Dynamic Chirality Control of (Xyl-)BIPHEP Ligands Leading to their Diastereomerically Pure Ru Complexes with a Chiral *N*-Substituted DPEN

Toshinobu Korenaga, Kohsuke Aikawa, Masahiro Terada, Susumu Kawauchi, Koichi Mikami*

Department of Applied Chemistry, Tokyo Institute of Technology, Meguro-ku, Ookayama 2-12-1, Tokyo 152-8552, Japan
Fax: (+81) 3-5734-2776, E-mail: kmikami@o.cc.titech.ac.jp

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Abstract: The metal complex of the chirally flexible biphenylphosphine (BIPHEP) exists as an equilibrium between the enantiomeric pairs due to the flexibility of BIPHEP. The dynamic chirality control of the BIPHEP ligands in enantiomerically pure forms to give diastereomerically pure metal complexes with respect to their Ru(II) complexes by their molecular design with the introduction of a substituent in the chiral diamines rather than in the biphenylphosphine is described.

Keywords: BIPHEP; diamine; dynamic chirality control; phosphine; ruthenium

Introduction

The development of an asymmetric catalyst is of central importance in modern synthetic and pharmaceutical chemistry,[1] wherein the design of a chiral ligand is the key to increase the catalyst activity from an achiral pre-catalyst and, hence, to induce chirality in a product ("ligand-accelerated catalysis"[2]). In order to obtain the enantiopure forms of chirally rigid, for example, Noyori's BINAP ligands,[3] asymmetric synthesis or resolution is required. By contrast, the chirally flexible biphenylphosphine (BIPHEP) counterparts (Figure 1) cannot be synthesized in enantiopure forms.[4] Accordingly, we have reported the use of the chirally flexible BIPHEP ligands without their asymmetric synthesis or resolution[4,5] in highly enantioselective hydrogenation by means of the corresponding Ru catalyst, instead of the enantiopure, chirally rigid BINAP counterparts.[6] Furthermore, the BIPHEP-Ru(II) complex can be obtained in enantioenriched forms, after complexation with a chiral diamine activator such as 1,2-diphenylethylenediamine, DPEN 1) to control the chirality through epimerization and 2) to increase the catalyst activity of the BIPHEP-Ru(II) complex in asymmetric hydrogenation of ketones ("asymmetric activation").[6a] Herein, we wish to report the dynamic chirality control of the BIPHEP ligands in enantiomerically pure forms to give diastereomerically pure Ru(II) complexes by their molecular design through introduction of a substituent in DPEN rather than in BIPHEP.

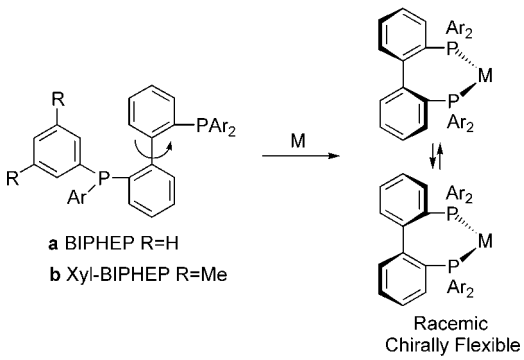

Figure 1. Chirally flexible BIPHEP ligand complex.

We have already reported that complexation of racemic $RuCl_2$[dm(i. e., xyl)biphep](dmf)$_n$ with the parent (*S*,*S*)-DPEN initially provides both diastereomeric $RuCl_2$(xylbiphep)[(*S*,*S*)-dpen] in an equal amount and finally a 3:1 diastereomeric ratio {with $RuCl_2$[(*S*)-xylbiphep][(*S*,*S*)-dpen] as major diastereomer}, after epimerization of the Xyl-BIPHEP ligand.[6,7] However, the parent $RuCl_2$(biphep)(dpen) was found to give lower (2:1) diastereomeric ratio under the same conditions in 2-propanol, suggesting a steric repulsion between the 3,5-substituents in BIPHEP and the amine hydrogens in DPEN (vide infra). Therefore, the diastereomeric ratio could be increased up to 100:0 by introducing larger substituents in the 3,5-positions in BIPHEP and/or on the amines in DPEN.

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Results and Discussion

The favorable complexation of 3,5-substituted (*S*)-BIPHEP-$RuCl_2$ (**1**) with *N*-substituted (*S*,*S*)-DPEN was highly predictable by molecular modeling studies (Figure 2, a and b). However, the 3,5-di-*tert*-butyl analogue of BIPHEP and/or *N*,*N*-dibenzyl-DPEN did not provide the corresponding Ru complexes. Fortunately, *N*,*N*-dimethyl-1,2-diphenylethylenediamine (DM-DPEN) (**2**) was found to complex not only with the parent BIPHEP-$RuCl_2$ (**1a**) but also with Xyl-BIPHEP-$RuCl_2$ (**1b**) to give the diastereomerically pure (Xyl-)BIPHEP-Ru/DM-DPEN complexes.

In principle, the dynamic chirality control can be classified into two extremes. We have already reported that complexation of racemic $RuCl_2$(xylbiphep)$(dmf)_n$ (**1b**) with the parent DPEN initially provides a 1:1 ratio of diastereomers, which then epimerize (Figure 3, a). The other possibility is selective complexation of the *N*-substituted DPEN with one enantiomer of a racemic BIPHEP-Ru (**1**) complex along with the remaining BIPHEP-Ru (**1**) enantiomer which eventually racemizes in order to complex with the *N*-substituted DPEN (Figure 3, b). Therefore, do we have the enantiomer-selective complexation of (*S*,*S*)-DM-DPEN (**2**) with (*S*)-(Xyl-)BIPHEP-$RuCl_2$ or a non-selective complexation, that is the question.

(*S*,*S*)-DM-DPEN (**2**) was found to complex with either enantiomer of the racemic Xyl-BIPHEP-Ru (**1b**) to provide $RuCl_2$[(*S*)-xylbiphep][(*S*,*S*)-dmdpen] (*S*)-**1b**/(*S*,*S*)-**2** and $RuCl_2$[(*R*)-xylbiphep][(*S*,*S*)-dmdpen] (*R*)-**1b**/(*S*,*S*)-**2** in equal amounts in dichloromethane as observed by ^{1}H NMR analysis.[8] However, the (*R*)-**1b**/(*S*,*S*)-**2** completely epimerized to (*S*)-**1b**/(*S*,*S*)-**2** in 2-propanol at 50 °C after 1 hour as observed by ^{1}H NMR analysis at room tempetature in $CDCl_3$. Indeed, the (*S*)-/(*S*,*S*)-configuration of the Xyl-BIPHEP-$RuCl_2$/DM-DPEN diastereomer was determined in its *trans*-configuration by X-ray analysis of the single-crystal obtained from dichloromethane-ether-hexane (Figure 4, b).

With respect to BIPHEP-$RuCl_2$ (**1a**), (*S*,*S*)-DM-DPEN (**2**) was also found to complex with either enantiomer in equal amounts. Although the BIPHEP li-

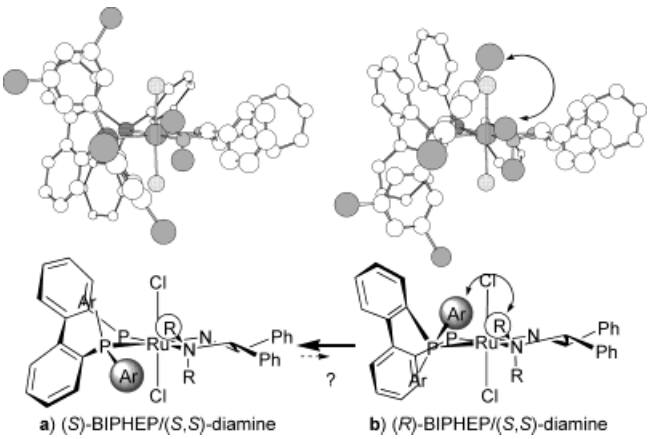

Figure 2. Model study for the control of the enantiomers of the BIPHEP ligand.

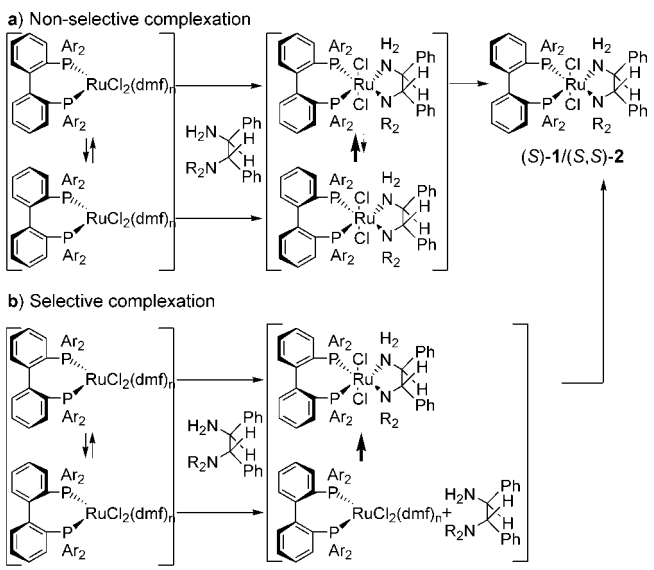

Figure 3. Classified dynamic chirality control.

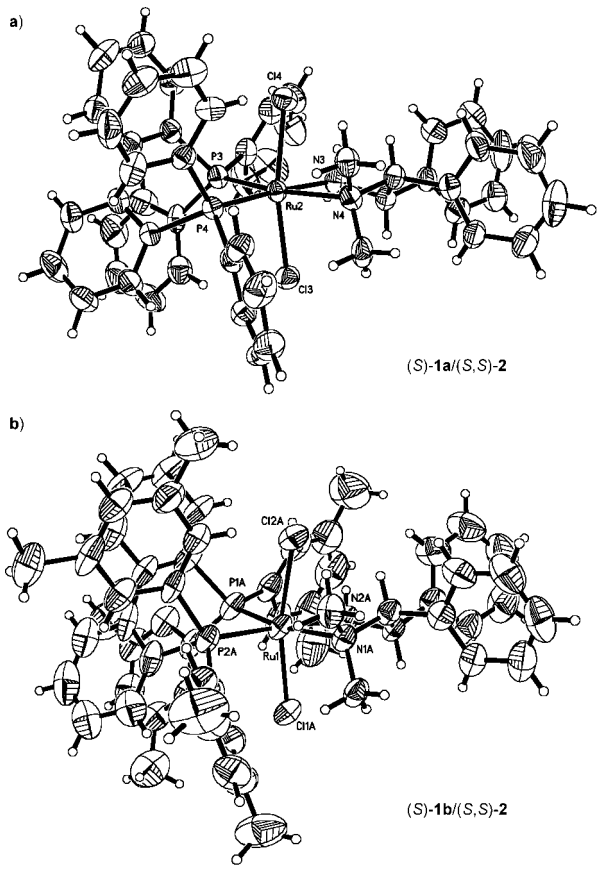

Figure 4. X-ray analysis of (Xyl-)BIPHEP-Ru/DM-DPEN complexes.

gand was less effective than the Xyl-BIPHEP ligand as shown by the ratios of epimerization of their DPEN complexes (2 : 1 as compared to the 3 : 1 ratio of the Xyl-BIPHEP-Ru/DPEN complex) (vide supra), the less favorable $RuCl_2$[(*R*)-biphep][(*S*,*S*)-dmdpen] (*R*)-**1a**/(*S*,*S*)-**2** completely epimerized to $RuCl_2$[(*S*)-biphep][(*S*,*S*)-dmdpen] (*S*)-**1a**/(*S*,*S*)-**2** in 2-propanol (Figure 4, a).[9]

In order to estimate the activation barrier of internal rotation between the biphenyl rings, we carried out a density functional calculation for a model catalyst. In the model, H atoms were used instead of phenyl rings attached to phosphorus atoms to reduce calculation costs. The B3LYP functional was used with the SDD basis sets implemented in the Gaussian 98 program.[10] As shown in Figure 5, a and c, we obtained two equilibrium structures with C_2 symmetry.[11] The geometrical differences were mainly found in a torsion ring composed of biphenylphosphine and ethylenediamine. However, the energy difference was quite small, only 0.2 kcal/mol. Then, the biphenyl rings were put on the same plane to optimize the other variables of the structure for obtaining the transition state (TS) of internal rotation of the biphenyl rings. The optimized structures are shown in Figure 5 (b).[12] The energy difference relative to the equilibrium structure, which is 35.9 kcal/mol,[13] gives a rough estimate of the activation barrier Phenyl substituents on phosphorus atoms will increase the activation barrier. This leads to the conclusion that internal rotation between the biphenyl rings in the real catalyst is a difficult process (Figure 5) and that stereomutation occurs through rupture of only one Ru-P bond rather than two bonds (Figure 6). In fact, no ligand exchange was observed between (Xyl-)BIPHEP and BINAP upon addition of BINAP to the solution of the (Xyl-)BIPHEP-Ru-(DM-)DPEN complex. Then solvent-assisted mutation[14] about the biphenyl single bond through the so-called cogwheeling effect[15] depending on the effective van der Waals radii[16] and recoordination of P to Ru would result in the epimerization to the favorable diastereomer, as we have already proposed.[6a,7]

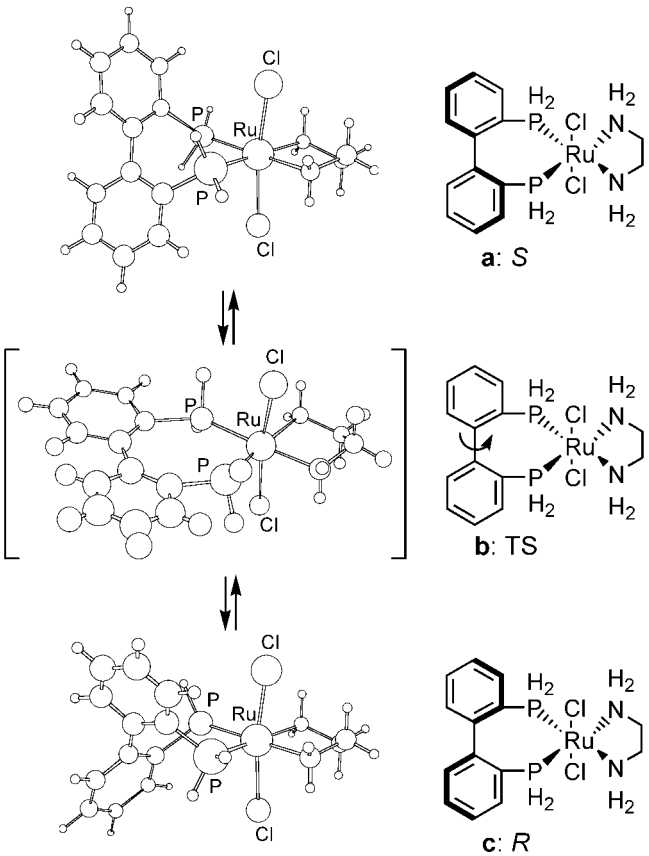

Figure 5. DFT caclulations of internal rotation of the biphenyl ring.

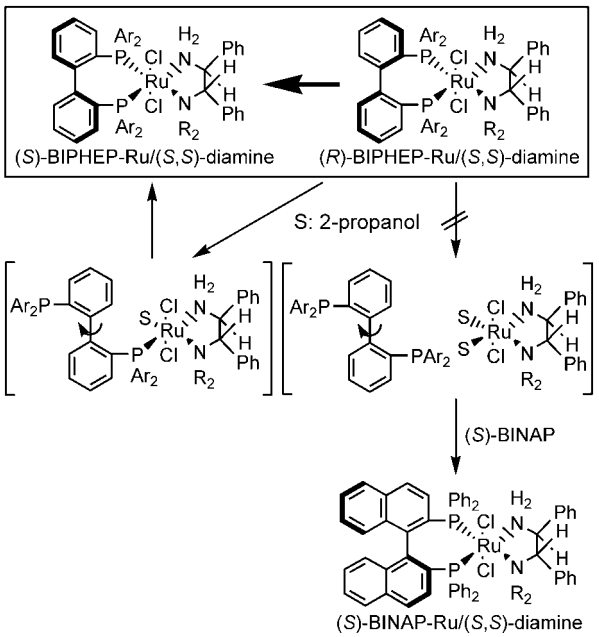

Figure 6. Mechanism of epimerization of BIPHEP-Ru(DM-)-DPEN complexes.

Conclusion

In summary, we have reported that the diastereomerically pure Ru complex of the (Xyl-)BIPHEP ligand can be envisioned through epimerization following non-selective complexation of *N*-substituted DPEN with (Xyl-)BIPHEP-$RuCl_2$, wherein the steric repulsion between the (3,5-dimethyl)phenyl group in BIPHEP and the *N*-methyl substituent in DPEN is operative in the dynamic chirality control.

Experimental Section

Procedure for (*S*)-1b/(*S,S*)-2

To a mixture of $RuCl_2$[(*S*)-xylbiphep](dmf)$_n$ (**1b**; 100 mg, 0.105 mmol) and (*S,S*)-DM-DPEN (**2**) (24 mg, 0.1 mmol) was added dichloromethane (10 mL) at room temperature under an argon atmosphere. After the mixture had been stirred for 30 min at room temperature, dichloromethane was removed under reduced pressure and then 2-propanol (10 mL) was added. After stirring for 1 h at 50 °C, the solvent was removed under reduced pressure. The residue was purified by florisil chromatography (eluent: dichloromethane) to give 104 mg of $RuCl_2$[(*S*)-xylbiphep][(*S,S*)-dmdpen] [(*S*)-**1b**/(*S,S*)-**2**] quantitatively. This complex was recrystalized from dichloromethane, ether, and hexane for X-ray analysis. ^{1}H NMR ($CDCl_3$): δ = 3.17–3.22 (m, 1H, CH–N*H*$_2$), 3.54–3.58 (m, 1H, CH–N*H*$_2$), 4.32–4.39 (m, 1H, C*H*–NH$_2$), 5.02 (d, 12.3 Hz, 1H, C*H*–NMe$_2$).

X-Ray Crystallography

$RuCl_2$[(*S*)-biphep][(*S,S*)-dmdpen] (*S*)-**1a**/(*S,S*)-**2**
The single crystal growth was grown from a dichloromethane-hexane mixed solvent system at room temperature. X-ray crystallographic analysis was performed with a Bruker SMART 1000 diffractometer (graphite monochromator, MoKα radiation, λ = 0.71073 Å). The structutre was solved by direct methods and expanded using Fourier techniques. Crystal data for $RuCl_2$[(*S*)-biphep][(*S,S*)-dmdpen]: $C_{52}H_{48}Cl_2N_2P_2Ru$, orange, crystal dimensions 0.26×0.34×0.41 mm^3, Tetragonal, space group P_1, a = 12.624(5), b = 13.987(5), c = 15.042(5) Å, V = 2436.8(15) Å^3, Z = 2, $\rho_{calc.}$ = 1.274 g cm^{-3}, μ(MoKα) = 1.43 cm^{-1}, T = 298 K, 36405 reflections were independent and unique, and 26970 with $I > 2\sigma(I)$ ($2\theta_{max}$ = 30.5°) were used for the solution of the structure. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. R = 0.0694, w$R2$ = 0.2063. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-156880. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB@ 1EZ, UK [fax:(+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk].

$RuCl_2$[(*S*)-xylbiphep][(*S,S*)-dmdpen] (*S*)-**1 b**/(*S,S*)-**2**
The single crystal was grown from a dichloromethane-ether-hexane mixed solvent system at room temperature. X-ray crystallographic analysis was performed with a Bruker SMART 1000 diffractometer (graphite monochromator, MoKα radiation, λ = 0.71073 Å). The structutre was solved by direct methods and expanded using Fourier techniques. Crystal data for $RuCl_2$[(*S*)-xyl-biphep][(*S,S*)-dmdpen]: $C_{60}H_{64}Cl_2N_2P_2Ru$, orange, crystal dimensions 0.17×0.23×0.55 mm^3, Monoclinic, space group C_2, a = 20.511(3), b = 19.540(3), c = 30.191(4) Å, V = 12099(3) Å^3, Z = 10, $\rho_{calc.}$ = 1.150 g cm^{-3}, μ(MoKα) = 1.43 cm^{-1}, T = 299 K, 31172 reflections were independent and unique, and 10966 with $I > 2\sigma(I)$ ($2\theta_{max}$ = 23.3°) were used for the solution of the structure. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. R = 0.0494, w$R2$ = 0.1380. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-156881. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB@ 1EZ, UK [fax:(+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk].

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[8] ^{1}H NMR of (*S*)-**1b**/(*S*,*S*)-**2**: δ = 4.32–4.39 (m, 1 H, C*H*–NH_2), 5.02 (d, *J* = 12.3 Hz, 1 H, C*H*–NMe_2). ^{1}H NMR of (*R*)-**1b**/(*S*,*S*)-**2**: δ = 4.12 (d, *J* = 12.3 Hz, 1 H, C*H*–NMe_2), 4.80–4.96 (m, 1 H, C*H*–NH_2). Assigned by comparison with Xyl-BINAP-Ru/(*S*,*S*)-**2**. ^{1}H NMR of (*S*)-Xyl-BINAP-Ru/(*S*,*S*)-**2**: δ = 4.26–4.32 (m, 1 H, C*H*–NH_2), 4.98 (d, *J* = 12.3 Hz, 1 H, C*H*–NMe_2). ^{1}H NMR of (*R*)-Xyl-BINAP-Ru/(*S*,*S*)-**2**: δ = 3.98 (d, *J* = 12.3 Hz, 1 H, C*H*–NMe_2), 4.82–4.94 (m, 1 H, C*H*–NH_2).

[9] ^{1}H NMR of (*S*)-**1a**/(*S*,*S*)-**2**: δ = 4.32–4.38 (m, 1 H, C*H*–NH_2), 4.94 (d, *J* = 12.3 Hz, 1 H, C*H*–NMe_2). ^{1}H NMR of (*R*)-**1a**/(*S*,*S*)-**2**: δ = 4.16 (d, *J* = 12.3 Hz, 1 H, C*H*–NMe_2), 4.72–4.80 (m, 1 H, C*H*–NH_2). Assigned by comparison with BINAP-Ru/(*S*,*S*)-**2**. ^{1}H NMR of (*S*)-BINAP-Ru/(*S*,*S*)-**2**: δ = 4.26–4.34 (m, 1 H, C*H*–NH_2), 4.89 (d, *J* = 12.3 Hz, 1 H, C*H*–NMe_2). ^{1}H NMR of (*R*)-BINAP-Ru/(*S*,*S*)-**2**: δ = 4.06 (d, *J* = 12.3 Hz, 1 H, C*H*–NMe_2), 4.74–4.84 (m, 1 H, C*H*–NH_2).

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