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Right or left – this is the question (enantioselective catalysis with transition metal compounds)

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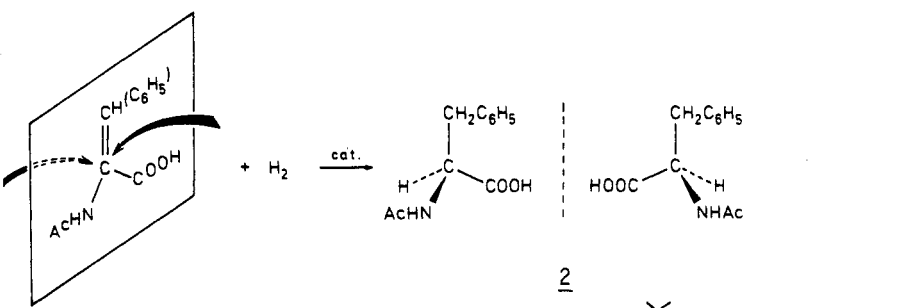
Abstract - New methods to prepare optically active phosphines for enantioselective transition metal catalysts are presented. The transfer hydrogenation of itaconic acid to give methylsuccinic acid using HCOOH is optimized to optical purity. The enantioselective monophenylation of meso-diols with $Cu(OAc)_2$/pyridineoxazoline catalysts is introduced as a new reaction. The stereochemistry of the stoichiometric cyclopropanation of styrene with the carbene ligand of a Fe complex is determined by the metal configuration, the optically active phosphine ligand making only a small contribution. Similarly, in the Khand-Pauson reaction of phenylacetylene with norbornene to give optically pure 3a,4,5,6,7,7a-hexahydro-2-phenyl-4,7-methano-1H-indene-1-one, the stereochemistry is determined by the cluster configuration and not by the optically active phosphine ligand. The conclusion is drawn that a control of the metal configuration during enantioselective catalysis would be of major importance for the optical induction.

INTRODUCTION

Enantioselective catalysis with transition metal compounds is a new approach to the synthesis of optically active compounds, needed in economy, starting from prochiral precursors. As the optically active catalyst reenters each catalytic cycle anew with its chiral information, it is a method to prepare large amounts of optically active compounds using only a small quantity of an optically active catalyst. Advantageously, the optically active catalyst is an in situ catalyst, consisting of a stable and commercially available metal compound (the procatalyst) and a stable and commercially available optically active ligand (the cocatalyst). The most celebrated example for this concept is the enantioselective hydrogenation of dehydroamino acids yielding amino acids. In Scheme 1 the most frequently used standard system is shown, the hydrogenation of (Z)-α-N-acetamidocinnamic acid 1 to give N-acetylphenylalanine 2 (ref. 1-3).

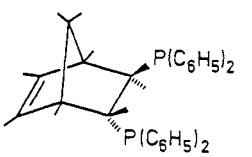
Scheme 1



1 2

cat.: $[Rh(cod)Cl]_2$/Norphos

Norphos =



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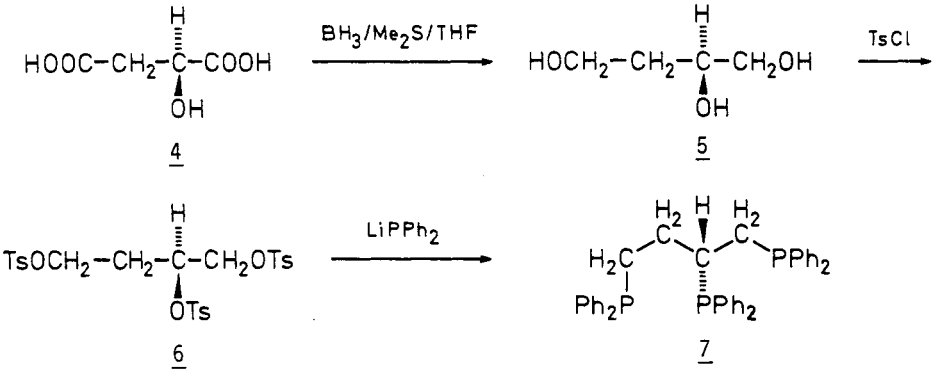
The procatalyst is a rhodium complex, such as $[Rh(cod)Cl]_2$, cod = 1,5-cyclooctadiene, and the cocatalyst is an optically active chelate phosphine, such as Norphos 3 (ref. 4,5). In this reaction N-acetylphenylalanine is formeded quantitatively and in an optical purity of close to 100 %. The oxide of Norphos (ref. 6) is resolved by dibenzoyltartaric acid, a methodology also applicable to the resolution of other phosphine oxides, e.g. the oxide of Binap (ref. 7). A large number of other optically active phosphines catalyzes the reaction of Scheme 1 as efficient as Norphos (ref. 1,2).

Optically active chelate phosphines are the best cocatalysts for transition metal catalysts in a variety of other reactions. However, in addition to the many optically active phosphorus ligands known to date, new optically active phosphines are required which contain additional functional groups for binding to the surface of a polymer or for helping to orient the substrate. Thus, in the following paragraph new methods to prepare optically active phosphines are described.

NEW OPTICALLY ACTIVE PHOSPHINE LIGANDS

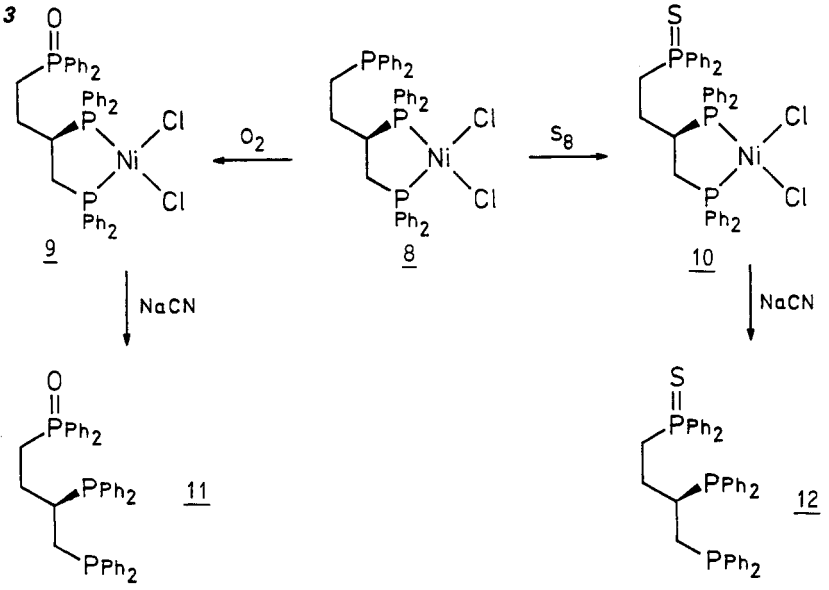
L-malic acid 4 is a cheap commercial product. Its reduction with BH_3xSMe_2 according to Scheme 2 yields triol 5, which is tosylated to give tritosylate 6. Reaction of 6 with $LiPPh_2$ results in the formation of the new tridentate phosphine 7, capable of forming five-membered and six-membered chelate rings (ref. 8).

Scheme 2



Although for some reactions tridentate ligands might be beneficial, for most reactions bidentate phosphines are more favourable. Therefore, the tridentate phosphine 7 is converted into the bidentate phosphines 11 and 12, derivatives of Prophos (Scheme 3).

Scheme 3

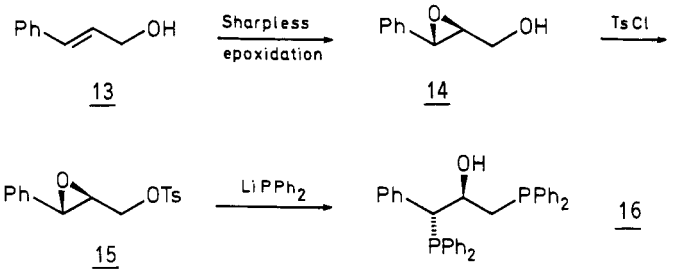


To this end, the Ni complex 8 is isolated from ethanol, which contains 7 as a bidentate ligand, coordinated by a five-membered ring. The dangling PPh_2 group can be oxidized to $POPh_2$ by molecular oxygen or to $PSPh_2$ by elemental sulphur. Addition of NaCN liberates the ligands 11 and 12 from the Ni complexes 9 and 10 and allows their isolation. The additional PO group of ligand 11 should be capable of forming strong hydrogen bonds with

suitable substrates. The same sequence of reactions can be carried out with (S)-(+)-5-exotetrahydrofuran-2-carboxylic acid obtained from L-glutamic acid (ref. 9).

The Sharpless epoxidation, one of the most valuable reactions of the last decade, can be used to prepare new optically active functionalised chelate phosphines. The principle is shown in Scheme 4 starting from the commercial cinnamic alcohol 11, which is epoxidized to 12 with 93 % ee, according to ref. 10. Tosylation of the epoxy alcohol 12 yields the solid tosylate 13, which is easily crystallized to optical purity. Reaction with 2 mol $LiPPh_2$ gives the chelate phosphine 14, one mol of PPh_2^- replacing the tosylate group and the other mol of PPh_2^- opening the three-membered ring by selective attack at the benzylic position. The OH group of 16 can be used for further derivatisation or for attachment to a surface. The concept can be extended to other allyl alcohols, such as geraniol (ref. 10).

Scheme 4

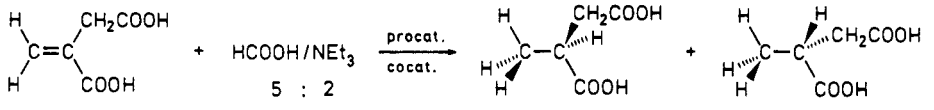


13 14 15 16

ENANTIOSELECTIVE TRANSFER HYDROGENATION OF ITACONIC ACID

The catalytic hydrogenation of itaconic acid 17 gives varying enantioselectivities. The best results have been obtained with the ligand BPPM 19 or derivatives thereof (ref. 11-13). We have found that molecular hydrogen can be replaced by formic acid as the hydrogen source, the commercial azeotrope $HCOOH/NEt_3$ ▫ 5:2 being a convenient choice (ref. 14). With the catalyst $[Rh(cod)Cl]_2$/BPPM in DMSO methylsuccinic acid 18 is obtained with an enantiomer ratio of 92:8 (Scheme 5), close to the enantioselectivity accessible with gaseous hydrogen. Surprisingly, not only Rh(I) compounds, such as $[Rh(cod)Cl]_2$, are suitable procatalysts, but also Rh(II) compounds, such as $Rh_2(OAc)_4$, or Rh(III) compounds, such as $RhCl_3$. Replacement of triethylamine by (R)-1-phenylethylamine, lowers the enantioselectivity of all the systems. With (S)-1-phenylethylamine, however, the enantioselectivities of all the systems are higher than for NEt_3, the catalysts $Rh_2(OAc)_4$/BPPM and $RhCl_3$/BPPM giving virtually complete optical induction (ref. 15).

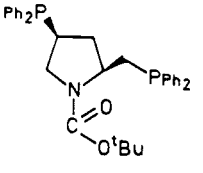
Scheme 5



17 18

cat.: $[Rh(cod)Cl]_2$/BPPM
$Rh_2(OAc)_4$/BPPM
$RhCl_3$/BPPM

BPPM =



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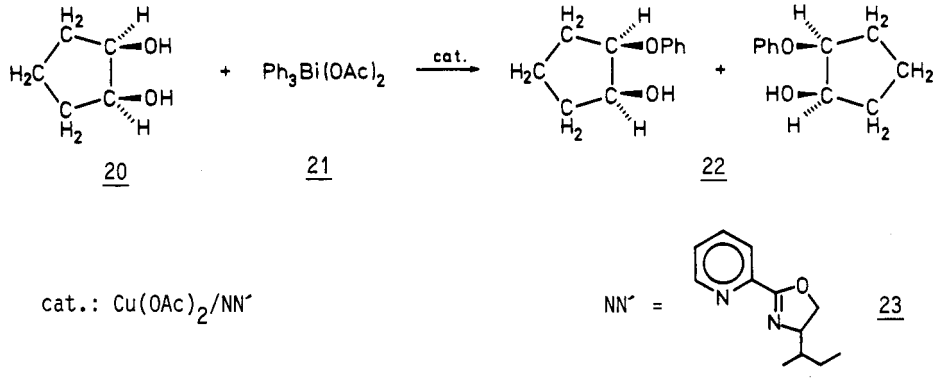
ENANTIOSELECTIVE MONOPHENYLATION OF DIOLS

Bismuth reagents are selective reagents in organic chemistry. Thus, $Ph_3Bi(OAc)_2$ 21 is a reagent for the monophenylation of diols which can be catalyzed by $Cu(OAc)_2$ (ref. 16). We have succeeded in rendering this reaction enantioselective as demonstrated in Scheme 6. The substrate is 1,2-cyclopentane-diol 20, a meso-compound containing a plane of symmetry. Monophenylation removes the plane of symmetry yielding a racemic mixture of 22. An in situ

system consisting of $Cu(OAc)_2$ as the procatalyst and the pyridineoxazoline 23 as the cocatalyst gives 50 % ee in the reaction of Scheme 6. This monophenylation reaction has been extended to a series of other meso diols (ref. 17,18).

Scheme 6

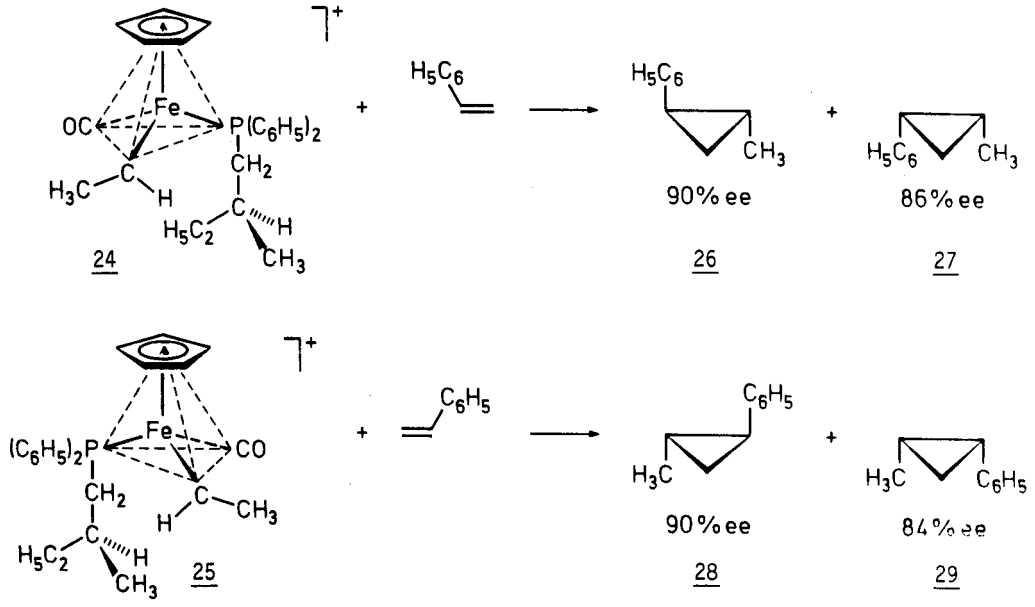


Different from the noble metal catalysts in Schemes 1 and 5, the catalyst in Scheme 6 is an inexpensive 3d-metal compound. Moreover, the optically active phosphine ligands 3 and 19, accessible only in lengthy syntheses, are replaced by the easy to get pyridineoxazoline ligand 23, derived from an optically active aminoalcohol. $Cu(OAc)_2$/phosphine catalysts do not give optical inductions in the monophenylation of diols according to Scheme 6. The reason is that the phosphine ligand, present in only small amounts, is oxidised by the Bi(V) compound 21, present as the substrate, whereas pyridineoxazoline ligands are stable towards oxidation (ref. 18).

ENANTIOSELECTIVE CYCLOPROPANATION OF STYRENE WITH FE-CARBENE COMPLEXES

Cationic $CpFe(CO)_2$carbene complexes are known to undergo a cyclopropanation reaction with olefins, a reactivity maintained on substitution of one of the CO ligands by a phosphine ligand. In the cations $[CpFe(CO)(PR_3)carbene]^+$ the Fe atom is a chiral center (ref. 19,20). In order to determine its influence on the stereochemistry of the cyclopropanation reaction, it was resolved using the optically active phosphine (S)-$PPh_2CH_2CHMeEt$, abbreviated PPh_2R^* (ref. 21). The two diastereoisomers differing only in the Fe configuration, $S_{Fe}S_C$- and $R_{Fe}S_C$-$[CpFe(CO)(PPh_2R^*)carbene]X$ 24 and 25 are shown in Scheme 7.

Scheme 7



In the reaction with styrene, the SS isomer 24 gives high optical yields of 90 and 86 % ee of (-)-trans- and (-)-cis-methylphenylcyclopropane 26 and 27, whereas the RS-isomer 25 gives high optical yields of 90 and 84 % ee of (+)-trans- and (+)-cis-methylphenylcyclopropanes 28 and 29 (ref. 21), according to Scheme 7. The reaction has been extended to other cationic Fe-carbene complexes and to other olefins (ref. 22).

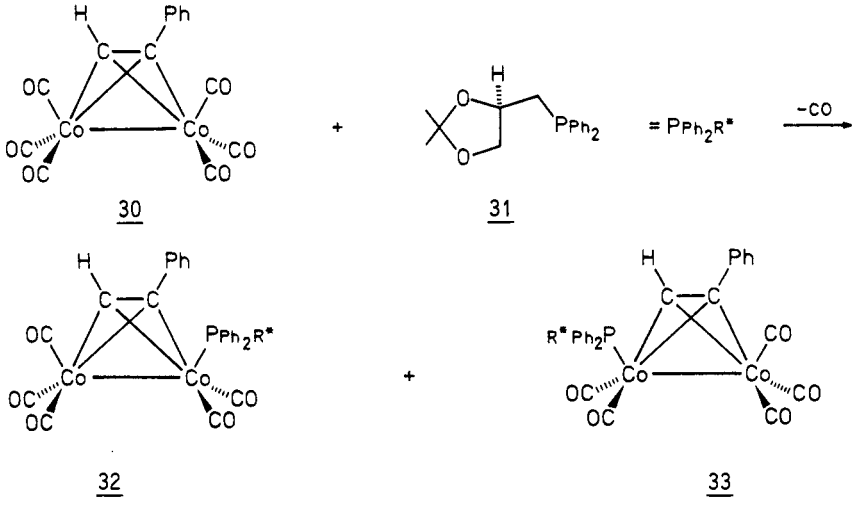
ROLE OF METAL CONFIGURATION VERSUS LIGAND CONFIGURATION

In enantioselective catalysis, in situ catalysts are used consisting of a metal component and a ligand, carrying the chiral information. It is to be assumed that in many catalytic reactions the metal atom itself becomes a chiral center which actively participates in the chirality transmission from the optically active ligand to the product. The stoichiometric system of Scheme 7 is analogous to an in situ catalyst in consisting of a metal atom at which the cyclopropanation reaction occurs and an optically active ligand PPh_2R', added as the only source of chirality at the beginning of the reaction sequence. Using the mixture of diastereomers 24 and 25 as formed in the synthesis would give cyclopropanes with only low enantioselectivity. It is the separation of the diastereoisomers with respect to the metal configuration which makes 24 and 25 induce high and opposite chirality into the product cyclopropanes. The chirality of the phosphine PPh_2R' obviously plays only a little role. Used as an "in situ system" without separating the diastereoisomers 24 and 25, the cyclopropanation of Scheme 7 would be considered to be a reaction with low stereoselectivity. The important role of metal/cluster configuration in organometallic reactions is also demonstrated by the next example.

ENANTIOSELECTIVE KHAND-PAUSON REACTION

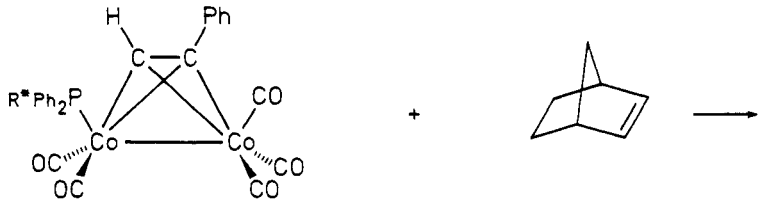
In the stoichiometric Khand-Pauson reaction, cyclopentenones are formed from binuclear cobalt-carbonyl-acetylene complexes and olefins (ref. 23). In the reaction of phenylacetylene with cobalt-carbonyl the Co_2C_2 cluster $Co_2(CO)_6(HCCPh)$ 30 is formed, which contains a plane of symmetry. In the reaction of 30 with the optically active phosphine PPh_2R^* 31, substitution of CO occurs at the two enantiotopic axial positions giving the monosubstitution products 32 and 33 (Scheme 8). In the tetrahedral unit, the clusters 32 and 33 contain two different asymmetric cobalt atoms and two different asymmetric carbon atoms. As these four asymmetric centers are coupled by the tetrahedral frame, only two isomers are possible, image and mirror image with respect to the tetrahedral unit. The two diastereomers 32 and 33 differ in their ^1H nmr spectra. They can be separated by column chromatography. Whereas 32 and 33 are configurationally stable at room temperature, approach to equilibrium at 60 °C in toluene occurs with a halflife of 170 min, the equilibrium composition being 32:33 = 60:40 (ref. 24).

Scheme 8



Using the equilibrium mixture of the Co_2C_2 clusters 32 and 33 in a Khand-Pauson reaction with norbornene, the product 2-phenyl-3a,4,5,6,7,7a-hexahydro-4,7-methanoindane-1-one 34 is formed in an enantiomer ratio of 68:32 (Scheme 9). The pure diastereoisomer 33, however, exclusively gives rise to optically pure 34 (ref. 24).

Scheme 9



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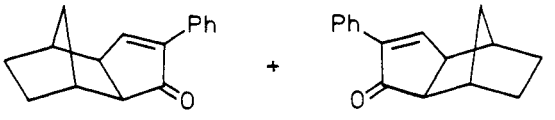

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CONCLUSION

The examples of Schemes 7 and 9 demonstrate that in organometallic systems, chiral at the metal center and chiral in the phosphine ligand, it is the metal (or cluster) configuration which determines the stereochemistry of product formation, the optically active ligand having only a marginal influence. Therefore, to control factors such as the metal configuration in transition metal catalysts, would be of great importance for the optical induction in enantioselective reactions.

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