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Terpene ligands in the coordination chemistry: synthesis of metal complexes, stereochemistry, catalytic properties and biological activity

Olga A. Zalevskaya, Yana A. Gur'eva, Aleksandr V. Kutchin

Institute of Chemistry of Komi Science Centre of the Ural Branch of the Russian Academy of Sciences, ul. Pervomaiskaya 48, 167000 Syktyvkar, Russian Federation

Published data on the synthesis and catalytic properties of metal complexes with chiral ligands containing a terpene moiety are integrated and systematized. The stereochemical features of transition metal complexes with terpene ligands are discussed. Structures of stable complexes of this type and the initial chiral ligands are presented. In view of the enormous structural diversity of the analyzed data, classification is based on the chemical functionality of terpene ligands. The results of application of terpene ligands in asymmetric transition metal catalysis are considered; the data are classified in terms of the type of chemical reaction. Data on the biological activity of some metal complexes with terpene ligands are presented. The bibliography includes 228 references.

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1. Introduction

The coordination chemistry of transition metals and biologically active ligands is an actively developing field of modern chemistry comprising contributions from asymmetric synthesis, metal complex catalysis, biochemistry, medicinal chemistry and pharmacology. Extensive information on new research in this area appears every year.

Endless possibilities for the design of new metal complexes are determined by the diversity of natural bioligands and semisynthetic derivatives and by the wide range of metals (almost all transition metals of the Periodic Table have been studied). Moreover, there are various types of compounds involving different types of bonds, including polymetallic and mixed-ligand complexes.

Nature is a high-class synthetic chemist creating a variety of chiral substrates with a high degree of stereochemical purity. These compounds are widely demanded by chemists. Blaser [1] cited an interesting analysis of abstracts published by the *Chemical Abstracts* journal between 1984 and 1986 with the key words 'enantioselective synthesis with transition metal catalysts'. It turned out that about two-thirds of the 329 described ligands were derived from natural molecules. The number of such ligands grows exponentially every year. Terpenes, being able to induce chirality, are not at the bottom of this list.

Terpenoids (isoprenoids) are a unique class of natural compounds.[2–4] They possess a wide range of biological action in living nature, the number of known compounds of this class amounts to tens of thousands and their structural diversity is represented by almost all classes of organic compounds. Terpenoids can be easily isolated from renewable plant raw materials as single stereoisomers. All this makes them valuable substrates for the synthesis of numerous new chiral derivatives, including ligands for coordination chemistry.

This review summarizes the key results concerning the synthesis and studying the structure and properties of metal complexes containing polyfunctional derivatives of natural terpenoids as ligands. The geographical area of these studies

O.A.Zalevskaya. Ph.D. (Chemical Sciences), Leading Researcher at the Institute of Chemistry of Komi Science Centre.
E-mail: zalevskayaoa@rambler.ru
Ya.A.Gur'eva. Ph.D. (Chemical Sciences), Researcher at the same Institute.
Telephone: +7(8212)229 – 327, e-mail: gurjeva-ja@chemi.komisc.ru
Current research interests of the authors: transition metal complexes, terpenes, asymmetric catalysis, stereochemistry.
A.V.Kutchin. Corresponding Member of the RAS, Doctor of Chemical Sciences, Professor, Head of a Laboratory at the same Institute.
Telephone: +7(8212)229 – 327, e-mail: kutchin-av@chemi.komisc.ru
Current research interests: stereoselective synthesis, chemistry of natural compounds, medicinal chemistry, stereochemistry.

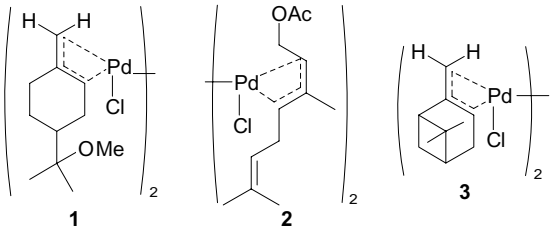
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is rather large covering > 20 countries. Among the main research teams who are actively working in this field, worthy of note are Russian researchers from the A.V.Nikolaev Institute of Inorganic Chemistry (NIIC SB RAS) and I.N.Vorozhtsov Novosibirsk Institute of Organic Chemistry (NIOC SB RAS, Novosibirsk), research teams from Switzerland (von Zelewsky and co-workers.), China (Kwong and co-workers) and Italy (Chelucci and co-workers) and a UK research team headed by Prof. Kocovsky.

The synthesis and characterization of transition metal complexes of terpenes were reported for the first time by Dunne and McOuillin in 1970.[5–7] The authors investigated the reactions of some monoterpenoids (*cis*- and *trans*-ocimenes, myrcene, linalyl acetate, nerolidyl acetate, limonene, pinene) with sodium tetrachloropalladate. They detected the formation of stable π-allyl complexes **1** – **3** and their analogues which they considered to be precursors of chemical transformations of the polyenes of interest. The complexes were isolated in a pure state. The results of these studies convincingly prove the important role of transition metal catalysts for isomerization, dimerization and cyclization of polyenes.

Structures 1 – 3



1 **2** **3**

The scope of this review does not include methods and details of the synthesis of terpene ligands. This information, valuable for synthetic chemists and available from most of the cited original publications, will be the subject of a separate discussion.

The following abbreviations are used:

AA — ascorbic acid
acac — acetylacetonate,
BQ — 1,4-benzoquinone,
BINAP — 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl,
Boc — *tert*-butoxycarbonyl,
BSA — *N*,*O*-bis(trimethylsilyl)acetamide,
CHP — cumene hydroperoxide,
cod — cycloocta-1,5-diene,
CPC — cyclopalladated complexes
dba — dibenzylideneacetone,
DPPH — 2,2-diphenyl-1-picrylhydrazyl,
de — diastereomeric excess,
ee — enantiomeric excess,
EDA — ethylenediamine.
IC_{50} — half-maximal inhibitory concentration,
LDA — lithium diisopropylamide,
Naph — naphthyl,
nbd — norbornadiene,
OTf — trifluoromethanesulfonate (triflate),
p-cymene — 1-isopropyl-4-methylbenzene,
rt — room temperature,
Ts — *p*-toluenesulfonyl (tosyl)

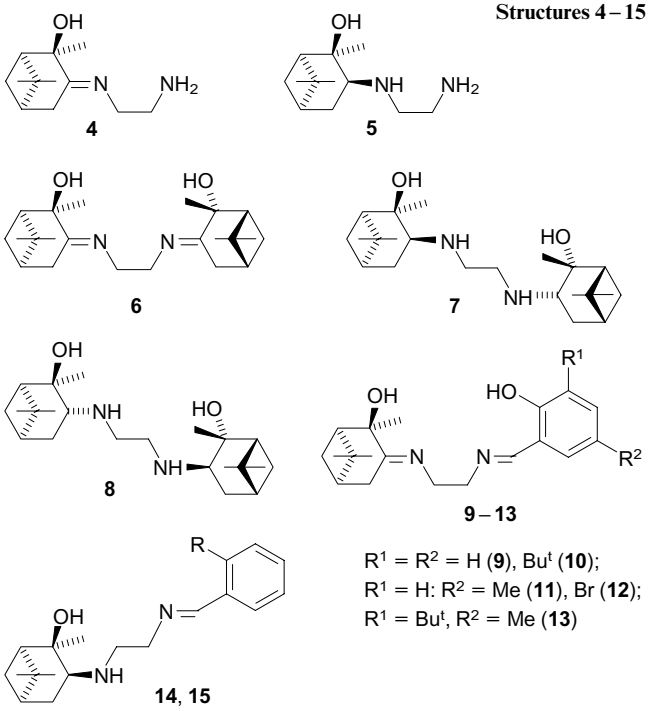
2. Synthesis of metal complexes with terpene ligands

2.1. Polydentate terpene ligands based on 1,2-diamines

It is known that ethylenediamine (EDA) derivatives are successfully used as ligands for the synthesis of metal chelates, which have a broad range of applicability. The preparation of terpene derivatives of EDA is described in several publications.[8–16] Since 2004, pinane and bornane derivatives of ethylenediamine belonging to the classes of imines, amines or polyfunctional compounds have been synthesized at the Institute of Chemistry, Komi Scientific Centre, Ural Branch of the RAS. Pinane ligands **4** – **29** were prepared starting from (−)-α-pinene (or its enantiomer), which was oxidized to give (+)-2-hydroxypinan-3-one and (−)-myrtenal. The condensation of these carbonyl derivatives with ethylenediamine afforded the corresponding mono- [structures **4** (Ref. 14) and **25** (Ref. 15)] and diimines [structures **6** (Ref. 14) and **27** (Ref. 15)]. The bifunctional nature of EDA makes it possible to introduce a certain additional structural moiety into the ligand to obtain unsymmetrical diimines **9**,[14] **10**[16] and **11** – **13**.[13] The reduction of the imines to amines doubles the number of synthesized ligands (see structures **5**, **7**, **8**, **14** – **16**, **19** – **24**,[13] **17**, **18**,[16] **26**, **28** and **29**).[15] Bornane derivatives of EDA **30** – **33** were obtained from (−)-3-bromocamphor.[10,12] The cited publications are also of interest for fine organic synthesis. Single stereoisomers of EDA terpene derivatives were isolated and characterized; the complexing behaviour of these compounds is considered below.

Ligands **9**, **10**, **17** and **33** containing a phenolic group can be classified as salen type N,N,O-tridentate ligands. They were shown[9,11,12] to behave in different ways under comparable complexation conditions (Li_2PdCl_4, MeOH, 1 : 1 molar ratio). Diimines **9**, **10** and **33** form bicyclic complexes **34** – **36** in which the starting ligand is

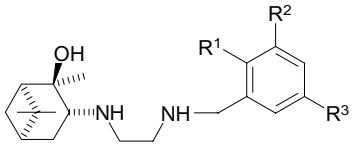
Structures 4 – 15



$R^1 = R^2 = H$ (**9**), Bu^t (**10**);
$R^1 = H$: $R^2 = Me$ (**11**), Br (**12**);
$R^1 = Bu^t$, $R^2 = Me$ (**13**)

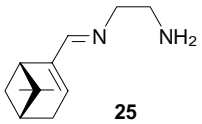
R = OH (**14**), H (**15**)

Structures 16 – 36

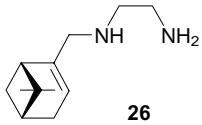


16 – 24

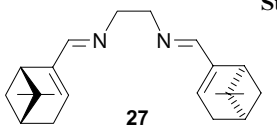
$R^1 = R^2 = R^3 = H$ (**16**);
$R^1 = OH$: $R^2 = R^3 = H$ (**17**), Bu^t (**18**);
$R^2 = H$, $R^3 = Me$ (**19**);
$R^2 = H$, $R^3 = Br$ (**20**);
$R^2 = Bu^n$, $R^3 = Me$ (**21**);
$R^2 =$ , $R^3 = Me$ (**22**);
$R^2 =$ , $R^3 = Me$ (**23**);
$R^2 =$ , $R^3 = Me$ (**24**)



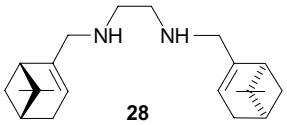
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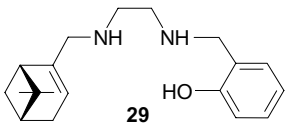
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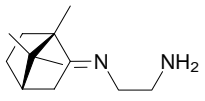
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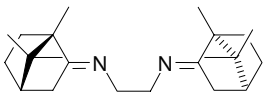
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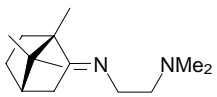
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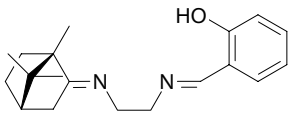
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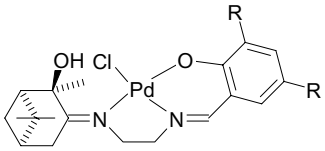
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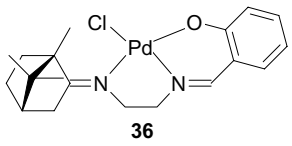
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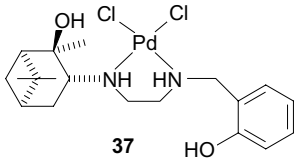


34, **35** [R = H (**34**), Bu^t (**35**)]

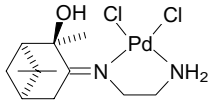


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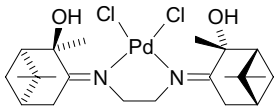
Structures 37 – 49



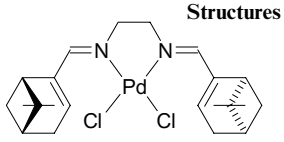
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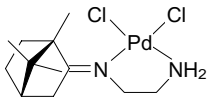
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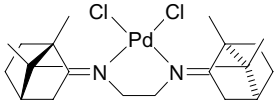
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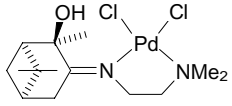
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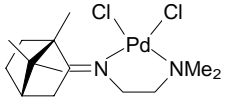
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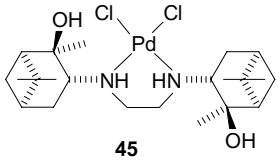
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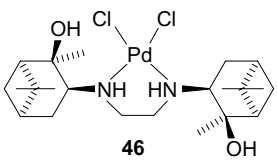
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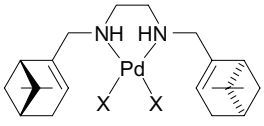
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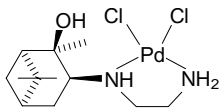


46



47, **48**

X = Cl (**47**), Br (**48**)



49

coordinated to the palladium cation *via* the imine nitrogen atoms and the phenolic hydroxy group. The structures of complexes **34** and **36** were confirmed by X-ray diffraction: the central atom has the expected distorted square planar configuration and the organic ligand forms two chelate rings. The six-membered ring is planar within 0.07 Å, while the five-membered ring has an envelope conformation. Unlike diimines, the corresponding diamine ligand **17** forms only one metal ring (**37**), while the phenolic hydroxy group is not involved in additional chelation. Several palladium chelate complexes of this type, compounds **38**, **39**,[11] **40**,[8] **41**, **42**,[12] **43** and **44**,[10] were prepared using terpene derivatives of EDA.

A peculiar behaviour is inherent in diamine ligands **5**, **7**, **8** and **28**. Complexation with these ligands locks the configuration of nitrogen, thus giving rise to two additional chiral N-donor centres. Detailed analysis of ^{1}H NMR and ^{13}C NMR spectra of complexes **45** – **49** demonstrated[8, 11] that chelation is highly stereoselective and affords single diastereomers.

Ethylenediamine terpene derivatives **5**, **7**, **8** and **11** – **24** were studied[13] as chiral ligands in the asymmetric nitroaldol condensation. The results of catalytic experiments are presented below (see Section 3.5). (More information about polydentate terpene ligands based on 1,2-diamines can be found in Sections 3.9, 3.12 and 4 of the review.)

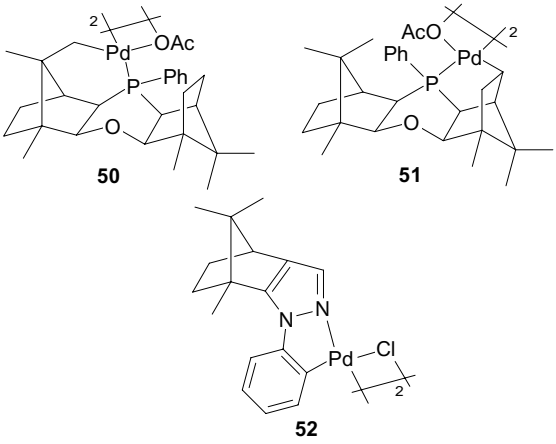
2.2. Cyclopalladated terpene ligands

A special group is comprised of cyclopalladated complexes (CPC) containing an activated metal – carbon bond. Unlike other organometallic compounds, CPC are synthesized rather easily and have high thermal, oxidative and hydrolytic stability. Quite a few CPC of various types were prepared and described to date.[17 – 20] It is known[21, 22] that chiral palladacycles are used rather actively in asymmetric synthesis and catalysis. A variety of derivatives of natural terpenoids have been studied as ligands for the preparation

of chiral CPC. A popular starting terpenoid is camphor, which is due, first of all, to its easy availability from renewable raw material.

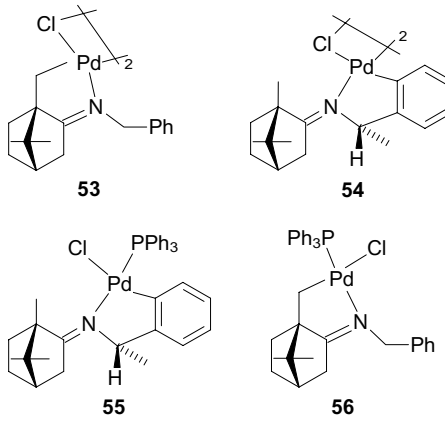
In 1983, Constable *et al.*[23] described an attempt to cyclopalladate D-camphor, resulting in the formation of a complex with only monodentate ligand coordination. The first products[24] of successful cyclopalladation of D-camphor derivatives are structures **50** and **51**, in which metallation involves the terpene moiety, and complex **52**, resulting from classical *ortho*-palladation into the aromatic ring of the substituent.[25]

Structures 50 – 52



Cyclopalladation of D-camphor derivatives at the methyl group in position 1 was first performed by our research team. The results were reported in our publications.[26,27] A study of the selectivity of palladium acetate-catalyzed cyclopalladation of α-substituted camphor benzylimines showed that the cyclometallation pathway appreciably depends on the structural features of the ligand. Only in the case of unsubstituted camphor benzylimine, was cyclometallation of the bornane moiety directed towards the 1-methyl group (structure **53**), whereas camphor α-methylbenzylimine formed *ortho*-palladated complex **54**. The structure of **53** was confirmed by X-ray diffraction.[27] Binuclear complexes of this type are known to undergo chloride bridge opening under the action of an additional ligand to give new mixed-ligand complexes. This approach was used to prepare coordination compounds **55** and **56**.

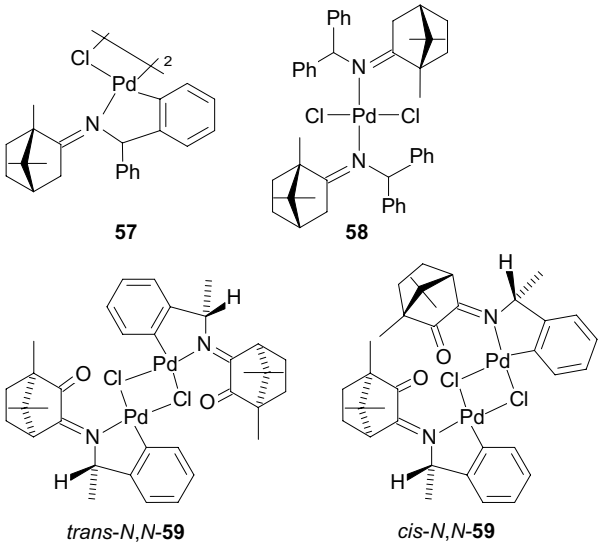
Structures 53 – 56



The α-phenyl-substituted derivative is cyclopalladated at the aromatic ring under the same conditions to be converted to compound **57**.[28] The outcome of the reaction depends considerably on the nature of the palladating agent: cyclometallation takes place with palladium acetate, while in the case of lithium tetrachloropalladate, complex **58** with monodentate ligand coordination is formed. The same trend was noted for other related ligands.

Interesting stereochemical results were obtained[28,29] in studies of the cyclopalladation of 2,3-camphorquinone benzylimines. The *ortho*-palladation of camphorquinone α-methylbenzylimine affords a mixture of geometric isomers — *trans*-*N*,*N*-**59** and *cis*-*N*,*N*-**59**.[28]

Structures 57 – 59

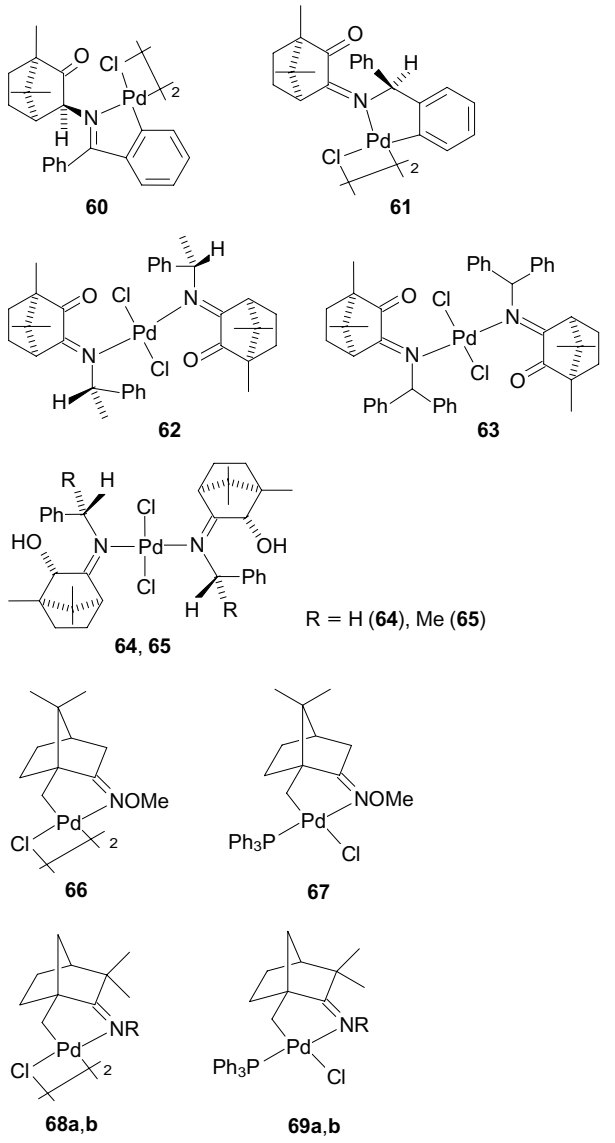


The cyclopalladation of α-phenylbenzylimine of 2,3-camphorquinone takes place only in the reaction with palladium acetate.[29] This gives two isomeric binuclear palladacycles and involves isomerization of the initial ligand. The formation of complex **60** is accompanied by structural rearrangement of the imine, while for compound **61**, the C=N bond configuration changes. In both cases, the diastereoselective formation of a new chiral centre takes place. The structure of CPC **61** was confirmed by X-ray diffraction. The bornane palladacycle **61** was tested[30] as a catalyst in asymmetric reactions of carbon – carbon bond formation. The hydroarylation of norbornene in the presence of this catalyst gave the product in a quantitative yield (90% – 97%), but with low asymmetric induction.

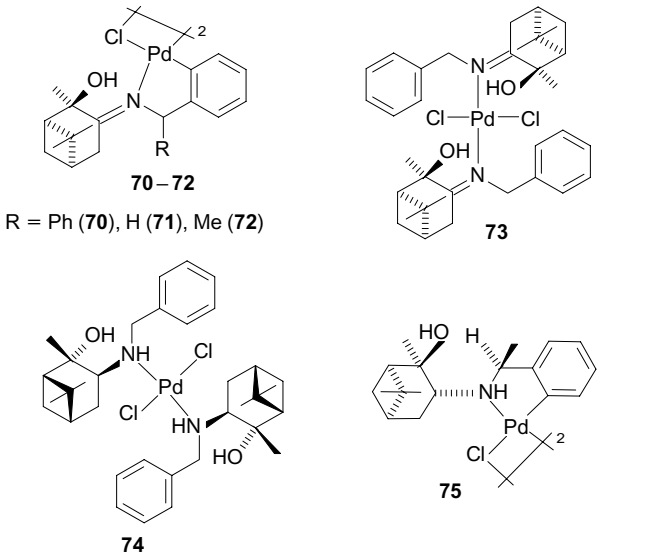
In the reaction of bornane benzylimine ligands with lithium tetrachloropalladate, no cyclopalladation takes place; instead, complexes **62** and **63** with monodentate ligand coordination are formed.[29] The structure of complex **62** was established by X-ray diffraction. However, 2β-hydroxybornan-3-one benzylimines could not be subjected to cyclopalladation, only complexes **64** and **65** being isolated in 58% and 64% yields, respectively.[28]

The successful results of cyclopalladation of bornane oximes giving a bond between the palladium atom and a saturated carbon atom of the terpene ring were reported by Smolyakova and co-workers.[31,32] The authors obtained the CPC of D-camphor methoxime and L-fenchone oxime and methoxime (structures **66** – **69**); the structures of compounds

Structures 60 – 69



Structures 70 – 75



67 and **68a**,**b** were confirmed by X-ray diffraction. The carbon centre activation can be used for chemical modification of the initial terpenoid.

Among the CPC involving a series of pinane ligands,[28, 33 – 35] note 2α-hydroxypinan-3-one benzylimines and palladacycles **70** – **72** based on them.[28] It was shown that pinane derivatives are cyclopalladated under milder conditions than the corresponding bornane ligands. Under the action of lithium tetrachloropalladate in the presence of a base, the reaction is directed towards the aromatic ring and gives CPC **70** – **72**. As in most cases, a complex with monodentate ligand coordination (*e.g.*, compound **73**) was obtained as a second reaction product.[26 – 29, 34 – 36] In some cases, these complexes are the only reaction products. For example, 3-benzylamino-2α-hydroxypinane forms only complex **74** under the reaction conditions, whereas the presence of an additional methyl group in the benzylic position favours the formation of palladacycle **75**.[34]

2.3 Terpenoid oximes and their polyfunctional derivatives

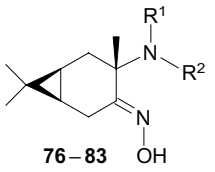
Polyfunctional oximes based on natural terpenoids are actively investigated by inter-institutional team comprising researchers from NIIC SB RAS and NIOC SB RAS and headed by S.V.Larionov and A.V.Tkachev. The reviews[37, 38] published in 2004 and 2012 summarize their results on the synthesis, structures and properties of chiral complexes of transition metals with several groups of hybrid ligands based on monoterpene hydrocarbons: α-pinene, 3-carene, limonene and caryophyllene (a sesquiterpene). One of the attractive reactions that can be used to introduce N-donor groups into a terpene molecule is nitrosochlorination, that is, the addition of NOCl to the C=C bond. This synthetic approach enabled the preparation of various chiral terpene ligands. Among them, three main groups can be distinguished: monoximes **76** – **91**, bisoximes **92** – **107** and macrocyclic derivatives **108** and **109**.

The review of Larionov[38] published in 2012 considers 32 new ligands and 79 transition metal complexes based on them. The compounds include Cu^{II}, Zn^{II}, Ni^{II}, Co^{II}, Pd^{II} and Pt^{II} complexes; the structures of 18 compounds were confirmed by X-ray diffraction. The magnetic properties of the obtained metal complexes were discussed; this allowed the authors to draw conclusions about the electronic state of the coordination centre. The studies along this line are in progress.[39 – 51]

Special mention should be made of a group of chiral palladium complexes that are of interest for their potential catalytic activity. The nature of the complexing metal strongly affects the structure of complexes. Palladium retains the ability to form a square planar environment and chelate rings of the same type with all of the studied ligands, in particular, with a PdN_2Cl_2 coordination unit for N,N-donor ligands **79**,[47] **80**,[41] **85**,[47] **87**,[39] **88**,[39] **92**,[52] **95**,[53] **96**,[48] **101**,[53] **104**,[54] **105**,[54] **106**,[53] **107** (Ref. 48) and with a $PdNSCl_2$ unit for N,S-donor ligands **84**,[55] **97**,[52] **98**,[46] **102**, **103**.[56] The complexes are diamagnetic, which is indicative of a low-spin configuration of the d^8-metal.

As examples, consider typical mononuclear complexes **110** and **111**.[47] An important stereochemical feature of α-amino oxime complexes containing a secondary amino

Structures 76 – 109

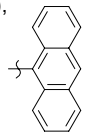


76 – 83

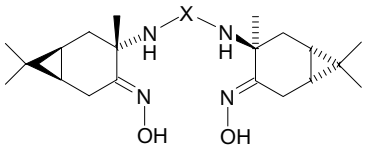
$R^1 = R^2 = Me$ (**76**);
$R^1 = H$: $R^2 = OH$ (**77**);
$(CH_2)_3NH_2$ (**78**),



(**79**),

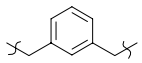


(**80**),
$CH(Bn)CO_2Me$ (**81**),
CH_2CO_2Na (**82**),
$CH(Ph)CO_2Me$ (**83**)

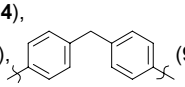


92 – 96

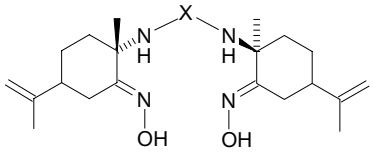
X = $(CH_2)_2$ (**92**), $(CH_2)_3$ (**93**),
$(CH_2)_2NH(CH_2)_2$ (**94**),



(**95**),

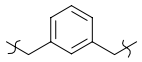


(**96**)

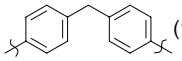


104 – 107

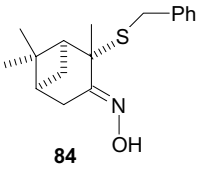
X = $(CH_2)_2$ (**104**), $(CH_2)_3$ (**105**),



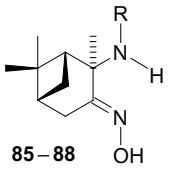
(**106**),



(**107**)

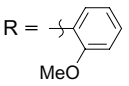


84

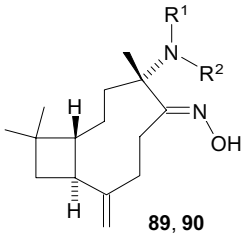


85 – 88

R =

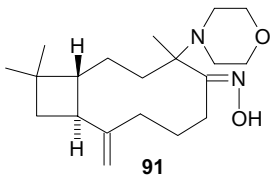


(**85**),
CH_2CO_2Na (**86**),
$(CH_2)_2CO_2H$ (**87**),
$(CH_2)_2CO_2Et$ (**88**)

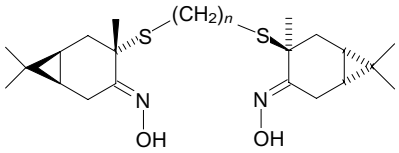


89, **90**

$R^1 = R^2 = Me$ (**89**);
$R^1 = H$, $R^2 = Bu^t$ (**90**)

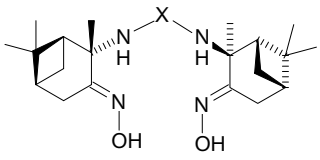


91



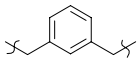
97, **98**

n = 2 (**97**), 3 (**98**)

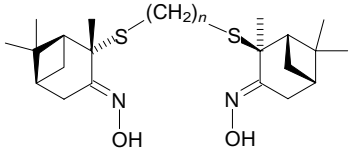


99 – 101

X = $(CH_2)_2$ (**99**), $(CH_2)_3$ (**100**),

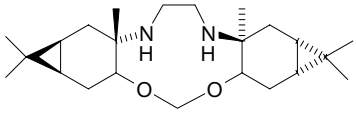


(**101**)

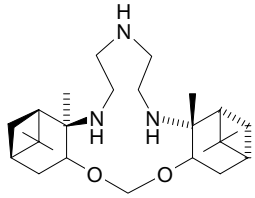


102, **103**

n = 2 (**102**), 3 (**103**)

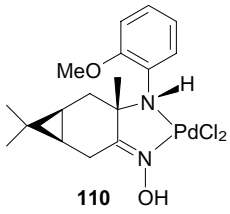


108

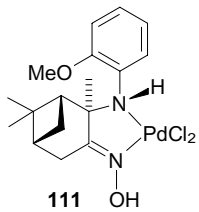


109

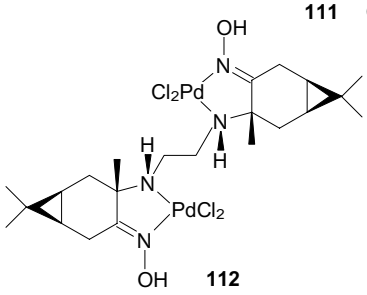
Structures 110 – 112



110



111



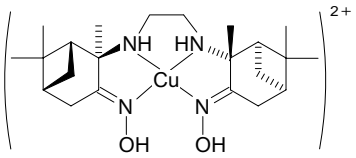
112

group is that coordination gives rise to a chiral N-donor centre and, hence, enables the formation of diastereomers. However, in most cases, a single diastereomer can be isolated in the crystalline state, which is confirmed by X-ray diffraction data. This is also typical of binuclear palladium complexes, for example, compound **112**.[52] This stereoselective complexation and the presence of a chiral centre directly bound to the metal enhance the value of these ligands for their potential application in the asymmetric transition metal catalysis.

Copper is an important metal in nature, as it is present in some enzymes. Copper complexes obtained from the above terpene mono(α-amino oximes) (**76**,[57] **78**,[58] **81**,[40] **82**,[44] **83**,[44] **86**,[40] **89**,[59] **90**,[59] **91**[60]), bis(α-amino oximes) (**92**,[61] **96**,[48] **99**,[62] **100**,[62] **105**,[63] **107**[48]) and their sulfur analogues (**84**,[55] **97**,[64] **102**,[56] **103**[56]) are of interest for bioorganic chemistry. In addition, they participate in numerous copper-catalyzed reactions (see Section 3). The composition and structure of copper complexes, unlike those of palladium compounds, are highly dependent on

the ligand type and preparation conditions. For example, in the case of bis(α-amino oximes) **92**,[61] **99**,[62] **100**,[62] **105** (Ref. 63) and **108**,[65] ionic paramagnetic copper complexes with a CuN_4 coordination unit are formed [*e.g.*, structure **113** (Ref. 62)].

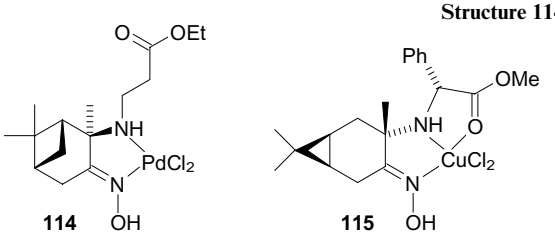
Structure 113



113

A new line of research pursued by Novosibirsk scientists is related to the synthesis of metal complexes based on terpene ligands **81** – **83** and **86** – **88** containing amino acid moieties.[39, 40, 44, 66] Unlike palladium complex **114**,[39] in the case of copper(II) complexes, the amino acid substituent is involved in the formation of an additional chelate ring, for example, in structure **115**.[44]

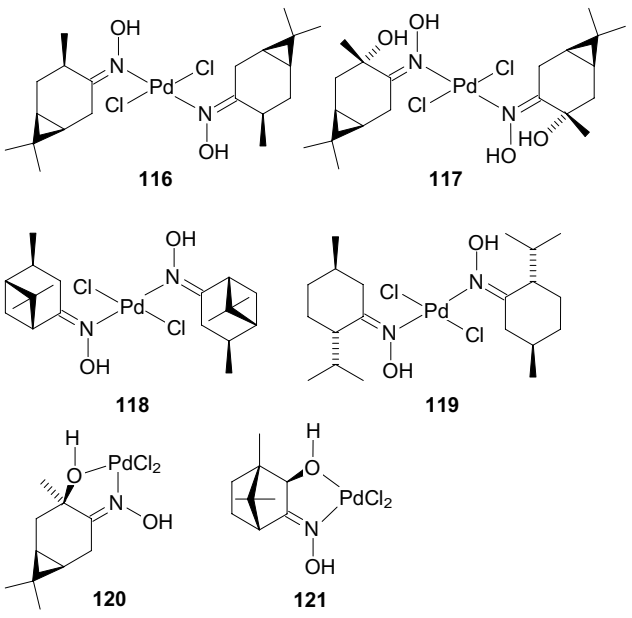
Structure 114, 115



114 **115**

Palladium complexes based on oximes of (−)-*cis*-caran-4-one, (+)-3α- and 3β-hydroxycaran-4-ones, (+)-*cis*-verbanone, (−)-menthone and (+)-2β-hydroxybornan-3-one were synthesized, with our participation.[67] The oximes were obtained by direct condensation of terpene ketones with hydroxylamine hydrochloride; the yields of single stereoisomers were 70% – 94%. The reactions of these ligands with lithium tetrachloropalladate in methanol result in the formation of stable complex compounds of various types: complexes containing monodentate ligands in the *trans*-configuration (**116** – **119**) and chelates (**120**, **121**). The structure of complex **120** was confirmed by X-ray diffraction. It is noteworthy that the formation of chelate **120** is accompanied by a change in the C=N bond configuration with respect to that in the initial ligand.

Structures 116 – 121

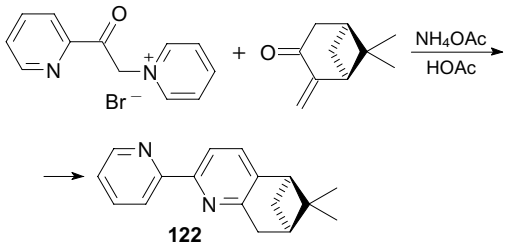


116 **117** **118** **119** **120** **121**

2.4. Terpene-pyridine ligands

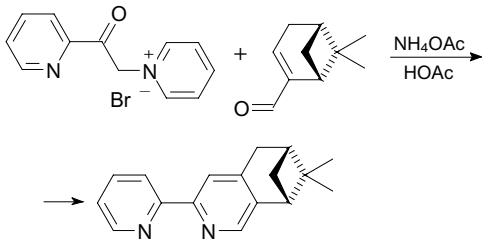
Pyridine derivatives are successfully utilized as building blocks for the design of N-donor ligands. Terpenoids are used for effective introduction of a chiral moiety into the molecule. Since 1992, research along this line has been actively carried out under supervision of Prof. von Zelewsky at the Institute of Inorganic Chemistry, University of Fribourg (Switzerland).[68, 69] Among the prepared bipyridine ligands, note compounds **122**, **123** and dimer **124** containing a pinane moiety. The introduction of chiral terpene groups into the bipyridine molecule was accomplished *via* annulation (Kröhnke condensation) using bicyclic monoterpenes, in particular, β- and α-pinene derivatives (Schemes 1 and 2). This gave 5,6- and 4,5-pinanepyridines **122** and **123**. Owing to high acidity of the CH_2 group of the terpene moiety and proton diastereotopicity, they can be converted to an endless number of derivatives, including dimers (*e.g.*, compound **124** in Scheme 3). The substitution reaction is stereoselective and gives a chiral bridge and, correspondingly, a single stereoisomer.

Scheme 1



122

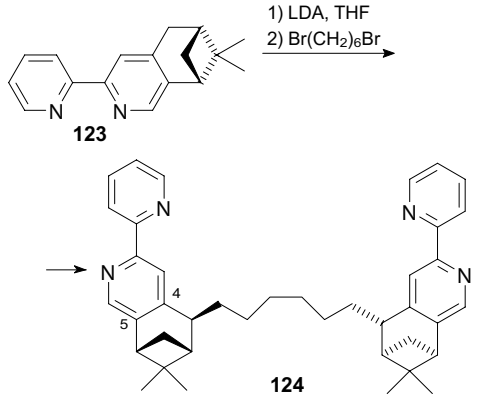
Scheme 2



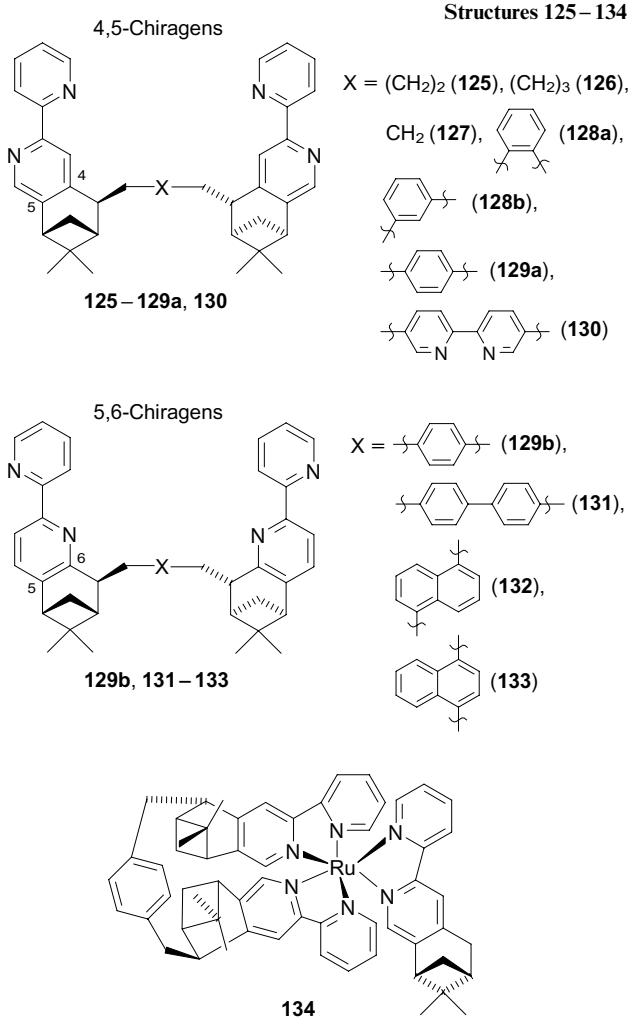
123

The interest in these tetradentate ligands is due to their diastereoselective self-assembly taking place during complexation to give a new helical chiral state. A number of studies[68 – 75] report the synthesis of tetradentate ligands **124** – **133**, which were called chiragens (from chirality generators). For example, ligand **124** is 4,5-chiragen[6], where digit 6 means the number of methylene units in the bridge. These compounds are composed of terpene bipyridine moieties linked by a chiral bridge. This bridge can be of variable length and can contain both aliphatic chains (compounds **125**,[71] **126**[71] and **127**[72]) and aromatic rings (**128a**,[70, 71] **128b**,[70, 71, 74] **129a**,[70, 71] **129b**,[74, 75] **130**,[70, 72]

Scheme 3



Structures 125 – 134

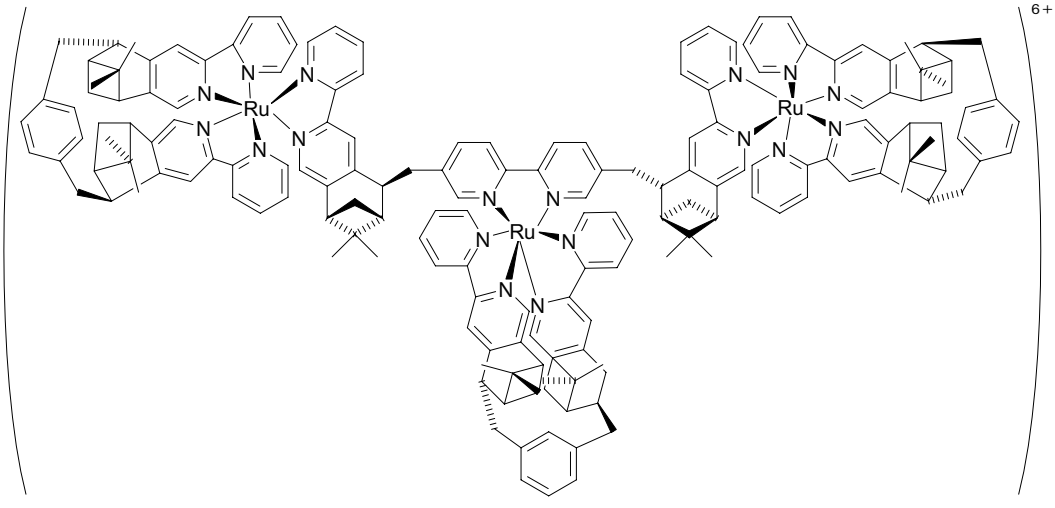


131,[75] **132**,[74, 75] **133**[74, 75]). The authors perceive such a ligand as a chiral basketball basket and a metal ion as a ball getting into the basket. A unique feature of these ligands is that the complexation is stereospecific: in particular, octahedral Ru^{II} complexes are formed as single enantiomers, most often, with Δ-configuration. Compound **134**, the structure of which was determined by X-ray diffraction, can be considered as an example of this type of complexes with topological chirality.[71]

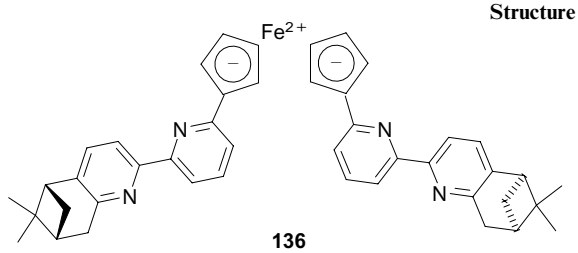
In the subsequent publications of this research team, the authors developed a strategy for the preparation of chiral transition metal complexes of the mentioned type with a predictable topology. According to reviews[76, 77] that summarize the interim results, about two hundred chiragen type pyridine and polypyridine ligands were synthesized. The stereochemistry of their complexation with metals, Ru^{II}, Cu^{I}, Ag^{I}, Cd^{II}, Zn^{II}, Fe^{II}, Co^{II} and Ni^{II}, was studied. The researchers revealed unique possibilities of stereospecific coordination of these ligands to give structures with a predictable configuration and various types of chirality. For example, trinuclear complex **135** was obtained from enantiomerically pure chiragen ligands.[72] The authors called these systems metallosupramolecular architectures capable of stereoselective self-assembly.

As noted above, chiragen type polypyridine ligands may assume a helical shape upon coordination to metal cations. In this case, the terpene moiety acts as a stereogenic unit determining the helix configuration (*P* or *M*). Von Zelewsky and co-workers[73] reported the synthesis and characterization of chiragen ligands with a ferrocene bridge (*e.g.*, compound **136**), which form a double helix upon interaction with metal cations such as Cu^{I}, Ag^{I} and Zn^{II}. The binuclear complexes $[Cu_2(\mathbf{136})_2](PF_6)_2$, $[Ag_2(\mathbf{136})_2](PF_6)_2$ and $[Zn_2(\mathbf{136})_2](PF_6)_4$ were prepared with this ligand. The struc-

Structure 135



Structure 136



136

tures of the first two mentioned compounds were confirmed by X-ray diffraction. For all complexes, the same type of organization was found: two metal atoms were located on the helix axis, while ferrocene units linked the upper and lower parts of the structure.

One more study of this research team [74] deals with the ability of chiragen ligands to chiral self-recognition during the formation of metal complexes with a definite helicity. They prepared a series of enantiomerically pure bipyridine ligands with an aromatic bridge, in particular, single enantiomers (+)-**129b** and (−)-**129b** and their hexanuclear Cu complexes. High stereoselectivity of complex formation involving these compounds was noted: for example, upon the reaction with Cu^{I}, enantiomer (−)-**129b** formed a homochiral circularly closed hexanuclear *P*-helix. When a racemic mixture of compounds (+)-**129b** and (−)-**129b** was used, a racemic mixture of *P*- and *M*-helical forms was obtained, indicating a 100% chiral self-recognition of enantiomers (Scheme 4). In the case of *meso*-form **129b**, the stereochemical outcome of the complex formation was completely different: oligomeric mixed complexes were generated. The self-assembly patterns of the chiragen metallosupramolecular systems identified by the authors make it possible to compare these systems with biochemical chiral recognition processes in living nature.

Scheme 4

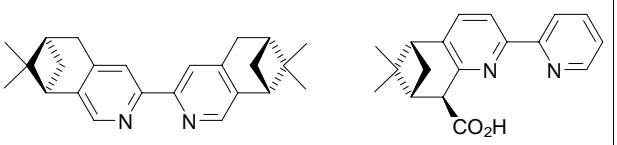
(+)-**129b** + (−)-**129b** $\xrightarrow{Cu^{+}}$

$\longrightarrow$ (*M*)-[Cu_6((+)-**129b**$)_6$]$(PF_6)_6$ + (*P*)-[Cu_6(−)-**129b**$](PF_6)_6$

Chiragen type pinane ligands have been reported in two papers.[75, 78] Quite recently, the synthesis of new bis(bidentate) ligands **131** and **133** was described.[75] The stereochemistry of their complexation with Ag^{I} was studied and compared with previously obtained data [74] for ligands **132** and **129b**, which differ in the bridge structure. The results of these studies confirmed that the nature of the bridge (the length, the type of substitution and the bulk) dictates the architecture of the whole ensemble. For example, ligand **131** with a biphenyl bridge forms, in solution, single discrete silver complexes with a circularly closed helix, whereas ligand **129** with one aromatic ring in the bridge gives a mixture of two helical polynuclear species. Compound **132** with a more bulky naphthyl bridge forms polymer-organized helices under these conditions.

Bipyridine ligands **137** and **138** show a specific behaviour. When they are complexed with transition metals, a helical architecture is also formed, with two possible configurations of the coordination unit, Δ and Λ, respectively. Bipyridine pinane ligand (−)-**137** was used to study [79] the diastereoselectivity of formation of tris(diimine) complexes of a number of transition metals (Fe^{II}, Ru^{II}, Os^{II}, Zn^{II}, Cd^{II}, Cu^{II}, Ni^{II}). It was shown that the nature of the metal determines the topology of the coordination unit. However, the diastereoselectivity of this complex formation was very low. For example, Fe^{II}, Ru^{II} and Os^{II} tris(bipyridine) complexes were formed as racemic mixtures, which proved to be separable. A study of the lability of the obtained optically active complexes in solutions under various conditions demonstrated that Δ-isomers are thermodynamically more preferable in all cases, except for Ru^{II} and Os^{II} compounds.

Structures 137, 138

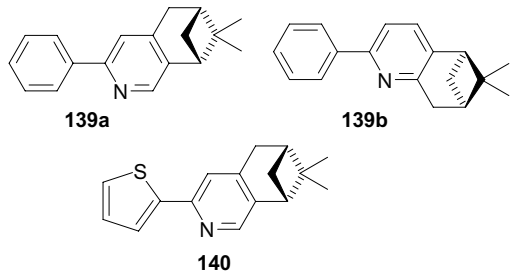


(−)-**137** (+)-**138**

A series of publications [80–83] describe the coordination of metals to carboxyterpene bipyridine derivative **138**. Trivalent lanthanides, La, Pr, Nd, Sm, Eu, Gd and Tb, were chosen as complexing metals. It was found that the architecture of the resulting complex considerably depends on the nature of the solvent. The self-assembly of the complex is diastereoselective: each metal ion has a helical environment composed of two N,N,O-tridentate ligands. The helix direction (left- or right-handed) is determined by the configuration of the terpene moiety of the starting ligand.

Using terpene-containing pyridine ligands,[84, 85] various chiral metal complexes, including cyclometallated iridium complexes, were prepared. Aryl-substituted terpenopyridines **139a**,**b**, **140** served as the starting compounds. The composition and structure of Ir^{III} complexes considerably depended on the structural position of the terpene moiety. In the case of 4,5-annulated derivative **139a** and its thiophene analogue **140**, tetranuclear complexes were formed, with a HEXOL type inner core, $[Ir(IrCl_2)_3]^{6+}$, surrounded by six chiral bidentate cyclometallated ligands.[84] Pyridine ligand **139b** containing a 5,6-terpene moiety, which provides a more sterically crowded coordination unit, formed the binuclear complex $[Ir(\mathbf{139b})_2(\mu\text{-}Cl)]_2$. In this complex, two cyclometallated moieties are connected by chloride bridges.[85] The luminescent properties of the obtained complexes were studied.

Structures 139, 140

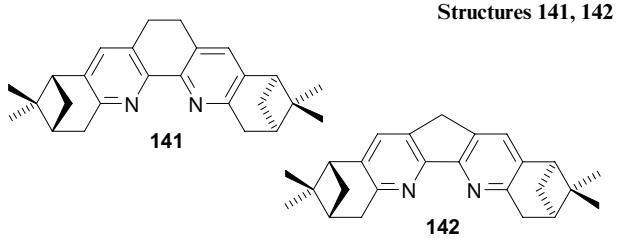


139a **139b**

140

Ligands **141**, **142** can be considered as bipyridine analogues, with their structure being locked by an additional methylene bridge. A group of Novosibirsk researchers [45, 50] synthesized and studied terpene-containing ligands of this type and prepared Zn^{II} and Cd^{II} complexes based on them. For both ligands, zinc formed mononulear complexes

Structures 141, 142



141 **142**

[Zn(**141** or **142**)Cl_2]. Cadmium compounds were chloride-bridged dimers or coordination polymers [Cd(**141** or **142**)$Cl_2]_n$.

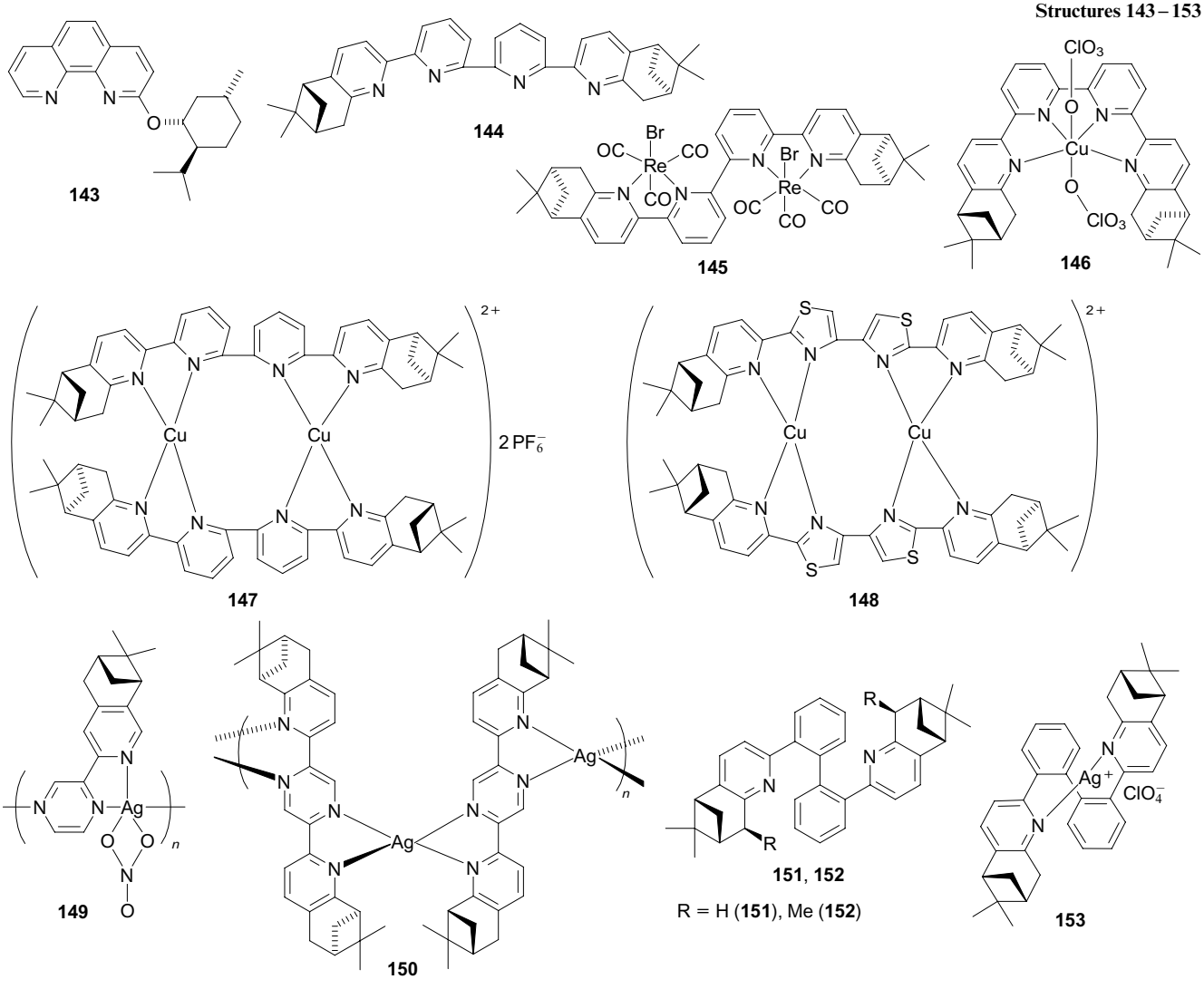
Larionov *et al.*[49] described the synthesis of ligand **143**, in which the menthane moiety inducing the chirality was introduced as a substituent into the phenanthroline ring. This ligand was utilized to prepare complexes of a number of trivalent lanthanides (Eu, Gd, Tb, Dy). All mononulear complexes with phenanthroline ligand **143** obtained by the authors had the composition [Ln(**143**)$_2$$(NO_3)_3$]; the Ln^{3+} coordination number in these compounds was 10. Hence, the metal was surrounded by two bidentate N,N-donor ligands and three bidentate chelating nitrate groups. Studying magnetic and photoluminescent properties of these complexes showed that the Eu^{III} complex has a long photoluminescence time (>1750 μs) and a very high quantum yield ($\varphi_f = 0.87$), which makes these compounds promising materials for optoelectronics.

Stereoselective formation of polynuclear metal complexes with a helical structure was studied by Kwong and co-workers.[86–89] They prepared a series of tetrapyridine ligands containing a chiral pinane moiety, in particular, compound **144**[86,87] and its structural analogues. It was shown that depending on the nature of the complexing metal, complexes of different geometry are formed with these ligands. Rhenium complexes [*e.g.*, compound **145** (Ref. 87)] are binuclear; they form a single helix as a mixture of two diastereomeric forms (*M* and *P*), which were separated by crystallization.

Yeung *et al.*[86] described copper complexes with analogous tetrapyridine ligands. Copper(II) forms a planar complex **146**, while copper(I) complex **147** is binuclear and exists as a double helix with different degrees of diastereoselectivity (52% – 99%), predominantly with *M* configuration. Copper(I) complex **148** of the same type is formed by the pyridinethiazole ligand.[88] It should be noted that the replacement of two pyridine rings by thiazole rings leads to the opposite stereochemical outcome: double *P*-helix is obtained in this case.

Attention is attracted by the diversity of types of ligands and, therefore, architectures of the resulting metal complexes reported by Chinese researchers.[89–91] The silver

Structures 143 – 153



143 **144** **145** **146**

147 **148**

149 **150**

151, **152**

R = H (**151**), Me (**152**)

153

coordination polymers **149** and **150** were prepared from pyridine-pyrazine ligands containing a pinane moiety.[91] In the latter case, stereoregular polymer **150** is formed, since a silver ion has a chiral tetrahedral environment with a certain alternation pattern of Λ- and Δ-configurations of Ag^{I}.

Axially chiral dipyridine ligands **151** and **152** were studied by the same Chinese research team.[90] These ligands tend to form two conformations (stereodescriptors *R* and *S*), which occur in equilibrium. The reactions with silver(I) or copper(I) ions lock the configuration. Planar chiral mononulear complexes [Ag(**151**)ClO_4] (**153**), [Ag(**152**)ClO_4], [Cu(**151**)I] and [Cu(**152**)I] were obtained. In all cases, mixtures of diastereomers were formed in which *S* isomer predominated.

Terpene-pyridine ligands are actively used in asymmetric transition metal catalysis (see Section 3). Additional numerous examples of ligands of this type and metal complexes based on them are presented below.

3. Terpene ligands in asymmetric transition metal catalysis

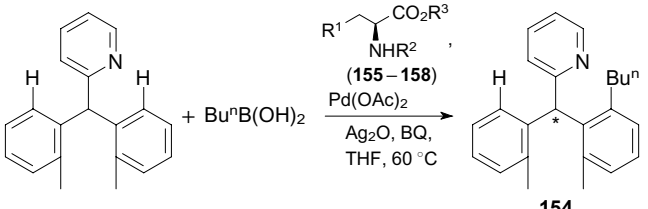
Asymmetric catalysis is a unique tool used to synthesize products with high enantiomeric purity. Natural compounds, including terpenoids and their semi-synthetic derivatives, are successfully used as chiral components of catalytic systems. The advances of asymmetric catalysis by metal complexes are reflected in numerous publications on this subject; furthermore, review publications appear every year. The range of studied reactions includes quite a number of transformations. In this Section, we analyze the results of studies of terpene-based ligands in the enantioselective catalysis of various types of reactions. Several international research groups are actively working along this line. An extensive review of Kwong *et al.*[92] summarizes the results of studies of chiral pyridine ligands (including terpene – pyridine ones) in asymmetric synthesis. Several more studies also address this subject.[93 – 96]

3.1. Cross-coupling reactions

Cross-coupling reactions have a special synthetic value, because they give new carbon – carbon bonds and form the basis of organic molecules. A review of Shi *et al.*[97] summarizes the latest achievements in the enantioselective C – H activation using the Suzuki and Mizoroki – Heck reactions as examples and focusing on the structural characteristic of the chiral ligands, among which terpene compounds were also present.

Shi *et al.*[98] employed natural amino acid derivatives containing an additional chiral menthyl block for chiral induction. In relation to asymmetric palladium-catalyzed alkylation (Scheme 5), an unusual influence of the structure of the chiral ligand on the yield and enantiomeric purity of product **154** was revealed (Table 1). This influence was

Scheme 5



BQ is 1,4-benzoquinone, Boc is *tert*-butoxycarbonyl

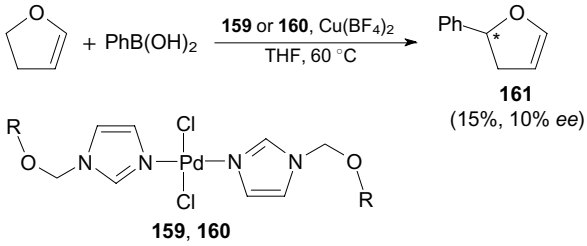
Table 1. Effect of ligands on the enantioselectivity of alkylation (see Scheme 5).[98]

Ligand	R^1	R^2	R^3	Yield of **154** (%)	*ee* (%)
155	Pr^i	H	H	0	0
156	Pr^i	Boc	Me	86	0
157	OH	Boc	H	65	88
158	Pr^i	C(O)O-(–)-Menth	H	91	87

demonstrated for leucine derivatives: in the case of leucine (**155**), the reaction did not proceed; with the N-acyl protected methyl ester (compound **156**), the product was obtained in 86% yield, but as a racemate. Acids **157** and **158** provided good product yields (up to 90%) and high enantioselectivity [up to 90% enantiomeric excess (*ee*)]. The best result was obtained with ligand **158**, containing menthyl (menth) as an additional chiral moiety.

Zawartka *et al.*[99] reported the synthesis of imidazoles with a chiral terpene substituent. These ligands were used to prepare palladium complexes **159** and **160**, which were tested in Heck type asymmetric cross-coupling (Scheme 6). Arylation of 2,3-dihydrofuran with phenylboronic acid was carried out in the absence of bases, but with addition of copper(II) salts, which gave rise to a redox pair with palladium and regeneration of the active catalyst species. Complexes **159** and **160** showed a moderate activity (the yield of product **161** was 15%) and low enantioselectivity (*ee* ⩽10%).

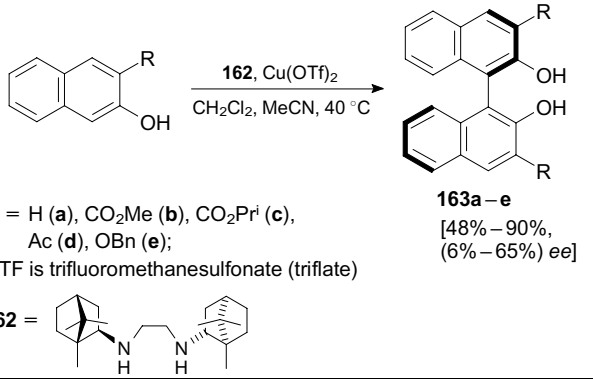
Scheme 6



R = (–)-bornyl (**159**), (+)-fenchyl (**160**)

Caselli *et al.*[100] synthesized bornane diamine **162** based on (+)-camphor and ethylenediamine and tested it in the copper-catalyzed oxidative coupling of naphthols with the aim to obtain axially chiral disubstituted binaphthyls **163a** – **e** (Scheme 7). The results of this reaction were mod-

Scheme 7



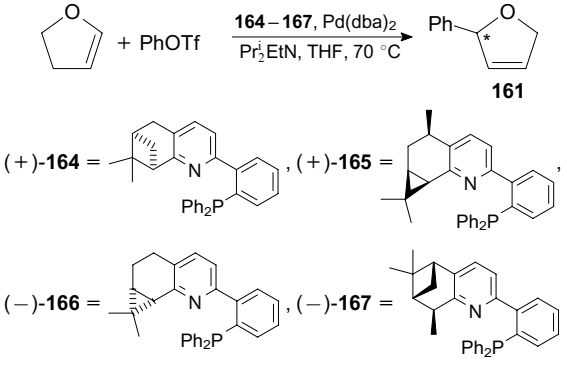
R = H (**a**), CO_2Me (**b**), CO_2Pr^i (**c**), Ac (**d**), OBn (**e**);
OTF is trifluoromethanesulfonate (triflate)

162 =

erate: the product yields were 48% – 90% and enantiomeric purity did not exceed 65%.

N,P-Donor pyridine ligands (+)-**164**, (+)-**165**, (−)-**166** and (−)-**167**, synthesized from (−)-β-pinene, (+)-3-carene, (+)-2-carene and (−)-α-pinene, respectively, were investigated as chiral ligands in the palladium-catalyzed Heck reaction (Scheme 8, Table 2).[101] Phenyl triflate reacts with dihydrofuran to give arylation product **161** with high enantiomeric purity and virtually without side products. The mechanism of this reaction, which is accompanied by double bond migration in the ring, was studied by Brown and co-workers.[102] It was shown[101] that ligand (+)-**164** induces the formation of product (*S*)-(−)-**161** with 59% *ee*, while ligand (+)-**165** shows higher enantioselectivity (70% *ee*). It is noteworthy that the use of quasi-enantiomer (−)-**166** leads to the product with the opposite configuration (*R*)-(+)-**161** (69% *ee*). Inversion of configuration for the aryl derivative also takes place in the case of pinanes: unlike compound (+)-**164**, ligand (−)-**167** gives rise to (*R*)-(+)-**161** (88% *ee*).

Scheme 8



dba is dibenzylideneacetone

Table 2. Effect of ligand nature on the enantioselectivity of Pd-catalyzed arylation of dihydrofuran (see Scheme 8).[101]

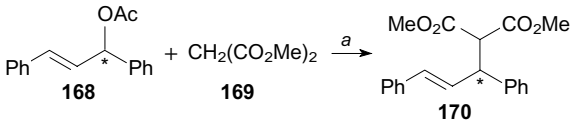
Ligand	Yield of **161** (%)	Configuration	*ee* (%)
164	45	*S*	59
165	–	*S*	70
166	–	*R*	69
167	68	*R*	88

3.2. Allylic substitution

Palladium-catalyzed asymmetric allylic substitution is a convenient method for the synthesis of single stereoisomers with a chiral carbon atom.[103, 104] Unlike other catalytic reactions, this method is applicable to the formation of various types of bonds (C – C, C – O, C – S, C – N) with the same catalytic system.

The model reaction chosen in most of the cited publications was palladium-catalyzed alkylation of racemic 1-acetoxy-1,3-diphenylprop-2-ene (**168**) with dimethyl malonate (**169**), which results in the formation of chiral substitution product **170** (Scheme 9). As a rule, the catalytic complex was formed *in situ*. Palladium(II) salts and complexes and the appropriate chiral ligand served as precursors. Ethylenediamine derivatives were studied by Bottari *et al.*[105] In order to estimate the contributions of the asymmetric

Scheme 9



(*a*) **171** – **190**, $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, CH_2Cl_2, MeCN, BSA, KOAc, rt; BSA is *N*,*O*-bis(trimethylsilyl)acetamide

Table 3. Effect of ligand nature on the enantioselectivity of Pd-catalyzed allylic substitution (see Scheme 9).

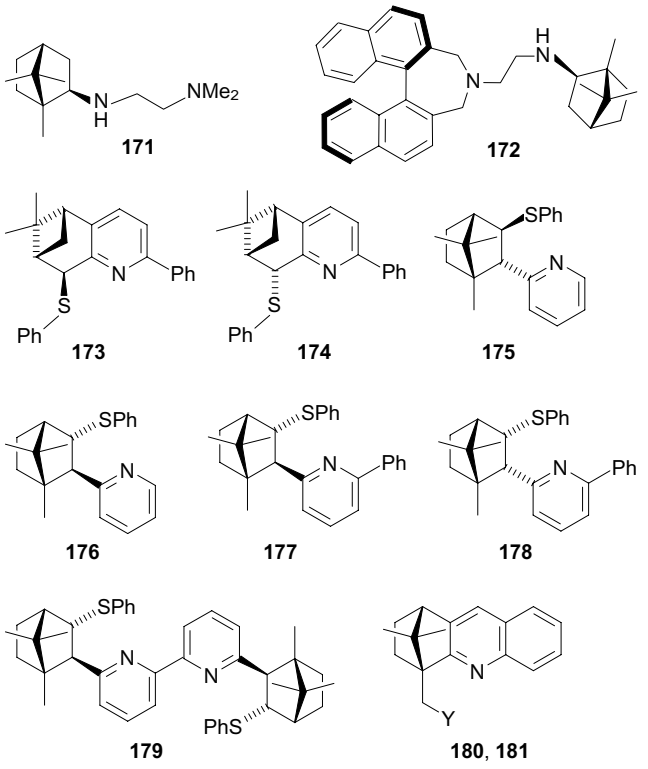
Ligand	Yield of **170** (%)	Configuration	*ee* (%)	Ref.
171	26	*S*	55	105
172	84	*S*	98	105
173	90	*R*	83	106
174	85	*S*	78	106
175	84	*S*	30	107
176	85	*R*	26	107
177	–	*R*	76	107
178	–	*S*	3	107
179	76	*R*	48	107
182	2	*S*	80	108
183	4	*R*	23	108
184	70	*R*	81	108
185	80	*R*	84	108
186	77	*S*	68	109
187	94	*R*	89	110
188	93	*R*	84	111
189	99	*R*	85	112
190	63	*R*	53	113

Note. A dash means that the yield is not indicated.

induction of particular chiral blocks, diamine **171** with a bornane moiety and ligand **172** containing additionally an axially chiral binaphthyl substituent were synthesized. In the latter case, it was possible to attain high enantioselectivity of the reaction (up to 98% *ee*) (Table 3). To confirm the *in situ* formation of the active complex, the authors[105] obtained palladium complexes based on ligands **171** and **172** in a pure state.

Pyridine derivatives are used rather efficiently in asymmetric catalytic reactions of various types.[92] Terpene-pyridine ligands **173** – **190** were studied in allylic substitution reactions (see Scheme 9 and Table 3). Among the variety of synthesized molecules, several groups can be distinguished. Ligands **173** – **179** and **181** – **185** are sulfur-containing pyridine derivatives, in particular, thiols. Chelucci *et al.*[106] considered pinane thioethers **173** and **174**, which exhibited high catalytic activity in the allylic substitution. These quasi-enantiomers promote the formation of allylic substitution products of the opposite configuration with high enantiomeric purity (83% and 78% *ee*). Using camphor as a chiral starting compound, thioether derivatives **175** – **179** were prepared.[107] It was shown that stereoselectivity of the allylic substitution reaction considerably depends on the spatial structure of the ligand. For example, in the case of thioether **177**, *ee* can reach 76%, while for its *cis*-stereoisomer **178**, *ee* is $\leqslant$3%. The authors give no explanation to this finding. It can also be noted that *cis*- or *trans*-position

Structures 171 – 181

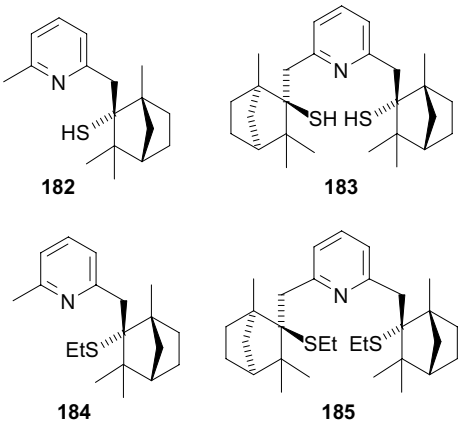


of hetero substituents in the terpene ring of the ligand is an important factor. It is likely that *trans*-orientation of the hetero donor substituents promotes more efficient chelation of the metal. In the presence of ligands with this structure (**175** – **177**), a higher enantioselectivity of Pd-catalyzed allylic substitution is attained (30% – 76% *ee*).

Koning *et al.*[108] described yet another group of efficient bornane ligands containing a thiol (**182**, **183**) or thioether (**184**, **185**) substituent. Compounds **182**, **184** and **185** show a high asymmetric induction (up to 84% *ee*), but differ considerably in the catalytic activity. Thiols, which tend to poison the catalyst, give very low yields of allylic substitution products ($\leqslant$10%).

Bipyridine and dipyridine ligands **186** – **189** containing an annulated terpene moiety were studied for chiral induction in the asymmetric allylic substitution reactions (see Scheme 9). Table 3 presents several most significant results for this reaction.[109 – 112]

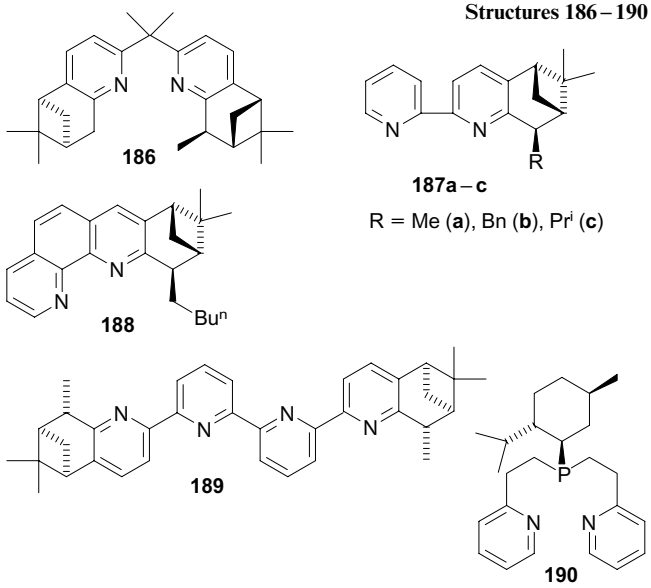
Structures 182 – 185



As indicated above, chiragen type ligands (see Section 2.4) are highly stereoselective chiral inducers. The first example of application of complexes of this type as asymmetric catalysts (allylic substitution reactions) was reported by Kwong *et al.*[112] The authors synthesized tetrapyridine ligand **189** and the chiral palladium complex with this ligand, $[Pd_2(\eta^3\text{-}C_3H_5)_2(\mathbf{189})](SbF_6)_2$, which had a helical binuclear structure. This catalyst and its analogues showed high enantioselectivity in this process (up to 85% *ee*), with the product yield being nearly quantitative.

An unusual P,N,N′-tridentate phosphine ligand **190** containing a menthyl substituent was reported by Minato *et al.*[113] This ligand used in the palladium-catalyzed allylic substitution provided a moderate enantioselectivity (up to 53% *ee*).

Structures 186 – 190



The above examples of studying terpene-containing ligands of various types in the asymmetric palladium-catalyzed allylic substitution demonstrate that good results can be obtained using various types of ligands, with terpene-pyridine derivatives appearing most promising.

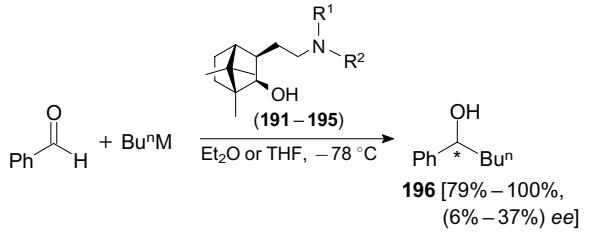
3.3. Addition to aldehydes and ketones

The reactions of organometallic compounds with aldehydes give secondary alcohols. It was ascertained that in the presence of chiral ligands (primarily, N,O-donors), the reaction is enantioselective and represents a facile and reliable route to chiral secondary alcohols.

(+)-Camphor-derived terpene amino alcohols **191** – **195** were investigated[114] for chiral induction in the enantioselective addition of Zn, Mg and Li organic compounds to aldehydes. The following features were identified. The addition of n-butyllithium and n-butylmagnesium bromide to benzaldehyde (Scheme 10) has al low selectivity ($\leqslant$37% *ee*) and considerably depends on the nature of the solvent which forms a complex solvate with the organometallic reagent. The best results (the highest yield of product **196**) were obtained in diethyl ether.

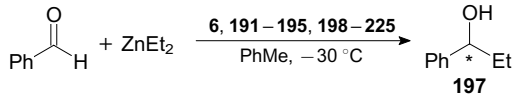
The addition of diethylzinc to benzaldehyde is more selective (Scheme 11).[114] In particular, when amino alcohol

Scheme 10



M = Li, MgBr; $R^1 = R^2$ = Et (**191**), Bu^i (**192**), Bu^n (**194**);
R^1 = Me, R^2 = Ph (**193**); $R^1 - R^2 = (CH_2)_2O(CH_2)_2$ (**195**)

Scheme 11



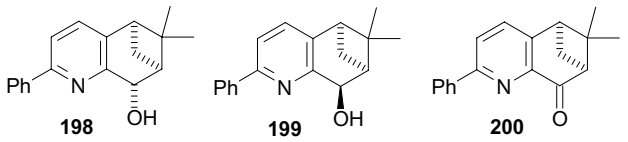
195 is used as the chiral ligand, the enantiomeric excess of the reaction product of 1-phenylpropan-1-ol (**197**) can be as high as 87%, while the yield is 94%.

It should be noted that the nucleophilic addition of diethylzinc to benzaldehyde in the presence of bornane β-amino alcohols (see Scheme 11) served as a model reaction for studying the non-linear effects in the dependence of reaction enantioselectivity on the enantiomeric purity of chiral ligands. This system was investigated in detail by a group of Japanese scientists headed by Noyori,[115, 116] while the first quantitative characterization of these non-linear effects was reported by Kagan and co-workers.[117, 118] Blackmond [119] demonstrated how the kinetic behaviour may promote more extensive use of non-linear effects as a diagnostic tool to identify active catalytic species and to establish the reaction mechanism.

The effect of terpene ligands of various types (**6**, **198** – **225**; for the structures, see below) on the enantioselectivity of addition of diethylzinc to benzaldehyde was investigated (see Scheme 11, Table 4). The most enantioselective reaction was described by Salehi *et al.*[120] In this case, ligand **6** (EDA- and 2-hydroxypinan-3-one-derived diimine) acted as a component of the catalytic system. In the presence of this compound, (*R*)-1-phenylpropan-1-ol was obtained with a high enantiomeric purity (up to 99% *ee*).

The pyridine ligands synthesized by von Zelewsky and co-workers [121, 122] were tested for chiral induction in the enantioselective addition of diethylzinc to benzaldehyde. Pinane-pyridine derivatives **198** – **200** showed a high enantioselectivity.[121] In the presence of ligand **199**, (*R*)-1-phenylpropan-1-ol was obtained in 98% yield and with 91% enantiomeric purity. Ligand **198**, which differs only in the C(8) configuration, affords the opposite enantiomer with a much lower selectivity (28% *ee*). The influence of the solvent nature was also ascertained: the replacement of toluene by more polar tetrahydrofuran inhibits the reaction.

Structures 198 – 200



The same catalytic reaction was addressed in the study of Collomb and von Zelewsky.[122] Bipyridine (**201** – **207**) and monopyridine (**208** – **214**) alcohols were synthesized and used as chiral ligands. Generally, tridentate ligands **201** – **207** had higher catalytic activity and enantioselectivity in this reaction than bidentate analogues **208** – **214**. The authors found no obvious relationship between the stereoselectivity of the addition reaction and the composition or spatial arrangement of the groups R^1 and R^2 in the ligands.

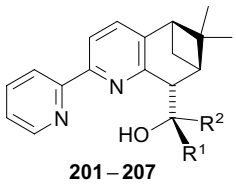
Bipyridine ligands containing terpene moieties, namely, menthane (**215**), bornane (**216**, **217**) or pinane (**218**) ones, were also studied [123] in the addition reaction of diethylzinc to benzaldehyde in which they showed a higher enantioselectivity (80% to 92% *ee*).

LeGoanvic *et al.*[124] reported the synthesis of a series of terpene-pyridine ligands: N,O,O-tridentate (**219** – **222**) and N,O-bidentate ones (**223** – **225**). Comparative analysis of application of these ligands demonstrated that the crucial

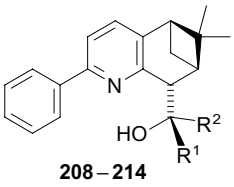
Table 4. Effect of ligands on the enantioselectivity of diethylzinc addition to benzaldehyde (see Scheme 11).

Ligand	Yield of **197** (%)	Configuration	*ee* (%)	Ref.	Ligand	Yield of **197** (%)	Configuration	*ee* (%)	Ref.
191	92	*S*	78	114	**209**	90	*R*	68	122
192	36	*S*	40	114	**210**	91	*R*	45	122
193	28	*S*	21	114	**211**	60	*R*	18	122
194	29	*S*	20	114	**212**	91	*R*	64	122
195	94	*S*	87	114	**213**	95	*R*	46	122
6	74	*R*	99	120	**214**	85	*R*	15	122
198	75	*S*	28	121	**215**	77	*S*	85	123
199	98	*R*	91	121	**216**	86	*R*	92	123
200	96	*R*	75	121	**217**	82	*R*	77	123
201	100	*R*	73	122	**218**	86	*R*	79	123
202	100	*R*	79	122	**219**	81	*S*	42	124
203	100	*R*	78	122	**220**	81	*S*	35	124
204	100	*R*	52	122	**221**	76	*R*	95	124
205	99	*S*	86	122	**222**	78	*R*	75	124
206	100	*S*	82	122	**223**	93	*S*	21	124
207	99	*R*	47	122	**224**	85	*S*	95	124
208	91	*S*	42	122	**225**	81	*R*	77	124

Structures 201 – 218

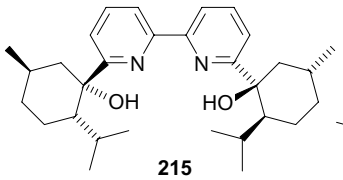


201 – 207

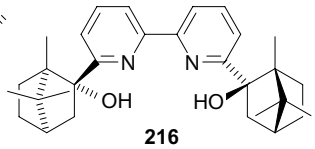


208 – 214

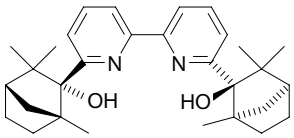
$R^1 = R^2 = Me$ (**201**, **208**), Ph (**202**, **209**); $R^1 = Ph$, $R^2 = Me$ (**203**, **210**); $R^1 = Me$: $R^2 = Ph$ (**204**, **211**); $R^2 = Me$: R^1 = 1-Naph (**205**, **212**), 2-Naph (**206**, **213**); $R^1 = Me$, R^2 = 1-Naph (**207**, **214**); Naph is naphthyl



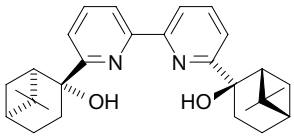
215



216



217

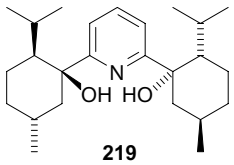


218

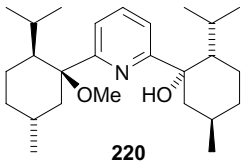
factor determining the enantioselectivity of addition of diethylzinc to benzaldehyde is the distance between the donor sites rather than their number. For example, the tridentate ligand **221** and its bidentate analogue **224**, which contain a menthol moiety, ensure 95% enantioselectivity. In the case of more rigid ligands **219**, **220** and **223**, in which the donor sites are located in positions 1 and 4 relative to each other, the enantiomeric excess does not exceed 42%.

Good results were obtained for enantioselective addition of diethylzinc to various aldehydes. Using pyridine ligands

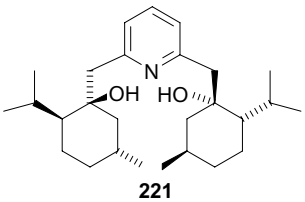
Structures 219 – 225



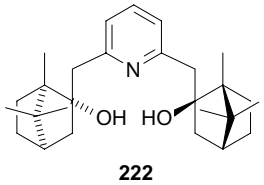
219



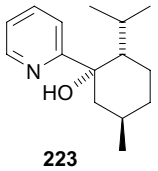
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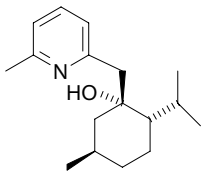
221



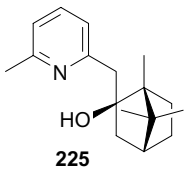
222



223

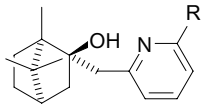


224

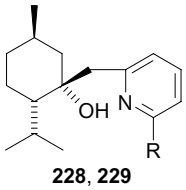


225

Structures 226 – 229



226, **227**



228, **229**

R = Me (**226**, **228**), H (**227**, **229**)

226 – 229,[125] the range of applicable substrates was extended.

The best selectivity in this reaction was found for ligand **229** (Scheme 12, Table 5). It is noteworthy that aliphatic aldehydes react with diethylzinc less selectively (54% – 61% *ee*) than aromatic aldehydes (94% *ee*).

Scheme 12

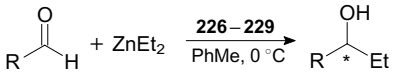


Table 5. Enantioselectivity of diethylzinc addition to aldehydes in the presence of ligand **229** (see Scheme 12).[125]

Starting aldehyde	Yield of the alcohol (%)	*ee* (%) (see [a])
Benzaldehyde	94	92
o-Methoxybenzaldehyde	92	84
p-Methoxybenzaldehyde	90	89
p-Methylbenzaldehyde	91	89
o-Chlorobenzaldehyde	82	83
p-Chlorobenzaldehyde	87	84
3,4-Dimethoxybenzaldehyde	97	89
4-Dimethylaminobenzaldehyde	98	76
1-Naphthaldehyde	92	94
2-Naphthaldehyde	90	83
Cinnamaldehyde	87	76
Dodecanal	83	60
Nonan-1-al	86	54
Cyclohexanecarboxaldehyde	80	61

[a] The value for *S*-enantiomer is indicated.

3.4. Hydrogenation of asymmetric ketones

The catalytic asymmetric reduction of ketones in the presence of chiral transition metal complexes is an important route to chiral secondary alcohols with high enantiomeric purity. There are three key reduction methods:

1) direct high-pressure hydrogenation with molecular hydrogen,

2) hydrogenation with a hydrogen atom transfer from a proton donor,

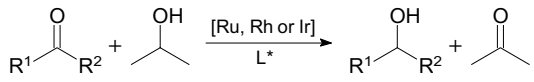
3) hydrosilylation of ketones followed by hydrolysis.

All of the three methods have been used with considerable success, which is reflected in relevant publications. First of all, mention should be made of classical studies [126 – 129] performed under supervision of Ryoji Noyori, Nobel Prize Laureate in Chemistry of 2001 (Japan). The versatile Noyori catalysts are Ru^{II} complexes with chiral diphosphine ligands [*e.g.*, with BINAP — 2,2′-bis(diphenyl-

phosphino)-1,1′-binaphthyl]. These studies served as the starting point for the search of new catalytic systems among chiral transition metal complexes. A review[130] discusses the achievements in the asymmetric reduction of ketones by various methods in the presence of iron complexes. The relevance of this study is associated with the goal to replace expensive and toxic ruthenium by other metals. Chiral iridium complexes were studied rather extensively as catalysts for the asymmetric reduction of ketones.[131] The search for new chiral ligands for such complexes, including those based on terpene derivatives, is in progress.

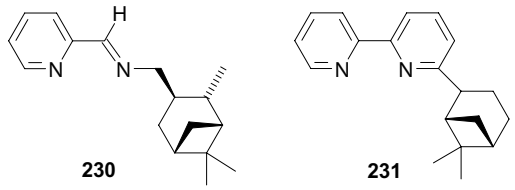
Homogeneous catalysis is an experimentally simple and efficient method for the asymmetric reduction of ketones;[132–135] in this case, 2-propanol can, for example, act as the proton donor (Scheme 13).

Scheme 13



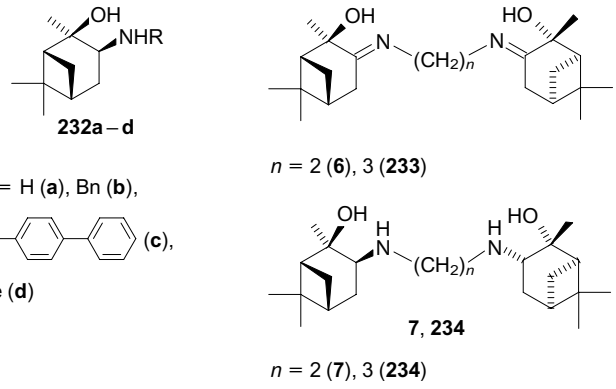
Historically, the first terpene ligand used in this reaction was pyridine derivative **230** described by Zassinovich *et al.*[136] in 1981. This ligand serves as the precursor for the design of chiral Ir- catalyst, and a number of aromatic and aliphatic ketones were investigated as substrates. However, the enantioselectivity of this reaction did not exceed 10%. Bipyridine ligand **231**, which was tested in the Rh-catalyzed reduction of acetophenone, also showed low enantioselectivity.[137]

Structures 230, 231

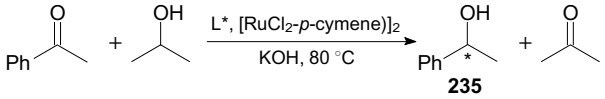


Pinane amino alcohols **232a – d**, and diimino- and diaminodiols **6**, **7**, **233** and **234** were tested[138] in the ruthenium-catalyzed asymmetric hydrogen transfer reaction (Scheme 14, Table 6). The active Ru complex was formed *in situ* from precursors. In all cases, high acetophenone

Structures 6, 7, 232 – 234



Scheme 14



p-cymene is 4-isopropyl-1-methylbenzene

Table 6. Effect of ligand nature on the enantioselectivity of Ru-catalyzed reduction of acetophenone (see Scheme 14).[138]

Ligand L*	Conversion of acetophenone (%)	*ee* (%) [a]
232a	85	18
232b	83	34
232c	77	45
232d	92	29
6	90	10
233	97	18
7	90	13
234	88	7

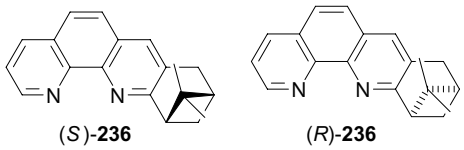
[a] The value for enantiomer (*R*)-**235** is indicated.

conversion was attained, but the enantioselectivity of formation of 1-phenylethanol (**235**) was moderate (less than 45% *ee*).

Moutet *et al.*[139] studied polypyridine ligands **122**, **123**, **129a** and **236** in the asymmetric hydrogenation of prochiral ketones, including acetophenone. The authors compared three methods: homogeneous hydrogen transfer reaction and homogeneous and heterogeneous electrocatalytic hydrogenation in the presence of chiral Rh^{III} complexes. Regarding enantioselectivity, neither variation of the ligands nor the change in the reduction procedure caused considerable differences. In all cases, the enantiomeric excess of the chiral alcohols did not exceed 20%.

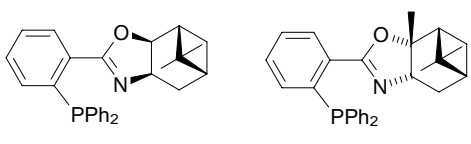
Chiral phosphine-oxazoline ligands **237** and **238** were

Structure 236



prepared and tested[140] in Ru-catalyzed reduction of a number of ketones. The catalytic complex was obtained in advance by the reaction of the appropriate ligand with $[Ph_3P]_3RuCl_2$ in 2-propanol, and then solutions of Ru complexes **237**-Ru and **238**-Ru were added to the reaction mixture. The hydrogen transfer reduction of acetophenone was chosen as the model reaction (see Scheme 13). A clear dependence of the yield and enantiomeric purity of the resulting alcohol on the catalyst concentration was identi-

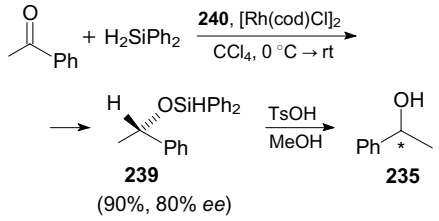
Structures 237, 238



fied. For example, a decrease in the proportion of complex **237**-Ru from 0.1 mol.% to 0.01 mol.% leads to an increase in *ee* from 76% to 90%. Note that catalyst **238**-Ru was less selective: *ee* was 37% at a concentration of 0.1 mol.%.

One more procedure for reduction of unsymmetrical ketones to chiral secondary alcohols is enantioselective hydrosilylation followed by hydrolysis of silyl ether **239** (Scheme 15). This reaction was investigated in detail by a German research team headed by Brunner.[141, 142] The chiral induction in the rhodium-catalyzed enantioselective hydrosilylation was accomplished using bipyridine ligands and several tens of amino- and iminopyridine derivatives containing terpene moieties.

Scheme 15

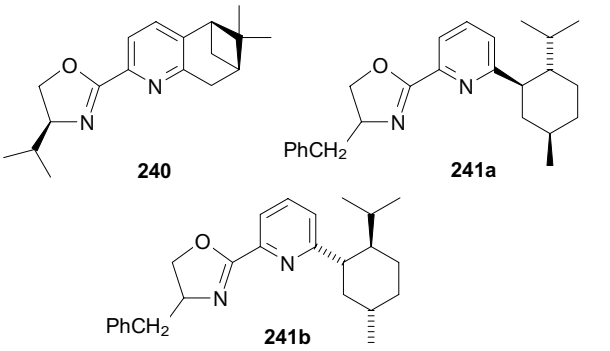


239 (90%, 80% *ee*) **235**

cod is cycloocta-1,5-diene, Ts is *p*-toluenesulfonyl (tosyl)

Brunner *et al.*[142] reported the synthesis of a number of terpene-pyridine ligands (*e.g.*, compounds **240** and **241a**,**b**), which incorporated a chiral oxazoline ring, and evaluation of their stereodifferentiating properties towards hydrosilylation of acetophenone with diphenylsilane (see Scheme 15). The best enantioselectivity was obtained for pinane ligand **240** (up to 80% *ee*). Menthyl derivatives **241a**,**b** showed virtually no selectivity, nor also with the use of rhodium(I) complex prepared in advance.

Structures 240, 241



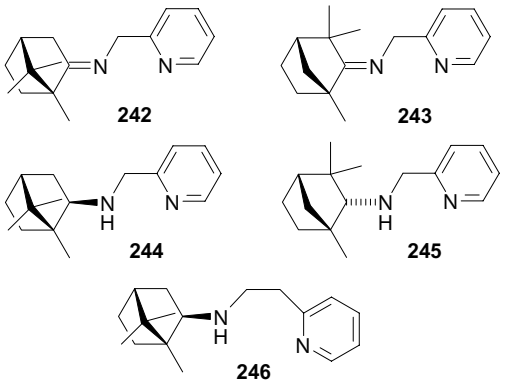
240 **241a** **241b**

3.5. Nitroaldol condensation

Nitroaldol condensation (Henry reaction) is one of the key catalytic reactions that give rise to a C–C bond. A review[143] published by Spanish researchers in 2007 is devoted to the achievements in the asymmetric catalysis of this reaction. The reaction of nitroalkanes with aldehydes or ketones yields β-nitro alcohols. Copper complexes with N,N-donor chelating ligands were found to be most efficient catalytic systems for this transformation.

Chiral ligands containing a terpene moiety were used for asymmetric catalysis of the Henry reaction. First of all, note publications of Blay *et al.*,[144–151] who described bornane imino- (**242**, **243**) and aminopyridines (**244**–**246**) and their

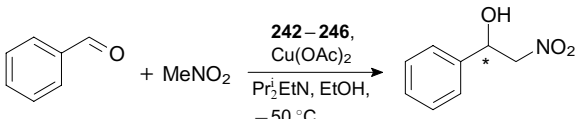
Structures 242 – 246



242 **243** **244** **245** **246**

derivatives. Quite a few aldehydes and ketones, in particular, benzaldehyde, were studied as substrates of this reaction (Scheme 16). The condensation of benzaldehyde with nitromethane was conducted in the presence of a catalytic system formed *in situ* from the ligand and copper(II) acetate or triflate. Virtually in all cases, with rare exceptions, the authors noted high catalytic activity (the chemical yield of alcohol **247** was in the 80% – 99% range) and enantioselectivity ($\geqslant$75% *ee*); the best properties were found for ligand **244**.

Scheme 16

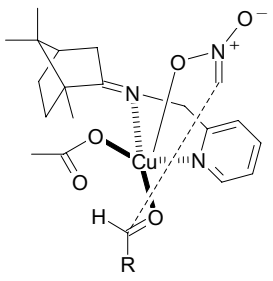


247 [80% – 99%, (75% – 98%) *ee*]

The results of the above studies were summarized in a review.[150] The authors proposed a stereochemical model of the transition state of the catalytic site (structure **248**) for the Cu-catalyzed Henry reaction in the presence of imine **242**. The first step is the formation of Cu^{II} chelate and a chiral ligand. Then, as a result of ligand exchange and the coordination capacity of complexing metal, the substrate and the reagent occupy the most favourable positions in the coordination environment of the metal. The enantiodifferentiation is controlled by the sterically optimal contact between the substrate and the reagent.

Ethylenediamine 2-hydroxypinan-3-one derivatives were investigated[13] as ligands in the copper-catalyzed asymmetric aldol condensation of nitromethane with 4-nitrobenzal-

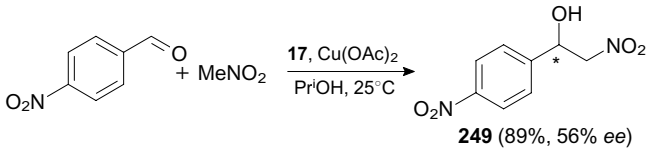
Structure 248



248

dehyde (Scheme 17). In order to estimate the effect of electronic and steric factors on the stereochemical outcome of the reaction, a series of stereoisomeric ethylenediamine pinane derivatives (**4** – **7**, **9**, **17**) containing various substituents in the ligand aromatic ring (see Section 2.1) were synthesized.

Scheme 17



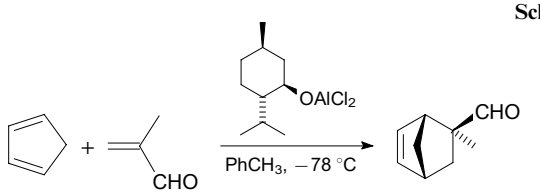
249 (89%, 56% *ee*)

It was found that diamine and copper acetate complexes formed *in situ* efficiently catalyze this reaction. The nitroaldol condensation proceeds under mild conditions to give product **249** in a high yield (up to 89%) and with moderate enantioselectivity. The best result (56% *ee*) was obtained with diamine ligand **17** (see Scheme 17).

3.6. Diels – Alder reaction

Cycloaddition reactions, including the Diels – Alder reaction, are activated in the presence of Lewis acids. Narasaka [152] analyzed the application of chiral Lewis acids in this type of asymmetric transformations. As a rule, the chiral catalyst is generated during the reaction from the corresponding precursors. There are known examples in which chirality is induced by terpenoids and their synthetic derivatives, for example, menthol.[153, 154] Thus, in the presence of menthyloxyaluminium dichloride, the reaction of 2-methylprop-2-enal with cyclopentadiene affords *exo*-adduct **250** with good enantioselectivity (72% *ee*) (Scheme 18).

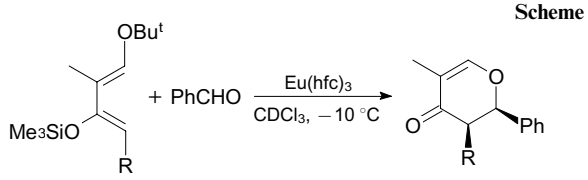
Scheme 18



250 (69%, 72% *ee*)

High stereoselectivity was attained in several hetero-Diels – Alder reactions catalyzed by the chiral europium(III) camphorate complex $Eu(hfc)_3$.[155, 156] For example, cycloaddition of benzaldehyde to polyfunctional diene (Scheme 19) is stereospecific and has a moderate enantioselectivity of formation of six-membered oxo ketones **251** (55% – 58% *ee*).

Scheme 19

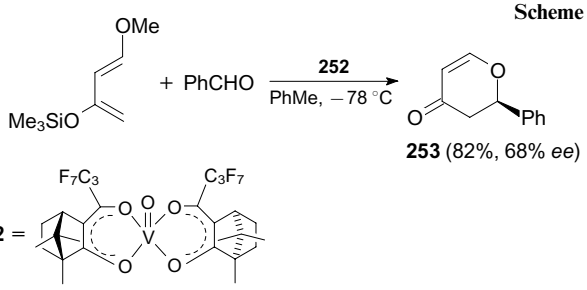


251 (55% – 58% *ee*)

R = Me, H; hfc is camphorate

Asymmetric Diels – Alder reactions were studied by Togni *et al.*[157, 158] Bis[3-(heptafluorobutyryl)camphorato]oxovanadium (**252**) was employed as the chiral catalyst. This complex efficiently catalyzes the cycloaddition of aldehydes to activated dienes (Scheme 20) giving oxopyran derivative **253**. The reaction has high stereoselectivity: diastereomeric excess (*de*) is 93% – 98% and *ee* can reach 85%. When the heptafluoropropyl substituent in the ligand is replaced by a trifluoromethyl or aromatic group, the cycloaddition is non-selective. With the goal to elucidate the stereochemistry of this reaction, the authors [157] carried out a detailed study of the structure of complex **252** and its adducts with the substrate and the reagent using X-ray diffraction and EPR and NMR spectroscopy. Lanthanide complexes of this type have found use as chiral NMR shift reagents.[159]

Scheme 20

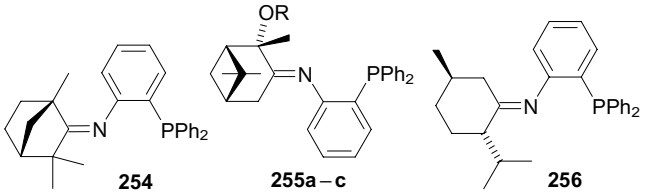


253 (82%, 68% *ee*)

The behaviour of the terpene ligands in palladium-catalyzed asymmetric Diels – Alder reactions has been discussed.[160, 161] Using (+)-fenchone, (+)-2-hydroxypinan-3-one, (−)-menthone, (+)-camphor and (+)-ketopinic acid as the starting compounds, the authors prepared iminophosphines **254** – **258** and palladium complexes **259** and **260**.

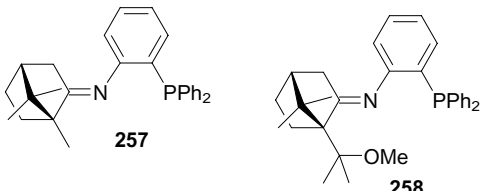
The effect of the composition of the catalytic palladium complex on the efficiency and stereoselectivity of the reaction of cyclopentadiene with dienophile **261** was studied

Structures 254 – 260

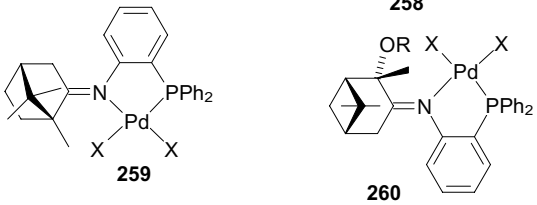


254 **255a – c** **256**

R = H (**255a**), Me (**255b**), Bn (**255c**)



257 **258**



259 **260**

X = Cl, SbF_6, ClO_4, OTf

(Scheme 21) by Hiroi and Watanable.[161] In the presence of chloride complexes **259** and **260**, cycloaddition does not take place. However, the replacement of a chloride anion by another ion gives rise to a high catalyst activity and stereoselectivity. For the anion exchange, chloride complexes formed upon the reaction of $PdCl_2(MeCN)_2$ with imino phosphine ligands **254** – **258** in refluxing methanol were treated with appropriate silver salts AgX (X = SbF_6, ClO_4, TfO). Some most significant results of these reactions are summarized in Table 7. It was found that in all cases, *endo*-adduct **262a** is predominantly formed. A considerable influence of the anionic ligand was elucidated: the highest activity and stereoselectivity were found for catalytic systems containing a hexafluoroantimonate anion. However, the authors[161] gave no explanation to this result. For comparable high yields of product **262** (89% – 99%), the best enantioselectivity was provided by catalytic systems based on bornane ligands **254** and **257** (72% and 84% *ee*, respectively).

Scheme 21

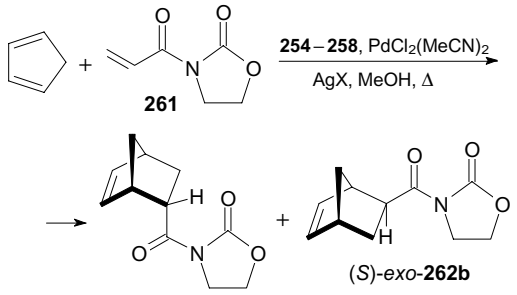


Table 7. Effect of ligand nature on the enantioselectivity of Pd-catalyzed Diels – Alder reaction (see Scheme 21).[161]

Ligand	Anion (X^-)	Yield of **262a** + **262b** (%)	**262a** : **262b** ratio	*ee* (%)[a] (configuration)
254	SbF_6	89	95 : 5	72 (*S*)
254	ClO_4	75	95 : 5	55 (*S*)
254	OTf	68	94 : 6	43 (*S*)
257	SbF_6	99	93 : 7	84 (*S*)
257	ClO_4	95	94 : 6	58 (*S*)
257	OTf	75	93 : 7	37 (*S*)
256	SbF_6	94	87 : 13	48 (*S*)
256	ClO_4	91	85 : 15	41 (*S*)
256	OTf	73	88 : 12	37 (*S*)

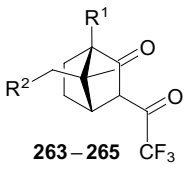
[a] The value for *endo*-isomer.

3.7. Cyclopropanation

A classical method for the preparation of three-membered carbocycles is the catalytic carbenoid synthesis.[162, 163] A challenging synthetic task is the possibility to prepare single stereoisomers. The stereoselectivity and, in particular, the effect of the nature of chiral inducing groups on the enantioselectivity of reactions between alkenes and diazo compounds were evaluated by studying metal complexes with terpene ligands of various types.

Copper(II) acylacetonate complexes based on trifluoroacetylcamphor **263** and its derivatives **264**, **265a** proved to be highly efficient catalysts for asymmetric cyclopropanation of styrene (Scheme 22).[164] For example, styrene reacts with 2-diazodimedone in the presence of a chiral Cu^{II} complex to give enantiomerically pure spirocyclic product **266**. The reactions were conducted using both homogeneous and heterogeneous catalysis. Heterogeneous catalyst **265b** was prepared by immobilization of the camphor derivative on a silicate substrate. With the heterogeneous catalyst, high enantioselectivity of cyclopropanation is retained (98% *ee*) and the advantages include simple catalyst removal and regeneration.

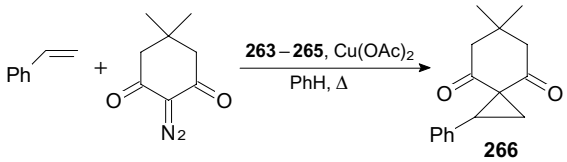
Structures 263 – 265



263 – **265**

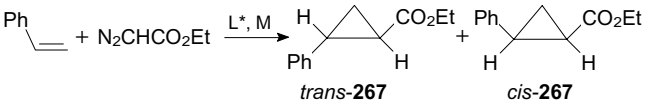
R^1 = Me: R^2 = H (**263**), I (**264**);
R^2 = H: R^1 = CH=CH_2 (**265a**),
$(CH_2)_2Si(OMe)_2OSiMe_3$ (**265b**)

Scheme 22



In most studies discussed below, the reaction of styrene with ethyl diazoacetate, resulting in a mixture of stereoisomeric cyclopropyl esters **267**, was chosen as the model reaction (Scheme 23). Numerous terpene-pyridine ligands were synthesized and tested in this reaction by Chinese researchers under supervision of Prof. Kwong.[165 – 174] Table 8 summarizes some most significant results and examples for comparison of the enantioselectivities of catalytic systems. The catalysts were metal complexes either pre-synthesized or formed *in situ*.

Scheme 23



Kwong and Lee[167] described the synthesis of tripyridine ligands **268a** – **d** for asymmetric copper-catalyzed cyclopropanation of styrene with ethyl diazoacetate (see Scheme 23, Table 8). The active Cu^{II} complex was formed *in situ*. In al cases, the reaction gave a mixture of *trans*- and *cis*-isomeric cyclopropyl esters **267** in high total yields (88% – 98%) and with high enantioselectivity (up to 94% *ee*). The authors studied the dependence of selectivity on the electronic and steric effects of substituents in the substrate and the reagent.

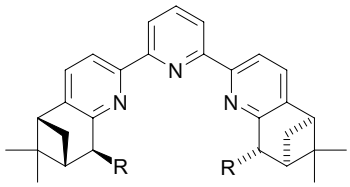
The *cis* – *trans* diastereoselectivity of cyclopropanation is dictated, first of all, by steric factors. This is indicated, for example, by the fact that a higher selectivity can be attained by replacing the ethyl group in ethyl diazoacetate by a bulkier group.[167] For example, styrene cyclopropanation with menthyl diazoacetate in the presence of ligand **268c** gives a mixture of isomeric cyclopropyl esters with *trans* : *cis* ratio of 91 : 9.

Table 8. Asymmetric cyclopropanation of styrene with ethyl diazoacetate (see Scheme 23).

Ligand	Metal	Yield of **267** (%)	*trans* : *cis* ratio	*ee* (*trans*) (%)	*ee* (*cis*) (%)	Ref.
268a	Cu^{II}	87	64 : 36	75	84	167
268c	Cu^{II}	96	69 : 31	90	94	167
268d	Cu^{II}	97	61 : 39	72	75	167
268a	Ru^{II}	83	65 : 35	0	0	175
268a	Rh^{III}	68	34 : 66	49	59	175
269	Rh^{III} (see [a])	73	71 : 29	10	12	176
270	Rh^{III} (see [a])	71	46 : 54	8	32	176
271	Rh^{III} (see [a])	78	37 : 63	52	64	176
269	Cu^{II}	78	72 : 28	22	20	176
270	Cu^{II}	73	72 : 25	32	34	176
271	Cu^{II}	33	67 : 33	7	4	176
269	Cu^{I}	73	64 : 36	20	18	176
270	Cu^{I}	71	67 : 33	18	16	176
271	Cu^{I}	22	70 : 30	6	4	176
268a	Cu^{II}	81	67 : 33	72	82	169
272	Cu^{II}	90	66 : 34	73	83	169

[a] An individual metal complex was prepared and studied.

Structure 268



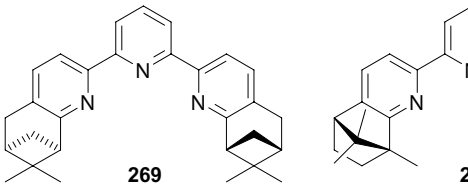
268a – d

R = Me (**a**), Pr^{i} (**b**), Bu^{n} (**c**), Bn (**d**)

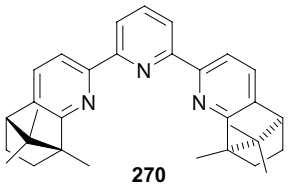
The same group of ligands was studied by Chelucci *et al.*[175,176] The authors[175] used pinane ligands **268a – d** to induce chirality in the rhodium(III)- and ruthenium(II)-catalyzed cyclopropanation of styrene. The reaction enantioselectivity substantially decreases with respect to that observed for Cu catalysts (see Table 8). Ligands **269 – 271** synthesized[176] from (−)-β-pinene, (+)-camphor and (+)-2-carene, respectively, were converted to Rh^{III} complexes. These complexes and copper(I and II) complexes formed *in situ* were studied in styrene cyclopropanation (see Scheme 23). All reactions gave mixtures of *trans*- and *cis*-isomers, with the former predominating is most cases. The enantioselectivity of the reaction did not exceed 64% (see Table 8). For rhodium complexes, the *cis*-isomer was the major product in some examples.

Kwong and co-workers[169] prepared mono- and di-N-oxides of the corresponding tripyridine ligands (*e.g.*, compounds **272** and **273**). Comparison of the performance of ligand **268a** and its oxide **272** (see Table 8) indicates that the introduction of the N-oxide group does not cause significant changes in the catalytic activity or catalyst enantioselectivity towards styrene cyclopropanation.

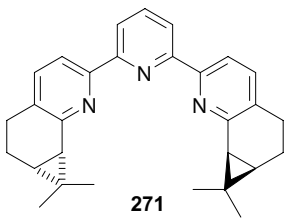
Structures 269 – 271



269

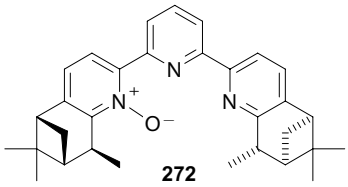


270

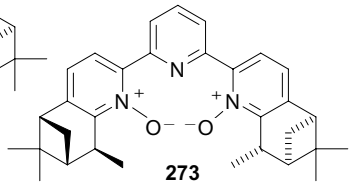


271

Structures 272, 273



272

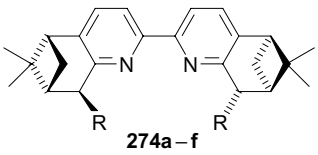


273

Lotscher *et al.*[177] discussed the results of studies of the enantioselective cyclopropanation of styrene in the presence of copper(II) complexes with chiral terpene-containing bipyridine ligands **274 – 277**. Two versions for conducting the catalytic cyclopropanation with ethyl diazoacetate were used. In one version, the active copper complex with chiral ligands was formed during the reaction and copper(I and II) triflates served as the starting copper compounds. In the second procedure, pre-synthesized copper complexes were used as the catalytic systems.

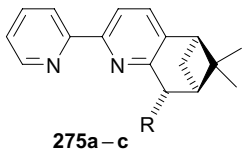
In all cases, stereoisomeric cyclopropanes were formed in high total yields (70% – 90%), but with low diastereoselectivity. Usually, the reactions gave mixtures of *cis*- and *trans*-isomers in which the *trans*-isomers slightly predominated. In some cases, high enantioselectivity was noted. The best result was attained by using the Cu^{II} complex with ligand **274b** as the catalyst: the *cis : trans* ratio was 22 : 78, with the enantiomeric purity of these isomers being 90% and 87%, respectively.

Structures 274 – 277



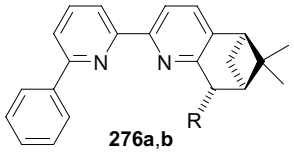
274a – f

R = H (**a**), Me (**b**), Et (**c**), Pr^n (**d**), Pr^i (**e**), Bn (**f**)



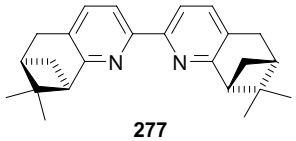
275a – c

R = Me (**a**), Et (**b**), Pr^i (**c**)



276a,b

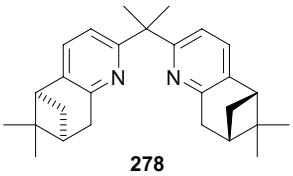
R = H (**a**), Et (**b**)



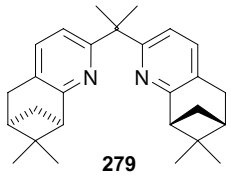
277

Dipyridine ligands of another type (compounds **278** – **280**) were obtained by Chelucci *et al.*[178] and tested in the copper-catalyzed cyclopropanation of styrene. The catalytic system was formed *in situ* from the corresponding ligand and copper(II) triflate. Ligands **278** and **279** showed low enantioselectivity for this reaction ($\leqslant$9% *ee*). Unexpectedly, ligand **280** with additional methyl substituents in the terpene moiety demonstrated a very high enantioselectivity of formation of disubstituted cyclopropanes (*ee* was 88% for the *trans*-isomer and 74% for the *cis*-isomer). This result attests to an unpredictable influence of structural factors on the stereochemical outcome of the reaction.

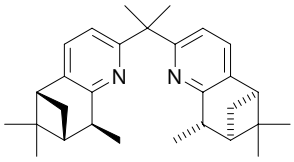
Structures 278 – 280



278



279

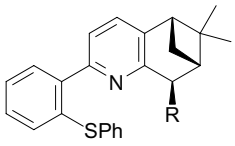


280

Chelucci *et al.*[179, 180] reported the synthesis of N,S-donor ligands **281a – c**, **282a,b** and investigation of these ligands in the copper-catalyzed cyclopropanation of styrene. The introduction of a sulfur atom into the ligand induced a sharp decrease in the enantioselectivity: *ee* did not exceed 5%.

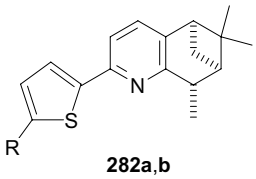
Analysis of the published data indicates that copper(II) complexes with tripyridine (**268**) and bipyridine (**274**) ligands are the most selective catalysts for asymmetric cyclopropanation of styrene with ethyl diazoacetate. In the presence of these catalysts, it is possible to obtain up to 70% of the *trans*-isomer of phenylcyclopropyl ester with enantioselectivity of at least 72%. In the case of rhodium complexes, *cis*-isomers are predominantly formed and the enantioselectivity decreases.

Structures 281, 282



281a – c

R = H (**a**), Pr^i (**b**), Bu^n (**c**)



282a,b

R = H (**a**), Ph (**b**)

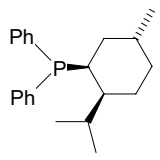
3.8. Hydrogenation of alkenes

Soluble rhodium complexes with phosphine ligands are classical catalysts for alkene hydrogenation (Wilkinson's catalysts). Terpene derivatives are often used to prepare chiral analogues of these ligands. For example, neomenthyldiphenylphosphine **283** was prepared as a chiral ligand.[181] The rhodium complex with this ligand showed a fairly high enantioselectivity (up to 60% *ee*) in the reduction of prochiral unsaturated acids.

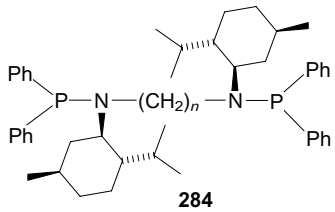
The studies[182, 183] describing attempted preparation of optically active α-amino acids from unsaturated precursors are of particular interest. Fiorini *et al.*[182] utilized rhodium chelate complexes with chiral aminophosphines, in particular, those containing a menthyl substituent (*e.g.*, compound **284**), to catalyze the asymmetric hydrogenation of alkenes. The reduction of cinnamic and acrylic acid derivatives proceeds with high enantioselectivity (70% – 93% *ee*).

Kinting *et al.*[183] paid primary attention to the synthesis of catalytic systems representing rhodium complexes with chiral phosphines **285a – c**. The chiral induction was accomplished by the menthyl group. The authors studied the homogeneously and heterogeneously catalyzed hydrogenation of substrates such as 2-acetamidocinnamic acid, 2-acetamidoacrylic acid and itaconic acid, which are prochiral precursors of optically active acids. For the preparation of the heterogeneous catalyst, the appropriate chiral phosphine ligands were immobilized on the silica gel surface. It was found that immobilized complexes are more stable and selective than their homogeneous soluble analogues. The hydrogenation of acetamidocinnamic and itaconic acids

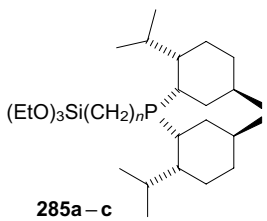
Structures 283 – 285



283



284



285a – c

n = 1 (**a**), 3 (**b**), 5 (**c**)

catalyzed by these complexes results in high optical yields (87% and 83%, respectively).

Bunlaksananusorn *et al.*[184] described the synthesis of several chiral P,N-donor pyridine ligands based on (+)-camphor and (+)-nopinone and their iridium(II) complexes. The iridium complexes obtained using two ligands (**286a**,**b**) were tested as catalysts for asymmetric hydrogenation of substituted styrenes **287a**,**b** giving products **288a**,**b** (Scheme 24, Table 9). Virtually all of these catalytic systems were highly efficient and highly selective, providing *ee* values above 90% for substrate conversion being 100%.

Scheme 24

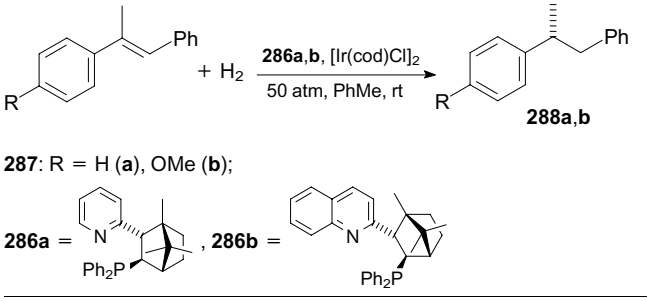


Table 9. Effect of ligand nature on the enantioselectivity of Ir-catalyzed hydrogenation of substituted styrenes (see Scheme 24).[184]

Ligand	Starting alkene	Conversion (%)	*ee* (%) [a]
286a	**287a**	100	95
286a	**287b**	87	91
286b	**287a**	100	95
286b	**287b**	100	95

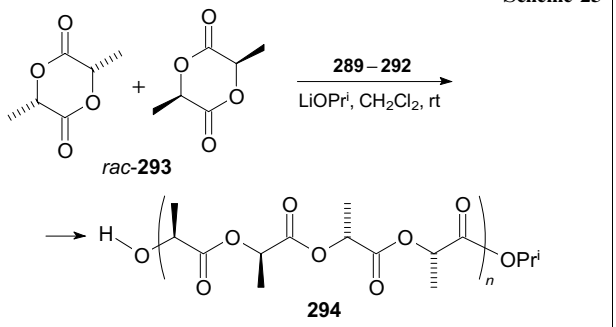
[a] The value for enantiomer (*R*)-**288** is indicated.

3.9. Stereoselective polymerization

In recent years, the success of chiral palladium complexes in the asymmetric catalysis has been shared by coordination compounds of other metals such as copper, zinc, nickel and cobalt. Kwon *et al.*[185–187] reported the synthesis of zinc and copper complexes **289** – **292** containing camphor imine derivatives as N,N-donor ligands. The structures of these compounds were proved by X-ray diffraction.

The prepared chiral zinc and copper complexes (as their alkoxy derivatives generated *in situ*) were studied and were found to have high catalytic activity in the stereoselective ring opening polymerization of racemic lactide **293** (Scheme 25). The reaction affords heterotactic polylactide **294** with a narrow polydispersity index (1.26 – 1.34). In the presence of copper complex **290a**, the resulting polymer has a higher degree of polymerization (number-average molecular mass of 14 000 Da) than the polymer formed in the presence of zinc complexes (7500 – 8500 Da).

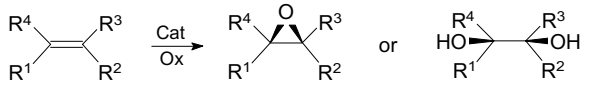
Scheme 25



3.10. Epoxidation reactions

The asymmetric catalytic oxidation of alkenes to epoxides or diols under the action of an oxidant (Ox) is a reliable routine synthetic route to chiral oxygen-containing derivatives (Scheme 26). Exhaustive data on various types of chiral catalytic systems used in these reactions is presented in reviews.[188, 189] The search for new catalysts is in progress; terpene ligands were also tested for asymmetric induction in the epoxidation.

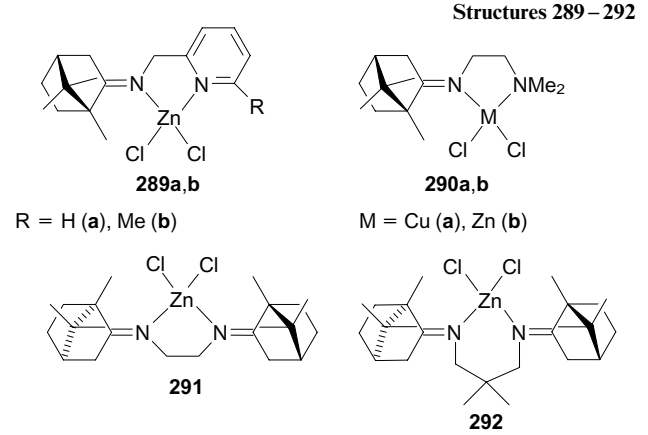
Scheme 26



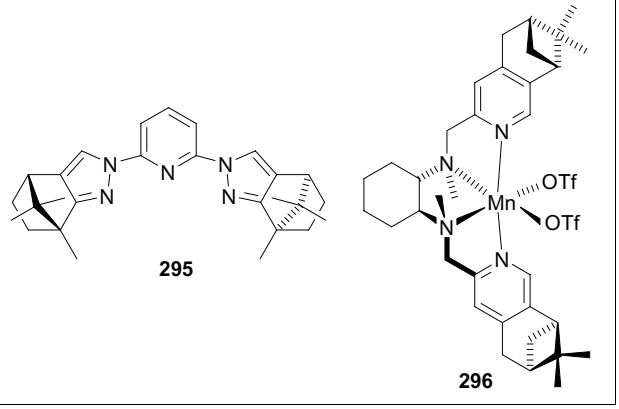
Fung *et al.*[190] prepared a ruthenium(IV) oxo complex based on ligand **295**. In the Ru-catalyzed asymmetric epoxidation of styrene and its derivatives, this complex showed moderate enantioselectivity (35% – 38% *ee*).

Costas and co-workers[191] investigated the catalytic epoxidation of alkenes in the presence of a salen type manganese(II) complex [Salen is *N*,*N*′-ethylenebis(salicylimine)] (**296**) containing a tetradentate terpene-pyridine

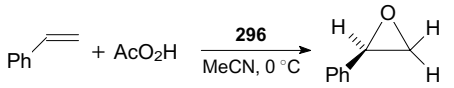
Structures 289 – 292



Structures 295, 296



Scheme 27



297 (80%, 40% *ee*)

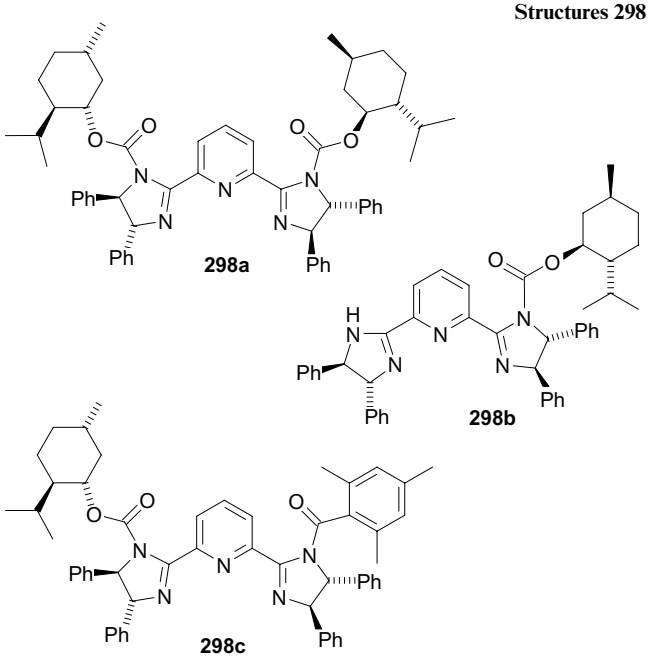
ligand (Scheme 27). The conditions of this reaction were optimized. The best results were obtained for styrene oxidation with peracetic acid in acetonitrile at 0 °C: the yield of epoxide **297** was 80% and *ee* was 40%. Epoxidation of a broad range of aromatic and aliphatic alkenes was performed under these conditions. The highest enantioselectivity (but *ee* not higher than 43%) was observed for styrene derivatives.

While considering the mechanism of reactions they studied, the authors noted an analogy between the action of these catalysts and classical salen type complexes;[192] in the authors' opinion, alkene epoxidation should be regarded as a concerted process in which the active oxygen is transported by high-valence $Mn^{V}O$ oxo species. This mechanism is evidenced by the fact that configurations of the starting *cis*- and *trans*-alkenes are retained during epoxidation. The possibility of alternative mechanisms, both radical and ionic ones, was not ruled out either.

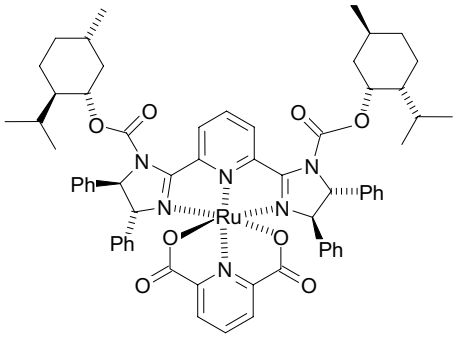
A series of tridentate pyridine-bis(imidazole) ligands, including menthyl-containing ligands **298a** – **c**, were prepared at the Leibniz Institute for Organic Catalysis (Rostock, Germany).[193] These chiral ligands were tested in the Ru-catalyzed asymmetric epoxidation of styrene and *trans*-stilbene (Scheme 28). Ruthenium(II) complexes were either prepared in a pure state or generated *in situ*. Complex **299** showed the best catalytic performance. For example, in the presence of this complex, *trans*-stilbene epoxide **300** was isolated in 97% yield with enantiomeric purity of 71%.

Pyridine ethers containing a menthyl (**301**, **302**) or pinane (**303**) moiety were introduced into epoxidation of a number of prochiral alkenes.[194, 195] These chiral ligands

Structures 298

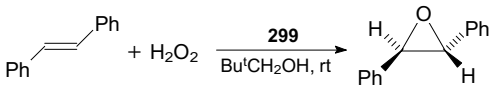


Structure 299



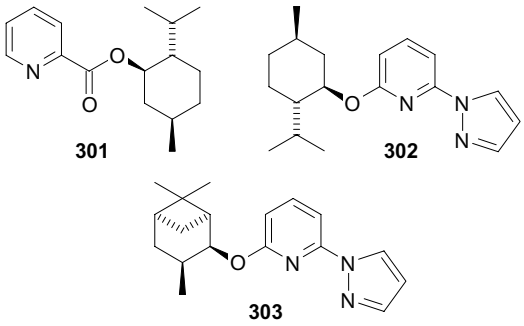
299

Scheme 28



300 (97%, 71% *ee*)

Structures 301 – 303



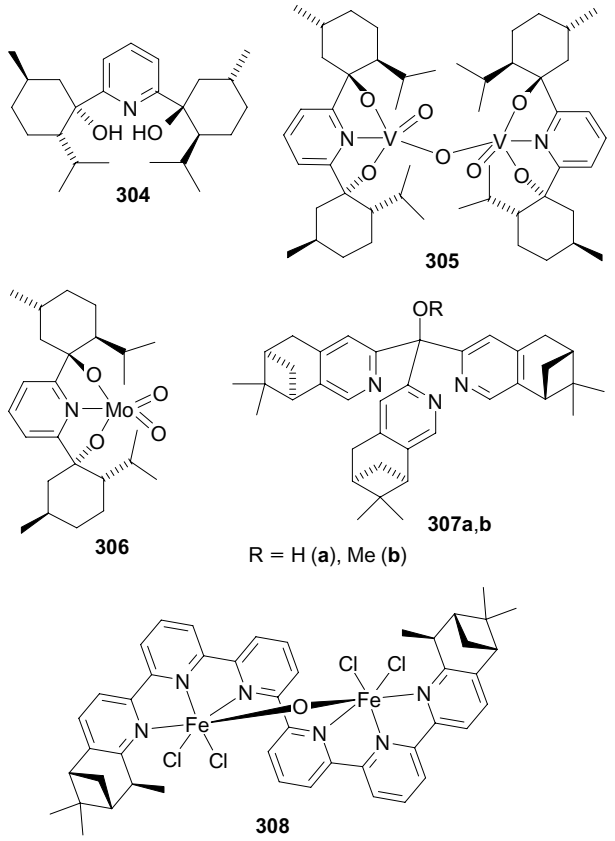
were used as precursors for rhenium(VII)- (Ref. 194) and molybdenum(VI)-catalyzed reactions.[195] However, these catalytic systems had very low enantioselectivity (2% – 12% *ee*).

Menthylpyridine ligand **304** and molybdenum(VI) and vanadium(V) oxo complexes with this ligand were reported by Bellemin-Laponnaz *et al.*[196] Catalysts **305** and **306** were active in asymmetric epoxidation of cyclohexene with enantioselectivity of up to 25%.

As shown above, the Swiss research team headed by von Zelewsky synthesized a large group of fused polycyclic terpene-pyridine ligands and studied their unique spatial structures (see Section 2.4). These ligands are actively used in asymmetric metal-catalyzed transformations. In particular, Sala *et al.*[197] described the synthesis of N,N,N-donor ligands **307a**,**b**. The ruthenium(II) complex prepared from ligand **307b** exhibited an moderate enantioselectivity in styrene epoxidation (36% *ee*).

Kwong and co-workers[198] prepared a pinane ligand containing six pyridine rings and iron(II) complex with this ligand (compound **308**). The catalytic activity of this complex was tested in the epoxidation of various alkenes. In particular, it was shown that epoxidation of styrene proceeds with a virtually 100% conversion in 3 min, with the enantioselectivity reaching 42%. After the catalytic cycle, the iron complex can be regenerated with a minor loss ($\sim$10%).

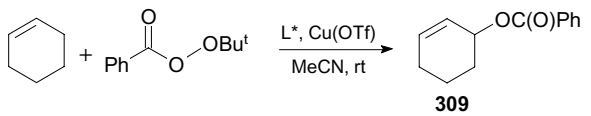
Structures 304 – 308



3.11. Allylic oxidation

The asymmetric allylic oxidation of cyclic alkenes (Kharasch – Sosnovsky reaction) is catalyzed most efficiently by copper(I) complexes. In the presence of chiral ligands, it is possible to obtain non-racemic oxidation products — allylic esters (*e.g.*, compound **309**). The oxidation of cyclohexene with *tert*-butyl perbenzoate was chosen as the model reaction in many of the studies discussed below (Scheme 29). Terpene ligands that were tested in this reaction are described in a number of publications.[199 – 205]

Scheme 29



Kwong and co-workers[202] reported the results of studying N,O-donor bipyridine ligands **215** – **218** and **310** – **313** in the copper-catalyzed allylic oxidation of alkenes with *tert*-butyl perbenzoate. The reaction was carried out at room temperature in acetonitrile using the appropriate ligands and copper(I) salts as precursors for the *in situ* formation of catalytic systems. It was found that variation of copper(I) salts has a pronounced effect on both the enantioselectivity of the reaction and the catalytic activity of the complex. Cyclopentene, cyclohexene, cycloheptene and cyclooctene were used as substrates for oxidation. All of the catalytic systems proved to be quite efficient towards the allylic oxidation of cyclo-

Structures 310 – 313

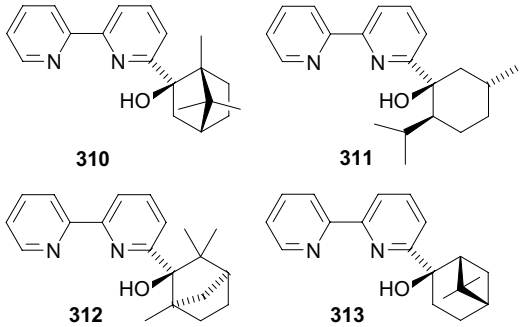


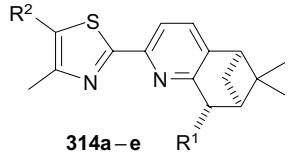
Table 10. Effect of ligand nature on the enantioselectivity of Cu-catalyzed allylic oxidation of cyclohexene (see Scheme 29).

Ligand	Yield of **309** (%)	Configuration	*ee* (%)	Ref.
216	57	*R*	52	202
215	79	*R*	22	202
217	44	*R*	31	202
218	47	*R*	30	202
310	43	*S*	65	202
314a	75	*R*	62	199
314b	95	*R*	61	199
314c	62	*R*	62	199
314d	63	*R*	55	199
314e	95	*R*	58	199
315	95	*S*	49	201
316	74	*S*	19	201
317	58	*S*	55	201
318	98	*R*	66	201

alkenes. Table 10 presents selected results on the oxidation of cyclohexene under optimized conditions. The highest enantioselectivity was provided by bornane ligands **216** and **310** (52% and 65% *ee*, respectively).

Thiazole ligands **314a** – **e** were also tested in the copper-catalyzed asymmetric oxidation of cyclohexene.[199] The enantioselectivity (50% – 60% *ee*) was comparable with that for bipyridine analogues, which were reported by Kocovsky and co-workers.[200, 201]

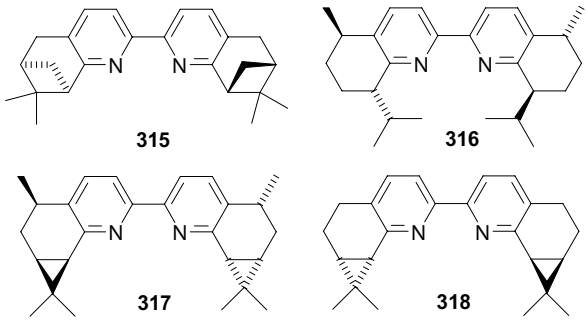
Structures 314



$R^1 = Pr^i$, R^2 = H (**a**);
$R^1 = R^2 = Pr^n$ (**b**), Bu^n (**c**),
Bn (**d**), CH_2SiMe_3 (**e**)

Kocovsky and co-workers[201] described the synthesis of bipyridine ligands containing pinane (**315**), menthane (**316**) and carane (**317**, **318**) moieties. The authors studied the enantioselectivities of various asymmetric reactions involving these compounds, in particular, copper-catalyzed allylic oxidation of cyclohexene. Copper(I) complexes with these ligands generated *in situ* showed high activity (the yields of oxidation product were up to 98%) and moderate enantioselectivity (up to 66% *ee*). If one compares the results obtained under similar conditions,

Structures 315 – 318

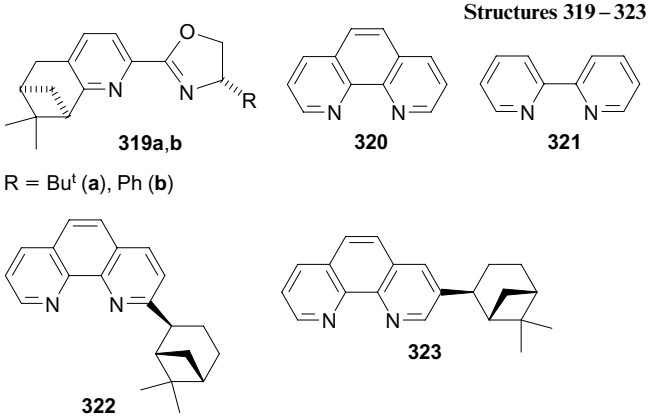


the catalytic system with menthane ligand **316** would turn out to be the least selective (19% *ee*).

In the subsequent studies, these authors expanded the range of pinane-pyridine ligands they studied. They synthesized derivatives **319a**,**b** containing an additional chiral centre in the oxazoline ring.[206] Testing the ligands in copper-catalyzed asymmetric allylic oxidation showed that the enantioselectivity of cyclohexene oxidation in the presence of ligands of this group did not exceed 60%.

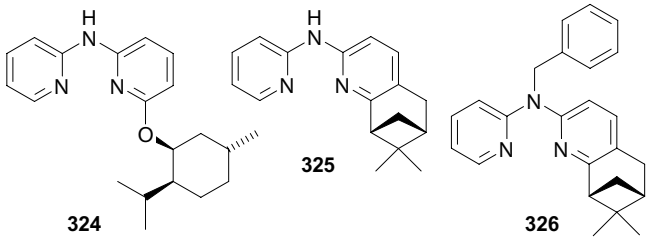
Chellucci *et al.*[205] comprehensively studied the effect of the structure of bipyridine (**122**, **123**) and phenanthroline (**322**, **323**) ligands containing terpene moieties on the catalytic activity of copper(I) complexes with these ligands towards the allylic oxidation of cyclohexene (see Scheme 29). Unsubstituted phenanthroline (**320**) and bipyridine (**321**), which do not show catalytic activity, were used for comparison. Unexpectedly, it was found that ligands **123** and **323** were also catalytically inactive. Thus, substitution of the pyridine ring in position 6 is a necessary condition for success: ligands **122** and **322** furnished allylic ester in 79% and 75% yields, respectively; however, the enantioselectivity was not higher than 20% in both cases.

Structures 319 – 323



Bolm *et al.*[204] investigated dipyridine ligands with an amine bridge containing a menthane (**324**) or pinane (**325**, **326**) moiety. These ligands had a very low selectivity in the allylic oxidation of cyclohexene: in the case of compound **326**, *ee* did not exceed 19%.

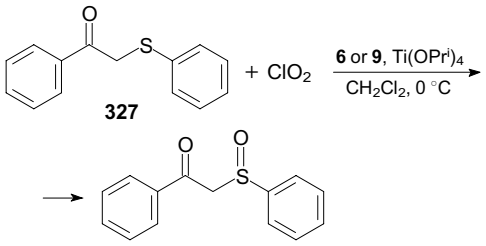
Structures 324 – 326



3.12. Asymmetric oxidation of sulfides

Asymmetric oxidation of sulfides is actively studied at the NIOC SB RAS and the Institute of Chemistry (Komi Science Centre of the Ural Branch of the RAS) with the goal to obtain enantiomerically pure biologically active sulfoxides with a chiral S-centre. The reactions are catalyzed by metal complexes in the presence of chiral terpene ligands. In particular, EDA derivatives **6** and **9** were tested as the ligands.[207 – 209] The oxidation of phenyl phenacyl sulfide **327** was conducted under various conditions in the presence of titanium(IV) or vanadium(IV) complexes formed *in situ* (Scheme 30). In some cases, satisfactory results were obtained: the yield of product **328** reached 80% with an enantiomeric purity of 47%.

Scheme 30



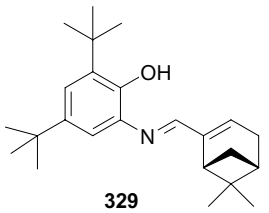
328 [69% – 80%, (6% – 47%) *ee*]

A series of terpene derivatives, Schiff bases, were synthesized to be used as chiral ligands in the asymmetric oxidation of various sulfides. A series of publications[210 – 215] are of interest as examples of efficient multistep syntheses. Imines **329** and **330** were prepared using the monoterpene (−)-myrtenal as the starting compound.[212] Imine **331** was obtained from the sesquiterpenoid caryophyllene.[212] Schiff bases **332**, **333** and **334a** – **j** were synthesized from (+)- and (−)-α-pinenes,[211] while imines **335a** – **f** were derived from (+)-3-carene.[210, 215] Il'ina *et al.*[213] described imines **336a**,**b** obtained using verbenol as the starting compound.

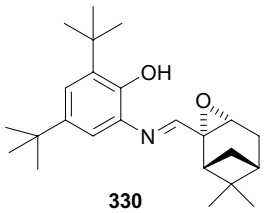
Schiff bases **332** and **333** with terpene and phenol moieties were investigated as chiral components of vanadium-containing catalytic systems in the model asymmetric oxidation of aryl sulfides **337a** – **c** to sulfoxides **338a** – **c** (Scheme 31).[210, 211, 213]

The asymmetric oxidation of sulfide **339** served as the basis for a new synthesis of esomeprazole (**340**), a clinically important antiulcer drug, which is widely and successfully used in practical medicine (Scheme 32).[215] The reaction is conducted in the presence of vanadyl complexes and chiral terpene Schiff bases, namely, ligands

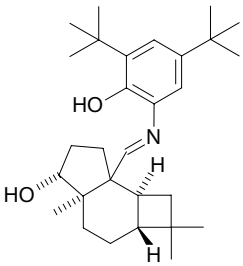
Structures 329 – 336



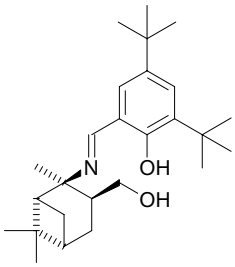
329



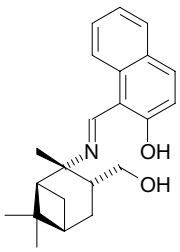
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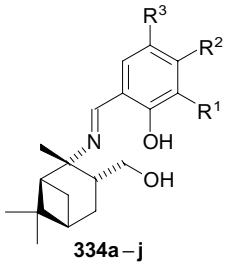
331



332

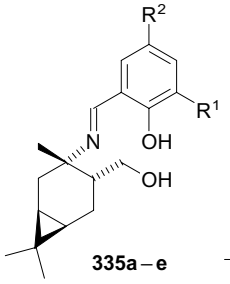


333

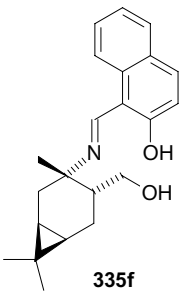


334a – j

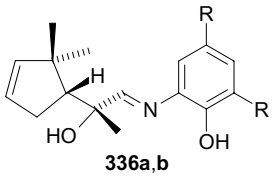
$R^1 = R^3 = Bu^t$, $R^2 = H$ (**a**);
$R^1 = R^2 = R^3 = H$ (**b**);
R^1 = , $R^2 = H$, $R^3 = Me$ (**c**);
$R^1 = R^3 = Me_2CPh$, $R^2 = H$ (**d**);
$R^1 = R^2 = H$, $R^3 = NO_2$ (**e**);
$R^1 = R^3 = NO_2$, $R^2 = H$ (**f**);
$R^1 = R^2 = H$, $R^3 = OMe$ (**g**);
$R^1 = OMe$, $R^2 = R^3 = H$ (**h**);
$R^1 = R^3 = H$, $R^2 = NEt_2$ (**i**);
$R^1 = Br$, $R^2 = NEt_2$, $R^3 = NO_2$ (**j**)



335a – e



335f

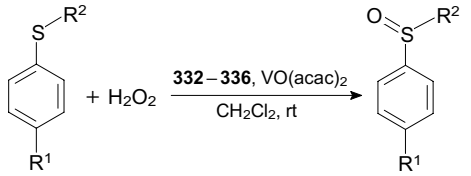


336a,b

R = H (**a**), Bu^t (**b**)

$R^1 = R^2 = Bu^t$ (**a**), H (**b**), NO_2 (**c**);
$R^1 = H$, $R^2 = OMe$ (**d**);
$R^1 = OMe$, $R^2 = H$ (**e**)

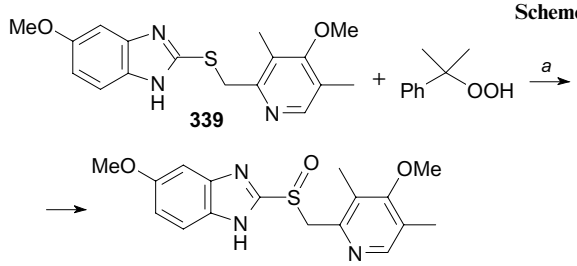
Scheme 31



337a – c **338a – c** [91% – 100%, (0% – 31%) *ee*]

$R^1 = H$: $R^2 = Me$ (**a**), Bn (**b**);
$R^1 = Br$, $R^2 = Me$ (**c**);
acac is acetylacetonate

Scheme 32



339

340 [80% – 99%, (2% – 31%) *ee*]

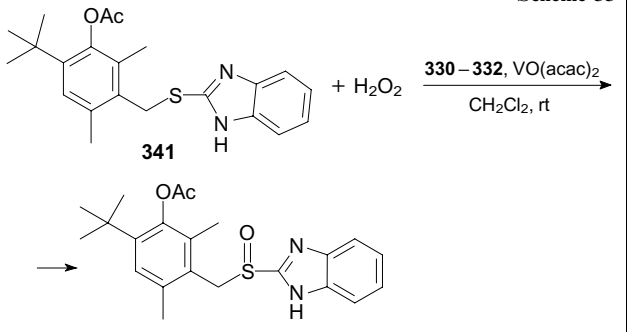
(*a*) **330 – 334**, $VO(acac)_2$, $PhPr^i$, 0 – 5 °C

330 – 334. The best stereochemical outcome (31% *ee*) was obtained with ligand **334b**.

Koneva *et al.*[215] gave a brief analysis of literature data on sulfide oxidation. It was noted that the first catalytic method for enantioselective oxidation of sulfide **339** proposed in 1996 [216] was based on a modification of the Kagan method. The application of the classical Kagan method,[217] consisting in sulfide oxidation with organic peroxides in the presence of $Ti(OPr^i)_4$ and optically active diethyl tartrate, resulted in the formation of a nearly racemic sulfoxide **340**.[216] It was found that the introduction of amines as bases into catalytic systems makes it possible to reach a high enantiomeric purity for esomeprazole (~100% *ee*); however, the product yields did not exceed 50%. Koneva *et al.*[215] used modification of the Bolm method [218] according to which sulfides are oxidized with aqueous hydrogen peroxide in the presence of a catalytic amount of a vanadyl complex with chiral Schiff bases.

Vanadium-containing oxidative systems containing ligands **330 – 332** were applied [218] for converting sulfide **341** to sulfoxide **342**, a structural analogue of esomeprazole (Scheme 33).

Scheme 33



341

342 [60% – 95%, (1% – 21%) *ee*]

All of the above-mentioned studies carried out by Novosibirsk researchers include thorough optimization of the conditions for transition metal-catalyzed asymmet-

ric oxidation of sulfides. In order to elucidate the influence of steric and electronic factors on the enantioselectivity, the authors evaluated a broad range of semisynthetic Schiff bases as chiral ligands, differing in both the terpene moiety and the nature of substituents in the aromatic aldimine moiety. No clear patterns were found for this influence. Most often, the chemical yields of sulfoxides were rather high: 80% – 99%; however, the enantioselectivity of sulfide oxidation was moderate: the best result was 37% *ee*.

4. Biological activity of metal complexes containing terpene ligands

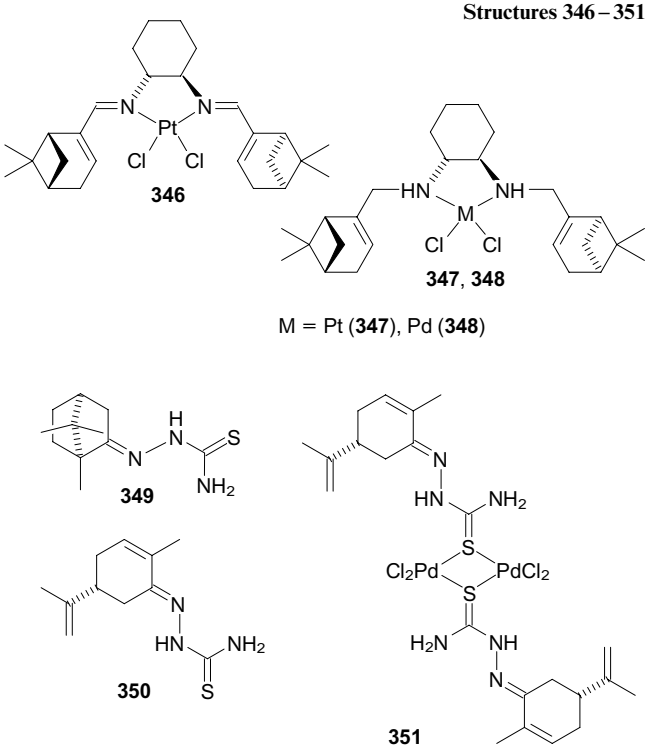
Metal complexes with diverse chiral ligands are widely investigated as promising prodrugs. Some reviews [219 – 222] are devoted to the most recent achievements and prospects for the application of metal complexes as anticancer agents. However, despite large diversity of the synthesized terpene-containing ligands and metal complexes based on them, the biological activity of these compounds has been scarcely studied.

Since the discovery of the anticancer activity of cisplatin,[223] platinum diamine complexes have been actively studied and already used in cancer therapy. An example of such agents is oxaliplatin (**343**), which is a platinum(II) oxalate complex containing a 1,2-diaminocyclohexane ligand. Amr *et al.*[224] synthesized terpene analogues of oxaliplatin — complexes **344** and **345** — based on pentacyclic triterpenoids (glycerrhetic and ursolic acid derivatives). The cytotoxicity of these complexes was assessed using the HT-29 colon carcinoma cell line. Under comparable conditions (incubation time of 48 h; concentration of the test agent of 100 mg ml^{-1}), the cancer cell death rate in the presence of these compounds was 44% (for **343**), 79% (**344**) and 86% (**345**).

The synthesis of platinum (**346**, **347**) and palladium (**348**) complexes based on bidentate ligands containing enantiomerically pure pinene moieties has been described.[225] Evaluation of the anticancer activity in L1210 leukemia cells demonstrated that complexes **346** – **348** suppress the cell growth more efficiently than commercial oxaliplatin (**343**). The half-maximal inhibitory concentration IC_{50} (concentration of the agent needed to kill 50% of cells) was 10.2 μmol litre^{-1} for compound **343** and 0.7 and 0.6 μmol litre^{-1} for platinum complexes **346** and **347**, respectively.

Novosibirsk researchers,[42, 43] who have a large inventory of synthesized terpene ligands and metal complexes of various types at their disposal, assessed the biological activity of these compounds. Optically active complexes of

Structures 346 – 351

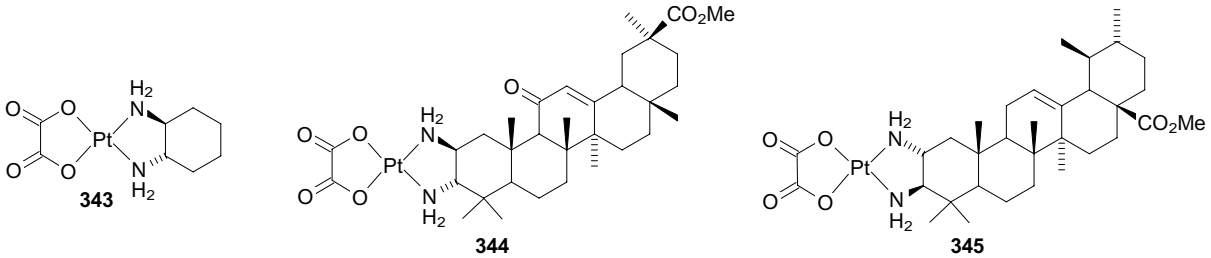


(+)-camphor thiosemicarbazone (**349**) — $[Zn(\mathbf{349})_2Cl_2]$, [Cu(**349**)Cl] and $[Pd_2(\mathbf{349})_2Cl_4]$ — were prepared and tested for cytotoxic activity.[43] The influence of (−)-carvone thiosemicarbazone (**350**) an its Pd complex **351** on cell viability was assessed in Hep2 adenocarcinoma cells (laryngeal cancer). The palladium complex exhibited markedly higher cytotoxicity than the free ligand: after 48 h incubation, the cell death rate reached 60% for complex **351** and 20% for ligand **350** (at 50 μmol litre^{-1} concentration).

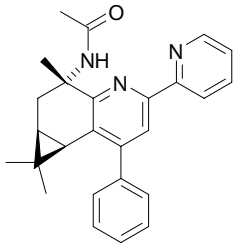
Kokina *et al.*[42] reported the data on the cytotoxic activity of ligand **349** and its complexes $[Zn(\mathbf{349})_2Cl_2]$, [Cu(**349**)Cl] and $[Pd_2(\mathbf{349})_2\,Cl_4]$ against the MCF-7 breast cancer cell line. For the free ligand, the IC_{50} value exceeded 50 μmol litre^{-1}, while for the complexes IC_{50} were in the range from 9.8 to 14.0 μmol litre^{-1}. The nature of the metal had almost no effect on the cytotoxic activity of the complexes under these conditions.

Carane-bipyridine ligand **352** and tetranuclear copper(I) complex $[Cu_4(\mathbf{352})_3I_4]$ were tested in Hep2 cell line.[51] It was additionally shown that complexation enhances the cytotoxic effect observed for the free ligand, which results in a

Structures 343 – 345



Structure 352



352

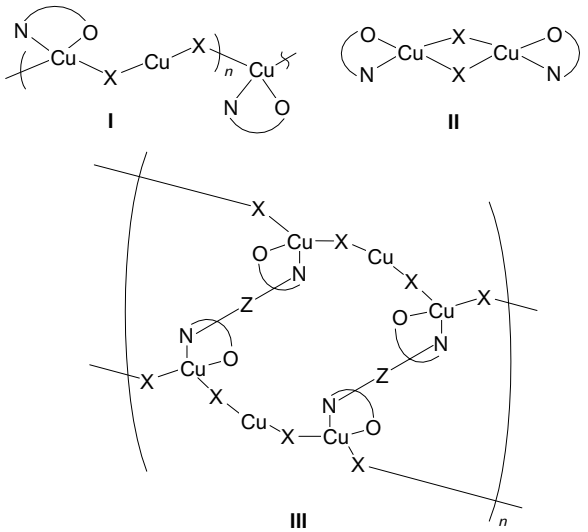
more than twofold decrease in IC_{50} for $[Cu_4(\mathbf{352})_3I_4]$ ($IC_{50} = 13.0 \pm 1.7$ μmol litre^{-1}) in comparison with free ligand **352** ($IC_{50} = 30.5 \pm 0.5$ μmol litre^{-1}). It is noteworthy that these cytotoxic agents had a much higher efficiency than thiosemicarbazone **350** and palladium complex **351** reported by Kokina *et al.*[43]

Fernandes *et al.*[226] studied the cytotoxicity of three types of polynuclear copper(I) complexes and camphor derivatives. Linear coordination polymers **I** and dimers **II** were prepared from camphorquinone hydrazones **353** – **356**, while double chain polymers **III** were derived from diimines **357** and **358**. The comparative influence of these compounds on the cell viability was assessed in the HT29 adenocarcinoma cell line. The copper complexes were not superior in the cytotoxic activity over the clinically known cisplatin with $IC_{50} = 26.3 \pm 1.1$ μmol litre^{-1}. Note the influence of the nature of the halide present in the molecule. For example, for the chloride coordination polymer **I** (X = Cl), $IC_{50} = 56.8 \pm 1.2$ μmol litre^{-1}, whereas for the bromide analogue (X = Br), this value is twice higher ($IC_{50} = 119.9 \pm 1.1$ μmol litre^{-1}). The structural changes in the ligand within complexes of the same type have virtually no effect on the cytotoxic activity (*e.g.*, IC_{50} for the group of chloride complexes **I** varies from 37 to 57 μmol litre^{-1}).

Copper(II), iron(III) and manganese(III) complexes (compounds **359** – **361**) based on a salen type ligand were synthesized from camphoric acid.[227] The cytotoxic activity of these complexes was tested in four cancer cell lines (HCC1806, MCF7, LS1034, WiDr). All of the agents were cytotoxic with $IC_{50} \leqslant 23$ μmol litre^{-1}. The best results were obtained for copper complex **359**, furthermore for all cell lines. For example, in the case of WiDr cells (colon cancer), the IC_{50} value for complex **359** was 1.24 μmol litre^{-1}, whereas for the chemotherapeutic agent 5-FU (5-fluorouracil), IC_{50} is 86.96 μmol litre^{-1}.

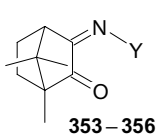
It is worth noting that Silva Serra *et al.*[227] drew a correlation between electrochemical data for metal complexes and the data on cytotoxic activity. An important aspect of the mechanism of biological activity of metal complexes is the possibility of redox reactions, which is due to the ability of the metal to easily change the oxidation state. This feature of complexes **359** – **361** was studied by differential pulse voltammetry. Copper complex **359** has a substantially larger electrochemical gap than iron (**360**) and manganese (**361**) complexes (2.3 V for Cu^{II}; 1.67 V for Fe^{III}; and 1.62 V for Mn^{III}). This accounts for higher stability of the copper complex to reduction and, hence, higher cytotoxic activity of complex **359**. These conclusions are not indisputable; nevertheless, with a reliable proof on numerous examples, this approach may be suitable for deriving structure – biological activity relationships for metal complexes.

Structures I – III



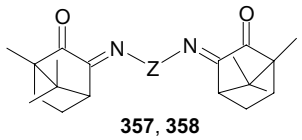
I **II** **III**

Structures 353 – 358



353 – 356

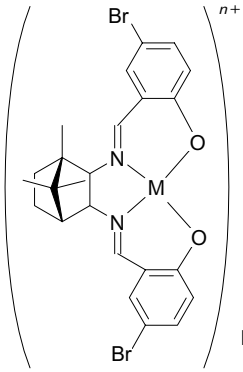
Y = NMe_2 (**353**), NH_2 (**354**), NHMe (**355**), $C_6H_4NH_2$-4 (**356**)



357, **358**

Z = *p*-phenylene (**357**), *m*-phenylene (**358**)

Structures 359 – 361

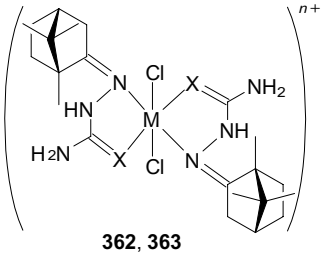


359 – 361

M = Cu^{II} (**359**), Fe^{III} (**360**), Mn^{III} (**361**);
n = 0 (**359**), 1 (**360**, **361**)

Balancing of the cellular redox metabolism is a promising approach to the therapy of quite a number of diseases. Most researchers believe that violation of redox processes in the body is related, first of all, to intensive formation of free radical species. The fraction of these species can be decreased by means of antioxidants. A relevant task is to search for new biologically active antioxidants among coordination compounds of transi-

Structures 362, 363



X = S: M = Fe^{III} (**362**-Fe), Co^{II} (**362**-Co), Cu^{II} (**362**-Cu);
X = O: M = Fe^{III} (**363**-Fe), Co^{II} (**363**-Co), Cu^{II} (**363**-Cu)
n = 0 (Co^{II}, Cu^{II}), 1 (Fe^{III})

362, **363**

Table 11. Antioxidant activity of metal complexes.[228]

Compound	IC_{50}/ μg ml^{-1}	Compound	IC_{50}/ μg ml^{-1}
AA	136.0	**362**-Cu	111.0
362-Fe	172.0	**363**-Fe	190.0
362-Co	> 1000	**363**-Co	> 1000
		363-Cu	> 1000

tion metals that contain bioligands or their hybrid forms. Indian researchers[228] reported the synthesis and antioxidant activity evaluation for Fe^{III}, Co^{II} and Cu^{II} complexes containing bidentate ligands — camphor thiosemicarbazone and semicarbazone (structures **362** and **363**). The results are summarized in Table 11 as the IC_{50} values corresponding to concentrations (in μg ml^{-1}) of added compounds providing a 50% inactivation of 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radicals. Results comparable with that of the reference compound, ascorbic acid (AA), were found for iron complexes **362**-Fe and **363**-Fe; the replacement of the oxygen atom in the ligand by sulfur virtually does not affect the activity of these metal complexes. Cobalt complexes **362**-Co and **363**-Co do not exhibit antioxidant behaviour under analogous conditions.

The above-presented data on the biological activity of the terpene-containing metal complexes indicate that this group of compounds deserves more extensive systematic research. Currently, it is difficult to ascertain what particular factor has a crucial influence on the biological activity of metal complexes, either the nature of the metal or the type of the terpene ligand, because no descriptions of correctly designed comparative experiments are available.

5. Conclusion

In this review, we tried to integrate, as fully as possible, systematically arrange and analyze the data published in the literature on the synthesis and properties of transition metal complexes with terpene ligands. A large body of valuable information, which is beyond the scope of this review, but would undoubtedly be of interest for synthetic chemists, can be additionally derived from the cited publications. Among this information are methods of chemical modification of natural terpenoids and synthesis of hybrid compounds.

In total, there are more than a thousand synthesized and described terpene ligands that were used to prepare metal complexes of various types or were used as precursors in the asymmetric catalysis by metal complexes. Terpene-pyridine ligands form the most numerous group. The most interesting results concerning the stereoselectivity of complexation and their enantioselective properties in catalytic reactions were also obtained for this group of ligands.

The first part of the review devoted to the synthesis of metal complexes is significantly supplemented by the information presented in the following parts. Most papers discussed as examples of using terpene ligands in asymmetric catalysis present also comprehensive information on the synthesis of ligands and metal complexes based on them. Most often, the catalytic properties of these systems are studied for practical purposes. The range of reactions is rather extensive. The results indicate that terpene ligands can show high asymmetric induction. For some reactions, high enantioselectivity was regularly attained, for example, for palladium-catalyzed allylic substitution and C – H-activation/cross-coupling reactions and copper-catalyzed cyclopropanation reactions in the presence of terpene-pyridine ligands. Ethylenediamine terpene derivatives are fairly efficient as catalytic ligands and provide high enantioselectivity of the addition of diethylzinc to aldehydes, which proves good prospects for these ligands in asymmetric metal complex catalysis. However, there are virtually no publications reporting in-depth studies of the mechanism of stereodifferentiating action of terpene ligands and its dependence of the metal complex structure. Studies in this area would considerably contribute to the theoretical grounds of the asymmetric transition metal catalysis.

Despite the diversity of metal complexes based on terpene ligands, their potential biological activity has been little studied. Nevertheless, considering known examples, it was ascertained that transition metal complexes with terpene ligands are active as anticancer agents and antioxidants. It is expedient to carry out more systematic research in this area in order to elucidate the structure – property relationships and develop new pharmaceutical drugs.

We hope that the presented material would be of interest for researchers working both in the field of asymmetric catalysis and in the chemistry of biologically active compounds.

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