

# Asymmetric Catalytic Hydrogenation. Design of New Ru Catalysts and Chiral Ligands: From Laboratory to Industrial Applications

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## ABSTRACT

This Account covers the design of Ru catalysts and ligands. Two classes of chiral phosphine ligands are prepared: the electron-rich *trans*-2,4-substituted phosphitanes, readily available from optically pure 1,3-diol cyclic sulfates, and atropoisomeric ligands (SYNPHOS, MeO-NAPhePHOS, bearing heterotopic biaryl moieties, and a chiral water-soluble diguanidinium binaphthyl diphosphine, *Digm*-BINAP). Applications of these ligands to rhodium- and ruthenium-mediated hydrogenation of ketones and olefins have been reported with high enantioselectivities. The recognition abilities of Ru-SYNPHOS for a wide range of ketones is superior to those observed with BINAP, MeO-NAPhePHOS, and MeO-BIPHEP. Several biologically active compounds have been prepared through dynamic kinetic resolution. This work gives access to a number of highly active catalysts of the type [Ru(biphosphane)(H)( $\eta^6$ -cot)]BF<sub>4</sub>. These catalysts have demonstrated their utility in the enantioselective hydrogenation of the tetrasubstituted cyclopentenone “dehydrodione”, which leads to the commercially important perfume component Paradisone (Firmenich).

## Introduction

Today, pharmaceuticals, agrochemicals, flavors, and fragrances as well as functional materials are increasingly produced as enantiomerically pure compounds.<sup>1</sup> This is due to the often superior performance of the single-enantiomer entities and/or because regulations demand the evaluation of both enantiomers of a biologically active compound before its approval. This trend has made the enantioselective synthesis of chiral compounds an important topic. Asymmetric catalysis has become one of the most powerful methods to produce a single-enantiomer drug, and it now provides one of the most cost-effective and environmentally responsible methods for the production of a vast array of structurally diverse, enan-

tiomerically pure compounds. Transition metal enantioselective catalysis is certainly among the most challenging and widely investigated areas in modern organometallic chemistry. Such a statement is undoubtedly fully confirmed by the award of the 2001 Nobel Prize in Chemistry to W. S. Knowles,<sup>2</sup> R. Noyori,<sup>3</sup> and K. B. Sharpless<sup>4</sup> for their work on asymmetric hydrogenation and oxidation reactions, respectively.

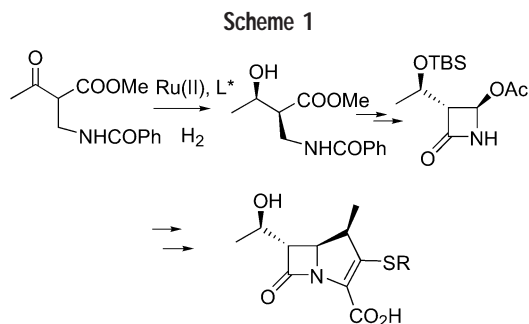
A great number of optically active compounds contain a hydrogen atom at the stereogenic center. As this hydrogen atom can be introduced into appropriate unsaturated precursors by hydrogenation, asymmetric hydrogenation is of particular importance to access highly enantiomerically pure compounds. In the first studies of homogeneous asymmetric hydrogenation, a modification of the achiral Osborn–Wilkinson’s catalyst was used in the hydrogenation of prochiral alkenes. Horner et al.<sup>5</sup> and Knowles and Sabacky<sup>6</sup> replaced triphenylphosphine by a chiral phosphine having the phosphorus atom as a stereogenic center, and very modest optical yields were obtained. Nevertheless, these pioneering experiments established the possibility of transforming rhodium(I) catalysts into chiral catalysts. A very important improvement was introduced when Kagan and Dang<sup>7</sup> demonstrated that a chiral phosphorus atom is not necessary if a chiral bidentate ligand is used, such as the C<sub>2</sub>-symmetric diphosphine ligand DIOP, with the chirality located within the carbon skeleton. The basic idea was that a suitable functionality and skeletal rigidity of the phosphine ligand would contribute to the differentiation of transition states needed to accomplish enantioselective catalysis. The rhodium(I)-DIOP catalyst was superior to monophosphine catalysts in asymmetric hydrogenation of dehydroamino acids. This was a seminal discovery, applicable across all homogeneous catalysis, which stimulated intense activity in various reactions: allylic substitution, hydroformylation, and hydrosilylation. By the early 1980s, however, the initial excitement had gone from asymmetric hydrogenation.

Today, asymmetric hydrogenation is a core technology.<sup>8</sup> The successful development of Rh-DIPAMP as a catalyst for L-DOPA with enantiomeric excess (ee) up to 96%<sup>9</sup> for many years enabled Monsanto to be the primary supplier of the main drug used in stabilizing the effects of Parkinson’s disease.

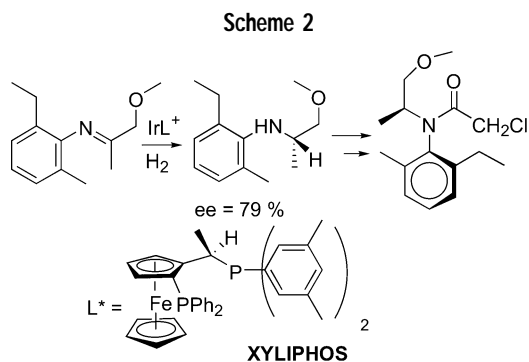
The next real breakthrough was Noyori’s demonstration that the well-defined, mononuclear Ru-BINAP catalysts had an incredible range of efficiency, which opened up many new classes of olefins<sup>10</sup> to asymmetric hydrogenation. The reaction could be successfully further extended to many types of keto groups.<sup>11</sup>

Noyori’s group developed an impressive technology by combining asymmetric hydrogenation with dynamic kinetic resolution, which together led to an important process developed by Takasago for the production of acetoxyazetidione (150 tons/year) (Scheme 1), a key intermediate in the synthesis of antibiotics.<sup>12</sup>

Jean-Pierre Genet was born in Tulle, France, on May 3, 1942. He received his education in Paris, obtaining a B.Sc. and a Ph.D. from the University of Pierre and Marie Curie with Professor Jacqueline Ficini. In 1975–1976, he did postdoctoral work with Professor B. M. Trost at the University of Wisconsin, Madison. He was appointed at the Université Pierre and Marie Curie as Assistant Professor in 1966, and then he became full Professor at the same university in 1980. In 1988, he moved to the Ecole Nationale Supérieure de Chimie de Paris. His research interests include organic synthesis, new synthetic reactions, catalysis in water, transition-metal-catalyzed reactions and synthesis of biologically active compounds.



The (*S*)-metolachlor hydrogenation process<sup>13</sup> (Scheme 2), using the Ir-XYLIPHOS catalyst of Ciba-Geigy Syngenta, demonstrates that enantioselective hydrogenation is also a feasible technology for large-volume products (15 000 tons/year).



Hoffmann-La Roche (Roche) has developed extremely efficient MeO-BIPHEP catalysts for rhodium and ruthenium hydrogenations. Pilot and bench-scale processes have been developed for the synthesis of vitamins, fine chemicals, and pharmaceuticals.<sup>14</sup>

In this Account, we will outline our efforts to design efficient syntheses of chiral ligands, and present a survey of our activities in the area of catalytic asymmetric hydrogenation. From a methodology point of view, our interests also focus on the development of general and new routes for the preparation of chiral Ru(II) complexes. The usefulness of these catalysts will be discussed, along with the successful enantioselective hydrogenation of prochiral olefins and ketones. Efficient syntheses of various complex biologically active molecules as well as a few industrial developments derived from our initial discoveries will be presented.

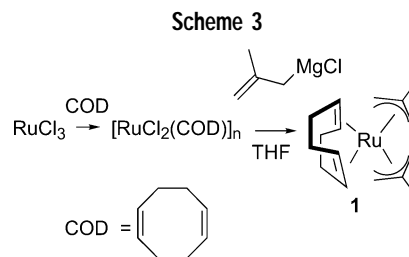
## Diversity in Chiral Ru Catalyst Preparations

Somehow it had been overlooked by the asymmetric hydrogenation community that James and co-workers had developed in 1975 the first chiral DIOP Ru catalysts.<sup>15</sup> It took 10 years to prove that chiral ruthenium-based catalysts could be employed efficiently using a BINAP ligand for asymmetric hydrogenation.<sup>16</sup>

Ikariya et al. prepared a dinuclear complex formulated as  $\text{Ru}_2\text{Cl}_4(\text{BINAP})_2(\text{NEt}_3)_3$ , later elucidated<sup>17</sup> as  $[\text{NH}_2\text{Et}_2][\text{RuCl}(\text{P}^*\text{P})_2(\mu\text{-Cl}_3)]$ , with  $\text{P}^*\text{P} = (R)\text{-}p\text{-MeO-BINAP}$ . The first mononuclear hexacoordinate ruthenium complex bearing BINAP a ligand has been reported by Noyori and was

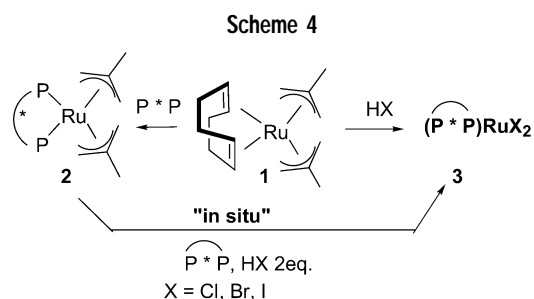
prepared from Ikariya's complex. A common limitation of the aforementioned method for the preparation of chiral Ru-BINAP catalysts was the harsh conditions (high temperatures and long reaction times) required.

Therefore, our efforts were focused on the design of a new, general, and mild synthesis of mononuclear hexacoordinate chiral complexes. The method is based on the easy availability of  $\text{Ru}(\text{COD})(\eta^3\text{-methylallyl})_2$  (**1**) from  $[\text{RuCl}_2(\text{COD})]_n$  by treatment with methylallyl Grignard (Scheme 3).<sup>18</sup>



Compound **1** is an excellent starting material for a facile synthesis of the well-defined mononuclear Ru( $\text{P}^*\text{P}$ )( $\eta^3\text{-methylallyl}$ )<sub>2</sub> (**2**). These complexes can be prepared by simple displacement of 1,5-cyclooctadiene (COD) from **1** by the appropriate chiral ligand  $\text{P}^*\text{P}$ , as shown in Scheme 4.

This method allowed us to prepare the first chiral mononuclear ruthenium(II) catalyst bearing tertiary diphosphines having stereogenic centers at phosphorus.<sup>19</sup> These preformed catalysts have been used for the preparation of the corresponding ruthenium dihalide complexes, defined by the empirical formula  $\text{Ru}(\text{P}^*\text{P})\text{X}_2$  (**3**), via addition of HX. Interestingly, in situ-generated catalysts  $\text{Ru}(\text{P}^*\text{P})\text{X}_2$  have been synthesized from  $\text{Ru}(\text{COD})(\eta^3\text{-methylallyl})_2$  and the appropriate chiral diphosphine by treatment with HX ( $\text{X} = \text{Cl}, \text{Br}, \text{I}$ ) at room temperature,<sup>19</sup> demonstrating the general nature of our method (Scheme 4).



This procedure allows screening of a large set of new chiral phosphines within their derived Ru(II) complexes in asymmetric hydrogenation, as shown in Figure 1. An interesting route to mononuclear  $\text{Ru}(\text{OAc})_2(\text{P}^*\text{P})$  ( $\text{P}^*\text{P} = \text{biphenyl ligand}$ ) was also reported using  $\text{Ru}(\text{COD})(\eta^3\text{-methylallyl})_2$ .<sup>20</sup>

Very recently, we have found simplified procedures for the preparation of chiral Ru(II) catalysts using commercially available  $[\text{RuCl}_2(\text{COD})]_n$ <sup>21</sup> and  $\text{RuCl}_3$  by simple addition of the chiral phosphine.<sup>22</sup> These established routes have several advantages for a rapid screening of

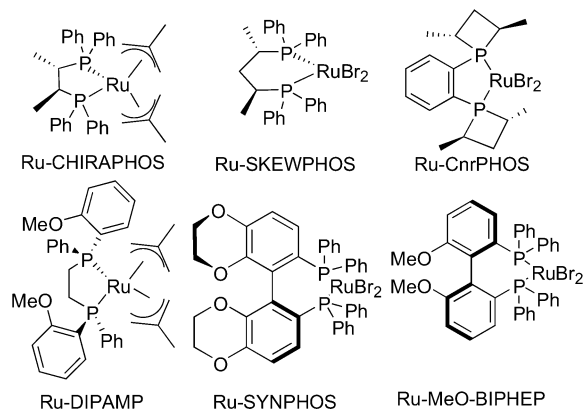
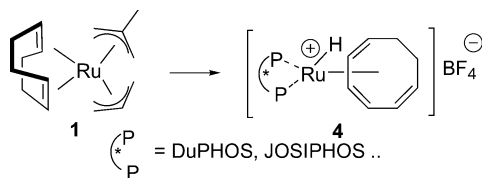


FIGURE 1. Chiral Ru(II) complexes prepared from Ru-(COD)( $\eta^3$ -methylallyl)<sub>2</sub>.

chiral ligands, as they do not require multistep reactions or isolation of intermediates.

In the course of collaboration with Firmenich, an industrial product-oriented project, the catalytic enantioselective hydrogenation of a substrate could not be achieved with any of the known catalysts. A new type of catalyst with high reactivity was discovered by treatment of Ru-(COD)( $\eta^3$ -methylallyl)<sub>2</sub> and various ligands P\*P (BINAP, DuPHOS, JOSIPHOS) in a weakly coordinating solvent (CH<sub>2</sub>Cl<sub>2</sub>) with HBF<sub>4</sub>. For example, as shown in Scheme 5, using (*R,R*)-Me-DuPHOS, a cationic monohydride ruthenium complex **4** was isolated and characterized by NMR spectroscopy and X-ray diffraction.<sup>23</sup>

Scheme 5



In the past decade, several other preparations of chiral Ru(II) complexes have been reported. Among these routes, a recent and versatile route to well-defined diphosphine Ru catalyst precursors using *trans*-RuCl<sub>2</sub>(NBD)Py<sub>2</sub> (NBD = norbornadiene, Py = pyridine) has been reported.<sup>24</sup>

Another part of the activity in the area of catalytic homogeneous enantioselective hydrogenation concerns ligand design. In asymmetric catalysis, a well-conceived class of ligands should possess one or more electronic and structural features that may be varied in a systematic fashion in order to optimize the design for a given substrate. In this context, two classes of bisphosphines have been considered in our program.

## Modular Phosphetanes Ligands

Electron-rich C<sub>2</sub>-symmetric diphosphines, in which the phosphorus atom is located in a cyclic moiety, have emerged recently as a valuable class of ligands in transition metal-promoted catalysis.<sup>25,26</sup> The low conformational flexibility of the four-membered ring is expected to have a positive effect on asymmetric reactions. The ability to

vary the phosphetane R substituent in a systematic fashion should allow interesting information to be obtained concerning the steric requirements of the catalytic reaction. Marinetti et al. have developed the first synthesis of chiral (diphosphetano) benzenes.<sup>27</sup> A general synthetic methodology (Figure 2) giving mono- and bisphosphetanes, involving the reaction between a primary mono- and diphosphine with a dielectrophile such as cyclic sulfate **6**, derived from enantiomerically pure 1,3-diols **5**, has been extensively studied at Ecole Nationale Supérieure de Chimie de Paris (ENSCP).

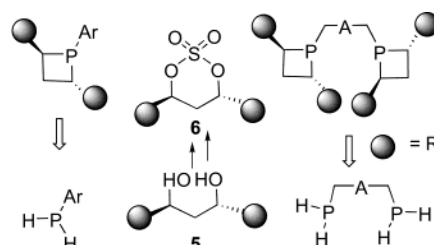


FIGURE 2. Synthetic approach to mono- and bisphosphetanes.

Given that a great number of preparations of primary phosphines exist, our synthetic approach was ensured by the convenient availability, in large scale and very high diastereomeric and enantiomeric excesses, of 1,3-diols by MeO-BIPHEP<sup>28</sup> ruthenium-catalyzed hydrogenation. Thus, the synthesis of a number of monodentate and bidentate phosphetanes **7–12** with various substituents (Figure 3) has been readily achieved according to the general method.<sup>29</sup>

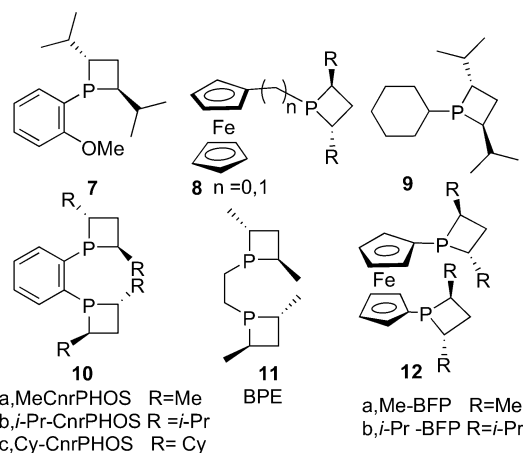


FIGURE 3. Representative examples of phosphetane ligands.

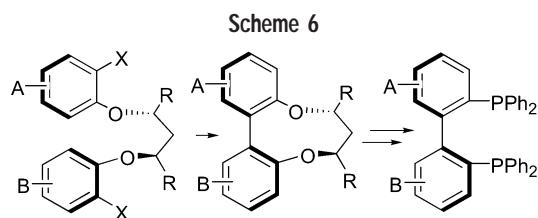
This overview shows that the structural features of the phosphetane ligands CnrPHOS, BPE, and BFP (bisferrocenyl phosphetanes)<sup>29c</sup> were easily modulated by the suitable choice of the primary phosphine and the starting chiral diol. A concurrent preparation of these phosphetanes by Chiroscience Ltd. has also been reported.<sup>30</sup>

## Atropisomeric Ligands

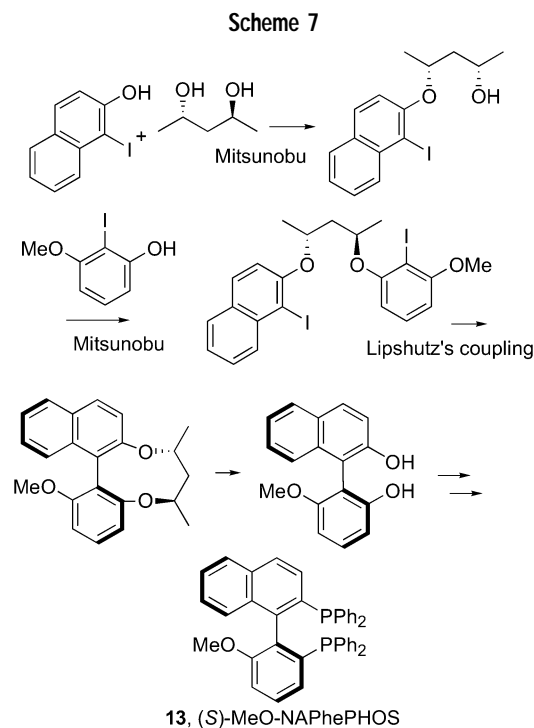
Atropisomeric diphosphines based on binaphthyl, biphenyl, and other biaryl backbones have also played a major role in the development of asymmetric catalysis.<sup>31</sup>

These ligands display uniformly high enantioselectivities in a number of catalytic reactions; variations of the biaryl skeleton induce fine-tuning of their properties. Concerning hydrogenation reactions, tentative correlation has been made recently between the observed enantioselectivities and the dihedral angle of the biaryl system.<sup>32</sup> These studies suggest that phosphines with smaller dihedral angles give higher selectivity in the ruthenium-catalyzed hydrogenation. Saito has designed, on the basis of the Cache MM2 calculation method, a new diphosphine ligand SEGPHOS.<sup>32b</sup>

In this context, with the purpose of industrial applications, we have been interested in the preparation of atropoisomeric ligands. We developed a versatile approach to new chiral, unsymmetrical atropoisomeric diphosphines. An important attribute associated with an unsymmetrical biaryl unit is the high modularity of these systems. Our approach, depicted in Scheme 6, takes advantage of the known stereoselective coupling between two aryl moieties connected by a chiral tether through ether linkages.

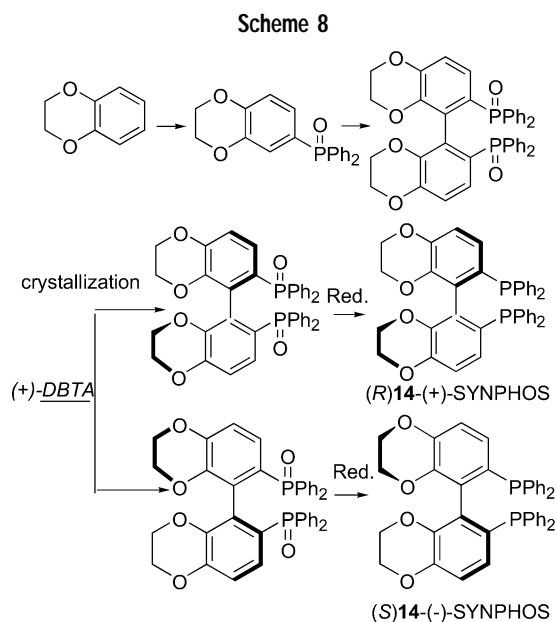


Thus, the stereoselective synthesis of the unsymmetrical ligand MeO-NAPhePHOS<sup>33</sup> was achieved (Scheme 7) from  $\alpha$ -iodo- $\beta$ -naphthol and 2-iodo-3-methoxyphenol. The diether derivative was prepared by two successive Mitsunobu reactions involving (*S,S*)-2,4-pentanediol. The aryl-aryl bond was then formed by applying Lipshutz's

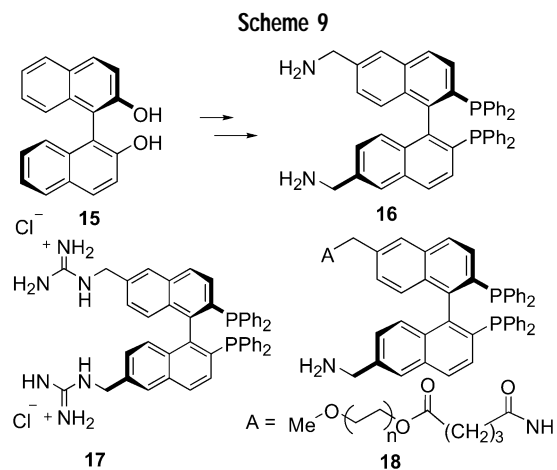


method,<sup>34</sup> leading to the biaryl derivative as a single diastereomer, which was easily converted into the corresponding diphosphine, MeO-NAPhePHOS (**13**), through Ni<sup>0</sup>-catalyzed coupling of the bistriflate with diphenylphosphane.<sup>33</sup>

We also reported very recently<sup>35</sup> the synthesis of symmetrical atropisomeric ligands bearing a benzodioxane core, (5,6,5',6'-bis(ethylenedioxy)biphenyl-2,2-diyl)-bis(diphenylphosphine), that we named SYNPHOS. (*R*) and (*S*) enantiomers of this ligand were efficiently synthesized from 1,2-ethylenedioxybenzene in five steps, as shown in Scheme 8.



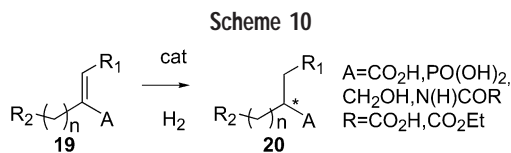
We have designed (Scheme 9) an atropoisomeric ligand derived from BINAP containing the guanidinium moiety (*R*)-Digm-BINAP (**17**). Another approach for the separation of the product from the catalyst involves a polymer, poly(ethylene glycol), monomethyl ether (MeO-PEG) ligand for one-phase catalysis and two-phase separation. Therefore, we have prepared PEG-(*R*)-Am-BINAP (**18**) containing a poly(ethylene glycol) chain.<sup>36</sup> Both ligands are available from the same intermediate **16**, which is easily prepared from optically pure BINOL **15**.





## Asymmetric Catalytic Hydrogenations

Asymmetric hydrogenation with electron-rich phosphines is capable of producing a wide range of chiral compounds.<sup>37</sup> The versatility of the new ligands and complexes designed in our laboratory may be highlighted by a survey of the types of prochiral substrates that can be reduced by various catalyst systems, as shown in Scheme 10.



## C–N Stereogenic Centers

Since the invention of well-designed Rh complexes containing DIOP<sup>7</sup> and DIPAMP<sup>9</sup> ligands, used for asymmetric hydrogenation of  $\alpha$ -(acylamino)acrylic acids, this reaction has become the model reaction to evaluate the efficiency of a new chiral phosphine. In our work as well, we have considered this reaction for an evaluation of the catalytic potential of our recently reported phosphetanes and the new atropisomeric ligands **13**, **14**, **17**,<sup>38</sup> and **18**. In this context, the electron-rich bis-phosphetane ligands **7–12** have revealed high efficiency in rhodium asymmetric hydrogenation of  $\alpha$ -dehydroamino acids to amino acids **21–23** (Figure 4).

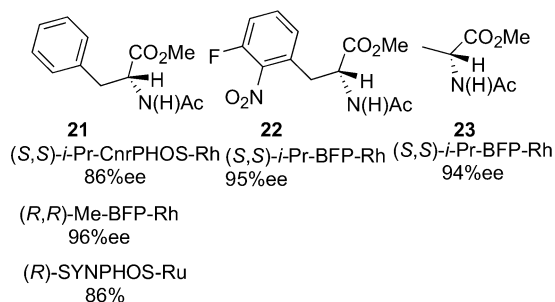


FIGURE 4. Rh and Ru hydrogenation of  $\alpha$ -dehydroamino acids.

Interestingly, Ru-(*R*)-SYNPHOS-Br<sub>2</sub>, Rh-(*S,S*)-*i*-Pr-CnrPHOS, and Rh-(*R,R*)-Me-CnrPHOS catalysts produced  $\alpha$ -amino acids of the same configuration.<sup>34a,39</sup> These ligands define the same chiral arrays in their complexes and block the same quadrants: upper left and bottom right. Elegant and very recent mechanistic studies<sup>40</sup> have unveiled some of the mysteries associated with asymmetric Ru-BINAP-catalyzed hydrogenation reactions. The reaction occurs via a monohydride Ru–H olefin insertion to the olefinic bond. The sense of the asymmetric hydrogenation is explained via the most stable Ru-H/enamide complex “stability-controlled mechanism” (Figure 5). Concerning the stereochemical course of the hydrogenation of dehydroamino acids derivatives with Rh-phosphetanes, the (*R*) configuration of the product is obtained. This promoted hydrogenation does not fit the Halpern–Brown kinetically controlled mechanism,<sup>41</sup> as phos-

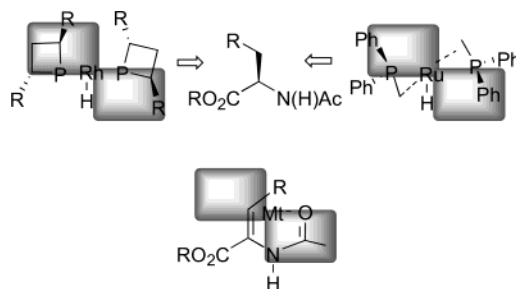


FIGURE 5. Stereochemical model of enamide hydrogenation with Rh-CnrPHOS, Rh-BFP, and Ru-SYNPHOS.

phetanes behave instead like other electron-rich phosphines.<sup>42</sup>

## C–C and C–P Stereogenic Centers

The formation of C–C and C–P stereogenic centers was also an important technology in asymmetric synthesis. Unsaturated carboxylic and phosphonic acids could be hydrogenated with high enantioselectivities to furnish products with new stereogenic centers at the  $\alpha$ -carbon (Scheme 10).

For example, carboxylic acids and derivatives **24**, **25**, and **29** have been obtained with high enantioselectivities using (*S*)-BIPHEMP-Ru( $\eta^3$ -methylallyl)<sub>2</sub> and (*S*)-BINAP-Ru( $\eta^3$ -methylallyl)<sub>2</sub> catalysts.<sup>43</sup> More recently, phosphonic acids **26** and **27** were prepared directly with reasonable ee up to 86% (Figure 6) through hydrogenation of the corresponding vinylphosphonic acids using (*R*)-MeO-BIPHEP-RuBr<sub>2</sub> catalyst.<sup>44</sup> This catalyst was also found to be particularly efficient for the synthesis of the highly functionalized allylic alcohol **28** precursor of carbapenem.<sup>45</sup>

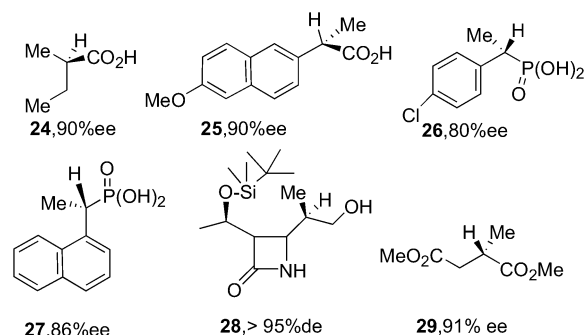
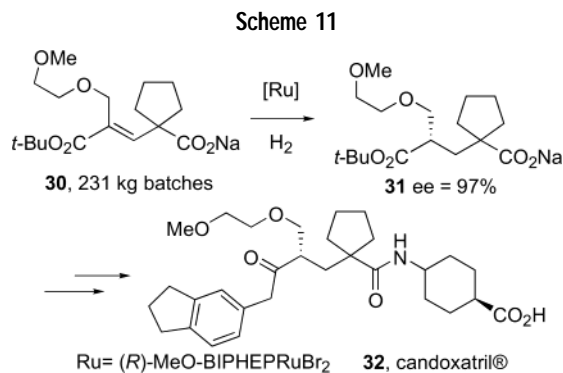


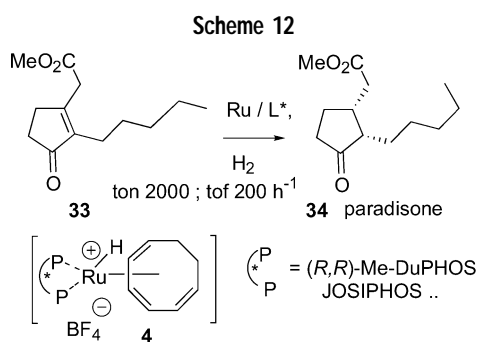
FIGURE 6. Enriched compounds produced via Ru hydrogenation.

Interestingly, we have found that bis-(2*R*,4*R*)-dimethyl-(phosphetano)ferrocene-Rh catalyst is highly efficient in asymmetric hydrogenation of itaconate ester to **29**. Thus, it appears that chiral phosphetane moieties gave better results than the corresponding phospholanes.<sup>37</sup>

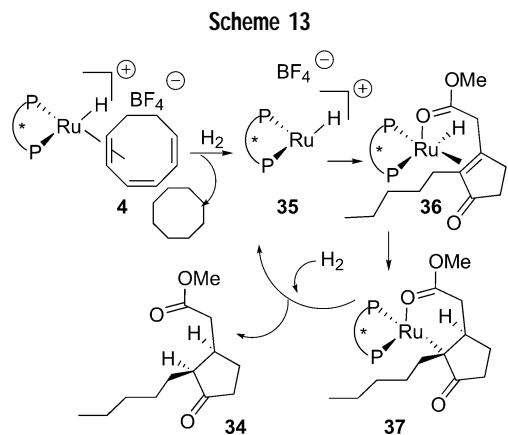
**Industrial Applications.** Our procedure for the preparation of chiral ruthenium dihalides has been used by PPG-SIPSY to prepare tons of a key chiral succinate intermediate,<sup>46</sup> **31**, from **30** (Scheme 11) for clinical trials of candoxatril (**32**), a cardiovascular drug (ANF potentiator) developed by Pfizer in the mid-1990s.



A considerable breakthrough in the hydrogenation of carbon–carbon double bonds was recently realized using [Ru(P\*P)(H)( $\eta^6$ -cot)]PF<sub>6</sub> (cot = cycloocta-1,3,5,7-triene) (**4**), prepared as shown in Scheme 5. In terms of practicality, the Firmenich–Genet procedure has the advantage of allowing the straightforward synthesis of a new generation of Ru complexes with a number of different phosphane ligands.<sup>23</sup> This new type of complex is highly active and has demonstrated its utility in the difficult enantioselective hydrogenation of a tetrasubstituted olefin. Thus, the enantioselective hydrogenation of the cyclopentenone “dehydrodione” **33** with [Ru-(*R,R*)-MeDuPHOS(H)-( $\eta^6$ -cot)]BF<sub>4</sub> leads directly to (+)-*cis*-methylidihydrojasmonate (**34**) with ee up to 90%<sup>23</sup> (Scheme 12), a commercially important perfume component named Paradisone.

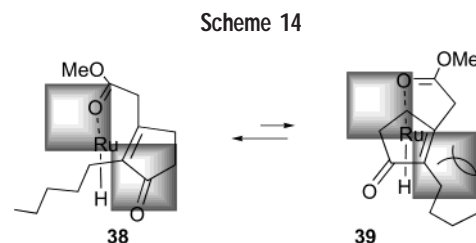


The success that we had in our system may be attributed, first, to the formation of the highly unsaturated ruthenium catalyst **35** formed under hydrogen pressure from **4**, which acts as a precatalyst (Scheme 13), and



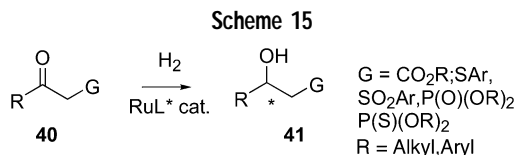
second, to the intrinsic advantage due to chelation of the ester, which entails metal binding to the double bond in **36** followed by olefin insertion to **37** and hydrogenolysis, to give **34** with regeneration of catalyst **35**.

Under these constraints, we envisioned that binding of the *re* face to the catalyst should afford an intermediate complex of structure **38**, whereas coordination of the *si* face should yield the diastomeric intermediate **39** (Scheme 14). Intermediate **39** has steric interactions between the methyl substituent of the ligand and the pentyl chain of the substrate, whereas **38** appears devoid of such unfavorable repulsions. This situation leads to substantial enantiomeric enrichment via the “stability control mechanism”.<sup>40</sup> It is important, however, to recognize that it is merely a simplistic model to explain the sense of enantioselectivity.



## C–O Stereogenic Centers

Asymmetric hydrogenation of prochiral ketones **40** has been extensively studied because of the synthetic significance of the corresponding alcohols **41** (Scheme 15).



In this area, the dominant ligand has been BINAP. The specificity of Ru-BINAP catalysts has been documented through the output from Noyori’s group in the mid-1980s. However, there is no universal ligand, and considerable efforts have been made to produce better selectivity. In this context, we had noticed through several examples in the past few years that MeO-BIPHEP exhibited high enantioselectivities in the ruthenium-mediated hydrogenation reactions of a series of functionalized ketones to give alcohols **42–50** (Figure 7).<sup>47</sup> Interestingly, the Ru-SKEWPHOS catalyst exhibits excellent enantioselectivities.<sup>48</sup>

We recently established in these reactions that unsymmetrical biarylphosphanes such as MeO-NAPhePHOS<sup>33</sup> (**13**) afforded alcohols **51–53** with enantioselectivity levels comparable to those of the C<sub>2</sub>-symmetrical analogues, BINAP and MeO-BIPHEP. Thus, the lack of C<sub>2</sub> symmetry was not detrimental to the catalytic properties of atropisomeric ligands. SYNPHOS-Ru catalyst was found to be highly efficient, giving compounds **54–56** (Figure 8).

Ruthenium complexes of phosphetanes have been used as catalysts in the enantioselective hydrogenation of

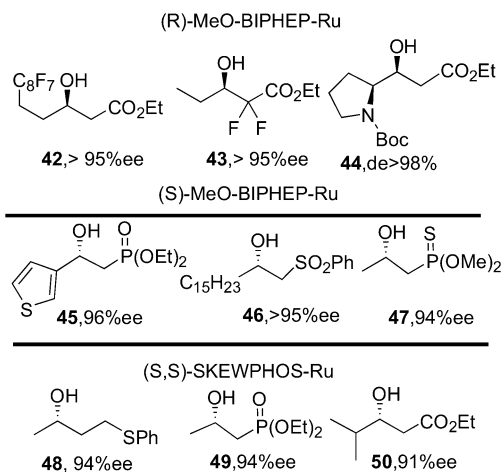


FIGURE 7. Alcohols produced via hydrogenation with MeO-BIPHEP and SKEWPHOS-Ru catalysts.

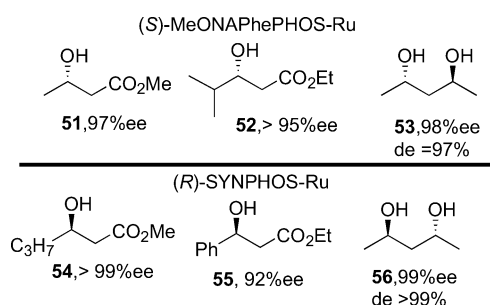
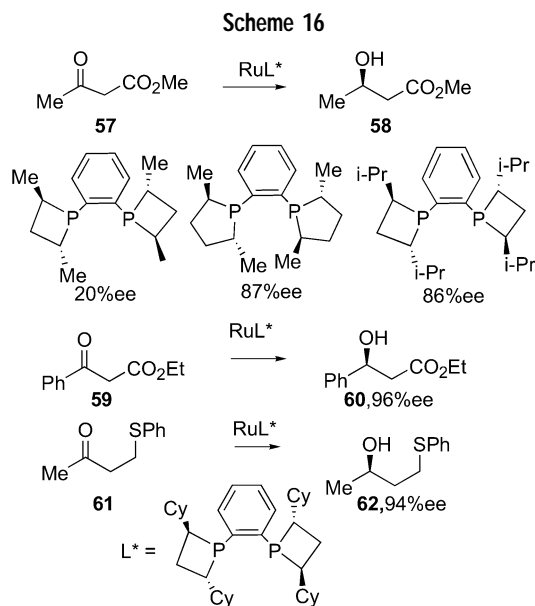


FIGURE 8. Enriched alcohols produced with MeO-NAPhePHOS and SYNPHOS.

$\beta$ -ketoesters and 1,3-diketones as model substrates.<sup>29</sup> Bidentate phosphetanes exhibit moderate to high enantioselectivities in hydrogenation reactions. Within each series, however, compared to the phospholane ligands, bulkier substituents are required for high enantioselectivity. For example, in the hydrogenation of substrates **57**, **59**, and **61** to alcohols **58**, **60**, and **62**, the highest enantioselectivity is attained by using sterically hindered ligands ( $R$  = isopropyl or cyclohexyl) (Scheme 16).



**Asymmetric Hydrogenation with Recoverable Ru Catalysts.** The Ru complex of the new guanidium phosphine (*R*)-*Digm*-BINAP ligand **17** hydrogenates various  $\beta$ -keto esters in ethyleneglycol to yield alcohols **63**–**65** with 90–99% ee (Figure 9). This catalyst was also robust and can be recycled five times without loss of activity.

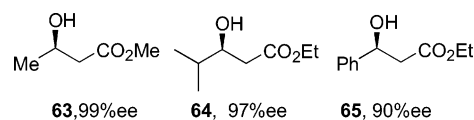


FIGURE 9. Alcohols produced with Ru-(*R*)-*Digm*-BINAP.

On the other hand, PEG-(*R*)-*Am*-BINAPRuBr<sub>2</sub> catalyst, prepared from **18**, also promoted highly enantioselective hydrogenations. Methyl acetoacetate was hydrogenated in methanol ( $S/C$ : 10 000) to give (*R*)-hydroxybutyrate in 99% ee. Recycling the catalyst was possible, as shown in Figure 10. Five cycles have been performed without significant loss of enantioselectivity.<sup>36</sup>

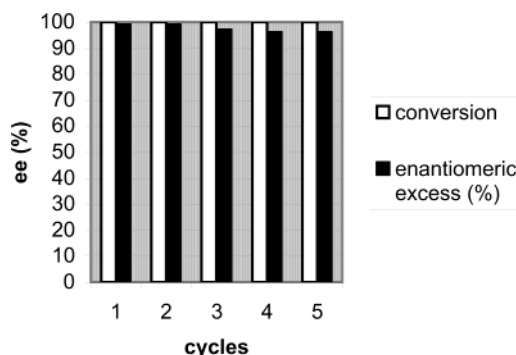


FIGURE 10. Recycling of the catalyst with Ru-PEG(*R*)-*Am* catalyst.

**Sense of the Enantioselectivity.** Noyori et al., using Ru-BINAP catalysts, have demonstrated that substituted ketones bearing functional groups **67** are reduced with high selectivity. They suggested a chelated intermediate **69** in which the Ru(II) atom interacts with the carbonyl group and the coordinating atom at the  $\alpha$  or  $\beta$  position. A recent elegant study by Bergens et al.<sup>49</sup> has established the mechanism of this important reaction. The stereochemical influence through interaction of the substrate with ruthenium-centered ligands such as BINAP, MeO-BIPHEP, DuPHOS, CnrPHOS, SKEWPHOS, MeO-NAPhePHOS, and SYNPHOS allows a general prediction of the absolute configuration of the alcohol. A specific relationship between chiral ligand and alcohol configuration is shown in Figure 11. When the ligand blocks the upper

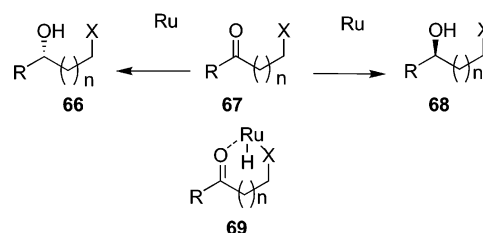


FIGURE 11. General sense of hydrogenation of functionalized ketones with Ru(II) catalysts.

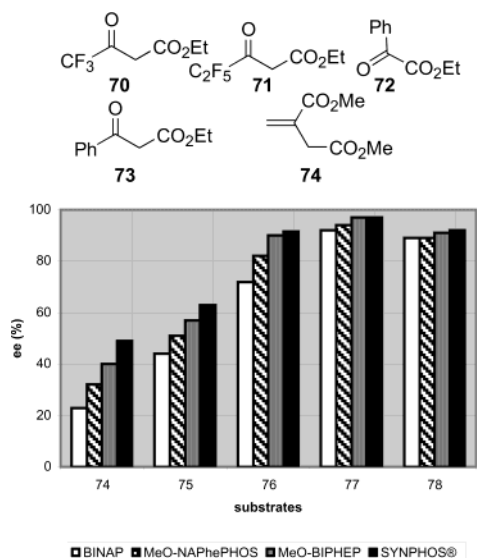
right and bottom left quadrants in the Ru catalyst, the major alcohol is **66**. The opposite configuration of the ligand gives **68**.

**Evaluation of the Steric Effects.** It is established that steric effects play a crucial role the steric consideration, based on the effect of varying the dihedral angles in the biaryl backbone, which may explain the differences in selectivity for BINAP vs SEGPHOS.<sup>32</sup> Having in hand two new ligands, MeO-NAPhePHOS and SYNPHOS, we decided to look at the dihedral angle of the biphenyl and binaphthyl systems. Recently, ruthenium hydride intermediates have been identified in these reactions as the enantio-determining step.<sup>49</sup> We decided to minimize the energy of ruthenium-mediated hydrogenation intermediate model complexes, bearing four diphosphane ligands (BINAP, MeO-BIPHEP, MeO-NAPhePHOS, and SYNPHOS), using the CAChe MM2 calculation method.

**Table 1. Dihedral Angles of Diphosphines in Ru Complexes**

diphosphine ligand	dihedral angle, $\theta$ ( $^\circ$ )
BINAP	80
MeO-NAPhePHOS	77
MeO-BIPHEP	76
SYNPHOS	75

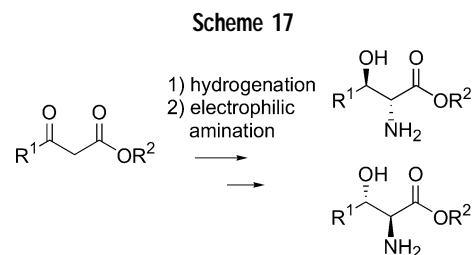
The calculated dihedral angles decrease in the order BINAP, MeO-BIPHEP, MeO-NAPhePHOS,<sup>50</sup> and SYNPHOS (Table 1).<sup>35a</sup> We then compared these ligands in the hydrogenation of substrates **70–74**. As shown in Figure 12, the enantioselectivities are remarkably influenced by the dihedral angle  $\theta$ . The narrower the dihedral angle, the higher the observed enantioselectivities.<sup>35c</sup>



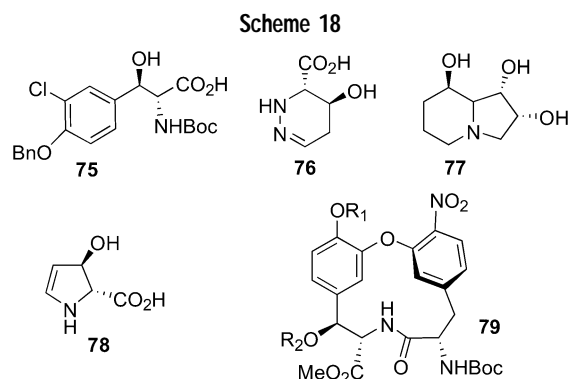
**FIGURE 12.** Comparison in the asymmetric hydrogenation of keto groups and olefins with Ru(II)-BINAP, MeO-NAPhePHOS, MeO-BIPHEP, and SYNPHOS.

**Synthetic Applications.** As shown above, functionalized  $\beta$ -hydroxy esters are obtained quantitatively with excellent enantiomeric excesses (>99% ee) by hydrogenation of  $\beta$ -ketoesters in the presence of chiral ruthenium catalysts.

This convenient methodology gives both antipodes with equal ease. By coupling the two sequential reactions—catalytic hydrogenation and diastereoselective amination of enolates—this method provides a direct approach to chiral anti  $\alpha$ -amino  $\beta$ -hydroxy esters, as shown in Scheme 17.

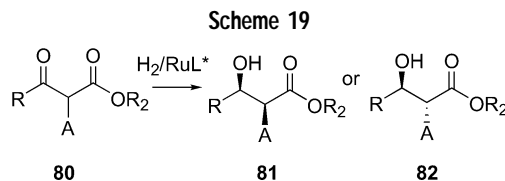


Different synthetic applications have been developed,<sup>51</sup> including the syntheses of the amino acid **75**, a key component of vancomycin, tetrahydropyridazine-3-carboxylic acid (**76**), (–)swainsonine (**77**), and a functionalized  $\Delta^2$ -pyrazoline (**78**) having important applications as 3-hydroxyproline surrogates (Scheme 18).<sup>52</sup> This powerful technology opens the way to the 14-membered ring system **79**, including  $\alpha,\beta$ -hydroxytyrosine, which is the direct precursor of cyclodityrosine (a potent antitumor agent).<sup>53</sup>



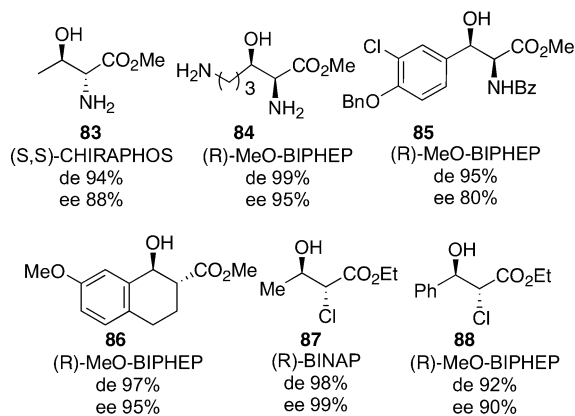
## Dynamic Kinetic Resolution (DKR)

Hydrogenation of racemic  $\alpha$ -substituted cyclic and acyclic  $\beta$ -ketoesters **80** should, in principle, provide four possible stereoisomers of hydroxy esters. However, it is possible to obtain a single product, *syn*-**81** or *anti*-**82**, with two contiguous stereogenic centers (Scheme 19).<sup>12</sup> Noyori et al.<sup>12</sup> and our group<sup>54</sup> discovered the first examples of stereo- and enantioselective hydrogenation through DKR.



The degree of selectivity (*syn* or *anti*) is highly dependent on the nature of the chiral Ru catalysts, the reaction conditions, and the substrates.<sup>55</sup> As shown in Figure 13, hydrogenation of racemic  $\alpha$ -acylamino  $\beta$ -ketoesters are hydrogenated with (*R*)- or (*S*)-MeO-BIPHEP-Ru complex

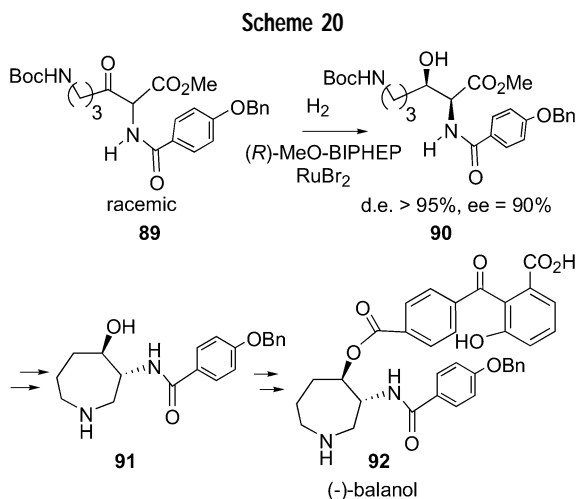




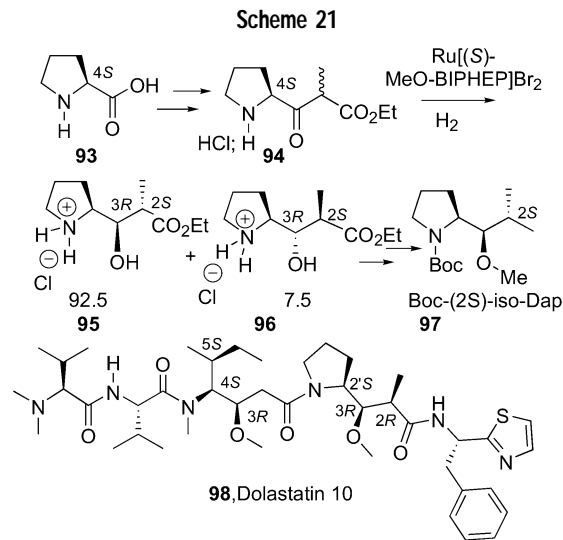
**FIGURE 13.** Synthesis of enantiomerically enriched alcohols via DKR.

to give (2*R*,3*R*)-*syn* amino esters in up to 99% ee. The reaction provides an efficient route to *syn*- $\beta$ -hydroxy- $\alpha$ -amino acids: threonine (**83**),<sup>54</sup> hydroxylysine (**84**),<sup>55</sup> and chlorohydroxyphenylalanine (**85**). The reduction through DKR of a tetralone gives the *trans* hydroxyester **86** with high selectivity.<sup>56</sup> Interestingly, hydrogenation of an  $\alpha$ -chloro substrate in the presence of an Ru-(COD)( $\eta^3$ -methylallyl)<sub>2</sub>/(*R*)-MeO-BIPHEP system gives exclusively the anti chlorohydrins **87–88** with ee's up to 99%.<sup>57</sup>

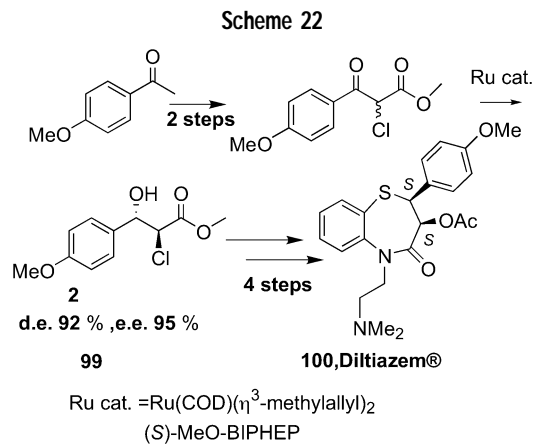
An  $\alpha$ -benzamido  $\beta$ -keto ester **89**, properly functionalized, was converted into a single product **90** with high diastereo- and enantioselectivity. This compound was subsequently transformed to the hexahydroazepane core in four steps (Scheme 20). This represents one of the shortest syntheses of the core unit **91** of (–)-balanol (**92**),<sup>58</sup> a natural product which has remarkable inhibitory properties toward protein kinase C.



Another application of this powerful technique involves the efficient multigram-scale synthesis of optically pure Boc-(2*S*,3*R*,3*S*)-isodolaproine (**97**) from proline **93**, as shown in Scheme 21. The catalytic asymmetric hydrogenation of ethyl (4*S*)-3-2-(2'-pyrrolidinyl)-3-oxo-2-methylpropanoate hydrochloride using in situ-generated Ru[(*S*)-MeO-BIPHEP]Br<sub>2</sub> catalyst furnishes the anti  $\alpha$ -methyl ester **95** with high selectivity.<sup>59</sup> This procedure opens access to an efficient preparation of analogues of dolastatin **98** (an anticancer agent).



Having in hand optimal conditions for the DKR of racemic  $\alpha$ -chloro  $\beta$ -keto esters to produce anti chlorohydrins with high enantioselectivity, we have developed from the enantiomerically pure compound **99** an efficient synthesis of diltiazem (**100**)<sup>60</sup> (Scheme 22), a potent calcium channel blocker used for treatment of hypertension.



## Conclusions

The successful hydrogenation reactions described herein proceed with high enantioselectivity. In particular, steric tuning of the phosphine, as well as the design of catalysts, proved to be successful. In this respect, the establishment of ligand diversity in the modular phosphetane and biphenyl series has truly found its utility in the hydrogenation of olefins and carbonyl compounds. In the course of an industrial product-oriented study, we discovered a new type of ruthenium catalyst, [Ru(P\*P)(H)( $\eta^6$ -cot)]BF<sub>4</sub>, that is particularly efficient for hydrogenation of a tetra-substituted olefin such as “dehydrodione” to (+)-*cis*-dihydrojasmonate in ee's up to 90%. This compound, named Paradisone, is now commercially produced in large quantities by Firmenich. From a synthetic viewpoint, asymmetric hydrogenation has been applied to the synthesis of a wide variety of bioactive compounds.

*This work has been carried out over the past 15 years at the Université Pierre and Marie Curie and Ecole Nationale Supérieure*

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