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COMMUNICATIONS

Published on Web 06/20/2006

Enantioselective Hydrogenation of Aromatic Ketones Catalyzed by Ru Complexes of Goodwin−Lions-type sp^2N/sp^3N Hybrid Ligands R-BINAN-R′-Py

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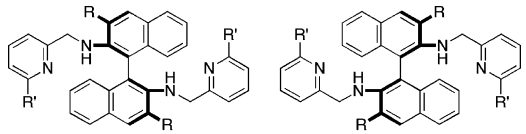
Homogeneous asymmetric hydrogenation of ketones using chiral diphosphine−Ru(II) complexes has been established as one of the most reliable strategies for the synthesis of optically active secondary alcohols since the BINAP−Ru method made its debut in 1987.[1] The invention of BINAP−Ru−diamine−base ternary catalytic systems has further expanded the scope of ketone hydrogenations.[2] Having apparently started a trend with BINAP−Ru systems, a tremendous number of hydrogenation-active Ru complexes with trivalent phosphorus ligating atoms have been reported.[3] The effectiveness has been examined and compared with the "privileged"[4] BINAP system and its derivatives. In comparison, asymmetric hydrogenation using non-phosphine-based Ru complexes is still in the developmental stage.[5,6] Herein, we report a catalytic system consisting of a new class of Goodwin−Lions-type[7] sp^2N/sp^3N combined ligand R-BINAN-R′-Py (**1**)[8] and a π-allyl Ru precursor, which hydrogenates aromatic ketones with high enantioselectivity.

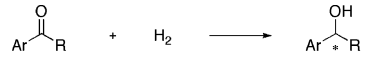


(*R*)-R-BINAN-R'-Py ((*R*)-**1**) (*S*)-R-BINAN-R'-Py ((*S*)-**1**)

a: R = C_6H_5; R' = H, **b**: R = R' = H, **c**: R = H; R' = CH_3

We have followed Noyori's leading concept of a donor−acceptor bifunctional catalyst[9] endowing Ru complexes with hydrogenation activity. The reaction site incorporates a H−sp^3N→Ru−H in the outer coordination sphere of the 18-electron Ru complex. Here, the interaction of the sp^3NH with the RuH synergistically enhances the NH acidity and the RuH nucleophilicity, facilitating the capture of the carbonyl of a ketonic substrate by the charge-alternating $H^{\delta+}-N^{\delta-}-Ru^{\delta+}-H^{\delta-}$ site via a NH···O═C hydrogen bond. Appropriate 3D assembly should allow enantioface-selective hydride transfer to the C═O group. The tetradentate pyridine/secondary amine N4 ligands R-BINAN-R′-Py satisfy the coordinative saturation of the octahedral Ru(II) species as well as the high potentiality of the wide range of structural perturbation on the planar pyridine and binaphthyl skeleton. Relatively high affinity of the sp^2N atom for Ru(II) and suppression of the hemilability of the sp^3NH function, because of the internal existence, are also advantageous to stabilize the corresponding Ru complexes.

Thus, Ph-BINAN-H-Py (**1a**) has been taken as the standard ligand and synthesized from 1,1′-binaphthyl-2,2′-diamine on the basis of an ortho-lithiation/halogenation/Suzuki−Miyaura coupling protocol.[10] The catalytic activity as well as the enantioselectivity in the hydrogenation of acetophenone (**2a**) was investigated by use of (*R*)-**1a** and a series of Ru precursors under the standard conditions: [**2a**] = 2 M, [(*R*)-**1a**] = 2 mM, [Ru] = 2 mM, [$KOC(CH_3)_3$] = 2 mM, substrate:catalyst ratio (S:C) = 1000, base:catalyst ratio (B:C) = 1:1, solvent = 2-propanol, no aging, 50 atm, 25 °C.



2 **3**

a: Ar = C_6H_5; R = CH_3
b: Ar = 4-$CH_3OC_6H_4$; R = CH_3
c: Ar = 4-$CH_3C_6H_4$; R = CH_3
d: Ar = 4-$CF_3C_6H_4$; R = CH_3
e: Ar = 2-naphthyl; R = CH_3
f: Ar = C_6H_5; R = CH_2CH_3
g: Ar = C_6H_5; R = $(CH_2)_7CH_3$
h: Ar = C_6H_5; R = $CH(CH_3)_2$
i: Ar = C_6H_5; R = *c*-C_6H_{11}
j: Ar = C_6H_5; R = $C(CH_3)_3$
k: Ar–R = C_6H_4-2-$(CH_2)_4$
l: Ar–R = C_6H_4-2-$(CH_2)_3$
m: Ar–R = C_6H_4-2-$(CH_2)_2$

Table 1 lists the results of these investigations. With Ru(π-$CH_2C(CH_3)CH_2)_2$(cod),[11] the reaction proceeds smoothly to give an (*R*)-1-phenylethanol ((*R*)-**3a**) in 93% ee after 15 h (entry 1). When the reaction is continued even after 100% conversion, 1-cyclohexylethanol is formed (24 h, 0.7% yield). Aging of (*R*)-**1a** and the π-allyl Ru precursor at 70 °C for 2 h also gave the same result (entry 3).[12] For operational simplicity, no aging was adopted as the standard condition. The base is not essential, but the reactivity without base is halved (entry 4).[13] The reaction proceeds at lower pressures (10 atm, S:C = 1000, B:C = 1, time = 108 h, 99% yield, 86% ee (*R*)), while no reaction occurs in the absence of H_2 (entry 5). The use of an S:C ratio of 10 000:1 is also successful with a high B:C ratio (entry 6). 2-Propanol and ethanol are the solvents of choice, but the efficiency drops dramatically in methanol, whereas aprotic solvents, such as CH_2Cl_2, THF, and toluene, cannot be used (entries 7−11). When the π-allyl Ru precursor is replaced with more commonly used Ru halides, such as $[RuCl_2(cod)]_n$, the level of conversion is halved and the enantioselectivity is lost (entry 12), while the reaction virtually stops with $[RuCl_2(C_6H_6)]_2$ or Ru(0)(cod)(cot) (entries 13 and 14). The enhancement of the reactivity by introduction of a methyl group at C(6) of the pyridine ring is observed with the simple ligand, (*R*)-H-BINAN-H-Py ((*R*)-**1b**) and its C(6) methyl analogue, (*R*)-H-BINAN-Me-Py ((*R*)-**1c**) (entries 15 and 16), although the enantioselectivities are low. Introduction of a *N*-methyl group into (*R*)-**1a** leads to virtually no reactivity under the standard conditions, showing the importance of H−sp^3N−Ru−H bifunctionality.

An electron-donating substituent, such as OCH_3 and CH_3, at the para position of the benzene ring of **2a** increases the enantiomeric excess up to 98%, while the value is lowered to 80% by introduction of the electron-withdrawing CF_3 group (entries 1 and 17−19). 2-Acetonaphthone (**2e**) is also hydrogenated in good yield and enantioselectivity (entry 20). With primary and secondary alkyl phenyl ketones, the enantiomeric excess ranges from 94 to 98%, but the presence of a tertiary alkyl group decreases it to 86% (entries 21−25). Cyclic aromatic ketones, such as **2k** and **2l**, are converted to the corresponding *R* alcohols in 94 and 99% ee, respectively

10.1021/ja062451a CCC: $33.50

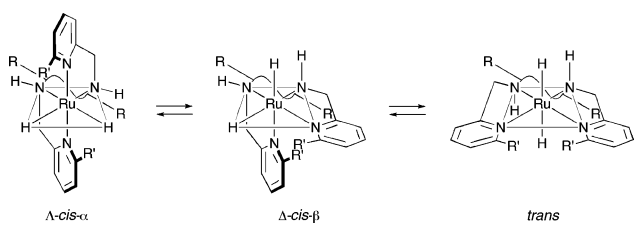
Table 1. Catalytic Asymmetric Hydrogenation of Aromatic Ketones Using R-BINAN-R′-Py and Ru Precursors[a]

entry	substrate	ligand	Ru precursor	% yield[b]	% ee (abs)[b]
1	**2a**	(*R*)-**1a**	**A**	>99	93 (*R*)
2	**2a**	(*S*)-**1a**	**A**	>99	93 (*S*)
3[c]	**2a**	(*R*)-**1a**	**A**	>99	93 (*R*)
4[d]	**2a**	(*R*)-**1a**	**A**	>99	94 (*R*)
5[e]	**2a**	(*R*)-**1a**	**A**	0	–
6[f]	**2a**	(*R*)-**1a**	**A**	>99	94 (*R*)
7[g,h]	**2a**	(*R*)-**1a**	**A**	90	87 (*R*)
8[i,h]	**2a**	(*R*)-**1a**	**A**	5.5	15 (*R*)
9[j,h]	**2a**	(*R*)-**1a**	**A**	0	–
10[k,h]	**2a**	(*R*)-**1a**	**A**	0	–
11[l,h]	**2a**	(*R*)-**1a**	**A**	0	–
12	**2a**	(*R*)-**1a**	**B**	51	0
13	**2a**	(*R*)-**1a**	**C**	0	–
14	**2a**	(*R*)-**1a**	**D**	4.3[m]	–
15[h]	**2a**	(*R*)-**1b**	**A**	29	55 (*R*)
16	**2a**	(*R*)-**1c**	**A**	>99	21 (*R*)
17	**2b**	(*R*)-**1a**	**A**	>99	98 (*R*)
18	**2c**	(*R*)-**1a**	**A**	>99	96 (*R*)
19	**2d**	(*R*)-**1a**	**A**	>99	80 (*R*)
20	**2e**	(*R*)-**1a**	**A**	>99	95 (*R*)
21	**2f**	(*R*)-**1a**	**A**	>99	98 (*R*)
22	**2g**	(*R*)-**1a**	**A**	>99	94 (*R*)
23	**2h**	(*R*)-**1a**	**A**	>99	98 (*R*)
24	**2i**	(*R*)-**1a**	**A**	>99	97 (*R*)
25	**2j**	(*R*)-**1a**	**A**	>99	86 (*R*)
26	**2k**	(*R*)-**1a**	**A**	>99	94 (*R*)
27	**2l**	(*R*)-**1a**	**A**	>99	99 (*R*)
28[n]	**2m**	(*R*)-**1a**	**A**	>99	93 (*R*)

[a] Reaction conditions: scale, 5.0 mmol; [**2**] = 2 M; [**1**] = [Ru] = [$KOC(CH_3)_3$] = 2 mM; H_2, 50 atm; solvent, *i*-C_3H_7OH; temp, 25 °C; time, 12−18 h. **A**: Ru(π-$CH_2C(CH_3)CH_2$)$_2$(cod). **B**: $[RuCl_2(cod)]_n$. **C**: $[RuCl_2(C_6H_6)]_2$. **D**: Ru(cod)(cot). The Ru precursors are not aged with **1**. [b] Determined by ^{1}H NMR, GC, or HPLC analysis.[10] [c] Aged at 70 °C for 2 h. [d] No base, 48 h. [e] H_2, 0 atm. [f] [**1a**] = [Ru]= 0.2 mM, 66 h. [g] C_2H_5OH. [h] 24 h. [i] CH_3OH. [j] CH_2Cl_2. [k] THF. [l] Toluene. [m] 1-Cyclohexylethanol was obtained in 95.7% yield with 14% ee (*R*). Intractable black solid was formed. [n] [**2m**] = 400 mM, no base.

(entries 26 and 27). 1-Indanone (**2m**) is not hydrogenated under the standard conditions, but instead without $KOC(CH_3)_3$, giving 1-indanol in 93% ee (entry 28). The presence of base may result in the enolization of the ketone that has relatively acidic α-proton,[14] thus retarding the reaction.

The mechanism is not clear at the present stage. Among many possibilities, we suppose that a dihydride mechanism is operating as proposed in the BINAP−Ru−diamine−base ternary system.[15] The RuH_2 formation would be facilitated by use of the Ru−π-allyl precursor possessing the easily hydrogenolyzed Ru−C bond. If so, the linear tetradentate chiral ligand (*R*)-**1** can theoretically form five geometrical isomers,[16] which are in equilibrium and have their own reactivity and enantioselectivity. Drawn below are the most plausible RuH_2 isomers, C_2-Λ-*cis*-α complex, the C_1 symmetric Δ-*cis*-*β*, and the C_2 symmetric *trans*. The overall enantioselectivity is expressed as an average of their contributions.[17] The R,R′ substituent effects as well as the aging effect[12,13] may be ascribed to the change in the relative ratios of these species. The detailed mechanistic study is now underway.



In summary, we have succeeded in highly enantioselective hydrogenation of aromatic ketones by combination of a Ru−π-allyl complex and an sp^2N/sp^3N-based chiral ligand R-BINAN-R′-Py. The new system catalyzes the reaction essentially in the absence of base. Although the efficiency does not exceed that of the original BINAP−Ru−diamine complexes, the present results should significantly expand the range of possibilities in designing catalysts not only for hydrogenation but also for many other reactions.[6,7]

Acknowledgment. This work was aided by the Grant-in-Aid for Scientific Research (No. 14078212) from the Ministry of Education, Science, Sports and Culture, Japan. We are grateful to Professor R. Noyori for valuable discussions, and to Messrs. T. Noda, K. Oyama, and Y. Maeda for their technical support.

Supporting Information Available: General procedure for the hydrogenation of acetophenone, determination of the enantiomeric excess and the absolute configuration of products, and synthetic procedures, and characterization of all ligands. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA062451A