The Chiral Pool as a Source of Enantioselective Catalysts and Auxiliaries

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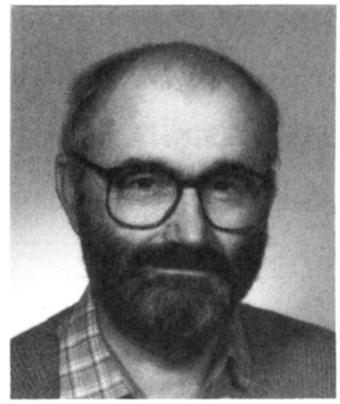

Hans-Ulrich Blaser was born in 1943 in Bischofszell, TG, Switzerland. He studied organic chemistry at the ETH in Zürich and carried out his Ph.D. thesis on metal-free corrins under the guidance of A. Eschenmoser. It was there that he learned to appreciate the potential and the esthetic qualities of simple mechanistic models. He spent the years 1971–1974 as Postdoctoral Fellow with J. Halpern at the University of Chicago and with J. Osborn at Harvard University. In this time he was initiated into the mysteries of kinetics and organometallic catalysis. After a short intermezzo as Research Associate at the now defunct Monsanto Research S.A. in Zürich, he joined the Central Research Laboratories of Ciba-Geigy in 1976. He now heads a small but dedicated team of researchers who study and apply homogeneous and heterogeneous catalysts for the synthesis of fine chemicals. He is more and more fascinated by the various ways molecules (and people) interact and tries to understand the reasons for their behavior. In his spare time he is an avid biker and skier.

I. Introduction

For many decades the chiral pool was the only source of enantiomerically pure catalysts or auxiliaries (ligands or modifiers) for enantioselective syntheses. Seemingly, the situation has changed because many of the most effective chiral agents described in the current literature have been designed and synthesized by organic chemists. While writing a review on the use of chirally modified solids for enantioselective heterogeneous catalysis we were therefore quite surprised to find that with few exceptions the modifiers used were all of natural origin.[1] In most cases the natural compounds were even used "as is" or with only small modifications. This made us curious as to whether the situation was really that different in the field of homogeneous enantioselective synthesis. A closer look at some very effective chiral ligands showed that in many cases they were derived from natural molecules. Usually, the carbon backbone, with the essential elements of chirality, was unchanged, but the functional groups were transformed and additional substituents were introduced in order to achieve the desired properties. A review by Brunner,[2] covering all *Chemical Abstract* references on enantioselective synthesis with transition metal catalysts between 1984 and 1986 confirmed this impression: about two-thirds of the 329 tabulated ligands were derived from natural molecules. This indicates that, even though the separation techniques for the resolution of racemates have improved, the chiral pool is still an attractive and economic source for enantiomerically pure chiral agents. Economic reasons and chemical interest led us to make a more extended survey.

This review is an attempt to present the state of the art of the application of naturally occurring chiral molecules and derivatives thereof as enantioselective agents (catalysts, modifiers, ligands, or metal-based reagents) in organic synthesis. Excluded are all approaches where the auxiliaries are covalently bound to one of the starting materials, i.e. diastereoselective reactions. In the first part, chiral reagents and catalysts derived from natural compounds are listed together

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Table 1. Chiral Reagents Derived from Alkaloids; Reaction Type and Best Optical Yield

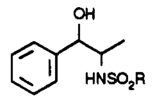
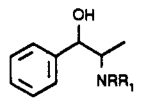
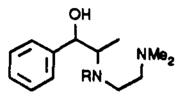
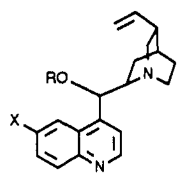
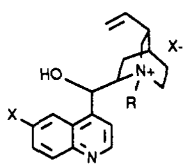
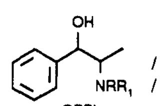
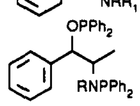
Entry	Chiral reagent		Reaction	ee	Ref.
1A	brucine	(/ Cu)	• decarboxylation of malonic acid deriv.	10	5, 13
	from ephedrine				
1B		/ $TiMe_4$	• addition of methyl group to aldehydes	90	14
1C		/ $LiAlH_4$	• reduction of ketones	98	15, 16
		/ BH_3;Rh	• hydroboration of olefins	56	17
1D			• addition of RCuM to enones	95	18, 19

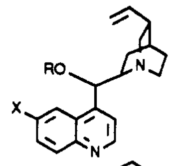
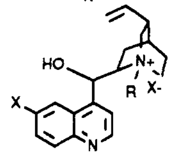
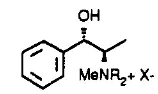
Table 2. Homogeneous Chiral Catalysts Derived from Alkaloids; Reaction Type and Best Optical Yield

Entry	Chiral catalyst		Reaction	ee	Ref.
	from cinchona alkaloids				
2A			• cycloaddition of ketene and aldehydes	>95	11b
			• addition of Et_2Zn to aldehydes	92	18, 20
			• Michael addition reaction	76	11b
			• addition of phosphites to aldehydes	80	11b
		/ Co	• hydrogenation of α-diketones	78	21, 22
		/ $Sn(OTf)_2$	• addition of Me_3SiCN to aldehydes	96	23
		/ Cu	• decarboxylation of malonic acid deriv.	31	13
			• addition of alcohols to ketenes	76	9, 24
		/ Os	• dihydroxylation of olefins	99	25
2B			• epoxidation of enones (PTC)	55	11b
			• α-alkylation of carbonyl compounds (PTC)	94	11a,18
	from ephedrine				
2C			• addition of R_2Zn to aldehydes	95	14, 18
		/ BH_3	• addition of Et_2Zn to aldehydes	95	14
		/ Ni	• Michael addition of Et_2Zn to enones	90	18
2D		/ Rh	• hydrogenation of enamides	80	26
2E	strychnine or brucine		• addition of alcohols to ketenes	40	9, 24
			• 2+2 cycloaddition of ketenes and aldehydes	72	27
2F	sparteine	/ Pd	• addition of RMgX to aldehydes	22	28
		/ Pd	• allylic alkylation reaction	85	29, 30
		/ Pd	• addition of RZnBr to aldehydes	95	31
		/ RLi	• polymerization of acrylic acid deriv.	≈100	32

with the type of reaction and the best optical yields reported for it. The goal of this compilation is to give the reader an impression of the diversity of both the structures of these auxiliaries and of the reaction types where they are applied. In the second part we have undertaken the endeavor to describe and classify different types of chiral ligands. Similarities and differences between successful inductor molecules are discussed and important structural elements that are beneficial for good optical induction are identified. From this analysis a few conclusions were drawn that may be useful for designing new chiral reagents and catalysts.

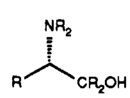
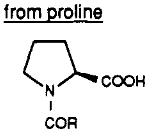
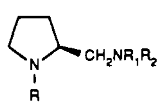
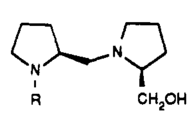
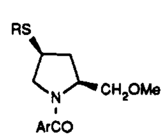
For obvious reasons, there is no simple way to search the literature in a systematic way for this particular topic. Much of the material of the present review is therefore based on the literature collections of several research teams in the Central Research Laboratories of Ciba-Geigy working on homogeneous and heterogeneous enantioselective catalysts and organometallic reagents.[3] Additional references were found by searching citations in reviews and research papers.[4] This overview is quite comprehensive for heterogeneous enantioselective systems, but only very effective (ee >80–90%) and/or interesting homogeneous catalysts and auxiliaries are tabulated, and it is possible that some relevant citations were missed entirely.

Table 3. Heterogeneous Chiral Catalysts Derived from Alkaloids; Reaction Type and Best Optical Yield

Entry	Chiral catalyst		Reaction	ee	Ref.[a)]
3A		/ Pt-support	• hydrogenation of α-ketoesters	95	H14
		/ Pt-support	• hydrogenation of C=N	15	H14
		/ Pd-support	• hydrogenolysis of C-Cl	50	H15
		/ Pd-support	• hydrogenation of C=C	30	H15
		/ Hg electrode	• reduction of ketones	16	E1, 33
3B		/ Hg electrode	• reduction of C=N	20	E2, 33
3C	ephedrine	/ Pd-support	• hydrogenation of C=O / C=N	10	H10
3D		/ Hg electrode	• reduction of C=O	26	E2, 33
		/ Hg electrode	• pinacole formation	26	E2, 33
3E	strychnine	/ Hg electrode	• reduction of C=O	48	E1, 33
		/ Hg electrode	• reduction of C-Cl	26	E1, 34
3F	emetine	/ Hg electrode	• reduction of C-Br	45	E1, 33
3G	sparteine	/ Hg electrode	• reduction of C=C	17	E1, 33

a) or number of catalytic system in ref. 1b

Table 4. Chiral Reagents Derived from Amino Acids; Reaction Type and Best Optical Yield

Entry	Chiral reagent		Reaction	ee	Ref.
4A	N,N'dibenzoylcystine	/ $LiBH_4$	• reduction of β-ketoesters	92	39
	from various amino acids				
4B		/ BH_3	• reduction of ketones and oximethers	100	40
		/ $LiAlH_4$	• reduction of ketones	100	139
	from proline				
4C		/ $NaBH_4$	• reduction of imines	86	15
4D		/ $LiAlH_4$	• reduction of ketones	95	41
		/ Li	• isomerization epoxide → allylic alcohol	92	18, 41
		/ $Sn(Tf)_2$	• addition of enolates to carbonyl compounds	>98	42- 44
		/ Sn	• monoacylation of diols	80	18
4E			• addition of BuLi to aldehydes	95	18, 41
	from hydroxyproline				
4F			• addition of RCuM to enones	94	18, 45

II. Enantioselective Catalysts and Reagents

A. Organization of Tables 1–16 and Figures 1–5

The different types of chiral reagents and catalysts are tabulated together with the reactions where they were applied successfully. For the sake of clarity and in order to facilitate the comparison among different auxiliaries, substituents are abbreviated. This may in some cases lead to a wrong impression about the steric requirements of a molecule. The material is divided into the following classes of natural compounds used as starting materials: alkaloids (Tables 1–3, Figure 1), amino acids (Tables 4–6, Figure 2), hydroxy acids (Tables 7–9, Figure 3), carbohydrates (Tables 10–12, Figure 4), terpenes (Tables 13–15, Figure 5), and miscellaneous systems (Table 16).

Each chapter comprises separate tables for stoichiometric reagents and for homogeneous and heterogeneous catalysts. The number of an entry tells in which

Table 5. Homogeneous Chiral Catalysts Derived from (A) Unfunctionalized Amino Acids, (B) Proline and Hydroxyproline, and (C) Functionalized Amino Acids; Reaction Type and Best Optical Yield

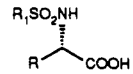
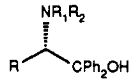
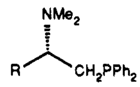
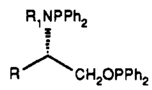
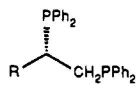
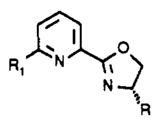
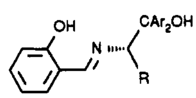
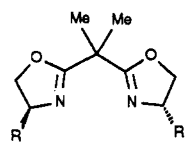
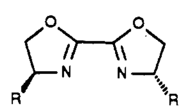
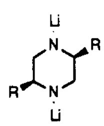
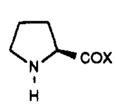
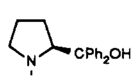
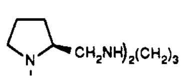
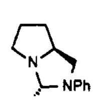
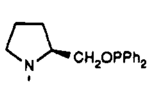
Entry	Chiral catalyst		Reaction	ee	Ref.
	A. Unfunctionalized Amino Acids				
5A		/ B	• Diels-Alder reaction	86	46
5B			• addition of Et_2Zn to aldehydes	97	47
5C		/ Ni	• Grignard cross coupling reaction	94	15
5D		/ Rh	• hydrogenation of enamides	94	2, 26
		/ Ni	• hydrovinylation of dienes	93	26
5E		/ Rh	• hydrogenation of enamides	99	48
5F		/ Cu	• monophenylation of diols	50	49
		/ Rh	• hydrosilylation of ketones	99	49, 140
5G		/ Cu	• cyclopropanation of olefins	92	50, 51
		/ Ti	• addition of Me_3SiCN to aldehydes	91	141
5H		/ Cu	• cyclopropanation of olefins	99	49
		/ Fe	• Diels-Alder reaction	86	49
5I		/ Ir	• transfer hydrogenation of ketones	91	49
		/ Pd	• allylic alkylation	77	49
		/ Rh	• hydrosilylation of ketones	84	52
5K			• addition of Et_2Zn to aldehydes	92	14
	B. Proline and Hydroxyproline				
	from proline				
5L	 X=OH		• cyclisation of tri-ketones	95	35, 53
		/ Cu	• allylic acetoxylation of olefins	30	54
	X=NHR	/ Rh	• hydrogenation of enamides	99	36
		/ Ni	• Michael addition reaction	61	55
5M			• addition of Et_2Zn to aldehydes	99	14,18
		/ B	• addition of Et_2Zn to aldehydes	99	56
		/ B	• Diels-Alder reaction	97	142
5N		/ Co	• decarboxylation of malonic acid derivatives	96	18
5O			• addition of Et_2Zn to aldehydes	96	57
5P		/ Rh	• hydrogenation of α-ketoamides	79	58
			• hydrogenation of enamides	96	48

Table 5. (Continued)

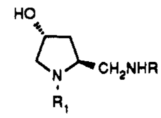
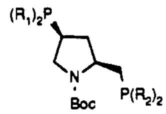
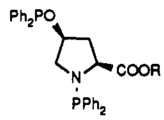
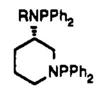
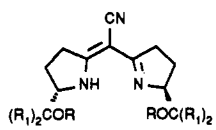
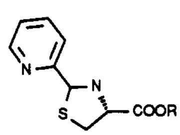
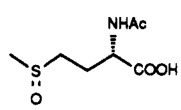
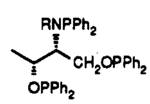
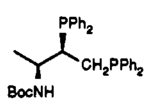
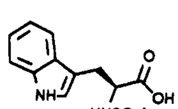
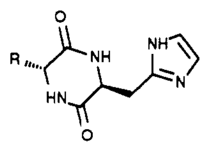
Entry	Chiral catalyst	Reaction	ee	Ref.
	from hydroxyproline			
5Q		• addition of RSH to enones	88	41
5R	 / Rh	• transfer hydrogenation of itaconic acid	97	143
	/ Rh	• hydrogenation of ketones	97	59, 60
	/ Rh	• hydrogenation of enamides	98	48,61
	/ Pt-$SnCl_2$	• hydroformylation of olefins	98	62
	/ Ir	• hydrogenation of imines	84	63
5S	 / Rh	• hydrogenation of enamides	92	64
		C. Functionalized Amino Acids		
	from ornithine			
5T	 / Rh	• hydrogenation of enamides	84	65
	from pyroglutamic acid			
5U	 / Cu	• cyclopropanation of olefins	93	50
	/ Co	• reduction of α,β-unsaturated amides	99	66
	/ Co	• reduction of α,β-unsaturated esters	96	66
	from cysteine			
5V	 / Rh	• hydrosylilation of ketones	98	2, 67
	from methionine			
5W	 / Rh	• transfer hydrogenation of ketones	75	68
	from threonine			
5X	 / Ni	• hydrovinylation of dienes	93	2, 69
5Y	 / Rh	• hydrogenation of enamides	94	70
	from tryptophan			
5Z	 / B	• Diels-Alder reaction	96	144

table it is located. The chiral auxiliaries are listed in order of increasing number of modified functional groups. The reason for this is our interest in the industrial application of enantioselective synthesis. There, a chiral auxiliary has to be easily available and not too expensive. This means that the fewer steps there are from the natural molecule to the auxiliary the better is the chance of its application. The structures of the natural products with their absolute configuration are given in Figures 1–5.

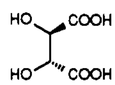
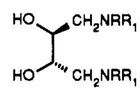
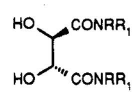
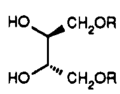
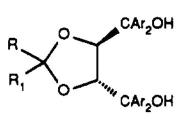
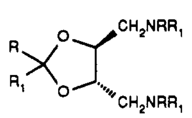
If a metal complex is the active reagent or catalyst, usually only the metal is given, although in some cases

Table 6. Heterogeneous Chiral Catalysts Derived from Amino Acids; Reaction Type and Best Optical Yield

Entry	Chiral catalyst		Reaction	ee	Ref.[a)]
6A	various amino acids	/ Raney-Ni	• hydrogenation of β-ketoesters	15	38
6B	tyrosine	/ Pd or Raney-Ni	• hydrogenation of C=C	50	H7, 71
6C	silk fibroin	/ Pd	• hydrogenation of C=C	66	H5
		/ Pd	• hydrogenation of C=N	30	H5
6D	synthetic polypeptides		• epoxidation of chalcones	99	M5,M11
		/ Pd; Ni; Ru	• hydrogenation of C=C	6	H11
		/ graphite electrode	• reduction of C=C	43	E4, 33
		/ Pt electrode	• oxidation of sulfides	93	E5, 33
	from histidine				
6E		in gel form	• addition of HCN to aldehydes	97	72

a) or number of catalytic system in ref. 1b

Table 7. Chiral Reagents Derived from Hydroxy Acids; Reaction Type and Best Optical Yield

Entry	Chiral reagent		Reaction	ee	Ref.
	from tartaric acid				
7A		/ $NaBH_4$	• reduction of ketones	86	73
7B		/ $EtAlCl_2$	• Diels-Alder reaction	94	74
7C		/ $B(OMe)_3$	• Diels-Alder reaction	92	75
		/ B-allyl	• allylboration of aldehydes	97	76
7D		/ $EtAlCl_2$	• Diels-Alder reaction	>98	74
7E		/ $Ti(OR)_2Cl_2$	• addition of MeLi to aldehydes	90	18
		/ $Ti(OR)_2Cl_2$	• addition of Me_3SiCN to aldehydes	96	75
		/ $Ti(OR)_2Cl_2$	• intramolecular ene reaction	>98	77
		/ $cpTiCl_3$	• addition of M-allyl to aldehydes	97	78
7F		/ OsO_4	• dihydroxylation of olefins	90	18

other essential ligands are mentioned as well. The highest enantiomeric excess (ee) described in the literature is reported as a useable value for judging the discriminating ability of a given auxiliary. It must be stressed that in most cases the best enantioselectivity can only be obtained under optimal conditions (substrate, chiral auxiliary, reaction conditions). While some of the enantioselective reactions are quite general, i.e. have been applied to different substrates, very often only one or two model substrates have been employed. Therefore, appropriate reviews have been cited in order to give the reader quick access to background information on the scope and limitations of a given chiral reagent or catalyst.

B. Sources for Effective Chiral Auxiliaries

1. Alkaloids (Tables 1–3, Figure 1)

Historically, alkaloids have played an important role in the discussions of the prospects of organic chemistry to mimic nature. From the time Fischer discovered that enzymes catalyze reactions enantioselectively, chemists have been challenged to find artificial systems with the same capability. The only enantiomerically pure compounds available at that time were of course of natural origin. The first positive results were obtained with alkaloids as chiral agents: Marckwald[5] reported in 1904 the enantioselective decomposition of the brucine salt of ethylmethylmalonic acid (entry **1A**). And in 1908, Bredig and Fajans[6] described the first kinetic resolution: nicotine catalyzed the decomposition of D- and L-camphocarbonic acid at different rates ($k_L/k_D \sim 1.17$). In 1912, the same group reported the first asymmetric catalytic synthesis: addition of HCN to aldehydes, catalyzed by cinchona alkaloids (ee ~2%) and in 1932 found the first heterogeneous catalysts for the same reaction (aminocellulose, ee ~22%, entry **12E**).[7] These results, together with those of Schwab[8] on the use of metals supported on quartz (entry **16B**), clearly laid to rest all suggestions that only nature could make chiral molecules selectively. The cinchona al-

Table 8. Homogeneous Chiral Catalysts Derived from Hydroxy Acids; Reaction Type and Best Optical Yield

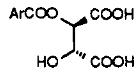
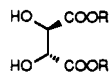
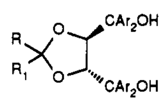
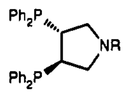
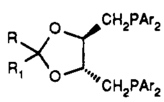
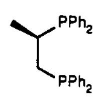
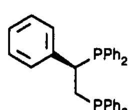
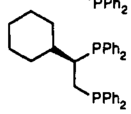
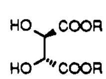
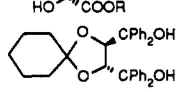
Entry	Chiral catalyst		Reaction	ee	Ref.
	from tartaric acid				
8A		/ B	• Diels-Alder reaction	96	18,75
			• allylation of aldehydes with allylsilanes	96	145
8B		/ Ti	• epoxidation of allylic alcohols	>98	79
			• oxidation of sulfides	97	53,80,81
			• addition of Me_3SiCN to aldehydes	91	82
			• photooxidation of olefins to epoxyalcohols	72	83
8C		/ Ti	• addition of MeLi to aldehydes	90	18
			• alcoholysis of thioesters (kinetic resolution)	92	18
			• Diels-Alder reaction	94	75
			• addition of Et_2Zn to aldehydes	99	84
			• 2 + 2 cycloaddition reaction	>98	75,85
			• addition of Me_3SiCN to aldehydes	96	146
8D		/ Rh	• hydrogenation of enamides	100	2,86
8E		/ Rh	• hydrosilylation of ketoesters	85	87
		/ Rh	• hydrogenation of itaconic acid derivatives	94	88
		/ Rh	• hydrogenation of enamides	94	2,89
		/ Rh	• hydroboration of olefins	82	90
		/ Rh	• intramolecular hydrosilylation of olefins	93	91
		/ Ir	• hydrogenation of imines	70	63
		/ Rh	• hydrogenation of aminoketones	95	48
	from lactic acid				
8F		/ Rh	• hydrogenation of enamides	91	92
		/ Co	• Diels-Alder reaction	81	93
	from mandelic acid				
8G		/ Rh	• hydrogenation of enamides	88	48
8H		/ Rh	• hydrogenation of enamides	98	48
		/ Rh	• hydrogenation of imines	91	94

Table 9. Heterogeneous Chiral Catalysts Derived from Hydroxy Acids; Reaction Type and Best Optical Yield

Entry	Chiral catalyst		Reaction	ee	Ref.[a]
	from tartaric acid				
9A	tartaric acid	/ Raney-Ni-NaBr	• hydrogenation of β-functionalized ketones	92	H9,38
9B	Zn-tartrate		• epoxide ring opening reactions	85	M7
9C	Cu-tartrate		• cyclopropanation of olefin	46	M8
9D		/ Ti-pillared clay	• epoxidation of allyl alcohols	98	M10
9E		crystalline chiral host	• Wittig reaction with cyclohexanones	57	M9,95
9F	malic acid	/ Raney-Ni	• hydrogenation of β-ketoesters	61	37

a) or number of catalytic system in ref. 1b

kaloid catalyzed addition of HCN to aldehydes was probably the first enantioselective reaction that was studied systematically and where a detailed mechanism was postulated.[9,10]

The results compiled in Tables 1–3 show that of the many types of alkaloids known today only a very few have been found to be effective chiral agents. The cinchona alkaloids are very versatile catalysts and ligands (entries **2A**), modifiers for heterogeneous catalysts (entry **3A**), and phase-transfer catalysts (entry **2B**). Interestingly, the unmodified alkaloids often exhibit the best enantioselection properties for a variety

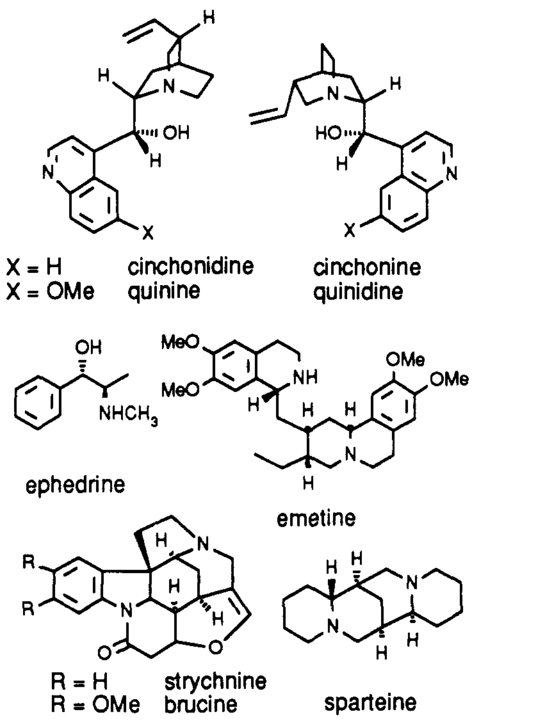


Figure 1. Structures and absolute configurations of the alkaloids used for preparing enantioselective catalysts and reagents described in Tables 1–3.

of transformations.[11b,12] Sparteine **2F**, strychnine or brucine **2E** and **3E**, and emitine **3F** are moderately effective without alteration either as catalysts or as chiral modifiers. Ephedrine derivatives are used mostly as ligands for organometallic reagents or catalysts, and the functionality is adapted accordingly (entries **1C**, **1D**, **2C**, and **2D**).

Some tentative conclusions can be drawn: High optical yields are observed for molecules with a basic nitrogen atom in a distinct asymmetric environment and an oxygen functionality in a 1,4-relationship. The multifunctionality of the cinchona alkaloids is rather unique.

2. Amino Acids (Tables 4–6, Figure 2)

Amino acids are obvious starting materials for enantioselective auxiliaries because a large series of closely

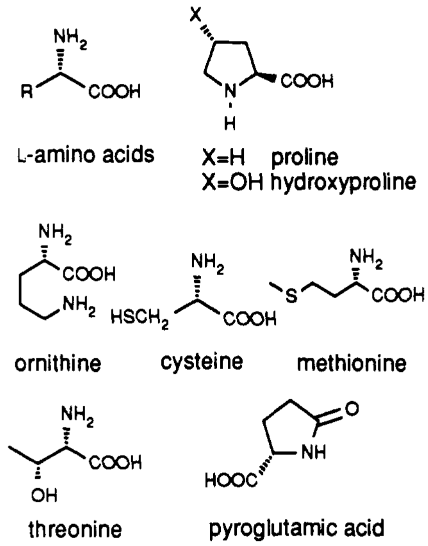
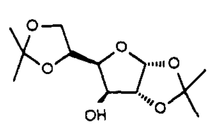
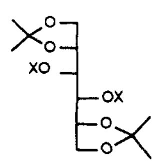


Figure 2. Structures and absolute configurations of the amino acids used for preparing enantioselective catalysts and reagents described in Tables 4–6.

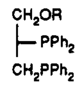
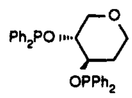
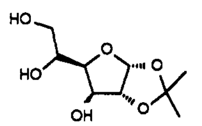
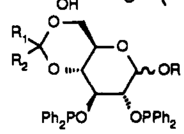
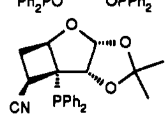
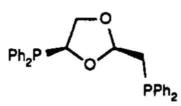
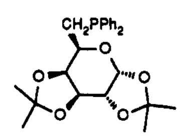
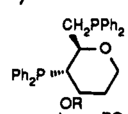
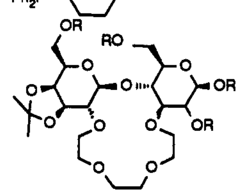
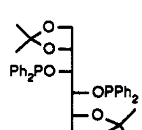
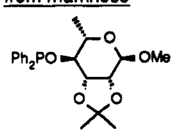
related analogs is available. There are so many outstanding homogeneous catalysts derived from amino acids that the results were subdivided as follows: unfunctionalized amino acids $RCH(NH_2)COOH$ (Table 5, part A), proline/hydroxyproline (Table 5, part B), and amino acids with an additional functional group (Table 5, part C). For most homogeneous applications, either both functional groups of the amino acids or an additional functional group was used to construct a bidentate ligand for various metal-mediated reactions (see below). There are interesting exceptions: Proline **5L** is an efficient catalyst for the cyclization of triketones (Hajos–Parrish–Wiechert reaction). Reported in the early 1970s, this was considered to be a spectacular achievement.[35] Just as spectacular is the recent report on the use of a simple amide of proline **5L** as a ligand for the Rh-catalyzed hydrogenation of enamides. If confirmed, this would represent the first efficient nonphosphine noble metal hydrogenation catalyst.[36] Other cases where only slight changes of the amino acid molecule are needed are the reduction reagents from *N,N'*-dibenzoylcystine/$LiBH_4$ **4A** and *N*-acylproline/$NaBH_4$ **4C** and the Diels–Alder catalyst **5A**.

Table 10. Chiral Reagents Derived from Carbohydrates; Reaction Type and Best Optical Yield

Entry	Chiral reagent		Reaction	ee	Ref.
	from glucose				
10A		/ cpTi	• addition of allyl groups to aldehydes	94	78
		/ cpTi	• addition of ester enolates to aldehydes	98	78
		/ BBN; KH[a)]	• reduction of ketones	100	16
10B	cyclodextrines		• epoxidation of benzoquinone	48	96
	from mannitol				
10C	 X				
	H	/ $EtAlCl_2$	• Diels-Alder reaction	94	74
	$SiMe_3$	/ $TiCl_4$	• Diels-Alder reaction	96	74

a) K-Glucoride; BBN = 9-borabicyclo[3.3.1]nonane

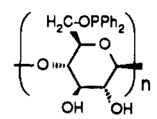
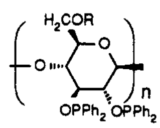
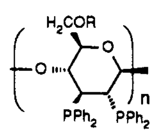
Table 11. Homogeneous Chiral Catalysts Derived from Carbohydrates; Reaction Type and Best Optical Yield

Entry	Chiral catalyst	Reaction	ee	Ref.
	from glyceraldehyde			
11A	 / Rh	• hydrogenation of enamides	86	2
	from xylose			
11B	 / Rh	• hydrogenation of enamides	90	97
	from glucose			
11C	 / $LiAlH_4$	• reduction of ketones	71	98
11D	 / Rh	• hydrogenation of enamides	99	99, 100
11E	 / Rh	• hydrogenation of enamides	92	2, 101
11F	 / Rh	• hydrogenation of enamides	90	2, 102
	from galactose			
11G	 / Ni	• Grignard cross coupling reaction	99	103
11H	 / Rh	• hydrogenation of enamides	73	104
11I		• Michael addition reaction	70	105
	from mannitol			
11K	 / Rh	• hydrogenation of enamides	78	135
	from rhamnose			
11L	 / Rh	• hydrogenation of itaconic acid deriv.	100	136

Amino acids are not very efficient for the modification of heterogeneous hydrogenation catalysts (entries **6A** and **6B**) but these modified systems together with the Pd/silk fibroin (a natural polypeptide) **6C** are historically important.[37,38] Very good optical yields were reported for the application of the synthetic polypeptides **6D** as epoxidation catalysts for enones and as modifiers for the electrochemical oxidation of sulfides. The dipeptides **6E** were used as catalysts for the addition of HCN to aldehydes. They exhibit good enantioselectivity only in gel form.[72b]

Tentative conclusions: Amino acids are versatile starting materials because of their simple structure with an O- and an N-functionality close to the asymmetric carbon atom. Analogs with additional functional groups

Table 12. Heterogeneous Chiral Catalysts and Reagents Derived from Carbohydrates; Reaction Type and Best Optical Yield

	Chiral catalyst or reagent		Reaction	ee	Ref.[a]
12A	glucose	/ Raney-Ni	• hydrogenation of C=C	≈10	H3
12B	fructose	/ ZnO	• bromination of C=C	<50	B1
	crystalline chiral hosts				
12C	cyclodextrines	/ BH_3; $NaBH_4$	• addition of XY to C=C (X,Y=H,Cl,Br) • reduction of ketones	100 91	M6 106, 107
	biopolymers				
12D	cellulose	/ Pd	• hydrogenation of C=C, C=O	<1	H12
12E	aminocellulose		• addition of HCN to aldehydes	22	B2
12F	gum arabicum	/ Pt sol	• various reactions	nd	H8
	complexes immobilized on cellulose-derivatives				
12G		/ Ru	• hydrogenation of enamides	35	21
12H		/ Rh	• hydrogenation of olefins • hydrogenation of enolphosphonates • hydrogenation of enamides • hydrogenation of itaconic acid	77 77 80 82	48 48 48 48
12I		/ Rh	• hydrogenation of olefins	40	108

a) or number of catalytic system in ref. 1b

are available. Five- and seven-membered chelates are easily accessible.

3. Hydroxy Acids (Tables 7–9, Figure 3)

Besides proline, tartaric acid is the single most important starting material for a variety of highly selective chiral agents. Again, in many cases only the backbone is left unchanged while the OH and/or the COOH groups are protected or transformed to give efficient ligands (see below). The most important catalyst here is probably the Sharpless epoxidation catalyst **8B** and **9D**. Other interesting exceptions where the tartrate molecule is not or only slightly changed are the well-publicized tartrate-modified Nickel catalysts for the hydrogenation of β-keto esters **9A**, the reducing agent **7A**, the Diels–Alder catalyst **8A**, and the Zn and Cu tartrate catalysts **9B** and **9C**. A few ligands derived

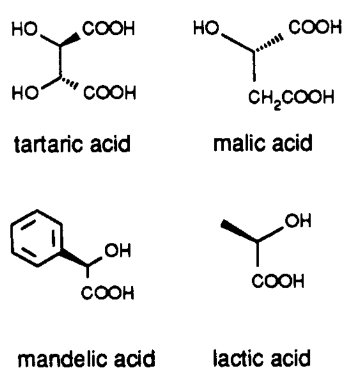


Figure 3. Structures and absolute configurations of the hydroxy acids used for preparing enantioselective catalysts and reagents described in Tables 7–9.

from monohydroxy acids are known (entries **8F–H**) and in some respect hydroxy acids offer a similar potential as starting materials as amino acids.

Tentative conclusions: Tartaric acid is a versatile starting material for a variety of different five- and seven-membered chelates with C_2 symmetry. In addition, both enantiomers are available.

4. Carbohydrates (Tables 10–12, Figure 4)

Carbohydrates are probably the class of natural compounds with the most asymmetric centers and potential ligand atoms per molecule. Their use as chiral auxiliaries is therefore very tempting. The results show, however, that more is not necessarily better. In most cases many or all of the hydroxy groups either have to be protected or removed in order to obtain an effective ligand for a diversity of metal-based reagents. This means that it is essentially the backbone and the bulky shape of the whole molecule that is used for chiral discrimination. With the exception of the mannitol derivative **11K**, the sugars are used in their cyclic form.

Sugars also occur naturally as oligomers (e.g. cyclodextrins) and polymers (e.g. cellulose). These materials have been applied with success as inclusion catalysts (entries **10B** and **12C**) and as polymeric ligands (entries **12G–I**). Their use as a chiral catalyst (entry **12E**) or catalyst support (entry **12D**) was less successful.

Tentative conclusions: There are often too many similar asymmetric elements and functional groups. Protected cyclic sugars have an interesting, bulky shape. Chelates attached to a ring are easily accessible.

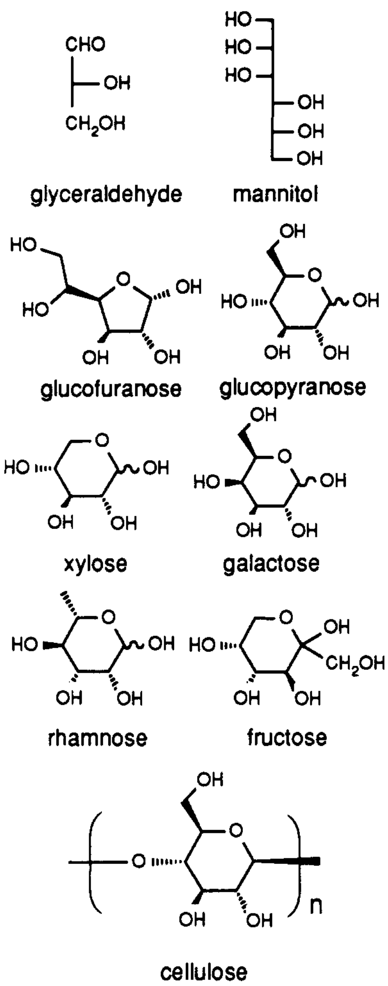


Figure 4. Structures and absolute configurations of the sugars used for preparing enantioselective catalysts and reagents described in Tables 10–12.

5. Terpenes (Tables 13–15, Figure 5)

The best-studied terpene-based chiral reagents are the versatile organoboranes (entries **13C,D,F**) developed by Brown over the last two decades.[76] Because the ligand is attached directly to the boron via a carbon atom, terpenes without heteroatoms are feasible as starting materials. Similar Al complexes **13E** have also been described. The lack of appropriate functional groups might be the reason that only two more terpenes have been used for other types of auxiliaries: camphor where additional functional groups must be introduced and menthol where the OH group was replaced in order to obtain suitable ligands. Both molecules are the starting point for several families of highly efficient ligands. There is one report of a rather unusual menthol/Rh catalyst **14D** which produces β-lactams by carbonylation of aziridines.

Tentative conclusions: Terpenes have rigid ring structures, but the lack of functional groups makes them less attractive as chiral auxiliary.

6. Miscellaneous Sources (Table 16, Figure 5)

This last chapter describes the only vitamin used as enantioselective catalyst (entry **16A**), a natural inorganic polymer (entry **16B**) employed as support, and two cases where the prochiral substrate crystallizes in chiral crystals which then lead to optical induction (entries **16C** and **16D**). These latter chiral systems are of no practical use at the moment either because of low optical yields or because the crystalline state is not a feasible reaction medium.

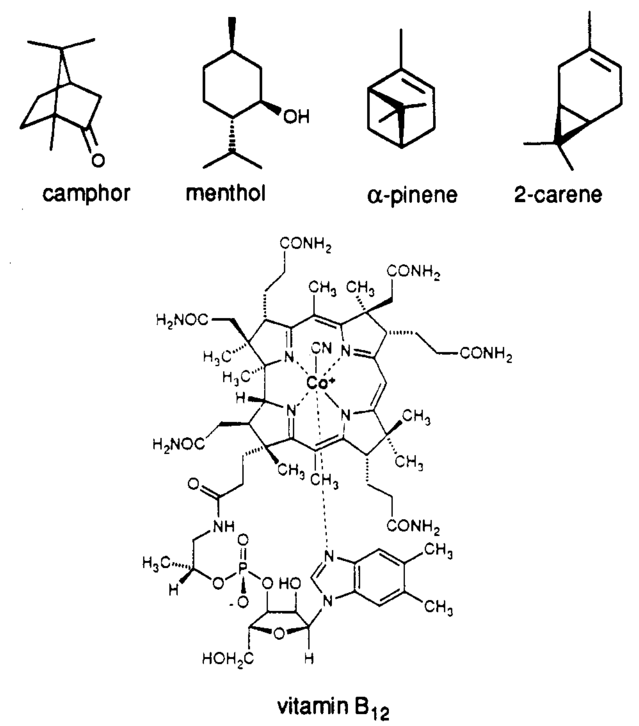
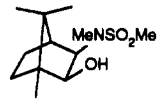
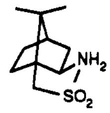
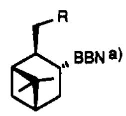
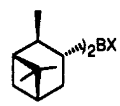
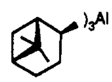
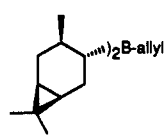


Figure 5. Structures and absolute configurations of the terpenes and of vitamin B_{12} used for preparing enantioselective catalysts and reagents described in Tables 13–16.

C. Chiral Auxiliaries from Non-Natural Starting Materials (Table 17)

As already pointed out, starting from enantiomerically pure natural products is only one way for obtaining chiral auxiliaries. One-third of the auxiliaries listed in the review of Brunner[2] have been prepared either by resolving racemic material or by enantioselective synthesis. Important examples have been listed in Table 17. This strategy has its own advantages: (i) the possibility to make chiral auxiliaries with chiral elements which do not exist in natural compounds, such as molecules with axial asymmetry (BINOL **17A** and BINAP **17B**), molecules with planar asymmetry like the ferrocene-derived phosphines **17D**, and ligands with an asymmetric P or Re atom (entries **17C** and **17E**); the BINAP ligand has especially expanded the scope of enantioselective hydrogenation;[122,123] (ii) the opportunity to design ligands with structural elements not occurring in nature (entry **17F**); (iii) both enantiomers of a given chiral agent can be made which is usually not possible when starting from natural compounds; (iv) auxiliaries with the same structural elements described in the previous chapters but without some of the natural residues or with more pronounced features can be synthesized. This approach of course requires at least an intuitive understanding of the function of different parts of the chiral agent. That is one reason we have tried to analyze the efficiency of different structures and substituents. Some very selective catalysts and reagents have been designed in this fashion and many of them are can be found in the cited reviews.

Table 13. Chiral Reagents Derived from Terpenes; Reaction Type and Best Optical Yield

Entry	Chiral reagent		Reaction	ee	Ref.
	from camphor				
13A		/ B-allyl	• allylboration of aldehydes	96	76
13B		/ EtAlCl$_2$	• Diels-Alder reaction	>98	74,75
	from pinene				
13C		/ tBuLi	• reduction of ketones	>99	76
		X			
13D		H	• hydroboration of olefins	>99	76
		Cl,I	• epoxide ring opening reaction	95	109
		H,Cl	• reduction of ketones	98	76
		allyl	• allylboration of aldehydes	>99	76
13E			• reduction of ketones	98	110
	from carene				
13F			• allylboration of aldehydes	>99	76

a) BBN = 9-borabicyclo[3.3.1]nonyl

Table 14. Homogeneous Chiral Catalysts Derived from Terpenes; Reaction Type and Best Optical Yield

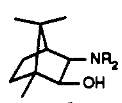
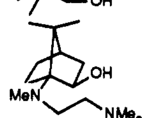
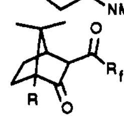
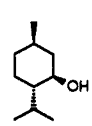
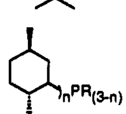
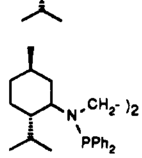
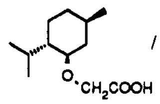
Entry	Chiral catalyst		Reaction	ee	Ref.
	from camphor				
14A			• addition of R$_2$Zn to aldehydes	99	18
			• protonation of photodienols	91	147
14B			• addition of R$_2$Zn to aldehydes	>96	14
14C		/ Cu	• cylopropanation of olefins	100	111
		/ Eu	• Hetero-Diels-Alder reaction	64	75, 112
		/V=O	• Hetero-Diels -Alder reaction	85	113
	from menthol				
14D		/ AlCl$_3$	• Diels-Alder reaction	72	75
		/ Rh	• carbonylation of aziridines	99	114
14E		/ Rh	• hydrogenation of enamides	87	115
		/ Rh	• hydrogenation of acrylic acid derivatives	61	116
		/ Ni	• hydrovinylation of norbornene	81	117
14F		/ Rh	• hydrogenation of enamides	93	118

Table 15. Heterogeneous Chiral Catalysts Derived from Terpenes; Reaction Type and Best Optical Yield

Entry	Chiral catalyst		Reaction	ee	Ref.[a]
15A		/ Pt black	• hydrogenation of C=N	18	H4
15B	camphor	/ Raney-Ni	• hydrogenation of C=O	24	H6

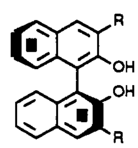
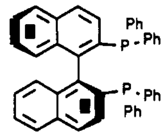
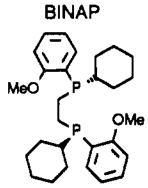
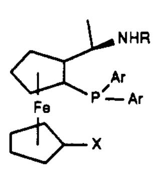
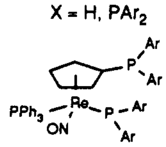
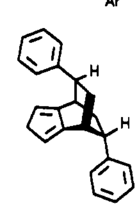
a) or number of catalytic system in ref. 1b

Table 16. Miscellaneous Chiral Systems; Reaction Type and Best Optical Yield

Entry	Chiral catalyst or reagent		Reaction	ee	Ref.[a]
16A	vitamine B_{12}		• isomerization epoxide → allylic alcohol	65	119
			• reduction of α,β-unsaturated ester	28	120
			• isomerization of N-acylaziridine	90	148
	inorganic polymer				
16B	quartz	/ Cu; Ni; Pd; Pt	• dehydrogenation of racemic alcohols	≈10	H1
	chiral substrate cystals				
16C	anthracene deriv.		• photodimerisation (kin. resolution)	90	M2
16D	α-ketoamide		• photolytic ring formation	93	M2

a) or number of catalytic system in ref. 1b

Table 17. Chiral Auxiliaries from Unnatural Sources; Type of Reaction and Best Optical Yield

Entry	Chiral catalyst or reagent		Reaction	ee	Ref.
17A	 BINOL	/ Al	• Hetero Diels-Alder reaction	97	75
		/ B	• Diels-Alder reaction	>98	75
		/ K[a]	• Michael addition reaction	99	121
		/ $LiAlH_4$	• reduction of ketones	100	15
17B	 BINAP	/ Rh	• isomerization of allylamines	99	122, 123
		/ Ru	• hydrogenation of β-functionalized ketones	>99	122
		/ Ru	• hydrogenation of acrylic acid deriv.	>99	122
		/ Ru	• hydrogenation of allylic alcohols	99	122
		/ Rh	• hydroboration of olefins	96	124
17C	 DIPAMP	/ Rh	• hydrogenation of enamides	97	48
17D	 X = H, PAr_2	/ Pd	• allylic alkylation reactio,	>98	125
		/ Pd	• Grignard cross coupling reaction	95	126
		/ Au	• aldol reactions of isocyanoacetates	96	125
		/ Rh	• hydrogenation of enamides	93	127
17E		/ Rh	• hydrogenation of enamides	98	128
17F		/ Ti	• hydrogenation of ethylstyrene	96	129

a) Chiral crown ether

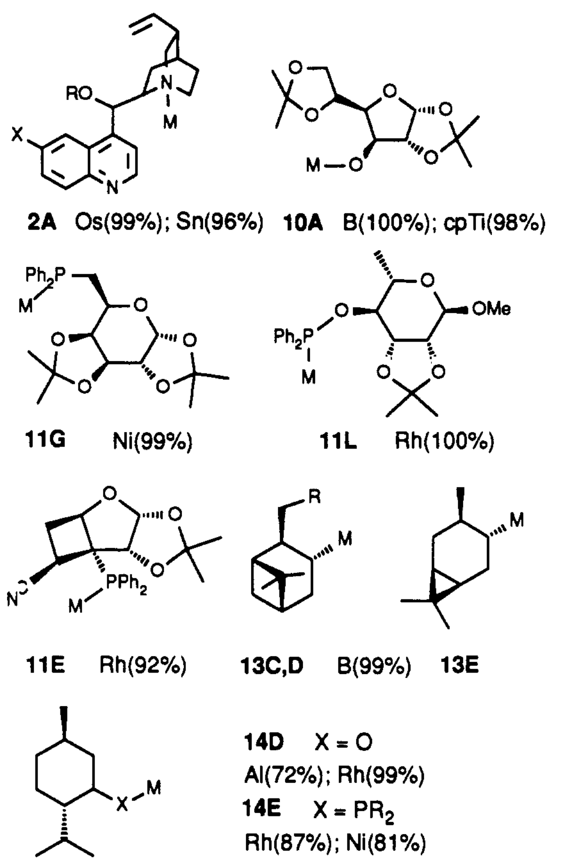


Figure 6. Structural elements and best optical yields of metal complexes with effective monodentate ligands.

III. Structural Analysis of Effective Chiral Ligands

The wealth of results collected in the preceding sections tempted us to carry out a simple structure analysis. For this purpose we chose a somewhat unusual approach. Instead of analyzing structural effects of related auxiliaries with high and low enantioselectivity we compared only highly efficient ones. We realize that the conclusions derived in this way might be biased for several reasons (choice of sample, lack of objectivity, wishful thinking), but we found it worth the effort. Because the majority of such cases deal with chiral auxiliaries that are used as ligands for enantioselective metal based catalysts or reagents, we concentrated on this class of chiral agents in order to find common structural elements. For this purpose the various kinds of ligands were distinguished according to the number and type of donor atoms. In Figures 6–11 the structures of the postulated metal complexes listed in Tables 1–16 are sketched in such a way that the essential factors are clearly visible: ligand atom, chelate size, type of backbone, and number and location of asymmetric centers. The drawings do not imply that the absolute configuration is always the same. The entry number gives the connection to Tables 1–16. Type of metal used and best optical yields are given in the figures. Note that entries starting with 1, 4, 7, 10, and 13 indicate stoichiometric reagents while those starting with 2, 5, 8, 11, and 14 are homogeneous catalysts.

A. Ligand Type and Enantioselectivity

1. Monodentate Ligands (Figure 6)

As a rule, monodentate ligands are less effective for the control of the stereochemical outcome of a reaction.

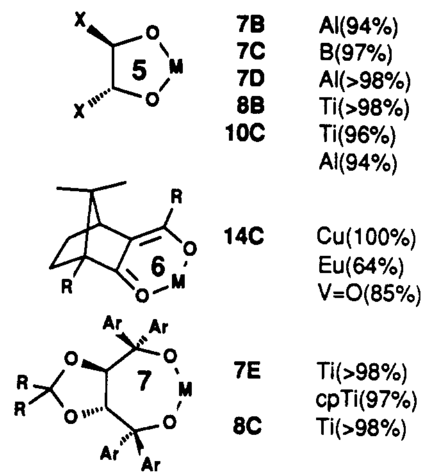


Figure 7. Structural elements and best optical yields of metal complexes with effective bidentate oxygen ligands.

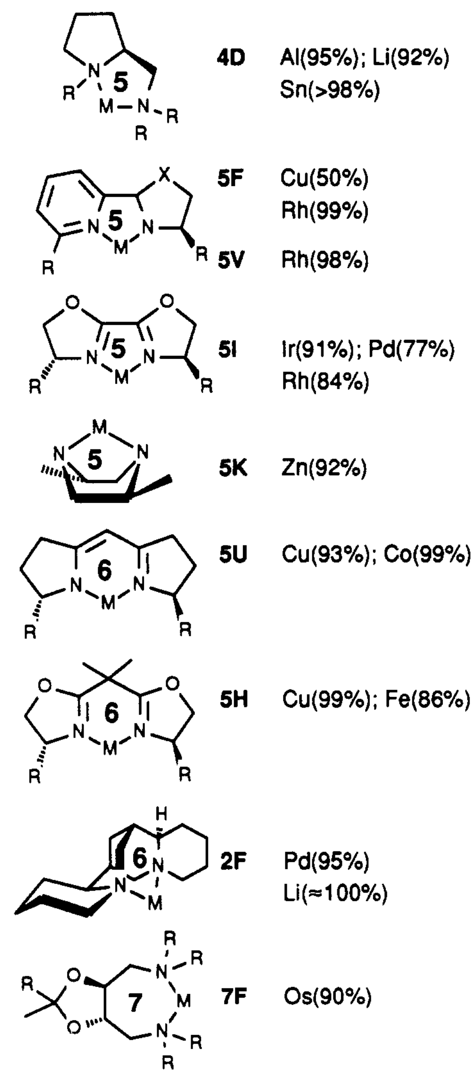


Figure 8. Structural elements and best optical yields of metal complexes with effective bidentate nitrogen ligands.

This is confirmed by the small number of effective catalysts listed here. The complexes depicted in Figure 6 are remarkable exceptions to this rule. They are similar in that all are cyclic structures, most of them are very bulky, and there is a unique and distinct ligand atom. They differ in that the distance of the metal from the next asymmetric center varies between one bond (directly bound to it) for **2A** and **13C–E** and three

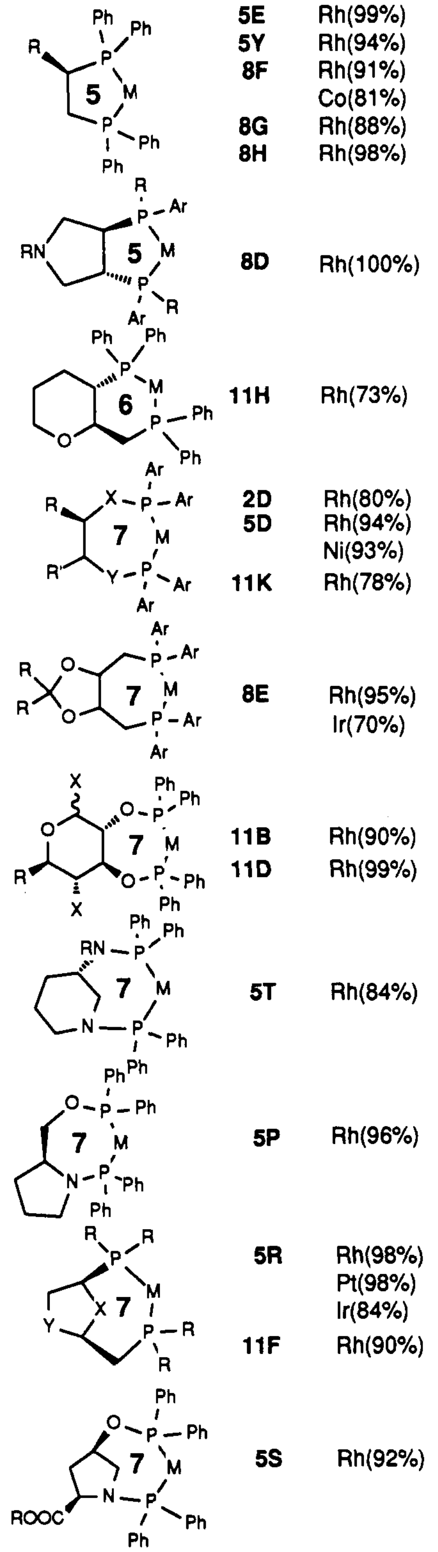


Figure 9. Structural elements and best optical yields of metal complexes with effective bidentate phosphine ligands.

bonds for **11L** and that the ligand atom can part be of a ring system, attached directly to the ring, or one atom removed.

2. Bidentate Oxygen Ligands (Figure 7)

The entries are arranged according to the ring size of the metal chelate complex. Not surprisingly, these ligands are used preferentially for first row and early transition metals and the majority of the reactions are stoichiometric. The variety of structural types is rather narrow, with only one ligand type for each chelate size.

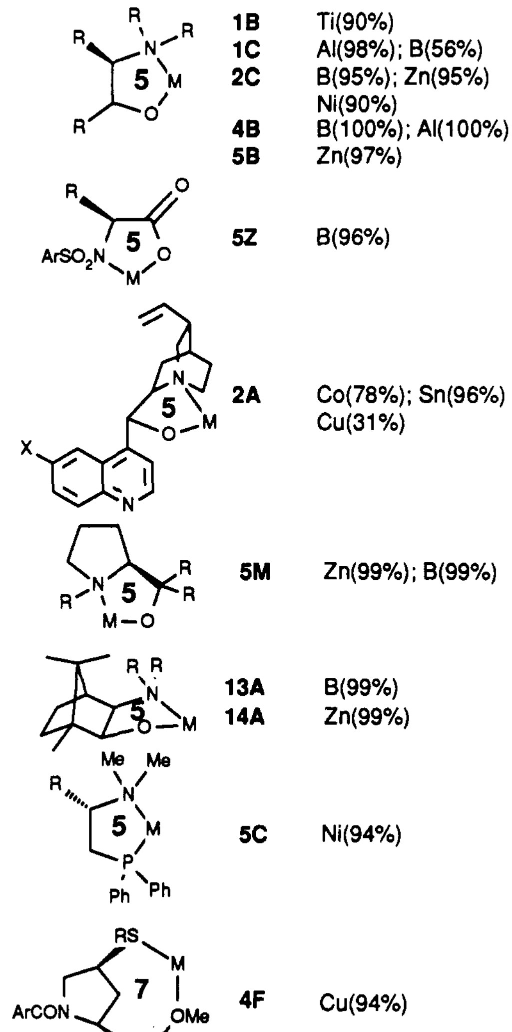
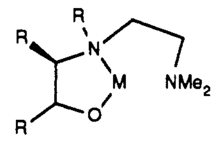


Figure 10. Structural elements and best optical yields of metal complexes with effective bidentate ligands with O, N, P, or S donor atoms.

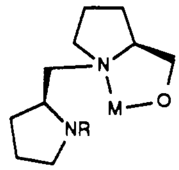
The five-membered chelates all have an acyclic backbone. The substituent X does not have to be very bulky. The heteroatoms that are usually present probably do not play a role for the enantioselection. For the seven-membered chelates, the aryl substituents α to the oxygen are essential for good optical yields. It is conceivable that they are involved in the transmission of the stereochemical information from the asymmetric centers which are quite far from the metal site.

3. Bidentate Nitrogen Ligands (Figure 8)

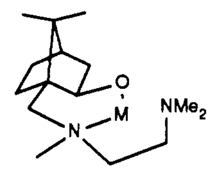
These ligands are used for the widest range of different types of catalysts and reactions. They are mostly derived from amino acids, and with the exception of **7F**, the ligand atom is part of a ring, in α-position to an asymmetric center. The two complexes **5K** and **2F** are rather unusual and probably also unique. **5K** could be called convex while **2F** is much more concave;[130] their mode of optical induction is therefore expected to be different but is at present not known. **4D** is a class of complexes developed by Mukaiyama that can be varied widely and has been applied for several types of reactions.[41] These and similar proline-derived reagents probably owe their properties to the rigid bicyclic structure. In contrast, the Os complexes **7F** with an unsubstituted seven-membered ring must be quite flexible. The other five entries (**5F**, **5V**, **5I**, **5U**, and



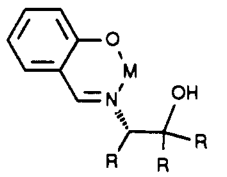
1D Cu/M(92%)



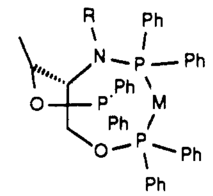
4E Li(95%)



14B Zn(>96%)



5G Cu(92%) Ti(91%)



5X Ni(93%)

Figure 11. Structural elements and best optical yields of metal complexes with various effective tridentate ligands.

5H) belong to a new and very promising type of catalyst complexes recently introduced by Brunner[67] and Pfaltz.[50]

4. Bidentate Phosphorus Ligands (Figure 9)

The seminal paper by Kagan,[131] where the first chiral bidentate ligand DIOP **8E** was introduced, had a profound effect on the field of homogeneous enantioselective catalysis. Today, the asymmetric hydrogenation of enamides with Rh diphosphine complexes is the most widely investigated catalytic enantioselective reaction. Diphosphine ligands are effective for other reaction types as well. This is partly due to the wide variety of different ligands available.[48] Some trends can be discerned: In most cases the ligating group is a diphenylphosphine; substituted phenyl groups (Ar),[88,132] or alkyl or cycloalkyl substituents (R)[26,59,60] can lead to improved optical yields; the P atom can be bound to the backbone via an O, N, or C atom. Ligands that can form five-membered chelates are effective both with an acyclic or a cyclic backbone but the former types are more versatile. It is possible that complexes of the type **8D** with two connected five-membered rings are so rigid that only few substrates fit optimally. A similar observation has been made for the synthetic ligand NORPHOS for the hydrogenation of aliphatic α-keto esters.[133] Six-membered chelates seem less suitable and indeed are very rare. The only effective one is the synthetic 2,4-bis(diphenylphosphino)butane where ee's up to 99% have been reported.[48] Ligands forming seven-membered metallacycles are the most numerous. It is not easy to see common structural features which might be advantageous because high optical yields are observed for very different arrangements: acyclic or cyclic backbones; five- or six-membered rings; the phosphine atom attached either directly to the ring or via C, N, or O links which can be in a 1,2 or 1,3 position.

5. Bidentate Ligands with O, N, P, or S Donor Atoms (Figure 10)

A number of different ligands with an O and a N donor atom that can form five-membered chelates have been developed in the last decade for a large variety of highly selective reactions. Structural elements are similar to the cases already discussed above. The ligand-accelerated addition of Et_2Zn to aldehydes is the best developed application of these auxiliaries.[14] **5C** is one of the few effective phosphine/nitrogen ligands, and **4F** is a rather rare example of sulfur as a ligating atom.

6. Potentially Tridentate Ligands (Figure 11)

The ligands of this series have many structural features in common with the bidentate types described above except that they have a further ligand atom of the same type which potentially can interact with the metal. The structures in Figure 11 are drawn in such a way that this should be visible. In most cases the authors make the plausible assumption that the third ligand atom does indeed coordinate to the metal and produces a better defined chiral environment. With the exception of **5G**, the detailed structures of these complexes have not been determined, and these conclusions are based on circumstantial evidence.

B. Tentative Conclusions on the Effect of Structural Elements

What can we learn from all the examples listed in Figures 6–11? Are there structural elements that guarantee high enantioselectivity? The answers to these questions are not clear. Yes, we think that there are structural elements that are common to many of the best ligands and that often are beneficial for obtaining high enantioselectivities. No, even if one succeeded in designing an auxiliary with all these structural elements there would still be no guarantee for success. Each chemical transformation demands its own type of chiral agent that has the ability to activate the substrate(s) on the one hand and to control the stereochemistry on the other. This requires a unique combination of donor atoms in a properly defined chiral environment.[138] Nevertheless some qualitative conclusions can be drawn concerning the beneficial effects of certain structural features. They might be of help in analyzing effects observed for a structural modifications of a given enantioselective agent or designing a new chiral auxiliary more systematically.

1. Position of Asymmetric Center(s)

The old rule that the asymmetric center should be as close as possible to the reacting center is still sound. But there are mechanisms which allow the transmittance of the chiral information via 2 or 3 bonds.

2. Chelating Agents

Very often ligands that can form chelates are preferential to monodentate ones. The optimal chelate ring size and type of backbone must be determined. Chelates which either have C_2 symmetry[134] or are distinctly unsymmetrical are among the most effective.

3. Ring Structures

Bidentate ligands with cyclic backbones have probably the best chance to give good results. The resulting bicyclic chelate complexes are spatially well defined because the number of accessible conformations is limited. In some cases the resulting complexes can be too rigid and as a result have a very narrow scope (high substrate specificity).

4. Bulky or Aromatic Substituents

It is plausible that bulky substituents will lead to a better-defined environment where the different orientations of the substrate(s) have substantially different energies. On the other hand, too much bulk will decrease the accessibility to the metal center thereby reducing its activity. Aromatic substituents are often essential and cannot be replaced by, for example, cycloaliphatic ones.

5. Essential Structures

Simple structures containing only the essential functions and structural elements are easier to modify systematically. Additional functional groups sometimes interfere negatively, and more asymmetric centers are not necessarily better. In a way one could talk of a "dilution effect" caused by superfluous components and substituents in a chiral auxiliary.

It is important to stress again that there are exceptions that can not be explained by any of these "rules of thumb". We would like to point out two such results: the hydrogenation of enamides with a simple prolinamide/Rh complex **5L** (ee 99%)[36] and the carbonylation of aziridines with a menthol/Rh system **14D** (ee 99%).[114] At the moment these results have not been confirmed, but it is clear that they do not fit into the picture presented above. There is no doubt, that other such examples exist.

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