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Recent advances in asymmetric catalysis. Synthetic applications to biologically active compounds*

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Abstract: New chiral cationic ruthenium complexes have been used for the industrial synthesis of (+)-dihydrojasmonate. A new class of electron-rich C_2-symmetric 2,4-disubstituted phosphetanes (CnrPHOS) was developed. Preliminary evaluation of their catalytic properties revealed high efficiency in rhodium and ruthenium-catalyzed asymmetric hydrogenations. A new stereochemical model is presented in which the phosphetane Rh-catalyzed hydrogenation follows an apparent stability-controlled mechanism.

INTRODUCTION

Among the various approaches by which chirality can be created, the catalytic asymmetric synthesis from prochiral compounds is a method of choice. For instance, the highly effective asymmetric hydrogenations with Binap-ruthenium catalysts have been extensively used since the pioneering work of Noyori [1]. Our contribution to this field has been the development of general synthetic approaches to chiral ruthenium(II) catalysts for hydrogenation reactions [2].

PREPARATION OF THE CATALYSTS

During the last few years, we have considered several approaches to ruthenium/chiral phosphine complexes to be used in catalytic hydrogenation reactions. These include the use of the polymeric $[RuCl_2(COD)]_n$ complex [3] and of the (diphosphine)Ru(2-methylallyl)$_2$ [4] complexes as the catalyst precursors. In the most general approach, ruthenium complexes bearing chiral diphosphines have been prepared from a 1:1 mixture of (COD)Ru(2-methylallyl)$_2$ **1** and the appropriate chiral phosphine, by treatment with 1.5 to 2 equiv of HX (X = Br, Cl, BF_4, PF_6) in acetone or dichloro methane (Fig. 1). This *in situ* preparation [4] affords ruthenium complexes defined by the empirical formula RuP*PX_2, which are excellent catalysts for the asymmetric hydrogenation of ketones and olefins [5].

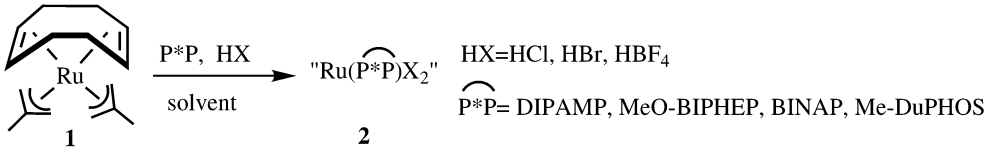

Fig. 1 Some examples of *in situ* preparation of chiral Ru(II) catalysts.

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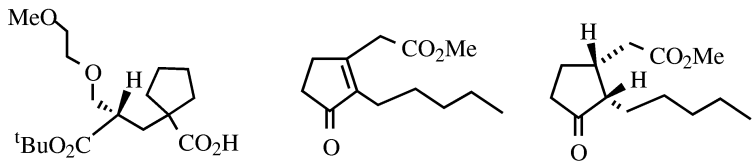
Among the major advantages of the established route, the rapid screening of ligands must be emphasized.

ENANTIOSELECTIVE HYDROGENATIONS

C=C bonds hydrogenations

Catalysts generated *in situ* according to Fig. 1, have been used in the large-scale preparation [6] of compound **3**, a key intermediate in the synthesis of candoxatril, an inhibitor of neutral endopeptidase.



3 ee = 98% **4** **5** ee 80-90%

Recently, we have found a new and highly efficient procedure for the hydrogenation of tetrasustituted olefins, by means of the cationic ruthenium complex Ru[(*R*,*R*)-Me-DuPHOS](H)(η^6-COT)BF_4. The efficiency of the method has been established by the commercial production of paradisone® [7] via asymmetric hydrogenation of the cyclopentenone derivative **4**.

C=O bonds hydrogenations

Catalysts **2** are also extremely efficient for the asymmetric hydrogenation of a wide range of functionalized ketones. We have established that ruthenium catalysts bearing chiral ligands are effective for the low-pressure (1 bar H_2) hydrogenation of β-keto esters [8]. Interestingly, 1,3 *anti* diols (Fig. 2) are produced through asymmetric hydrogenation of 1,3-diketones by using Me-DuPHOS, BINAP, or MeO-BIPHEP ruthenium-catalysts [9].

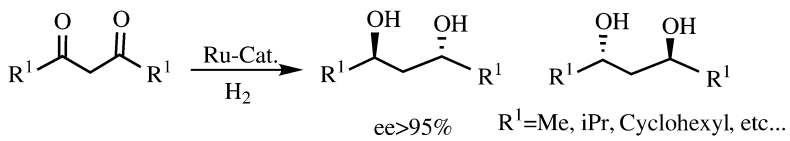


Fig. 2 Chiral 1,3-diols produced through asymmetric hydrogenation of 1,3-ketones.

Synthesis of phosphetane ligands

The optically pure 1,3-diols were used for the preparation of C_2-symmetric 2,4 disubstituted phosphetanes, a new class of electron-rich diphosphines (CnrPHOS) [10]. A wide range of

phosphetanes are available through the cyclization reaction between 1,3-diol cyclic sulfates and lithiated diphosphines as shown in Fig. 3.

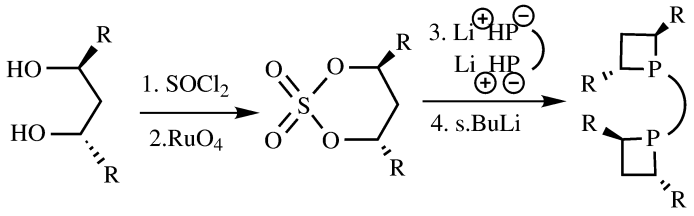


Fig. 3 Synthesis of chiral phosphetanes.

Phosphetane ligands in asymmetric catalysis

The new phosphatene ligands **6a–c** ligands (Fig. 4) proved to be efficient in asymmetric hydrogenation. A preliminary evaluation of the catalytic properties is established through a survey of the ruthenium-catalyzed hydrogenations of functionalized carbonyl derivatives and rhodium-catalyzed hydrogenations of olefins (Fig. 5).

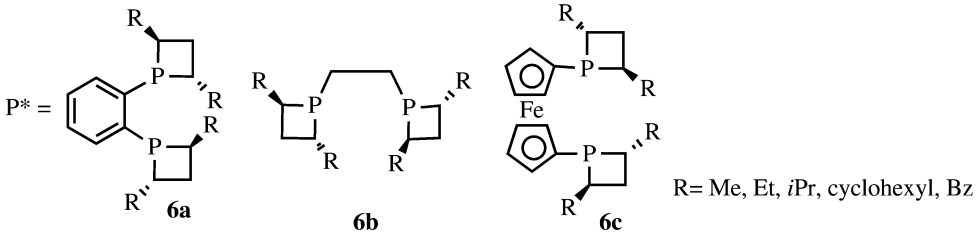


Fig. 4 Chiral phosphetanes ligands prepared from chiral 1,3-diols.

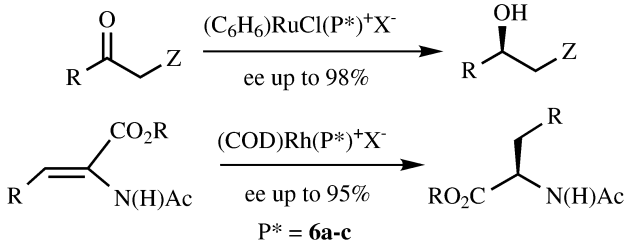


Fig. 5 Rhodium(I) and ruthenium(II) asymmetric hydrogenation with phosphetanes ligands.

The electron-rich nature of phosphetanes **6a–c** and the ring strain associated with the cyclic moiety, induce peculiar behaviors in their coordination chemistry and catalytic properties. Thus, for instance, the stereochemical issue of the rhodium-catalyzed hydrogenations of dehydroaminoacid derivatives is opposite to that anticipated by the generally accepted models: the (*S*,*S*)-1,2-bis(2,4-diisopropylphosphetano)benzene **6a** (R=*i*-Pr) which hinders the upper-left and bottom-right quadrants around the rhodium atom should afford *S*-configurated amino acid derivatives. Instead, the *R*-configurated species are obtained (Fig. 6) [11].

Accordingly, an unusual effect of the H_2 pressure on the enantioselectivity is noticed, since increased ee are obtained at higher hydrogen pressure. The results above may suggest that the phosphetane-catalyzed hydrogenations follow either a stability-controlled "olefin mechanism" or a

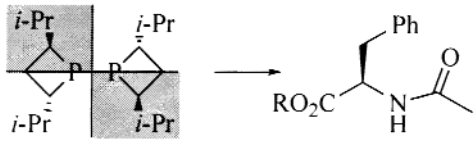


Fig. 6 Stereochemical model for the Rh-catalyzed hydrogenation.

"hydride mechanism". This seems to be the case for other electron-rich diphosphines, including DuPHOS, which affords stability-controlled hydrogenation products, in opposition to the initial claims [12]. Detailed mechanistic studies on these hydrogenation reactions are in progress.

Synthetic applications of the Ru-catalyzed hydrogenation via dynamic kinetic resolution (DKR) [13]

A racemic starting material such as α-substituted β-keto esters bearing a configurationally labile stereogenic center and a prochiral unsaturated moiety can be converted to one major *syn* or *anti* stereoisomer (Fig. 7), among the four possible stereoisomers. An efficient synthesis of 3-hydroxylysine derivatives, key intermediates for the synthesis of (-)balanol [14], was achieved using this technology. Interestingly, we have found that the hydrogenation of racemic α-chloro-β-keto esters under optimized conditions gave α-chloro β-hydroxy esters with *anti* diastereoselectivity and enantioselectivity up to 99% [15].

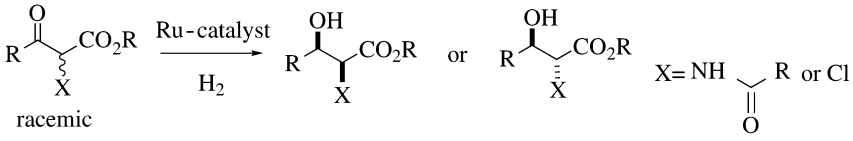


Fig. 7 Asymmetric hydrogenation of 2-substituted β-keto esters.

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