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REVIEW

Amino-Acids, Peptides and Their Derivatives: Powerful Chiral Ligands for Metal-catalyzed Asymmetric Syntheses

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Keywords: chiral synthesis; metal catalysis; amino-acid; peptide; asymmetric reactions

1 INTRODUCTION

Catalytic asymmetric reaction is one of the most powerful ways to produce optically active compounds, which have been utilized to synthesize a wide variety of products and intermediates in the pharmaceutical, agricultural and other industries.[1,2] Organometallic compounds with optically active organic molecules as chiral ligands can be practical catalysts for asymmetric reactions. Tremendous effort has been put into the development of metal-catalyzed asymmetric reactions. Design of the chiral ligand, therefore, is essential to achieve highly selective asymmetric catalysts. A number of natural and/or unnatural organic molecules, such as alkaloids, terpenes, sugars and binaphthyl compounds and their derivatives, are candidates for the successful 'designed ligand', and various highly selective catalytic asymmetric reactions have been realized using such molecules.

In addition to the optically active organic molecules mentioned above, amino-acids and peptides, which are polymers or oligomers of amino-acids, have also been potential candidates for a highly selective chiral ligand, since these are readily available and well known optically active compounds.[3] In this review, we would like to introduce strategies for the design of catalytic asymmetric reactions using amino-acids, peptides and their derivatives which are quite powerful chiral ligands of main-group and transition-metal complexes for various organic reactions.

In the design of asymmetric catalysts using α-amino-acids and their derivatives as ligands for metallic species, there are some advantages and disadvantages as summarized below.

(1) Natural L(generally *S* form)-amino-acids are readily available and most of the natural amino-acids are inexpensive. On the other hand, unnatural D-amino acids (the enantiomers of natural amino-acids) are not necessarily easy to obtain.
(2) Since several amino-acids which possess a variety of side-chain groups are available (polar/nonpolar, bulky/less bulky, neutral/acidic/basic, etc.), it is quite easy to 'tune' the design of asymmetric catalysts by changing te amino-acid residues.
(3) Since amino-acids bear amino and carboxylic groups, several modifications of such groups can easily convert them to β-amino-alcohols, 1,2-diamines and other functional groups without losing the chiralities. These converted compounds can also be chiral ligands for metal-catalyzed asymmetric reactions.
(4) Amino-acids and peptides sometimes epimerize under basic conditions, which, of course, causes trouble in asymmetric reactions.

Thus, the above characteristic advantages and disadvantages need to be taken into careful consideration in order to design asymmetric catalysts using amino-acid derivatives. We hereafter

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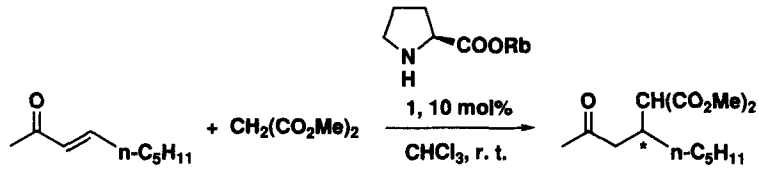


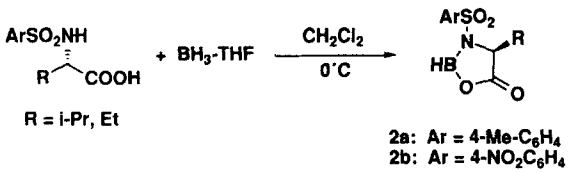
[1]

review examples of the asymmetric synthetic reactions catalyzed by metallic species with ligands composed of amino-acids (Section 2), peptides (Section 3) and other derivatives (Section 4).

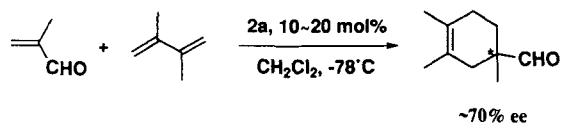
2 AMINO-ACIDS INCLUDING *N*-MODIFIED DERIVATIVES AS CHIRAL LIGANDS

Alkali-metal salts of amino-acids can be used in base-catalyzed C–C bond-forming reactions. The rubidium salt of (*S*)-proline (**1**) catalyzes asymmetric Michael addition of active methylene compounds to enones with an enantioselectivity of ~65% (Eqn [1]).

Yamamoto and Helmchem independently reported asymmetric Diels–Alder reactions catalyzed by boron complexes of an *N*-toluenesulfonyl (tosyl) amino-acid (valine or α-aminobutyric acid), which is generated by mixing *N*-tosylated amino-acid with BH_3–THF in CH_2Cl_2 at 0 °C (Eqn [2]).[5,6] The structure of the complex is considered to be **2a**. When the reaction of 2,3-dimethylbutadiene with methacrolein is carried out at −78 °C in the presence of 10–20 mol % of the catalyst **2a**, the corresponding cycloadduct is obtained in good yield with enantiopurities up to



[2]



[3]

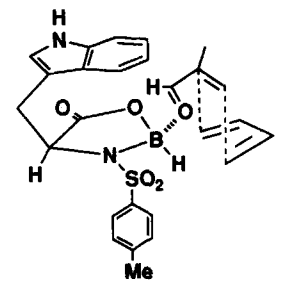
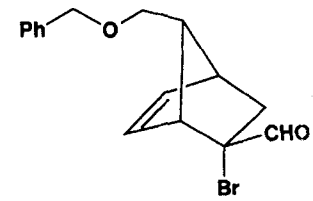


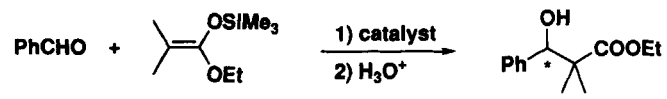
Figure 1

74% (Eqn [3]). On the other hand, Corey reported that the enantioselectivity of a similar asymmetric Diels–Alder reaction was improved if tryptophan was used as the amino-acid residue. 2-Bromoacrolein and cyclopentadiene undergo a smooth Diels–Alder reaction to give the cycloadduct with 200:1 enantioselectivity and 96:4 (*exo*/*endo*-CHO) diastereoselectivity. In addition, the course of the stereochemistry of the asymmetric reaction is opposite to that using valine as the amino-acid residue due to the 'attractive intramolecular interaction' of the aromatic aring of the tryptophan residue with the dienophile, as shown in Fig. 1. The process can be applied to the asymmetric synthesis of a prostaglandin intermediate (**3**).[7–9]



3

The borane complex of the *N*-tosyl amino-acid **2a** is also reported to catalyze asymmetric aldol reaction of ketene silyl acetals with aldehydes to yield the corresponding aldol adduct with enantiomeric excesses of up to 98%.[10] Although the reaction requires the use of a stoichiometric amount of borane complex **2a**, the modification of the *N*-arene sulfonyl group to *p*-nitro (**2b**)[11] or the



[4]

catalyst: **2a** (100 mol%): ~98% ee
2b, 4 (20 mol%): ~99% ee

employment of an α-alkylamino-acid (**4**)[12,13] enables the reaction to be effected in a catalytic manner (Eqn [4]).

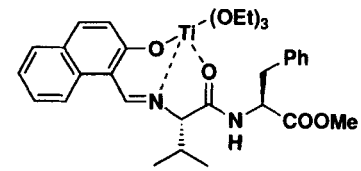
4

3 PEPTIDES

Because of recent progress in the chemical synthesis of peptides, it is quite easy to synthesize peptides of any combination of amino-acid sequences without epimerization.[14] Therefore, peptides are potential candidates for the molecular design of the chiral ligands of metallic species. Based upon the above background, the authors have designed a 'peptide–metal complex' and employed it in catalytic asymmetric syntheses. In order to facilitate the coordination of the peptide moiety to the metal, the *N*-terminal of the peptide was modified to a phenolic Schiff base (**7**) by treatment of the peptide (**6**) with salicylaldehyde derivatives (**5**). The phenolic Schiff base would form a metal phenoxide whose metallic species constitute a chelate structure by coordination of the nitrogen atom of the Schiff base as represented in Scheme 1.

Syntheses of the peptide ligands are quite easy and practical. As shown in Scheme 2, a dipeptide ester bearing a phenolic Schiff base was obtained via the coupling of an *N*-benzyloxycarbonyl (Z) amino-acid with an amino-acid ester by the mixed-anhydride method (i-BuOCOCl/Et_3N) followed by hydrogenolysis of the Z-group and treatment with a salicylaldehyde derivative.

When titanium(IV) alkoxide is chosen as the metallic species (a peptide–titanium complex), the catalyst system is very efficient for the asymmetric addition of hydrogen cyanide to aldehydes to give optically active cyanohydrins with high enantiomeric purities. The peptide–titanium complex (**8**) is synthesized by mixing (in 1:1 molar ratio) titanium(IV) ethoxide with Nap-Val-Phe-OMe (**9**), which was synthesized



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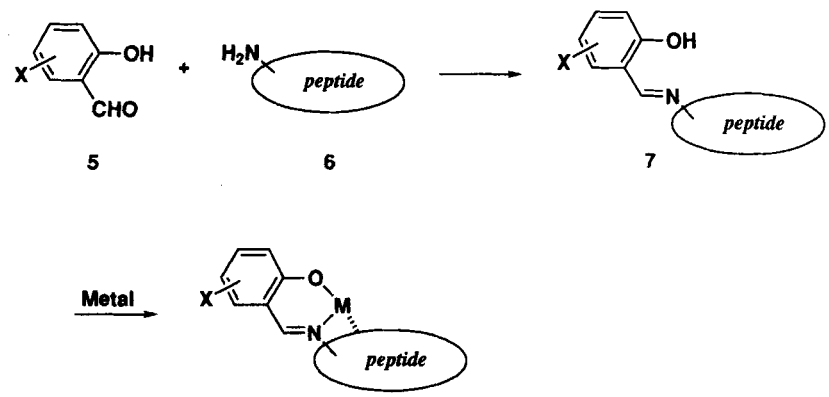
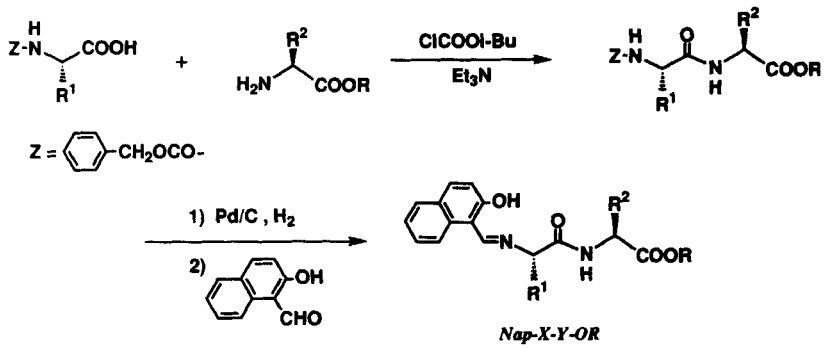
from the dipeptide ester (Val-Phe-OMe) and 2-hydroxy-1-naphthaldehyde. The reaction of ben-

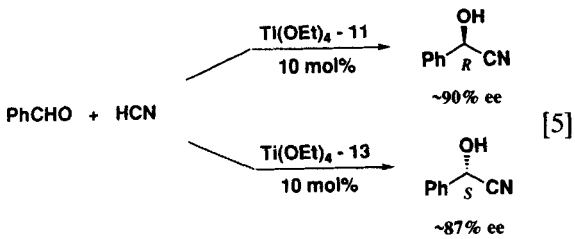


Scheme 1



Scheme 2

zaldehyde with HCN in the presence of 10 mol % **8** affords the corresponding *R*-cyanohydrin with



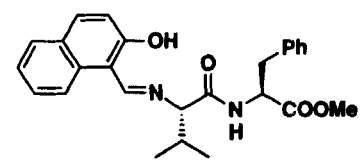
[5]

an enantiopurity of 90% (Eqn [5]).[15] Several combinations of amino-acid residues in dipeptides were examined. The results are summarized in Table 1. It is noteworthy in Table 1 that the use of a dipeptide as the ligand to the metal is important to obtain high *R*-selectivity. In contrast, the amino-acid piperidine amides, Ps-Val-Pip (**12**) and Dbs-Val-Pip (**13**), exhibited high *S*-selectivities. The design of the structure of the

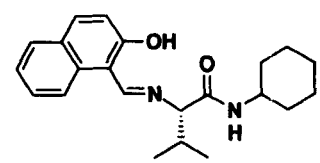
Table 1 Asymmetric addition of HCN to benzaldehyde catalyzed by peptide–titanium complexes

Peptide[a]		*ee*[b]	Configuration
Nap-Val-Phe-OMe	(**9**)	89	*R*
Nap-(*R*)-Val-Phe-OMe		38	*S*
Nap-Val-OMe		0	—
Nap-Val-NHCy	(**10**)	40	*R*
Nap-Val-Val-OMe		87	*R*
Nap-Val-Trp-OMe	(**11**)	90	*R*
Nap-Ala-Phe-OMe		59	*R*
Ps-Val-NHCy		70	*S*
Ps-Val-Pip	(**12**)	83	*S*
Dbs-Val-Pip	(**13**)	87	*S*
Dbs-Val-Phe-OMe	(**14**)	34	*R*

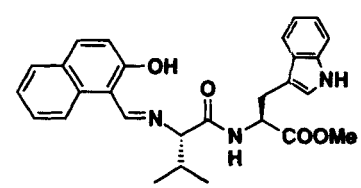
[a] Abbreviations: Nap, *N*-[(2-hydroxy-1-naphthyl)methylene]; Ps, *N*-(3-phenylsalicylidene)-; Dbs, *N*-(3,5-dibromosalicylidene)-; Pip, piperidide; Cy, cyclohexyl. [b] Enantiomeric excess (%).



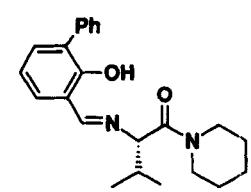
Nap-Val-Phe-OMe 9



Nap-Val-NHCy 10

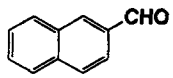
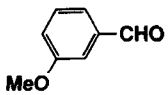
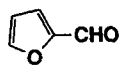
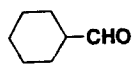
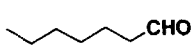


Nap-Val-Trp-OMe 11



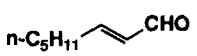
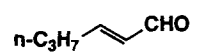
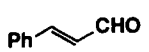
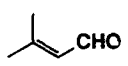
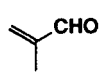
Ps-Val-Pip 12

Table 2 Asymmetric addition of HCN to aldehydes catalyzed by peptide–titanium complexes

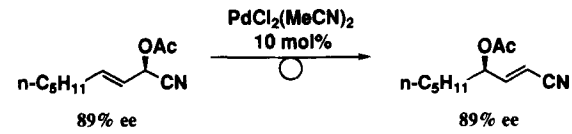
Aldehyde	Dipeptaide	*ee* (%)	Configuration
	**11**	90	*R*
	**11**	85	*R*
	**11**	87	*S*
	**9**	54	*R*
	**9**	76	*R*

Schiff base moiety is also significant in determining the routes to obtain both the enantiomers of the cyanohydrins by using peptides from natural *S*-amino-acid residues as metallic ligands.[16] The reactions of several aldehydes with HCN in the presence of **8** were also examined and the results are summarized in Tables 2 and 3. The asymmetric addition of HCN to α,β-alkenyl aldehydes followed by [3.3]sigmatropic chirality transfer of the corresponding cyanohydrin acetate catalyzed by a palladium complex (Eqn [6]) offers a facile synthetic route to optically active γ-cyanoallylic alcohols.[17]

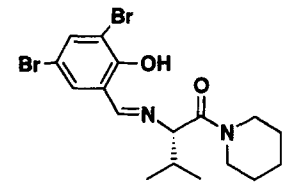
Table 3 Asymmetric addition of HCN to α,β-alkenyl aldehydes catalyzed by peptide (**9**)–titanium complexes

Aldehyde	*ee* (%)	Configuration
	89	*R*
	85	*R*
	81	*R*
	70	—[a]
	72	—[a]

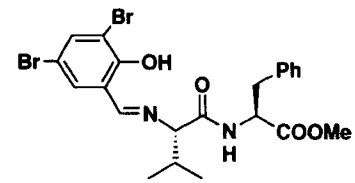
[a] Not determined.



[6]

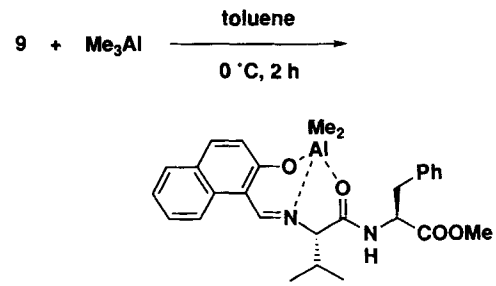


Dbs-Val-Pip 13



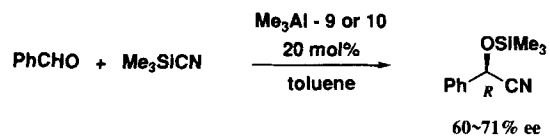
Dbs-Val-Phe-OMe 14

A peptide–aluminum complex was found to be useful as a chiral Lewis acid. Treatment of the peptide **9** with a stoichiometric amount of trimethylaluminum forms a peptide–aluminum complex (**15**) (Eqn [7]). The complex catalyzes asymmetric addition of cyanotrimethylsilane to aldehyde (asymmetric cyanosilylation) to give the



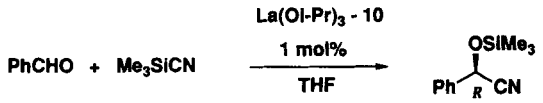
15

[7]



[8]

cyanohydrin trimethylsilyl ether (Eqn [8]) with high selectivity.[18,19] The aluminum complex of the amino-acid amide (**10**) also shows high selectivity.

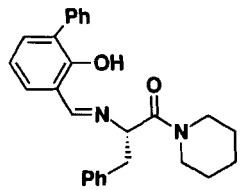


>99%, 70% ee

[9]

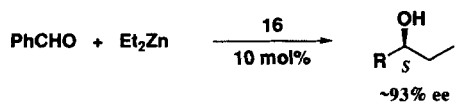
The reaction catalyzed by this aluminum complex requires 10–20 mol % of the catalyst. The asymmetric cyanosilylation reaction also proceeds rapidly in the presence of 1 mol % of the lanthanoid–peptide complex as catalyst, which is composed of lanthanum tri-isopropoxide and the peptide **10**, to give the corresponding product in good yield with selectivity of up to 70% (Eqn [9]) (A. Mori, D. Yu and S. Inoue, unpublished results).

The peptide Ps-Phe-Pip (**16**) was found to catalyze asymmetric alkylation of aldehyde with dialkylzinc. The alkylation of benzaldehyde with diethylzinc in the presence of 10 mol % **16** yields



Ps-Phe-Pip 16

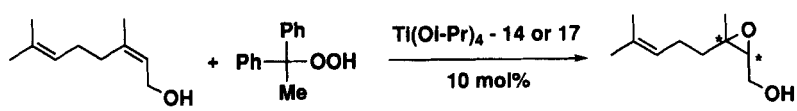
the secondary alcohol in good yield with considerably high enantioselectivity (Eqn [10]). The asymmetric alkylation is considered to proceed catalyzed by a peptide–zinc complex which is generated by the reaction of the peptide with excess dialkylzinc.[20]



~93% ee

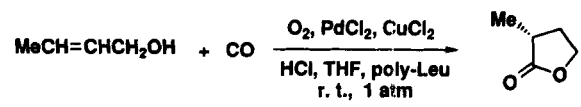
[10]

The peptide–titanium complex catalyzes the asymmetric epoxidation of allylic alcohols (Katsuki–Sharpless epoxidation) using organic hydroperoxides. Epoxidation of nerol with 1,1-diphenylethyl peroxide catalyzed by a mixture of the peptide Dbs-Val-Phe-Ome (**14**) and $Ti(OEt)_4$ yields the corresponding epoxy-alcohol in moder-



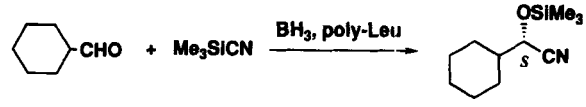
~68% ee

[11]



61% ee

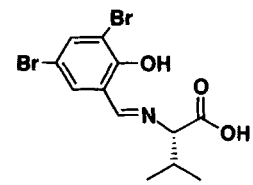
[12]



43% ee

[13]

ate to good enantioselectivity (Eqn [11]). In addition, the reaction is also effectively catalyzed by the titanium complex of amino-acid Dbs-Val (**17**).[21]

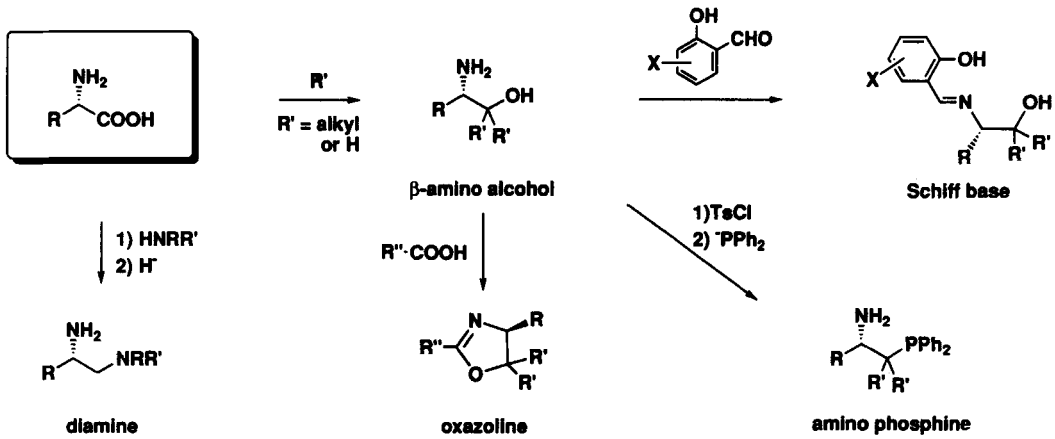


Dbs-Val 17

Polypeptides are also utilized as ligands for asymmetric catalysts. Polyleucine of molecular weight of about 20 000 can be used for a palladium-catalyzed cyclocarbonylation of 2-buten-1-ol to give the corresponding γ-lactone in 61% ee [Eqn [12]).[22] The authors used a mixture of BH_3–THF and polyleucine as a catalyst for asymmetric cyanosilylation [13]) (A. Mori, S. Toki and S. Inoue, unpublished results).

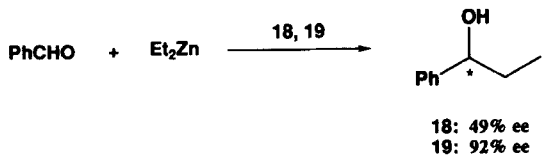
4. AMINO-ALCOHOLS AND RELATED COMPOUNDS

The carboxylic group of α-amino-acids can be easily converted to a hydroxymethyl group to give β-amino-alcohols by alkylation using carbanions or reduction by hydrides. Chiral β-amino-alchols thus obtained can themselves be ligands of metallic compounds. In addition, the amino-alcohols



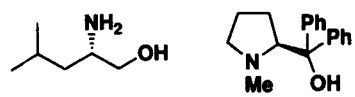
Scheme 3

are able to be transformed to further derivatives, which are also available as effective chiral ligands. Transformations of chiral β-amino-alcohols to a series of derivatives are summarized in Scheme 3. Asymmetric synthetic reactions of organometallic catalysts using these compounds as ligands are introduced hereafter.



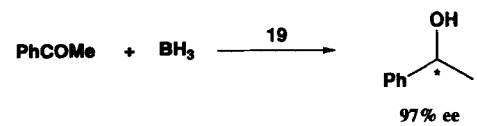
[14]

It is well known that optically active β-amino-alcohols catalyze the alkylation of aldehydes with dialkylzinc (Eqn [14]). Although these amino-alcohols are not necessarily derived from α-amino-acids, the catalyst of the first reported



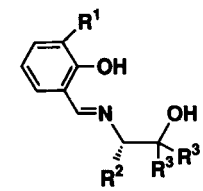
18 19

asymmetric alkylation of aldehydes using dialkylzinc by Oguni was leucinol (**18**), which was obtained by the reduction of leucine, to yield the secondary alcohol with a selectivity of 49% ee.[23] The amino-alcohol **19**, synthesized by alkylation of proline, is a highly selective catalyst for asymmetric alkylation.[24] The amino-alcohol **19** also forms the borane complex by reaction with BH_3, which catalyzes asymmetric reduction of ketones (Eqn [15]).[25]



[15]

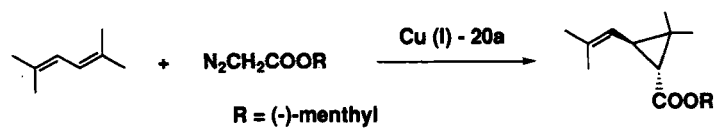
The primary amino group of the amino-alcohols can be modified to the Schiff base of salicylaldehyde derivatives, which is similar to the



20a: R^1= H, R^2=Me, R^3= Ar

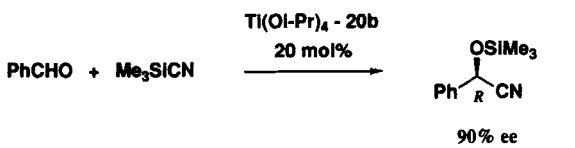
20b: R^1=t-Bu, R^2= i-Pr, R^3= H

peptides described in the previous section. Using the copper complexes of these Schiff bases (**20a**) as catalysts, Aratani reported asymmetric cyclo-



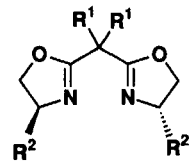
[16]

trans: cis = 93 : 7
94% ee (trans)



[17]

propanation of olefins by diazoacetic acid esters (Eqn [16]). Hayashi and Oguni also utilized the Schiff bases (**20b**) as ligands of a titanium complex for asymmetric cyanosilylation of aldehydes (Eqn [17]).[26,27]

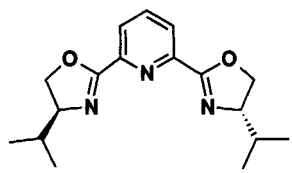


21
(R^1: Me or H
R^2: t-Bu, i-Pr, Ph)

Cu: cyclopropanation

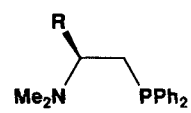
Fe, Mg: Diels-Alder reaction

The chiral amino-alcohols are converted to oxazoline derivatives by treatment with carboxylic acids or their synthetically equivalent compounds. Bisoxazolines (**21**, **22**) which are synthesized form malonic acid or pyridine-2,6-dicarboxylic acid are quite efficient asymmetric

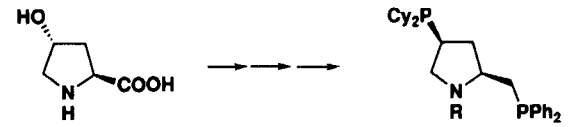


22
Rh: hydrosilylation

catalysts for several reactions, e.g. the copper complex for asymmetric cyclopropanations,[28,29] the magnesium or iron complex for asymmetric Diels–Alder reactions and the rhodium complex for asymmetric hydrosilylation.[31]

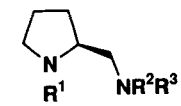


23
(R=i-Pr, i-Bu, t-Bu, ...)
NI: cross coupling



24
(R=CONHPh,COOt-Bu)
Rh: hydrogenation

The hydroxy groups of amino-alcohols are easily substituted by phosphorus groups to lead to aminophosphines (**23**), which can be chiral ligands of nickel for asymmetric cross-coupling reactions.[32] Diphosphine **24** from hydroxyproline is a highly selective ligand in a rhodium complex for asymmetric hydrogenation of olefins.[33–35]



25

Al: reduction (R^1=H, NR^2R^3=NHPh)

Ll: alkylation (R^1=Me, NR^2R^3=N)

Sn: aldol reaction (R^1=Me, NR^2R^3=N)

Diamines are synthesized by the reduction of amino-acid amides. The diamines obtained from proline (**25**) have been employed to modify aluminum hydrides and organolithiums to undergo asymmetric reductions and alkylation reactions.[36–40] Kobayashi and Mukaiyama recently reported catalytic asymmetric aldol reactions using these diamines as ligands of tin(II) compounds.[41–43]

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