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# BICHEP—Ru Complexes, Highly Efficient Catalysts for Asymmetric Hydrogenation of Carbonyl Compounds

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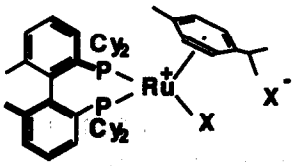
***Abstract:*** *Newly prepared [RuX(p-cymene)(bichep)]X (X = I, Cl) and Ru(OAc)$_2$(bichep) (bichep = 2,2'-bis(dicyclohexylphosphino)-6,6'-dimethyl-1,1'-biphenyl) proved to be highly efficient catalysts for asymmetric hydrogenation of carbonyl compounds bearing phenylglyoxyloyl group under mild conditions.*

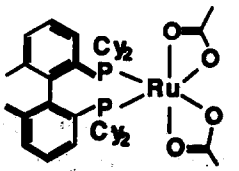
Electron-rich chiral diphosphines have been attracting considerable attention as ligands of transition metal catalysts for asymmetric reactions. Of particular interest are Rh(I) complexes of CyDIOP,[1a,b] *t*-BuCAPP,[1c] CyCHIRAPHOS,[1b] alkyl-AMPP,[1d] and MCCPM[1e]; these are highly active catalysts for reduction of carbonyl compounds, while CyBINAP[1f] and DuPHOS[1g,h]—Rh(I) complexes were used successfully as catalysts for asymmetric hydrogenation of prochiral olefins. Thus, Rh(I) complexes bearing electron-rich chiral diphosphines are well-documented,[1,2] but their Ru(II) complexes have rarely been used as catalysts for asymmetric reactions.[3]

We recently reported synthesis of electron-rich chiral diphosphine BICHEP (**1**)[1i] and showed that BICHEP—Rh(I) complexes are excellent catalysts for asymmetric hydrogenation of various prochiral olefins.[2] In this paper, we report synthesis of new cationic and neutral BICHEP—Ru(II) complexes, [RuX(*p*-cymene)(bichep)]X (**2**: X = Cl, **3**: X = I) and Ru(OAc)$_2$(bichep) (**4**), and show their high efficiency as catalysts for enantioselective hydrogenation of prochiral carbonyl compounds having phenylglyoxyloyl group.

The cationic BICHEP—Ru(II) complexes (*R*)-**2** and (*R*)-**3** were readily prepared from the reaction of [RuX$_2$(*p*-cymene)]$_2$ with an equimolar amount of optically pure (*R*)-(-)-**1** in a 1:2 mixture of dichloromethane and EtOH at 55 °C.[4] The brown solid obtained after removal of the solvents followed by washing of the residue with ether was recrystallized from a 4:1 mixture of dichloromethane and ether to give brown purple crystals in 60% yield for (*R*)-**2** and 75% yield for (*R*)-**3**. These complexes were fully characterized by $^1$H and $^{31}$P-NMR spectroscopy.[5]



X = Cl ; (*R*)- 2
I ; (*R*)- 3



(*R*)- 4
Cy= $C_6H_{11}$

The neutral (*R*)-BICHEP—Ru(II) complex (*R*)-4 was synthesized by the reaction of (*R*)-BICHEP with $[RuCl_2(cod)]_n$ in toluene in the presence of triethylamine at 110 °C followed by the treatment of the resulting brown solution with sodium acetate in *t*-BuOH.[6] Recrystallization of the crude product from a 2:5 mixture of toluene and hexane gave $Ru(OAc)_2$[(*R*)-bichep][(*R*)-(4)] as yellow microcrystals in 24% yield. The structure was fully identified based on $^1H$, $^{13}C$, and $^{31}P$ NMR spectra.[7]

These BICHEP—Ru(II) complexes 2—4 exhibited a very high level of enantioselectivity and catalytic activities in the hydrogenation of prochiral carbonyl compounds having phenylglyoxyloyl group under mild conditions. The results are summarized in Table 1. The *ee*'s listed are higher than any of the previously reported values for these substrates.[1a,d]

Under the reaction conditions described, hydrogenation of methyl phenylglyoxylate (5a) catalyzed by (*R*)-3 afforded methyl (*S*)-mandelate [(*S*)-6a] in almost complete enantioselectivity (>99% *ee*) (entry 1). This value is much higher than that (45% *ee*) obtained in the reaction catalyzed by RuI[{(*S*)-binap}(*p*-cymene)]I (substrate/catalyst 430/1, in MeOH, 30°C, $H_2$ 100 atm, 95 h, 100% conv.)[8] Interestingly, catalysis with (*R*)-3 gave (*S*)-6a, while hydrogenation with the (*S*)-BINAP-Ru (II) complex afforded (*S*)-6a. Phenylglyoxylamides 5b and 5c were also rapidly reduced to (*S*)-benzylmandelamides (*S*)-6b and (*S*)-6c in high *ee*'s (entries 2—7).


5

6 a, R = $OCH_3$
b, R = $NHCH_2Ph$
c, R = $NH^tBu$

The neutral Ru(II) analogue (*R*)-4 is less active as catalyst for the hydrogenation of *N*-*t*-butylphenylglyoxylamide (5c) to give (*S*)-6c in 81% *ee* after 2 days reaction. Interestingly, the anionic ligands of 2 and 3 are found to play important role in enantioface differentiation. The iodide complex (*R*)-3 achieved complete selectivity for the hydrogenation of methyl phenylglyoxylate (5a) to give (*S*)-6a (entry 1), whereas reduction with the chloride complex (*R*)-2 gave the product in only 61% *ee* with 13% conversion.

Notably, hydrogenation of **5a** catalyzed by RuCl[{(*S*)-binap}(benzene)]Cl gave (*S*)-**6a** in 79% *ee* (substrate/catalyst = 560/1, in MeOH, 30 °C, $H_2$ 100 atm, 94 h, 100% conv.).[8] Thus, the effects of anions on the enantioselectivities and catalytic activities seem reverse between the complexes of BICHEP and BINAP. On the contrary, (*R*)-**2** exhibited high efficiencies for the reduction of phenylglyoxylamide (entries 3, 4, and 6), but the reaction catalyzed by (*R*)-**3** resulted in lower enantioselectivities with similar reaction rates (entries 5 and 7).

Table 1. Asymmetric Hydrogenation of Carbonyl Compounds Catalyzed by BICHEP—Ru Complexes [a]

| entry | R | catalyst | solvent | $H_2$ (atm) | % *ee* (confign.) |
|---|---|---|---|---|---|
| 1 | -OMe [b] | (*R*)-**3** | EtOH | 5 | >99 (*S*) |
| 2 | -NHCH$_2$Ph [c] | (*S*)-**2** | MeOH | 1 | 81 (*R*) |
| 3 | | (*S*)-**2** | MeOH | 5 | 88 (*R*) |
| 4 | | (*S*)-**2** | MeOH | 40 | 96 (*R*) |
| 5 | | (*R*)-**3** | MeOH | 5 | 72 (*S*) |
| 6 | -NH$^t$Bu [c] | (*R*)-**2** | MeOH | 5 | 93 (*S*) |
| 7 | | (*R*)-**3** | MeOH | 5 | 85 (*S*) |
| 8 | | (*R*)-**4** | MeOH | 5 | 81 (*S*) |

(a) Reactions were carried out at 25 °C with 2—20 mM solutions of the substrate and the catalyst (0.02—0.2 mM), unless otherwise noted. Complete conversions were usually obtained in 1—10 h. Absolute configurations of the products were determined based on the signs of optical rotation.[1] (b) Enantiomeric excesses of methyl mandelate were obtained by HPLC analysis (DICEL CHIRALCEL OD column, 4.6 x 250 mm, hexane : *i*-PrOH = 9:1). (c) Enantiomeric excesses were calculated on the basis of the reported values; (*S*)-(+)-*N*-benzylmandelamide,[1] $[\alpha]_D$ +79.9° (*c* 1.09, $CHCl_3$); (*S*)-(+)-*N*-*t*-butylmandelamide, **6a** $[\alpha]_D$ +58.5° (*c* 0.545, MeOH).

Hydrogen pressure often exerts large effects on the enantioselectivities of the hydrogenation. In contrast to the hydrogenation of *N*-benzylphenylglyoxylamide catalyzed by BICHEP—Rh complexes,[2] the increase in the initial hydrogen pressure in the reaction with (*S*)-**2** from 1 atm to 40 atm (entries 2—4) remarkably enhanced the enantioselectivities (81% — 96%) (entries 2—4).

Since the results of the asymmetric hydrogenation of the substrates **5** utilizing Ru(II) complexes bearing other aryldialkyl- or trialkyl-phosphine ligands are unsatisfactory, we think that the dissymmetric structure of BICHEP ligand is important for preferable matching between the catalyst and the substrates leading to high enantioselectivities.

With the cationic BICHEP—Ru(II) complex (*R*)-3 and triethylamine ( 25 °C, 2 h), tiglic acid was smoothly hydrogenated in methanol to (*S*)-2-butyric acid in >95% *ee* in quantitative yield, while ethyl (*Z*)-α–benzamidocinnamate and dimethyl itaconate were reduced to (*S*)-*N*-benzoylphenylalanine ethyl ester and dimethyl (*S*)-2-methylsuccinate in 43% *ee* and 38% *ee*, respectively.

Further studies on asymmetric hydrogenation of the other unsaturated prochiral substrates are now in progress.

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5. [RuCl(*p*-cymene){(*R*)-bichep}]Cl [(*R*)-2]; $^1$H-NMR (400 MHz, $CDCl_3$) δ 1.40—3.50 (m, $C_6H_{11}$, $CH_3$, 53H), 1.22, 1.24 (d, $J$ = 7.0Hz, $CH(CH_3)_2$, 6H), 3.75 (q, $J$ = 5.7Hz, *p*-cymene, 4H), 6.50—7.80 (m, aromatic, 6H); $^{31}$P-NMR (162 MHz, $CDCl_3$) δ 44.7, 56.9 (d, $J_{p\text{-}p}$ = 23Hz) (downfield of external $H_3PO_4$ in $D_2O$). [RuI(*p*-cymene){(*R*)-bichep}]I [(*R*)-3]; $^1$H-NMR ($CDCl_3$) δ 0.31—2.04, 2.80—3.41 (m, $C_6H_{11}$, 44H), 1.18, 1.21 (s, $J$ = 6.9Hz, $CH(CH_3)_2$, 6H), 1.98, 2.08 (s, $CH_3$, 6H (BICHEP)), 2.29 (s, $CH_3$ of *p*-cymene, 3H ), 2.93 (sep, $CH$ $(CH_3)_2$, 1H), 5.24—5.48 (m, *p*-cymene, 4H), 7.20—7.46 (m, phenyl, 6H) ; $^{31}$P-NMR ($CDCl_3$) δ 69.4, 77.6 (d, $J_{p\text{-}p}$ = 40Hz).
6. T. Ohta, H. Takaya, and R. Noyori, *Inorg. Chem.*, **1989**, *27*, 566.
7. $Ru(OAc)_2$[(*R*)-bichep] {(*R*)-4]; $^1$H-NMR ($CDCl_3$) δ 0.30—2.71 (br, $C_6H_{11}$, 44H), 1.69, 2.02, 2.18, 2.32 (s, $CH_3$, 12H), 6.65—7.69 (m, aromatic, 6H). Assignment of the methyl signals were made by comparison with those of Ru(bichep)$(OCOCD_3)_2$ which was prepared using $CD_3COONa$ instead of $CH_3COONa$. ; $^{13}$C-NMR (100 MHz, $CDCl_3$) δ 25—30 ($C_6H_{11}$), 39, 41 ($CH_3$-Ph), 123—149 (aromatic), 177, 183 ($CH_3CO_2$); $^{31}$P-NMR ($CDCl_3$) δ 61.4, 61.8 (s).
8. Unpublished results.


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