ³⁵ , ³⁶		(<i>S</i>)=0.66	98.67 (<i>R</i>)	GC-5
		(<i>R</i>)=0.17	*99.67 (<i>S</i>)	
Potential human dopamine D4 antagonists synthesis ³⁷		(<i>S</i>)=0.17	*99.67 (<i>R</i>)	GC-6
		(<i>R</i>)<0.01	>99.99 (<i>S</i>)	
<div>1 Preparation of Evans Auxiliary³⁸, ³⁹</div> <div>2 Chemoenzymatic synthesis of the polyketide macrolactone10-deoxymethynolide⁴⁰</div> <div>3 Asymmetric total synthesis of (+)-migrastatin, a potent cell migration inhibitor⁴¹</div>		(<i>S</i>)=0.37	99.26 (<i>R</i>)	GC-7
		(<i>R</i>)<0.01	*>99.99 (<i>S</i>)	

Use in Asymmetric Synthesis and References	Name and Structure of Chiral Compound	Enantiomeric Composition		Method Number ^b
		%enantiomeric contaminant	enantiomeric excess (e. e.) ^a	
		(S)=6.49 (R)=3.29	*87.03 (R,R) 93.43 (S,S)	
Ring-closing metathesis to cyclic sulfamide peptidomimetics ⁴²				GC-8
<ol style="list-style-type: none"> Starting material of chiral diamine-chelated aryllithiums ⁴³ Synthesis of a novel arylpiperazine as potent and selective agonist of the melanocortin subtype-4- receptor⁴⁴ Fast microwave promoted palladium-catalyzed synthesis of Phthalides⁴⁵ 	2-Bromo-α-methylbenzyl-alcohol	(S)=0.36 (R)=0.14	*99.29 (R) 99.73 (S)	GC-9
<ol style="list-style-type: none"> Synthesis of 2, 3-diminopyridine bradykinin B1 receptor antagonists⁴⁶ Preparation of substituted N-(aryl/methyl)aryloxy arylcarboxamide antagonists for the PGE2 receptor EP4⁴⁷ 	1-(4-Bromophenyl)ethylamine	(S)=0.24 (R)=0.42	*99.53 (R) 99.16 (S)	GC-10
<ol style="list-style-type: none"> Total synthesis of 17,18,19,20-d4-iPF2a-III ³², for animal metabolism studies⁴⁸ Synthesis of kinsenoside and goodyeroside A⁴⁹ Control of regioselectivity of the pivalaldehyde acetalization⁵⁰ 	1,2,4-Butanetriol	(S)=0.84 (R)<0.01	*98.33 (R) >99.99 (S)	GC-5

Use in Asymmetric Synthesis and References	Name and Structure of Chiral Compound	Enantiomeric Composition		Method Number ^b
		%enantiomeric contaminant	enantiomeric excess (e. e.) ^a	
Synthesis of 1,2-dihydroxyimino-3,7-di-aza-9,10- O-iso-propylidene decane, a vic-dioxime derivative for its metal complex study ⁵¹		(S)=0.12	99.76 (R)	GC-11
		(R)=0.28	*99.45 (S)	
<ol style="list-style-type: none"> Used as substrates in transesterification of vinyl esters⁵² Lanthanide (III) triflate-catalyzed thermal and microwave-assisted synthesis of benzyl ethers⁵³ Synthesis of 3-phenoxypipropyl piperidine analogues as ORL1 receptor agonists⁵⁴ Preparation of fluoxetine analogues, a novel class of anti-candida agents⁵⁵		(S)=0.39	*99.22 (R)	GC-12
		(R)=0.24	99.53 (S)	
<ol style="list-style-type: none"> Synthesis and structure-activity relationship study of ethacrynic acid analogues on glutathione-s-transferase P1-1 inhibition⁵⁶ Synthesis of a peroxime proliferator activated receptor (PPAR) α/γ agonist⁵⁷		(S)=2.79	*94.42 (R)	GC-5
		(R)=0.38	99.25 (S)	
<ol style="list-style-type: none"> Synthesis of C₁-C₁₁ fragment of batilomycin A¹⁵⁸ Used in DMF promoted xylosylation of terpenols⁵⁹ Total synthesis of brasoside and littoralisone⁶⁰ Synthesis of marine sponge alkaloid hachijodine B⁶¹ Stereoselective synthesis of Fusarium toxin equisetin, a potent		(S)=1.38	*99.42 (R)	GC-13
		(S)<0.01	>99.99 (R)	

Use in Asymmetric Synthesis and References	Name and Structure of Chiral Compound	Enantiomeric Composition		Method Number ^b
		%enantiomeric contaminant	enantiomeric excess (e. e.) ^a	
<div>1 Study of a new method to oxidize primary alcohols to carboxylic acids⁶³</div> <div>2 Study of the influence of the nature of chiral auxiliaries on the diastereoselective hydrogenation of o-methoxy benzoic acid⁶⁴</div> <div>3 Used in the study of reductive alkylation of aromatic carboxylic acid derivatives⁶⁵</div>	<div>1-(2-Methoxybenzoyl)-2-Pyrrolidinemethanol</div> <div> </div>	(S)<0.01	>99.99 (R)	LC-1
		(R)<0.01	>*99.99 (S)	
<div>1 Preparation of chiral crown ethers^{66–68}</div> <div>2 Starting material for the synthesis of (3<i>R</i>,4<i>S</i>)-3,4-dihydroxy-5-oxohexyl phosphonic acid⁶⁹</div> <div>3 Synthesis through Mitsunobu reaction of chiral diesters and chiral diamines as macrocyclic frameworks⁷⁰</div>	<div>2,3-<i>O</i>-Benzylidene-D-threitol</div> <div> </div>	(-)=0.20	*99.60 (+)	GC-14
		(+)=7.42	85.16 (-)	
Synthesis of lower alkyl 4-cyano-3-hydroxybutyrate ⁷¹	<div>Ethyl 4-bromo-3-hydroxybutyrate</div> <div> </div>	(S)=0.37	99.26 (R)	GC-15
		(R)=0.36	*99.29 (S)	

Use in Asymmetric Synthesis and References	Name and Structure of Chiral Compound	Enantiomeric Composition		Method Number ^b
		%enantiomeric contaminant	enantiomeric excess (e. e.) ^a	
1 Substrate for enzymatic ammonolysis ⁷² 2 Synthesis of 4-cyano-3-hydroxybutyric acid esters ⁷³ 3 Preparation of epoxybutanoic acid esters ⁷⁴		(S)=0.49	*99.02 (R)	GC-15
		(R)=0.04	99.93 (S)	
1 Alkanol absolute configuration study with cyclopenta[b]furan derivative ⁷⁵ 2 Ruthenium-catalyzed quinoline synthesis through 2-aminobenzyl alcohol cyclization with secondary alcohols ⁷⁶ 3 Parallel carbonylation of aryl halides ⁷⁷ 4 Palladium-catalyzed heteroannulation of bromobenzylaldehyde ⁷⁸ 5 Enzymatic synthesis of aroma compound xylosides via transfer reaction ⁷⁹		(S)=0.12	*99.77 (R)	GC-16
		(R)=1.32	97.36 (S)	
Synthesis of analogs of antitumor agents for action mechanism study of XK469 and SH8080, 81		(S)<0.01	>99.99 (R) ^c	LC-2
1 Starting material for the synthesis of a new class of antiatherosclerosis agents, the NO-donor antioxidants ⁸² 2 Buiding block for novel potent inhibitors of lipid peroxidation with protective effects against reperfusion arrhythmias ⁸³ 3 Synthesis of CX-659S and its related compounds for the study of their effects on hypersensitivity reaction ⁸⁴ 4 Vitamin E precursor ⁸⁵		(S)<0.01	>99.99 (R)	LC-3
		(R)<0.01	>*99.99 (S)	

Use in Asymmetric Synthesis and References	Name and Structure of Chiral Compound	Enantiomeric Composition		Method Number ^b
		%enantiomeric contaminant	enantiomeric excess (e. e.) ^a	
<ol style="list-style-type: none"> Substrate for enantiomerically pure 4 or 5 substituted lactones⁸⁶ Study of oxidation of cyclic ketones by CH₃ReO₃/H₂O₂ catalytic system in room temperature ionic liquids through Baeyer–Villiger reaction⁸⁷ Synthesis of 3,4-bridged 1, 6, 6aλ4-trithiapentalenes⁸⁸		(S)=0.10	99.80 (R) ^c	GC-17
		(S)=0.13	*99.75 (R)	
		(R)=0.15	99.71 (S)	
<ol style="list-style-type: none"> Synthesis of the 5-HT₃ receptor probe⁸⁹ Fullerene substitution with piperazine⁹⁰ Preparation of 1, 4-benzothiazine analogues, thymocyte apoptosis and thymus inducers⁹¹		(S)=0.01	*99.99 (R)	GC-18
		(R)=0.62	98.76 (S)	
Synthesis of 10-azaprostaglandinE ₁ ⁹²		(S)=0.01	*99.99 (R)	GC-18
		(R)=0.62	98.76 (S)	
Efficient Synthesis of Cyclopentenones from Enynyl Acetates ⁹³		(S)=0.20	*99.61 (R)	GC-19
		(R)=0.17	99.77 (S)	

Use in Asymmetric Synthesis and References	Name and Structure of Chiral Compound	Enantiomeric Composition		Method Number ^b
		%enantiomeric contaminant	enantiomeric excess (e. e.) ^a	
1 Preparation of prochiral phosphinic acid derivatives for the synthesis of P-Stereogenic phosphinates ⁹⁴ 2 Synthesis of a methyl ketone as a substrate for samarium (II)-promoted aromatic ring spirocyclization ⁹⁵	4-Penten-2-ol	(S)=1.11	*97.79 (R)	GC-13
		(R)=0.39	99.22 (S)	
1 Starting material for the synthesis of 1-aryl[methyl-3-(1-methyl-2-amino) ethyl-5-aryl-6-methyl]uracils, a new class of small molecule GnRH antagonists ⁹⁶ 2 Preperation of tri- and tetra-substituted ureas as a novel class of steroid mimics ⁹⁷	3-Pyrrolidinol	(S)=0.04	99.92 (R)	GC-20
		(R)=0.54	*98.92 (S)	
Used in the study of enantioselective palladium(II)-catalyzed aerobic Alcohol oxidations with(–)-sparteine ^{98, 99}	α-(Trifluoromethyl) benzyl alcohol	(S)=1.06	97.88 (R)	GC-2
		(R)=1.32	*97.36 (S)	
Important synthetic component of ferroelectric liquid crystals ¹⁰⁰	1,1,1-Trifluorooctan-2-ol	(S)=0.90	98.20 (R)	GC-21
		(R)=0.56	*98.88 (S)	
Catalyst/catalyst ligands				

Use in Asymmetric Synthesis and References	Name and Structure of Chiral Compound	Enantiomeric Composition		Method Number ^b
		%enantiomeric contaminant	enantiomeric excess (e. e.) ^a	
Solid support catalysis for hydrosilylation of ketones ¹⁰¹		(1 <i>S</i> ,2 <i>R</i>)<0.01	*>99.99 (1 <i>R</i> ,2 <i>S</i>)	GC-22
		(1 <i>R</i> ,2 <i>S</i>)<0.01	99.60 (1 <i>S</i> ,2 <i>R</i>)	
Solid support catalysis for hydrosilylation of ketones ¹⁰¹		(<i>S</i>)=0.23	*99.54 (<i>R</i>)	GC-3
		(<i>R</i>)=0.74	98.52 (<i>S</i>)	
Solid support catalysis for hydrosilylation of ketones ¹⁰¹		(<i>S</i>)=2.15	*95.70 (<i>R</i>)	GC-20
		(<i>R</i>)=3.17	93.66 (<i>S</i>)	

Use in Asymmetric Synthesis and References	Name and Structure of Chiral Compound	Enantiomeric Composition		Method Number ^b	
		%enantiomeric contaminant	enantiomeric excess (e. e.) ^a		
<div>1 High throughput ruthenacycle-catalyzed asymmetric transfer hydrogenation102</div> <div>2 Enantiotopic lithiation of prochiral benzamide chromium complex103</div> <div>3 Used in asymmetric addition of silane to cyclohexanone104</div> <div>4 Asymmetric synthesis of (+)-anatoxina105</div>	<div>Bis (α-methylbenzyl)amine</div> <div> </div>	(S)<0.01	*≥99.99 (R)	LC-4	
		(S)=0.61	98.79 (S)		
	<div>1 HBr scavenger to increase the yield of photoinduced addition reaction product of 1,4-dibromo-2,5-piperazinedione and 1-alkenes106</div> <div>2 Exchange reactions of ethylene oxides and Et₂CH₂CHROH107</div>	<div>Epoxybutane</div> <div> </div>	(S)=0.13	99.74 (R)	GC-23
			(R)=0.01	*99.98 (S)	
<div>Accelerators for hydrosilation of unsaturated organic compounds108</div>	<div>1-Phenyl-2-propyn-1-ol</div> <div> </div>	(S)=2.02	95.96 (R)	GC-24	
		(R)=0.15	*99.70 (S)		
Chiral auxiliaries					

Use in Asymmetric Synthesis and References	Name and Structure of Chiral Compound	Enantiomeric Composition		Method Number ^b
		%enantiomeric contaminant	enantiomeric excess (e. e.) ^a	
Asymmetric alkylation of aromatic ketones ¹⁰⁹		(S)=1.26	*97.49 (R)	LC-5
		R<0.01	>99.99 (S)	
<div>1 Synthesis of (S)-fontalin and its antipode¹¹⁰</div> <div>2 Synthesis of maltingolide, a marine antibiotic¹¹¹</div> <div>3 Synthesis of sarcophytol A, an anticarcinogenic marine cembranoid¹¹²</div>		(S)=9.18	*81.64 (R)	LC-6
		(R)=4.98	90.04 (S)	
Scholkopf chiral auxiliary ^{113–117}		(S)=4.59	*90.83 (R)	GC-11
		(R)=2.37	95.26 (S)	

Use in Asymmetric Synthesis and References	Name and Structure of Chiral Compound	Enantiomeric Composition		Method Number ^b
		%enantiomeric contaminant	enantiomeric excess (e. e.) ^a	
1 Synthesis of α-(1-methylethyl)-α-(3-oxopropyl) benzeneacetoneitriles118 2 Chiral resolution of 6-phenyl-4-phenylethynyl-1,4-dihy dropyridines, A3 adenosine receptor antagonists119		(S)=2.23	95.55 (R)	GC-25
		(R)=2.40	95.21 (S)	
NMR configuration assignment of α-carboxylic acids120		(S)=13.8	72.50 (S)	LC-7
		(R)=11.1	77.80 (R)	
Dynamic kinetic resolution of α bromoesters121		(S)=1.10	97.80 (R)	GC-15
		(R)=1.12	97.77 (S)	

^aThe first eluted peaks are indicated with the sign *.

^bGC=gas chromatography, LC=liquid chromatography (here high pressure chromatography). Each method is taken from Table 1 and Table 2 where the specific condition for each separation is listed

^cFor these two compounds, only one enantiomer is tested because the other enantiomer is not commercially available.