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Organic and Inorganic Chemistry 2018: Recent advances in organic chemistry and asymmetric catalysis: Applications - Vidal Virginie-Ecole Nationale Superieure de Chimie de Paris- Chimie ParisTech

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Over the past few years, significant research has been directed toward the development of new methods for synthetic efficiency and atom economical processes. Among them, the potential of transition metal-catalyzed reactions has been steadily demonstrated, as they provide a direct and selective way toward the synthesis of highly valuable products. We focus on the development of catalytic methods for the synthesis of bio-relevant targets. More specifically, we have been interested in hydrogenation and transfer hydrogenation reactions, which provide important catalytic approaches to fine chemicals. There is no doubt that chiral ligands are at the heart of any enantioselective homogeneous process. In this context, our contribution to this field is the development of atropisomeric diphosphanes named SYNPHOS and DIFLUORPHOS with complementary stereoelectronic properties. Some applications in organic chemistry will be presented.

Introduction:

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

Preparation of Catalysts:

For the period of the last few years, we have considered several methods to ruthenium/chiral phosphine com- plexes to be used in catalytic hydrogenation reactions. These include the use of the polymeric [RuCl2(COD)]n complex and of the (diphosphine)Ru(2-methylallyl)2 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, BF4, PF6) in acetone or dichloro methane (Fig. 1). This in situ preparation affords ruthenium complexes well-defined by the empirical formula RuP*PX2, which are exceptional catalysts for the asymmetric hydrogenation of ketones and olefins

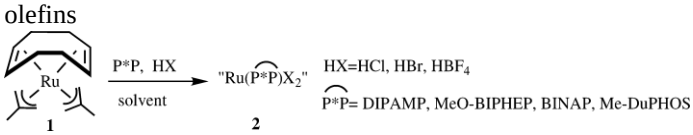


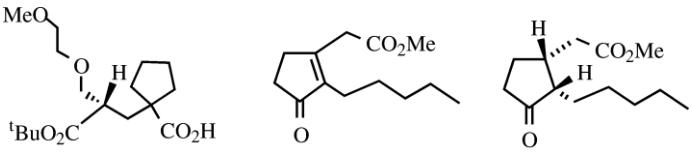
Fig. 1 Some examples of in situ preparation of chiral Ru(II) catalysts.

Among the most important advantages of the recognized route, the rapid screening of ligands must be emphasized.

Enantioselective Hydrogenations

C=C bonds hydrogenations

Catalysts generated in situ according to Fig. 1 are utilized in the large-scale preparation of com- pound three, a key intermediate within the synthesis of candoxatril, associate matter of neutral endopeptidase.



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

Recently, we've found a brand new and extremely efficient procedure for the hydrogenation of tetra- sustituted olefins, by means that of the ion ruthenium complicated Ru[(R,R)-Me-DuPHOS](H)(6- COT)BF4.

The efficiency of the tactic has been established by the industrial production of paradis- one via uneven hydrogenation of the cyclopentenone derivative

C=O bonds hydrogenations

Catalysts a pair of also are extremely efficient for the asymmetric hydrogenation of a large range of function- alized ketones. we've established that ruthenium catalysts bearing chiral ligands are effective for the low-pressure (1 bar H2) hydrogenation of Beta-keto esters Interestingly, 1,3 anti diols (Fig. 2) are pro- duced through arasymmetric hydrogenation of one,3-diketones by exploitation Me-DuPHOS, BINAP, or MeO- BIPHEP ruthenium-catalysts.

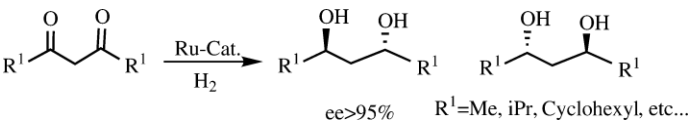


Fig. 2 Chiral 1,3-diols produced through asymmetric hydrogenation of 1,3-ketones

Synthesis of phosphetane ligands:

The optically pure 1,3-diols were used for the preparation of C2-symmetric 2,4 disubstituted phosphetanes, a new class of electron-rich diphosphines (CnrPHOS) . A wide range of phosphetanes are available through the cyclization reaction between 1,3-diol cyclic sulfates and lithiat- ed diphosphines as shown in Fig. 3.

This work is partly presented at 5th International Conference on Organic and Inorganic Chemistry during July 12-13, 2018 in Paris, France.

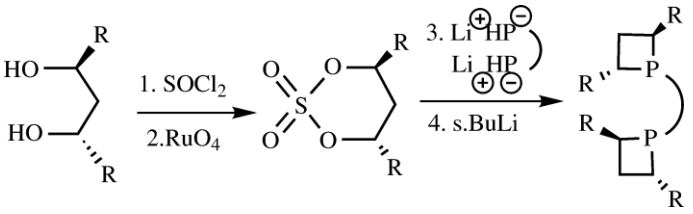


Fig. 3 Synthesis of chiral phosphetanes

Phosphetane ligands in asymmetric catalysis

The new phosphatene ligands 6a–c ligands (Fig. 4) verified to be efficient in asymmetric hydrogenation.A preliminary analysis 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).

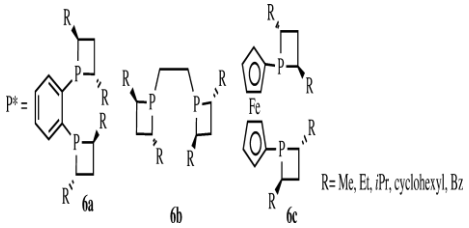


Fig. 4 Chiral phosphetanes ligands prepared from chiral 1,3-diols.

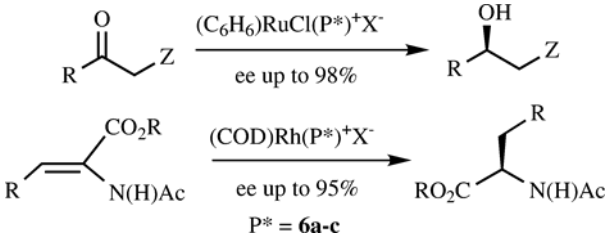


Fig. 5 Rhodium(I) and ruthenium(II) asymmetric hydrogenation with phosphetanes ligands. The electron-rich nature of phosphetanes 6a–c and also the ring strain related to the cyclic moi- ety, induce peculiar behaviors in their coordination chemistry and catalytic properties. Thus, for instance, the stereochemical issue of the rhodium-catalyzed hydrogenations of dehydroaminoacid derivatives is opposite to it anticipated by the widely accepted models: the (S,S)-1,2-bis(2,4-diiso- propylphosphetano)benzene 6a (R=i-Pr) that (Fig. 6) .

Accordingly, an uncommon impact of the H¬2 pressure on the enantioselectivity is noticed, since increased are obtained at higher hydrogen pressure.

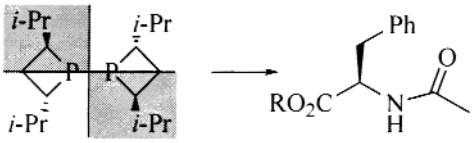


Fig.6 Stereochemical model for the Rh-catalyzed hydrogenation.

The results higher than might recommend that the phosphetane-catalyzed hydrogenations follow either a stability-controlled “olefin mechanism” or a “hydride mechanism”. This looks to be the case for different electron-rich diphosphines, as well as DuPHOS, that affords stability-controlled hydrogenation products, in opposition to the initial claims elaborated mechanistic studies on these hydrogenation reactions are ongoing.

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

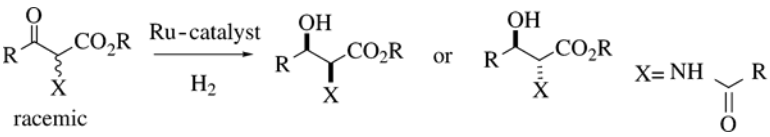


Fig. 7 Asymmetric hydrogenation of 2-substituted β-keto esters.

A racemic beginning material such as α-substituted β-keto esters bearing a configurationally labile stere- ogenic center and a prochiral unsaturated moiety are often regenerate to at least one major syn or anti stereoiso- mer (Fig. 7), among the four possible stereoisomers. An efficient synthesis of 3-hydroxylysine deriva- tives, key intermediates for the synthesis of (-)balanol, was achieved using this technology. Apparently, we've got 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.