SYNTHESIS OF NEW CHIRAL DIPHOSPHINE LIGANDS PINENE DERIVATIVES AND THEIR APPLICATION IN ENANTIOSELECTIVE REACTIONS

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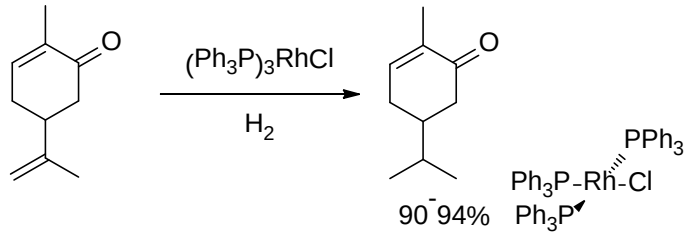
Nowadays, most of the reactions carried out in a laboratory as well as industrial scale utilize catalysts. They allow to increase efficiency, reduce time and sometimes even decrease expenses of processes. However, the use of catalysts on a big scale can be difficult because of recycling and values of catalysts. Cheap substrates and simple syntheses of ligands would solve these problems. Complexes of transition metals with bisphosphine ligands are successfully used as catalysts. Unfortunately bisphosphines are not cheap or easy to obtain. That is why there is a need to find the other ways of receiving chiral bisphosphine ligands in optically pure form, high yields and low costs. Natural compounds, such as monoterpenes are a good source of chirality. Terpenes are cheap and easily accessible. In this work, we attempted the synthesis of chiral ligands based on a rigid bicyclic structure of pinane.

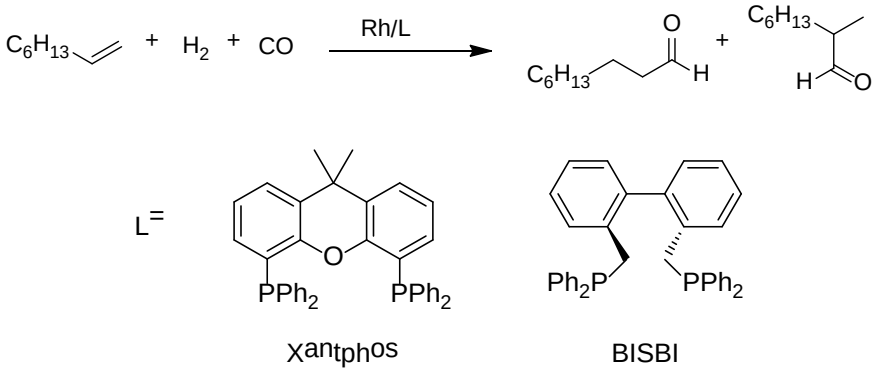
The discovery of the catalytic properties of [$RhCl(PPh_3)_3$], known as Wilkinson`s catalyst, in hydrogenation of olefins (*Scheme 1.*) opened the interest in this type of complexes. [1,2] An extension of these studies was the introduction of bisphosphine ligands.



Scheme 1. Hydrogenation with Wilkinson`s catalysts

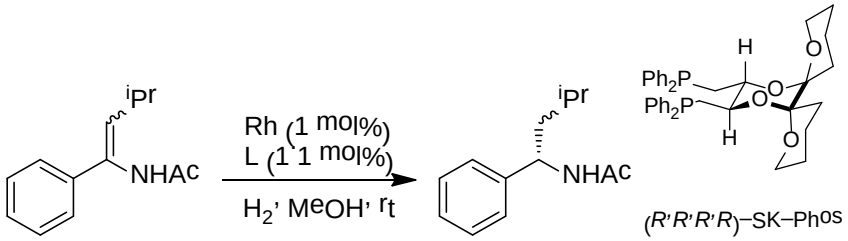
The most important property of bisphosphine structure is a bite angle. [3] It is an angle between phosphorus and metal atom. The way of coordination depends on a value of bite angle. [4] For P-donor ligands a P-M-P angle should be 120°. It determines chelation bis-equatorials. For both *Xantphos* and *BISBI* a value of this angle is close to the perfect one

(*Scheme 2.*). That is why they coordinate in position equatorial-equatorial in complexes with rhodium. These complexes catalyze the hydroformylation reaction (*Scheme 2.).* [4,5]



Scheme 2. Rhodium catalyzed hydroformylation with bisphosphine ligands

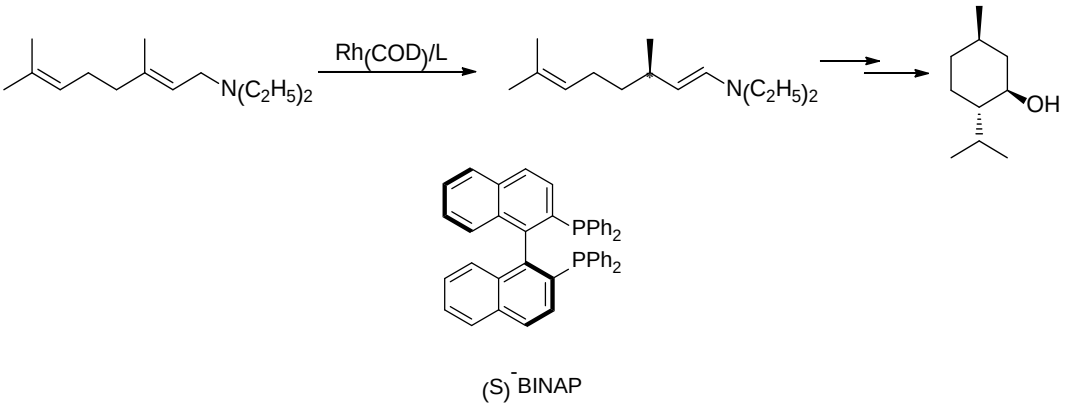
Metal complexes with chiral bisphosphine ligands can catalyze also asymmetric reactions. On these reactions bisphosphine ligands form with a metal chelating rings, which flexibility affects asymmetric reactions. [6]



Scheme 3. Asymmetric hydrogenation of enamide

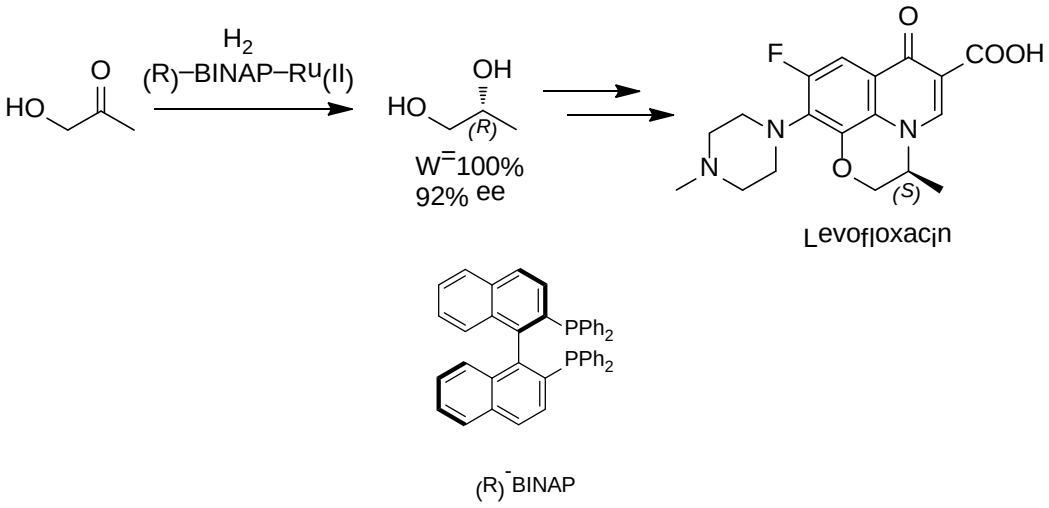
Asymmetric hydrogenation of N-(1-phenylvinyl)acetamide (*Scheme 3.*). catalyzed by the rhodium complex with (*R*,*R*,*R*,*R*)-Sk-Phos occurs with 98% enantiomeric excess. [7]

Another type of asymmetric reaction catalyzed by metal-bisphosphine complexes are isomerization. The best known compound with ruthenium are used as catalyst for asymmetric isomerization of allylamines to vinylamines is $[Rh\{(S)\text{-BINAP}\}(COD)]^+$. [8]



Scheme 4. Asymmetric isomerization of geranyldiethylamine

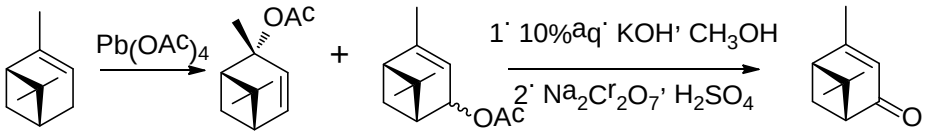
Isomerization of geranyldiethylamine in the presence of rhodium complex with BINAP is a key step in the industrial process of synthesis of L-menthol. [8] Both of BINAP`s enantiomers can be used as ligands. However, only (*S*)-BINAP leads to a natural menthol with 97%ee. [8] On the other hand, ruthenium-BINAP complex is used as a catalyst in asymmetric reduction of 2-hydroxyacetone. This reaction is used in production of antibiotic Levofloxacin (*Scheme 5.*). [9]



Scheme 5 Asymmetric hydrogenation of 2-hydroxyacetone

As it is shown above chiral bisphosphine ligands complexed with metals can be used in many catalytic reaction giving high yields and high stereoselectivities.

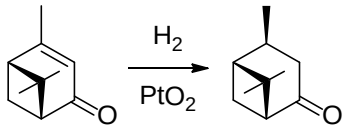
In our studies (+)–α–pinene as a substrate for the synthesis of region–isomers bisphosphorus ligands.



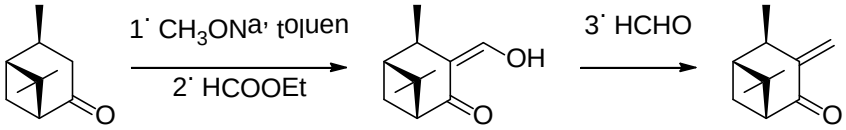
Scheme 6

In the first step, (+)–α–pinene ($[\alpha]_D^{22} + 47{,}1$) was oxidized with lead tetraacetate procedure. [10] The mixture of acetates was hydrolized under alkaline conditions and obtained alcohols oxidized to furnish (+)–verbenone (*Scheme 6*). A product of *Scheme 6* is (+)–verbenone. It was distilled under reduced pressure (bp. 81-83°C/6 mmHg) to yield 42% of verbenone with specific rotation $[\alpha]_D^{24} + 214$ (c 5,0, $CHCl_3$).

Hydrogenation of verbenone over Adams catalyst with 1 atm. of hydrogen proceeded only from less hindered side of the molecule. Product of this reaction ((1*R*,4*S*,5*R*)–4,6,6–trimethylbicyclo[3.1.1]heptan–2–one) was obtained in 93% yield (*Scheme 7*).

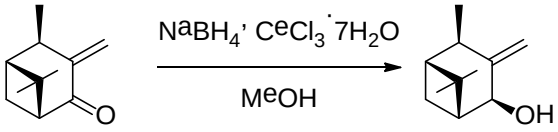


Scheme7



Scheme 8

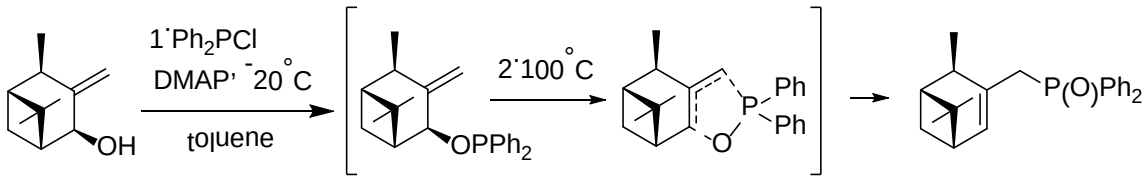
Next stape of the synthesis, presents on *Scheme 8* includes enolization of verbanone with sodium methoxide and condensation with ethyl formate followed by transaldolization with formaldehyde. The obtained product, (+)–α–methylene–verbanone, was isolated in 78% yield. After purifing cation of the ketone by column chromatography on silica gel (eluent: hexane:ethyl acetate 90:10) a specific rotation was $[\alpha]_D^{23} + 25$ (c 1,4; $CHCl_3$).



Scheme 9

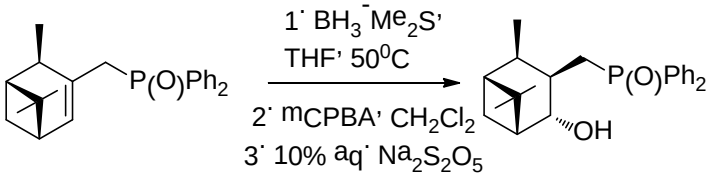
α,β–unsaturated ketone was then reduced to allylic alcohol using Luche protocol, which includes the reaction of carbonyl group within the presence of cerium (III) chloride in methanol (*Scheme 9*). This method allows the selective reduction of the carbonyl group in the α,β–unsaturated ketones, without reducing a double bond. Allylic alcohol was purified by column chromatography on silica gel (eluent: hexane:ethyl acetate 90:10) to give compound with $[\alpha]_D^{23} + 59$ (c 3,4; $CHCl_3$). Melting point of the product is 72–77°C.

The key step in the synthesis is the thermal [2,3]–sigmatropic rearrangement of allylic diphenylphosphinite to diphenylphosphine oxide (*Scheme 10*).



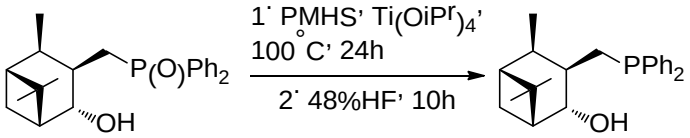
Scheme 10

Diphenylphosphinite was formed in the reaction of allylic alcohol with diphenylphosphine chloride in the presence of DMAP (–20°C). The phosphinite intermediate in high temperature undergoes [2,3]-sigmatropic rearrangement as it is shown on *Scheme 10*. The conversion of the intermediate into the phosphine oxide was followed by ^{31}P NMR ($ROPPh_2$ δ=113ppm; $RP(O)Ph_2$ δ=30ppm). Product was purified by column chromatography on silica gel (eluent: dichloromethane:diethyl ether50:50) to give an oxide in 98% yield, mp. 121–133°C, $[\alpha]_D^{25} - 98$ (c 2,4; $CHCl_3$).



Scheme 11

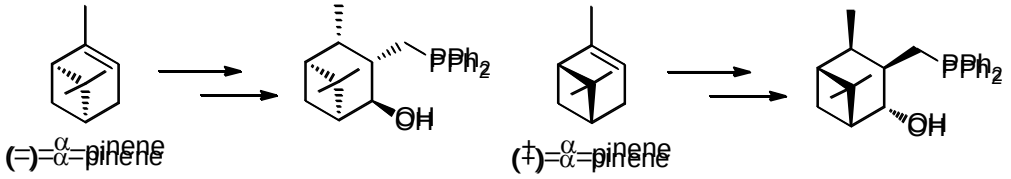
Allylic diphenylphosphine oxide was subjected to a hydrogenation–oxidation reaction in order to introduce a hydroxyl group. Hydroboration step was carried out with borane–dimethylsulfide adduct followed by the oxidation with m-chloroperbenzoic acid. A (((1*R*,2*R*,3*R*,4*R*,5*R*)–2–hydroxy–4,6,6–trimethylbicyclo[3.1.1]heptan–3–yl)methyl)diphenylphosphine oxide was purified by column chromatography on silica gel (eluent:dichloromethane:diethyl ether 10:90) to obtain 39% yield.



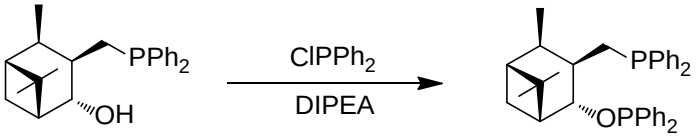
Scheme 12

In order to obtain phosphine derivative, phosphine oxide was reduced with poly(methylhydrosiloxane) in the presence of titanium (IV) isopropoxide (*Scheme 12*). Unfortunately, the yield of the phosphine (after column chromatography on silica gel with hexane:ethyl acetate 80:20) was only 22%.

The same protocol of synthesis was applied to (–)–α–pinane to furnish enantiomeric hydroxylphosphine (Scheme 13).



Scheme 13 Phosphine derivatives



Scheme 14

Conversion of the hydroxyl group into a leaving group and its substitution attempts with potassium diphenylphosphide have failed. For this reason, we conducted the reaction of hydroxyl group with chlorodiphenylphosphite substitution (*Scheme 14*).

Further studies towards the synthesis of the rhodium and iridium complexes with phosphine-phosphite ligands are continued.

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