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Highly Efficient Asymmetric Hydrogenation of α,β-Unsaturated Carboxylic Acids Catalyzed by Ruthenium(II)-Dipyridylphosphine Complexes

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Dedicated to Professor Masakatsu Shibasaki on the occasion of his 60th birthday.

Abstract: Two types of catalysts [RuL(benzene)Cl]Cl and $Ru(OCOCH_3)_2L$ with the dipyridylphosphine ligands P-Phos and Xyl-P-Phos were applied in the asymmetric hydrogenation of α,β-unsaturated carboxylic acids. The cationic complexes [RuL(benzene)Cl]Cl were found to be superior to the corresponding neutral complex $Ru(OCOCH_3)_2L$ in this type of reactions. The catalysts exhibited excellent activities and enantioselectivities (up to 97% *ee*) in the asymmetric hydrogenation.

Keywords: asymmetric hydrogenation; dipyridylphosphine; P-Phos; ruthenium complexes; α,β-unsaturated carboxylic acids; Xyl-P-Phos

Optically active carboxylic acids are important building blocks for the synthesis of new materials such as ferroelectric liquid crystals (FLCs),[1] non-steroidal anti-inflammatory (NSAI) agents[2] and other bioactive compounds.[3] The enantioselective hydrogenation of α,β-unsaturated carboxylic acids provides a simple, straightforward and quantitative route to this type of important compound. Ru(BINAP)-type catalysts were found to be highly effective in this class of reactions,[4] and H_8-BINAP was later proved to be superior to BINAP as the chiral ligand for these reactions.[5] Other types of effective ligands also have been reported for this type of asymmetric hydrogenation.[6] From both scientific and practical points of view, it is of high interest to develop more effective catalysts for the asymmetric hydrogenation leading to high-valued products.[7] Recently, SFDP ligands bearing a spirobifluorene structure with a large dihedral angle were developed and their ruthenium complexes gave excellent results in the asymmetric hydrogenation of α,β-unsaturated carboxylic acids.[8] Rhodium-catalyzed asymmetric hydrogenations of cinnamic acid derivatives were also carried out using a combination of monodentate phosphoramidite and PPh_3 ligands.[9]

The pyridylphosphine ligand P-Phos and its derivatives can be conveniently prepared and have been successfully used in a variety of asymmetric catalytic reactions such as the asymmetric hydrogenation of β-keto esters and ketones, the asymmetric hydrosilylation of ketones, the asymmetric Pauson–Khand reaction and the asymmetric carbocyclization reaction.[10] The transition metal complexes containing these ligands are quite air-stable even in solution, making their application in organic synthesis very convenient and the expansion of their scope of application attractive. Herein we report the application of P-Phos and Xyl-P-Phos ligands in the enantioselective hydrogenation of α,β-unsaturated carboxylic acids.

Two types of catalysts $Ru(OCOCH_3)_2L$ and [RuL(benzene)Cl]Cl (Figure 1) were prepared *in situ* following similar procedures as previously described,[7b,11] and were directly used for the asymmetric hydrogenation of α,β-unsaturated carboxylic acids without further purification (Scheme 1). The corresponding saturated carboxylic acids were obtained in essentially quantitative yields in most cases (Table 1).

It is noteworthy that [RuL(benzene)Cl]Cl (**1a** and **1b**) were found to be more effective than $Ru(OCOCH_3)_2L$ (**2a** and **2b**) (L = P-Phos or Xyl-P-

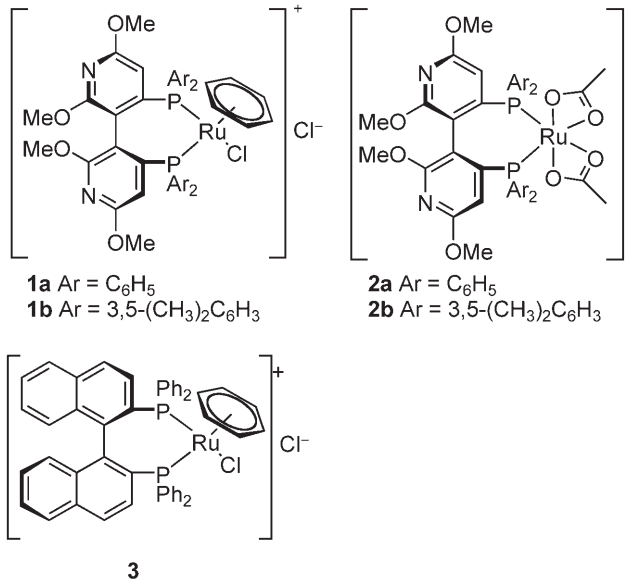
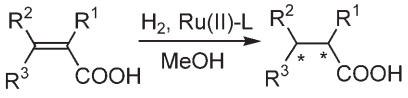
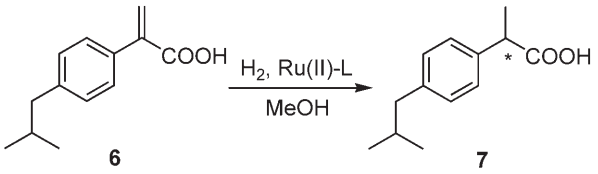


Figure 1. Structures for catalysts **1**–**3**.



	R^1	R^2	R^3
a	Me	Me	H
b	Me	Et	H
c	Me	Pr	H
d	Et	Pr	H
e	Me	Ph	H
f	H	CF_3	Me

Scheme 1. Asymmetric hydrogenation of α,β-unsaturated carboxylic acids.



Scheme 2. Asymmetric hydrogenation of 2-(4-isobutylphenyl)propenoic acid.

Phos) in these reactions. This is in sharp contrast to the Ru(BINAP)-type catalysts, e.g., $Ru(OCOCH_3)_2$-H_8-BINAP was reported to be superior to [Ru-H_8-BINAP(benzene)Cl]Cl in both activity and enantioselectivity.[5a,b] As shown in Table 1, in the presence of 0.25 mol% of catalyst **1a** or **1b**, the hydrogenation of tiglic acid (**4a**) proceeded smoothly at room temperature and under low hydrogen pressure (6 bar), affording (*S*)-2-methylbutanoic acid (**5a**) in high *ee*s (96% and 97%, respectively, entries 1 and 2). Compound (*S*)-**5a** and its esters are important materials for preparing fruit flavors (e.g., apple, strawberry, grape). Substrates **4a**–**e** were found to give high *ee*s under low hydrogen pressure. Similarly high *ee*s (95–97%) were also obtained in the hydrogenation of other (*E*)-2-alkyl-2-alkenoic acids (**4b**–**d**) when **1b** was used as catalyst. The reaction temperature had little effect on the enantioselectivity even though a higher reaction temperature was indeed beneficial to the rate of hydrogenation. The substrates were fully converted to the corresponding products at 50 °C even when S/C ratios were increased to up to 10,000/1 without causing a notable change in enantioselection (entries 5, 10, 17 and 20). The activity of the catalyst system with the Xyl-P-Phos ligand also was found to surpass those of $Ru(OCOCH_3)_2$-H_8-BINAP and $Ru(OCOCH_3)_2$-SFDP.[5a,b,8] In the hydrogenation of 2-methylcinnamic acid (**4e**) the reactivity and enantioselectivity of the present catalysts decreased significantly. A similar effect was previously observed with the BINAP system.[5b] The reaction proceeded very slowly at room temperature, giving less than 10% conversion after 65 h. The target compound **5e** was obtained with moderate *ee*s when the reaction temperature was raised to 60 °C.

The hydrogenation of β,β-disubstituted acrylic acids such as fluorinated **4f** required higher hydrogen pressure for high product *ee*s. When catalyst **1b** was used, product **5f** with 97% *ee* was obtained (entry 31). To our knowledge, this is the highest *ee* obtained for **5f** through asymmetric hydrogenation. When catalysts **2b** and **3** were used, 96% *ee* and 87% *ee*, respectively, were obtained (entries 32 and 33).

Catalysts **1a** and **1b** were also used for the hydrogenation of substrate **6** (Scheme 2), whose product (**7**) with the (*S*)-configuration is an effective anti-inflammatory agent [(*S*)-ibuprofen]. It was noteworthy that P-Phos was superior to Xyl-P-Phos in the hydrogenation of **6** (92% *ee vs.* 89% *ee*, entries 34 and 35).

In summary, we have applied two types of P-Phos catalysts, [RuL(benzene)Cl]Cl and $Ru(OCOCH_3)_2L$ (L = Xyl-P-Phos and P-Phos), in the asymmetric hydrogenation of α,β-unsaturated carboxylic acids. The experimental results indicated that the cationic complexes [RuL(benzene)Cl]Cl were superior to the neutral species $Ru(OCOCH_3)_2L$, which was distinctly different from other previously reported systems. The catalysts exhibited excellent activity and enantioselectivities (up to 97% *ee*).

Experimental Section

General Procedure for Asymmetric Hydrogenation of α,β-Unsaturated Carboxylic Acids

A glass-lined stainless steel autoclave was charged with an α,β-unsaturated carboxylic acid (0.1 mmol, unless otherwise

Table 1. Asymmetric Ru-catalyzed hydrogenation of α,β-unsaturated carboxylic acids.[a]

Entry	Substrate	Catatalyst	S/C ratio	H_2, [bar]	Time [h]	Conversion [%]	*ee*[b] [%]	Configuration
1	**4a**	**1a**	400	6	36	>99	96	(*S*)
2	**4a**	**1b**	400	6	36	>99	97	(*S*)
3	**4a**	**2b**	400	6	36	>99	94	(*S*)
4	**4a**	**3**	400	6	36	>99	88	(*R*)
5[c]	**4a**	**1b**	10,000	6	24	>99	96	(*S*)
6	**4b**	**1a**	500	6	36	>99	92	(*S*)
7	**4b**	**1b**	500	6	36	>99	96	(*S*)
8	**4b**	**2b**	500	6	36	>99	91	(*S*)
9	**4b**	**3**	500	6	36	>99	84	(*R*)
10[c]	**4b**	**1b**	10,000	6	40	>99	95	(*S*)
11	**4c**	**1a**	400	6	36	>99	93	(*S*)
12	**4c**	**1b**	400	6	36	>99	97	(*S*)
13	**4c**	**3**	400	6	36	>99	82	(*R*)
14[d]	**4c**	**1b**	400	6	36	>99	94	(*S*)
15[e]	**4c**	**1b**	400	6	36	1%	nd	(*S*)
16	**4c**	**2b**	400	6	36	>99	92	(*S*)
17[c]	**4c**	**1b**	10,000	6	24	>99	95	(*S*)
18	**4d**	**1a**	400	6	36	>99	94	(*S*)
19	**4d**	**1b**	400	6	36	>99	95	(*S*)
20[c]	**4d**	**1b**	10,000	6	36	>99	96	(*S*)
21	**4d**	**2b**	400	6	36	>99	94	(*S*)
22	**4d**	**3**	400	6	36	>99	88	(*R*)
23	**4e**	**1a**	400	6	65	7.2	nd	
24	**4e**	**1b**	400	6	65	4.1	nd	
25	**4e**	**3**	400	6	65	2.7	nd	
26[f]	**4e**	**1a**	400	6	24	>99	55	(*S*)
27[f]	**4e**	**1b**	400	6	24	>99	77	(*S*)
28[f]	**4e**	**2b**	400	6	24	>99	76	(*S*)
29[f]	**4e**	**3**	400	6	24	>99	36	(*R*)
30	**4f**	**1a**	400	95	16	>99	95	(+)
31	**4f**	**1b**	400	95	16	>99	97	(+)
32	**4f**	**2b**	400	100	16	>99	96	(+)
33	**4f**	**3**	400	100	16	>99	87	(−)
34	**6**	**1a**	200	100	8	>99	92	(*S*)
35	**6**	**1b**	200	100	8	>99	89	(*S*)
36	**6**	**2a**	200	100	8	>99	89	(*S*)
37	**6**	**3**	200	100	8	>99	88	(*R*)

[a] *Reaction conditions:* 0.1 mmol for substrates **4a–f** except for entries 5, 10, 17 and 20 (2.5 mmol substrates), 0.05 mmol for substrate **6**; 700 μL MeOH as solvent; room temperature reaction unless otherwise stated.

[b] The *ee* values were determined by chiral HPLC analysis with an OD-H column for the anilide derivative of **5a**, an OB column for the anilide derivative of **5e**, an OJ-H column for the anilide derivative of **5f** (the anilide derivatives were prepared by reaction of **5a**, **5e** and **5f** with aniline) or by chiral GC with a 25 m × 0.25 mm CP-CYCLODEX β 236M column for **5b–d**, or a 25 m × 0.25 mm Chirasil-DEX CB column for the methyl ester of **7**. The optical roation of **5f** was determined in $CHCl_3$.

[c] At 50 °C.

[d] Non-degassed solvent was used.

[e] Charged in air.

[f] At 60 °C.

stated) and a catalyst according to the given S/C ratio in methanol (0.7 mL) under a nitrogen atmosphere. After purging three times with H_2, the autoclave was pressurized to the desired pressure with H_2. The solution was magnetically stirred well at the given temperature for 8–65 h. After releasing the hydrogen pressure, the conversion of the substrate was determined by ^{1}H NMR analysis of the residue obtained on concentration of the reaction mixture. The enantiomeric excess of the product was determined by chiral HPLC or chiral GC (either directly or after derivatization to the corresponding methyl ester or anilide followed by silica gel column purification). The absolute configuration was determined by comparison with the corresponding known compound described in the literature.

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References

[1] a) H. Nohira, S. Nakamura, M. Kamei, *Mol. Cryst. Liq. Cryst.* **1990**, *180B*, 379–388; b) S. Nakamura, H. Nohira, *Mol. Cryst. Liq. Cryst.* **1990**, *185*, 199–207.

[2] a) T. Y. Shen, *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 460–472; b) D. Lednicer, L. A. Mitscher, *The Organic Chemistry of Drug Synthesis* Wiley, New York, Vols. 1 and 2, **1977** and **1980**; c) J.-P. Rieu, A. Boucherle, H. Cousse, G. Mouzin, *Tetrahedron* **1986**, *42*, 4095–4131; d) C. Botteghi, S. Paganelli, A. Schinato, M. Marchetti. *Chirality* **1991**, *3*, 355–369.

[3] a) T. Sturm, W. Weissensteiner, F. Spinder, *Adv. Synth. Catal.* **2003**, *345*, 160–164; b) I. Churcher, K. Ashton, J. W. Butcher, E. E. Clarke, T. Harrison, H. D. Lewis, A. P. Owens, M. R. Teall, S. Williams, J. D. J. Wrigley, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 179–183; c) Y. Yuasa, Y. Yuasa, H. Tsuruta, *Aust. J. Chem.* **1998**, *51*, 511–514; d) M. L. Bray, D. Gorbacheva, H. Jahansouz, M. J. Kaufman, K. Ishikawa, N. Harada, K. Suzuki, *Chem. Pharm. Bull.* **2001**, *49*, 1–4; e) Y. Lu, T. M.-D. Nguyen, G. Weltrowska, I. Berezowska, C. Lemieux, N. N. Chung, P. W. Schiller, *J. Med. Chem.* **2001**, *44*, 3048–3053.

[4] T. Ohta, H. Takaya, M. Kitamura, K. Nagai, R. Noyori, *J. Org. Chem.* **1987**, *52*, 3174–3176.

[5] a) X. Zhang, T. Uemura, K. Matsumura, N. Sayo, H. Kumobayashi, H. Takaya, *Synlett* **1994**, 501–503; b) T. Uemura, X. Zhang, K. Matsumura, N. Sayo, H. Kumobayashi, T. Ohta, K. Nozaki, H. Takaya; *J. Org. Chem.* **1996**, *61*, 5510–5516; c) K. Mashima, K.-h. Kusano, N. Sato, Y.-i. Matsumura, K. Nozaki, H. Kumobayashi, N. Sayo, Y. Hori, T. Ishizaki, S. Akutagawa, H. Takaya, *J. Org. Chem.* **1994**, *59*, 3064–3076; d) H. Kumobayashi, T. Miura, N. Sayo, T. Saito, X. Zhang, *Synlett* **2001**, 1055–1064.

[6] a) J. P. Genêt, C. Pinel, V. Ratovelomanana-Vidal, S. Mallart, X. Pfister, L. Bischoff, M. C. Caño De Andrade, S. Darses, C. Galopin, J. A. Laffitte, *Tetrahedron: Asymmetry* **1994**, *4*, 675–690; b) T. Benincori, E. Brenna, F. Sannicolo, L. Trimarco, P. Antognazza, E. Cesarotti, F. Demartin, T. Pilati, *J. Org. Chem.* **1996**, *61*, 6244–6251; c) T. Benincori, E. Cesarotti, O. Piccolo, F. Sannicolo, *J. Org. Chem.* **2000**, *65*, 2043–2047; d) U. Berens, M. J. Burk, A. Gerlach, W. Hems, *Angew. Chem. Int. Ed.* **2000**, *39*, 1981–1984.

[7] a) L. Qiu, J. Qi, C.-C. Pai, S. Chan, Z. Zhou, M. C. K. Choi, A. S. C. Chan, *Org. Lett.* **2002**, *4*, 4599–4602; b) L. Qiu, J. Wu, S. Chan, T. T.-L. Au-Yeung, J.-X. Ji, R. Guo, C.-C. Pai, Z. Zhou, X. Li, Q.-H. Fan, A. S. C. Chan, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5815–5820; c) L. Qiu, F. Y. Kwong, J. Wu, W. H. Lam, S. Chan, W.-Y. Yu, Y.-M. Li, R. Guo, Z. Zhou, A. S. C. Chan, *J. Am. Chem. Soc.* **2006**, *128*, 5955–5965.

[8] X. Cheng, Q. Zhang, J.-H. Xie, L.-X. Wang, Q.-L. Zhou, *Angew. Chem. Int. Ed.* **2005**, *44*, 1118–1121.

[9] R. Hoen, J. A. F. Boogers, H. Bernsmann, A. J. Minnaard, A. Meetsma, T. D. Tiemersma-Wegman, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *Angew. Chem. Int. Ed.* **2005**, *44*, 4209–4212.

[10] a) C.-C. Pai, C.-W. Lin, C.-C. Lin, C.-C. Chen, A. S. C. Chan, *J. Am. Chem. Soc.* **2000**, *122*, 11513–11514; b) C.-C. Pai, A. S. C. Chan, U. S. Patent 5,886,182, **1999**; *Chem. Abstr.* **1999**, *130*, 209822; c) J. Wu, H. Chen, Z.-Y. Zhou, C.-H. Yeung, A. S. C. Chan, *Synlett* **2001**, 1050–1054; d) J. Wu, H. Chen, W.-K. Kwok, K.-H. Lam, Z.-Y. Zhou, C.-H. Yeung, A. S. C. Chan, *Tetrahedron Lett.* **2002**, *43*, 1539–1543; e) G. A. Grasa, A. Zanotti-Gerosa, W. P. Hems, *J. Organomet. Chem.* **2006**, *691*, 2332–2334; f) G. A. Grasa, A. Zanotti-Gerosa, J. A. Medlock, W. P. Hems, *Org. Lett.* **2005**, *7*, 1449–1451; g) J. Wu, J.-X. Ji, A. S. C. Chan, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 3570–3575; h) F. Y. Kwong, Y.-M. Li, W. H. Lam, L. Qiu, H. W. Lee, C. H. Yeung, K. S. Chan, A. S. C. Chan, *Chem. Eur. J.* **2005**, *11*, 3872–3880; i) P. A. Evans, K. W. Lai, J. R. Sawyer, *J. Am. Chem. Soc.* **2005**, *127*, 12466–12467; j) P. E. Maligres, S. W. Krska, G. R. Humphrey, *Org. Lett.* **2004**, *6*, 3147–3150; k) G. Chen, F. Y. Kwong, H. O. Chan, W.-Y. Yu, A. S. C. Chan, *Chem. Commun.* **2006**, 1413–1415; l) J. Wu, A. S. C. Chan, *Acc. Chem. Res.* **2006**, *39*, 711–716.

[11] **2a:** ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 1.74$ (s, 6H), 3.36 (s, 6H), 3.60 (s, 6H), 6.03–6.06 (m, 2H), 7.02–7.60 (m, 20H); ^{31}P NMR ($CDCl_3$, 202 MHz): $\delta = 63.84$. **2b:** ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 1.73$ (s, 6H), 2.15 (s, 12H), 2.30 (s, 6H), 3.44 (s, 6H), 3.72 (s, 6H), 6.19–6.22 (m, 2H), 6.83–7.30 (m, 12H); ^{31}P NMR ($CDCl_3$, 202 MHz): $\delta = 63.83$.

