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Recent studies on asymmetric hydrogenation. New catalysts and synthetic applications in organic synthesis*

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Abstract: CODRu(η^3methylallyl)$_2$ is a versatile starting material for the preparation of a wide range of chiral bisphosphines ruthenium(II) complexes: (P*P)Ru(η^3methylallyl)$_2$ **2**, Ru[X_4(P*P)$_2$] **3**, and cationic monohydride ruthenium complex **4**. A facile synthesis of new C_2 electron-rich chiral phosphines, bis(phosphetano)benzene **8** and 1,1′bis(phosphetano)ferrocene **10** is presented. Dynamic kinetic resolution was used for efficient syntheses of key components of the hexahydroazepane core **16** of balanol and of optically pure Boc-(2*S*,3*R*,3*S*)-iso-dolaproïne **19**. Catalyst **4** was used in asymmetric hydrogenation of **22** to give (+)-*cis*-methyl dihydrojasmonate in high enantioselectivity.

INTRODUCTION

In the 1970s, the discovery of chiral phosphine-modified Rh complexes as catalysts has led to the standard method to synthesize optically active amino acids. Spectacular enantioselectivities (up to 99%) were obtained with rhodium(I) catalysts. There are many reviews and chapters of books covering the field [1–6]. In spite of impressive achievements [7] and improvements in the design of new ligands for the rhodium(I) catalysts, the scope of this chemistry is not so wide in comparison with Ru-catalyzed hydrogenation reactions. The first chiral Ru(II)-complex was reported by James [8]. A breakthrough came by the discovery of ruthenium complexes containing the highly effective BINAP ligands [9–10]. In the application of such chemistry to the synthesis of optically active compounds, chemists are facing the task of designing broad libraries of such chiral ruthenium(II) catalysts. In our ongoing research program on transition-metal catalysis we have developed a general route for the preparation of chiral Ru(II) complexes the usefulness of these catalysts will be briefly presented with the successful development of enantioselective hydrogenation of prochiral olefins and ketones, for the synthesis of various complex biologically active molecules.

DIVERSITY IN CATALYSTS PREPARATION

Our catalyst preparation starts with RuCOD(η^3-methylallyl)$_2$ (COD = cycloocta-1,5-diene) complex **1** which is transformed into a wide range of chiral ruthenium complexes **2** by the displacement of cyclooctadiene (COD) ligand by a wide range of chiral phosphine. A subsequent protonation by HX (X = Br, Cl) produces ruthenium(II) catalysts of type **3** (Scheme 1) [11–12].

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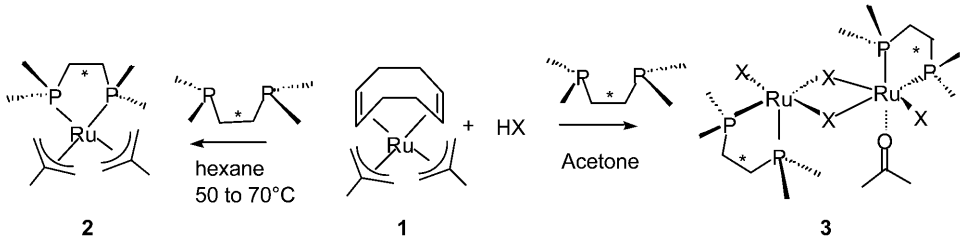
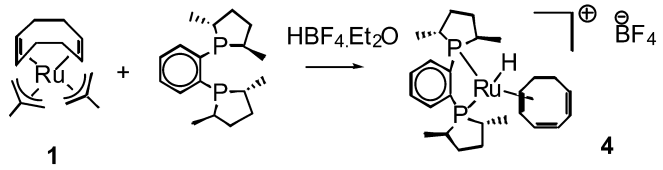


Scheme 1

A convenient one-step *in situ* preparation of Ru(II)-catalysts **3** has been developed [13] from (COD) Ru(η^3-methylallyl)$_2$ by protonation with HX in the presence of appropriate chiral phosphine.

Very recently, we have found simplified procedures for the preparation of chiral Ru(II)-catalysts using commercially available [$RuCl_2$(COD)]n [14] and $RuCl_3$ [15] by simple addition of the chiral diphosphines. The established routes have several advantages, a rapid screening of ligands. We also discovered that the treatment of Ru(COD)(η^3-methylallyl)$_2$ and various chiral diphosphane ligands P*P-(DUPHOS, JOSIPHOS) in CH_2Cl_2 with HBF_4 generates *in situ* a new type of catalysts (Scheme 2).



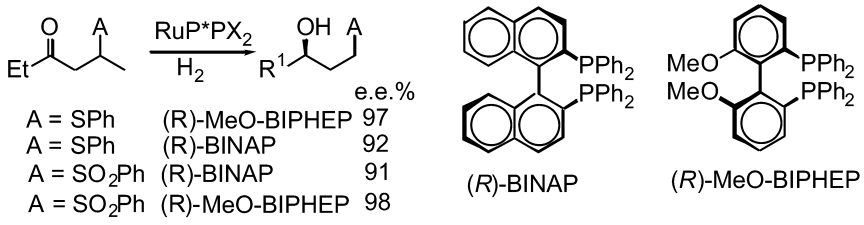
Scheme 2

For example, using (R,R DUPHOS), a cationic monohydride ruthenium complex **4** was isolated and characterized by NMR spectroscopy and X-ray diffraction [16]. The usefulness of all these catalysts will be demonstrated in the asymmetric hydrogenation of prochiral ketones and olefins.

ASYMMETRIC HYDROGENATIONS OF KETO GROUPS

We have found that the *in situ* prepared catalysts are extremely efficient for the asymmetric hydrogenation of a wide range of β-keto esters, β-thioketones, and β-keto-phosphonates. These catalysts exhibit high catalytic activity and enantioselectivity. We have established that SKEWPHOS also named BDPP (2,4-bis-diphenylphosphino) pentane is an efficient ligand up to 95% ee for ruthenium asymmetric hydrogenation of functionalized ketones under optimized conditions [17].

The catalytic behavior of Ru(II) catalysts containing atropisomeric ligands such as BINAP and MeO-BIPHEP has been investigated for a wide range of substrates. These catalysts are highly efficient for β-keto esters, β-keto phosphonates. However, our studies reveal some significant differences



Scheme 3

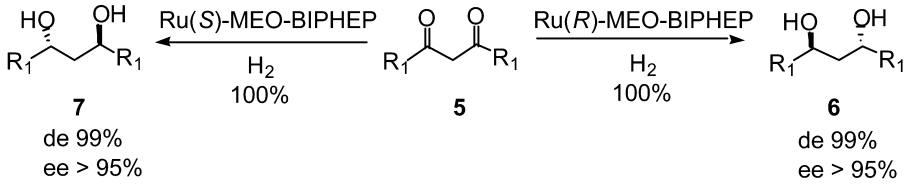
between BINAP and MeO-BIPHEP for some type of substrates (Scheme 3). For example, a better recognition in the reduction of β-keto sulfides [18] and β-sulfones [19] with MeO-BIPHEP vs. BINAP ligand was observed.

The better recognition of MeO-BIPHEP vs. BINAP could be due to the influence of the dihedral angle in the biaryl backbone. These steric effects have been estimated by CAChe MM2 calculation of dihedral angle of chiral bisphosphines and the corresponding Ru-complexes.

	MeO-BIPHEP	BINAP
dihedral angle bisphosphine	77.4°	86.2°
dihedral angle Ru-bisphosphine complex Ru_2X_4 $(P^*P)_2$	72.5°	78.9°

The smaller dihedral angle of the Ru-complex containing MeO-BIPHEP increases of the steric interactions in ruthenium-substrate complex and affects the enantioselectivity [20].

The ruthenium asymmetric hydrogenation of symmetrical 1,3-diketones **5** into *anti* 1,3-diols **6** or **7** has been achieved using (*R*) and (*S*) MeO-BIPHEP, with outstanding enantiomeric and diastereomeric excesses up to 99% (Scheme 4) [21].

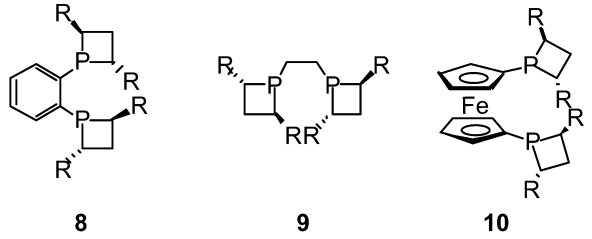


Scheme 4

SYNTHESIS OF NEW CHIRAL LIGANDS

Electron-rich bisphosphines

From a practical viewpoint, these optically pure 1,3-diols have been used for the preparation of a new class of C_2 electron-rich symmetric phosphines bis(phosphetano)benzene: CnrPHOS **8** bis(phosphetano)ethane **9** and 1,1′-bis(phosphetano)ferrocene **10** [22–25]. These optically pure ligands (Scheme 5) are easily accessible in both enantiomeric form; they display significant enantioselectivity in ruthenium- and rhodium-catalyzed hydrogenation, respectively.

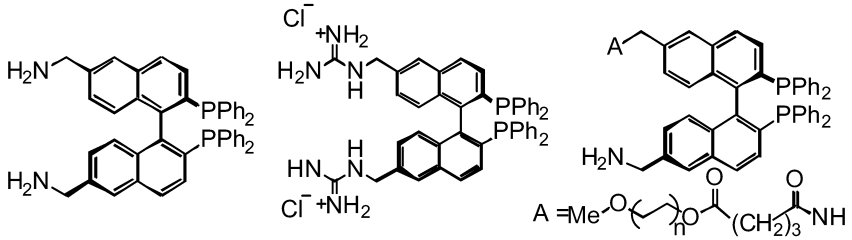


Scheme 5

It appears that the presence of the 4-membered phosphetane ring with bulky substituents (R = isopropyl, cyclohexyl) in the diphosphine; for example, the ferrocenyl phosphetane brings about peculiar properties and specific applications with respect to the phospholane analogs [23,25].

Recoverable ligands

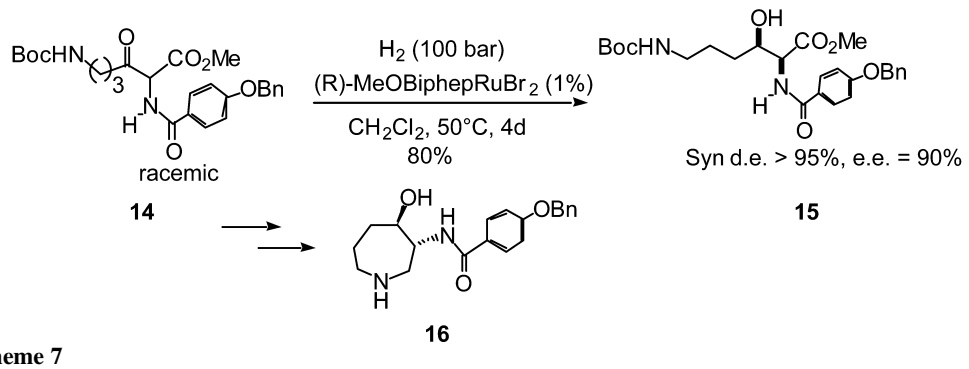
A major problem associated with the most homogeneous catalyst systems is the separation and recycling of the expensive catalyst. One way to solve this problem is to use water-soluble ligand for a two-phase systems or polymer-bounded ligand for one-phase catalysis and two-phase separation. In this context, we have prepared two new recyclable BINAP-type ligands from 6-6′ diamino (*R*)-BINAP **11**, the cationic diguanidinium **12**, and PEG-bound BINAP **13** (Scheme 6). These new ligands are highly efficient in rhodium- and ruthenium-catalyzed hydrogenation, respectively (catalyst/substrate ratio up to 1:10000 ee up to 99%) [26].



Scheme 6

DYNAMIC KINETIC RESOLUTION (DKR): SYNTHETIC APPLICATIONS

In this process, a racemic material such as α-substituted β-keto esters bearing a configurationally labile stereogenic center and a prochiral carbonyl moiety can be converted to one major *syn* or *anti* stereoisomer, through enantioselective hydrogenation via dynamic kinetic resolution (DKR). This technique is now widely used in organic synthesis [27]. The reaction provides an efficient route to *syn* β-hydroxy α-amino acids. Recently, we have reported an efficient formal synthesis of (–)-balanol [28] (Scheme 7). The α-amido β-keto ester **14** properly functionalized was converted into a single diastereomer with high diastereo- and enantioselectivities (de = 93%; ee = 94%).

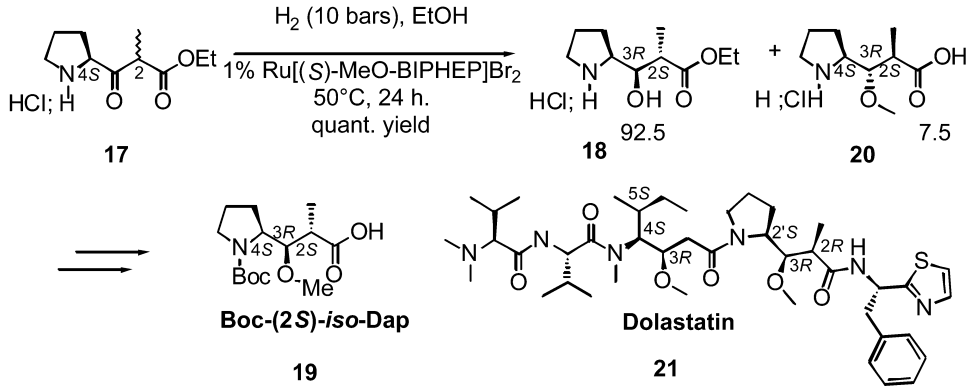


Scheme 7

This compound was subsequently transformed to the hexahydroazepane core **16** in four steps. This represents one of the shortest synthesis of balanol, in which compound has been found remarkable inhibitory properties toward protein kinase C (PKC).

Another example of this powerful DKR has been used for an efficient multigram-scale synthesis of optically pure Boc-(2*S*,3*R*,3*S*)-iso-dolaproïne **19**. The catalytic asymmetric hydrogenation of ethyl (4*S*)-3-(2′-pyrrolidinyl)-3-oxo-2-methyl propanoate hydrochloride **17** using *in situ* generated Ru[(S)-MeO-Biphep]Br_2 catalyst affords the *anti* β-hydroxy α-methyl ester **18**, quantitatively.

Synthesis of Boc-(2*S*)-iso-dap, was achieved in two subsequent steps (Scheme 8). This technology opens access to an efficient preparation of Dolaproïne key component of Dolastatin 10 **21**.

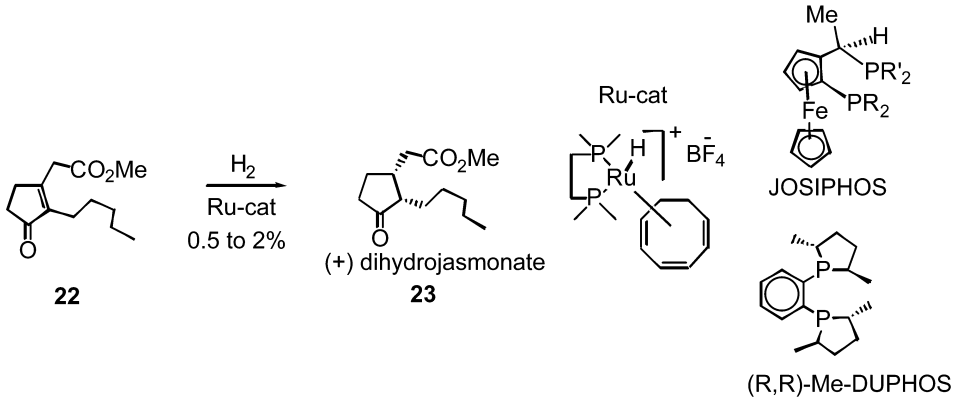


Scheme 8

ASYMMETRIC HYDROGENATIONS OF OLEFINS

The Ru(P*P)Br_2 catalysts **4** displayed good efficiency in asymmetric hydrogenation of α, β unsaturated acids and dehydroamino acids. An important application of this technique is the enantioselective preparation in large scale (2.3 t) of a key intermediate [30] of candoxatril (Pfizer) an inhibitor of neutral eudopeptidase for the treatment of congestive heart failure.

Methyl dihydrojasmonates, due to their olfactive properties, are greatly appreciated in perfumery and are commercialized by Firmenich. However, it was recently established that the (+)-*cis*-dihydrojasmonate is indeed the only steroisomer that has an odor. In principle, the most direct route to (+)-dihydrojasmonate was the enantioselective catalytic hydrogenation of the tetrasubstituted cyclopentenone **22**. All attempts to use catalysts **3** in the hydrogenation of **22** failed. However, we found that cationic catalysts **4** are highly effective. Electron-rich P*P ligands are required for high activity and enantioselectivity (up to 90% ee) and 99% *cis* selectivity. DUPHOS and JOSIPHOS were found as the best ligands [16].



Scheme 9

This discovery has led to the industrial synthesis by Firmenich of (+)-*cis*-methyl dihydrojasmonate **23** (Scheme 9) and commercialized under the trade name of Paradisone®.

CONCLUSIONS

COD Ru(η^3-methallyl)$_2$ complex is a very convenient starting material for the preparation of Ru-catalysts by protonation with a wide range of ligands. This technique has led to the discovery of highly active cationic monohydride ruthenium catalysts: Ru(P*P)(H)($\eta^6C_8H_{11}$)$^+BF_4^-$. Homogeneous asymmetric hydrogenation of β-keto esters α-substituted using chiral ruthenium(II) catalysts is a powerful tool (DKR) that can provide entry to the synthesis of highly functionalized, optically enriched building blocks.

ACKNOWLEDGMENTS

I would like to thank the coworkers who were contributors of the results presented in this lecture. Their names are quoted in the list of references.

REFERENCES

1. R. Noyori and M. Kitamura. In *Modern Synthetic Methods*, R. Scheffold (Ed.), Vol. 5, p. 115, Springer, Berlin (1989).
2. R. Noyori. In *Asymmetric Catalysis in Organic Synthesis*, Chap. 2, Wiley VCH, New York (1994).
3. J. P. Genet. In *Reduction in Organic Synthesis. Recent Advances and Practical Applications*, D. F. Abdel-Magid (Ed.), ACS Symposium Series 641, Chap. 2, American Chemical Society, Washington DC (1996).
4. T. Ohkuma, R. Noyori, H. U. Blaser, F. Spindler. In *Comprehensive Asymmetric Catalysis*, E. N. Jacobsen, A. Pfaltz, H. Yamamoto (Eds.), Vol. I, Chap. 6, Springer, Berlin (1999).
5. J. M. Brown and R. L. Halterman. In *Comprehensive Asymmetric Catalysis*, E. N. Jacobsen, A. Pfaltz, H. Yamamoto (Eds.), Vol. I, Chap. 5, Springer, Berlin (1999).
6. T. Ohkuma, M. Kitamura, R. Noyori. In *Catalytic Asymmetric Synthesis*, I. Ojima (Ed.), 2nd ed., Chap. 1, Wiley VCH, New York (2000).
7. H. B. Kagan. *Bull. Soc. Chim. Fr*. 846 (1988).
8. B. R. James, D. Wang, R. F. Voight. *J. Chem. Soc. Chem. Commun*. 574 (1975).
9. T. Ikariya, I. Ishii, H. Kawano, T. Arai, M. Saburi, S. Yoshikawa, S. Akutagawa. *J. Chem. Soc. Chem. Commun*. 922 (1985).
10. R. Noyori, M. Ohta, Y. Hsiao, M. Kitamura, H. Takaya. *J. Am. Chem. Soc*. **108**, 7117 (1986).
11. J. P. Genet, S. Mallart, C. Pinel, S. Jugé, J. A. Laffitte. *Tetrahedron: Asymmetry* **2**, 43 (1991).
12. J. P. Genet, C. Pinel, S. Mallart, S. Jugé, N. Caihlol, J. A. Laffitte. *Tetrahedron Lett*. **33**, 3433 (1992).
13. J. P. Genet, C. Pinel, V. Vidal, S. Mallart, X. Pfister, M. C. Caño de Andrade, J. A. Laffitte. *Tetrahedron: Asymmetry* **5**, 675 (1994).
14. P. Guerreiro, M. C. Caño de Andrade, J. C. Henry, J. P. Tranchier, P. Phansavath, V. Ratovelomanana-Vidal, J. P. Genet, T. Homri, A. R. Touati, B. Ben Hassine. *C.R. Acad. Sci. Paris*, t. 2, Serie IIc, 175 (1999).
15. J. Madec, X. Pfister, P. Phansavath, V. Ratovelomanana-Vidal, J. P. Genet. *Tetrahedron* **57**, 2563 (2001).
16. D. A. Dobbs, K. P. M. Vanhessche, E. Brazzi, V. Rautenstrauch, J. Y. Lenoir, J. P. Genet, J. Wiles, S. H. Bergens. *Angew. Chem., Int. Ed*. **39**, 11, 1992 (2000).
17. D. Blanc, J. C. Henry, V. Ratovelomanana-Vidal, J. P. Genet. *Tetrahedron Lett*. **38**, 6603 (1997).
18. J. P. Tranchier, V. Ratovelomanana-Vidal, J. P. Genet, S. Tong, J. Cohen. *Tetrahedron Lett*. **38**, 17, 2951 (1997).

19. (a) P. Bertus, P. Phansavath, V. Ratovelomanana-Vidal, J. P. Genet, A. R. Touati, T. Homri, B. Ben Hassine. *Tetrahedron Lett*. **40**, 3175 (1999); (b) P. Bertus, P. Phansavath, V. Ratovelomanana-Vidal, J. P. Genet, A. R. Touati, T. Homri, B. Ben Hassine. *Tetrahedron: Asymmetry* **10**, 1369 (1999).
20. This working hypothesis has been recently reported for the design of new atropisomeric ligands: (a) T. Saito, T. Yokozawa, T. Ishizaki, T. Moroi, N. Sayo, T. Miura, H. Kumobayashi. *Adv. Synth. Catal*. **343** (3), 264 (2001); (b) Z. Zhang, H. Qian, J. Longmire, X. Zang. *J. Org. Chem*. 6223 (2000).
21. D. Blanc, V. Ratovelomanana-Vidal, A. Marinetti, J. P. Genet. *Synlett* **4**, 480 (1999).
22. A. Marinetti, J. P. Genet, S. Jus, D. Blanc, V. Ratovelomanana-Vidal. *Chem. Eur. J*. **5**, 1160 (1999).
23. A. Marinetti, F. Labrue, J. P. Genet. *Synlett* **12**, 1975 (1999).
24. A. Marinetti, S. Jus, J. P. Genet, L. Ricard. *Tetrahedron* **56**, 95 (2000).
25. A. Marinetti, S. Jus, J. P. Genet, L. Ricard. *J. Organomet. Chem*. **624**, 162 (2001).
26. P. Guerreiro, V. Ratovelomanana-Vidal, J. P. Genet, P. Dellis. *Tetrahedron Lett*. **42**, 3423 (2001).
27. V. Ratovelomanana-Vidal and J. P. Genet. *Can. J. Chem*. **78**, 746 (2000) and references cited therein.
28. P. Phansavath, S. Duprat de Paule, V. Ratovelomanana-Vidal, J. P. Genet. *Eur. J. Org. Chem*. 3903 (2000).
29. D. Lavergne, C. Mordant, V. Ratovelomanana-Vidal, J. P. Genet. *Org. Lett*. **3**, 12, 1909 (2001).
30. (a) J. P. Genet. In *Current Trends in Organic Synthesis*, C. Scalastico and F. Nicotra (Eds.), p. 229 Kluwer, Dordrecht (1999); (b) M. Bulliard, B. Lahoue, J. Lastennet, S. Roussiasse. *Org. Proc. Res. Develop.* **5**, 438 (2001).