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General Asymmetric Hydrogenation of Hetero-aromatic Ketones

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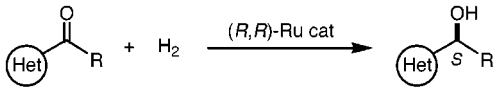
ABSTRACT



Het = hetero-aromatic ring
(*R*,*R*)-Ru cat = *trans*-$RuCl_2$[(*R*)-xylbinap][(*R*)-daipen]

***trans*-$RuCl_2$[(*R*)-xylbinap][(*R*)-daipen] or the *S*,*S* complex acts as an efficient catalyst for asymmetric hydrogenation of hetero-aromatic ketones. The hydrogenation proceeds with a substrate-to-catalyst molar ratio of 1000–40000 to give chiral alcohols in high ee and high yield. The enantioselectivity appears to be little affected by the properties of the hetero-aromatic ring. This method allows for asymmetric synthesis of duloxetine, an inhibitor of serotonin and norepinephrine uptake carriers.**

A variety of chiral transition metal catalysts effect the asymmetric hydrogenation of C═C and C═O bonds, assisted by the coordination of a neighboring heteoatom to the metallic center.[1] It is only during recent years that certain homogeneous catalysts have been used to enantioselectively hydrogenate simple ketones lacking coordinative functional groups.[2] In this regard, however, the substrates have been limited largely to simple aromatic[3] and olefinic ketones.[4] Asymmetric hydrogenation of hetero-aromatic ketones is also important because the chiral alcoholic products are useful as building blocks of biologically active compounds[5] and chiral ligands.[6,7] A ternary system consisting of $RuCl_2$[(*R*,*R*)-bicp](tmeda), (*R*,*R*)-1,2-diphenylethylenediamine, and KOH is known to enantioselectively hydrogenate certain heterocyclic, mostly thienyl, ketones.[8] However, it is highly

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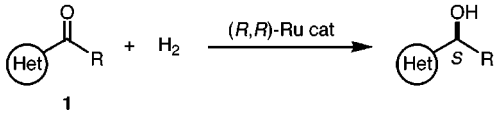
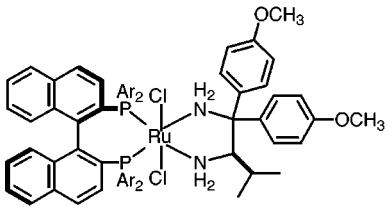
desirable to broaden the scope and to improve the enantioselectivity (currently alcoholic products in 86−93% ee) and turnover number (<500 mol product/mol catalyst). We here describe a highly efficient enantioselective hydrogenation of a wide range of heterocyclic ketones catalyzed by a combined system of a chiral $RuCl_2$(diphosphine)(1,2-diamine) complex and a strong base. This method can employ as substrates various ketones possessing a π-electron-rich or -deficient hetero-aromatic substituent, greatly broadening the scope and utility of the Ru-catalyzed asymmetric hydrogenation.

Scheme 1



1

a: Het = 2-furyl; R = CH_3
b: Het = 2-furyl; R = n-C_5H_{11}
c: Het = 2-furyl; R = $(CH_2)_3C{=}CH_2$
d: Het = 2-thienyl; R = CH_3
e: Het = 3-thienyl; R = CH_3
f: Het = 2-(1-methyl)pyrrolyl; R = CH_3
g: Het = 2-[1-(4-toluenesulfonyl)]pyrrolyl; R = CH_3
h: Het = 2-thiazolyl; R = CH_3
i: Het = 2-pyridyl; R = CH_3
j: Het = 2-pyridyl; R = $(CH_3)_2CH$
k: Het = 3-pyridyl; R = CH_3
l: Het = 4-pyridyl; R = CH_3



(*R*,*R*)-**2**: Ar = 3,5-$(CH_3)_2C_6H_3$

Examples are given in Table 1. The hydrogenation was mostly conducted in 2-propanol containing *trans*-$RuCl_2$[(*R*)-xylbinap][(*R*)-daipen] [(*R*,*R*)-**2**][9] and *t*-C_4H_9OK, with a substrate-to-catalyst molar ratio (S/C) of 2000−5000 under 8 atm of H_2 at 25 °C. The corresponding *S* alcohols were obtained in high ee and near-quantitative yield. The reaction of the 2-furyl ketone **1a** afforded the *S* product, (*S*)-**3a**, in 99% ee without reduction of the furan ring.[10] Hydrogenation of 110 g (1.0 mol) of **1a** in 100 mL of 2-propanol (5.0 M solution) was attainable with only 30 mg of (*R*,*R*)-**2** (S/C = 40000) at 50 atm.[11] The higher analogue **1b** was hydrogenated to (*S*)-**3b** in 98% ee, which is convertible to the cinerulose A moiety of B-58941, a macrolide antibiotic,[5e,13] and a naturally occurring γ-lactone.[5d] Hydrogenation of the

Table 1. Asymmetric Hydrogenation of Hetero-aromatic Ketones[a]

ketone	Ru cat				alcohol	
no.	config	S/C[b]	H_2 (atm)	time (h)	no.	ee[c] (%)
1a	*R*,*R*	5000	8	12	(*S*)-**3a**	99
1a[d]	*R*,*R*	40000	50	12	(*S*)-**3a**[e]	99
1b	*R*,*R*	2000	8	12	(*S*)-**3b**	98
1c	*R*,*R*	2000	8	2	(*S*)-**3c**	97
1d	*R*,*R*	5000	8	12	(*S*)-**3d**	99
1d	*S*,*S*	1000	1	17	(*R*)-**3d**	99
1e	*R*,*R*	5000	8	5	(*S*)-**4**	99.7
1f	*S*,*S*	1000	8	20	**3e**[f]	97
1g[g]	*R*,*R*	1000	8	18	(*S*)-**3f**[h]	98
1h	*R*,*R*[i]	2000	8	12	(*S*)-**5**	96
1i	*R*,*R*[i]	2000	8	3	(*S*)-**6a**	96
1j	*R*,*R*	2000	8	12	(*S*)-**6b**	94
1k	*R*,*R*	5000	8	12	(*S*)-**7**	99.6
1l	*R*,*R*	5000	8	12	(*S*)-**8**	99.8
9	*R*,*R*	10000	8	17	(*S*)-**10**[j]	100
11	*R*,*R*	5000	8	17	(*S*)-**12**	91
13	*R*,*R*	2000	8	7	(*S*)-**14**	92

[a] Unless otherwise stated, reactions were conducted using 1.25−10.0 mmol of ketone in 2-propanol (0.2−1.1 M) containing **2** and *t*-C_4H_9OK at 25 °C. The yields determined by GC or ^{1}H NMR analysis were >99%. [b] Substrate/catalyst molar ratio. [c] Determined by chiral GC or HPLC analysis. [d] Reaction using 110 g of **1a** in 100 mL of 2-propanol (5.0 M). [e] The yield determined by GC analysis was 93%. [f] 61% conversion. Absolute configuration was not determined. [g] Reaction in a 1:10 DMF−2-propanol mixture. [h] 93% isolated yield. [i] $B[OCH(CH_3)_2]_3$ (ketone/borate = 100:1) was added. [j] The meso isomer was not detected.

olefinic furyl ketone **1c** saturated the carbonyl group selectively to give (*S*)-**3c** with 97% ee.[4a] The 2- and 3-thienyl ketones **1d** and **1e** gave (*S*)-**3d** and (*S*)-**4**, respectively, in >99% ee and 100% yield. The sulfur-containing heterocycle did not disturb the catalytic activity. The reaction of **1d** was accomplished even under atmospheric pressure. Currently, no reliable methods for the asymmetric reduction of 2-pyrrolyl ketones are available. Hydrogenation of the *N*-methyl compound **1f** gave highly unstable **3e** in 97% ee with only 61% yield. However, the reaction of **1g** possessing an electron-withdrawing *p*-tosyl group at the nitrogen produced (*S*)-**3f** in 98% ee and 93% isolated yield.[14]

2-Thiazolyl ketones were difficult substrates. Under the standard conditions, the ketone **1h** was hydrogenated very sluggishly. Fortunately, the addition of a small amount of $B[OCH(CH_3)_2]_3$ [ketone:(*R*,*R*)-**2**:borate = 2000:1:20] greatly

(8) Cao, P. Zhang, X. *J. Org. Chem.* **1999**, *64*, 2127−2129. (*R*,*R*)-BICP = (2*R*, 2′*R*)-bis(diphenylphosphino)-(1*R*,1′*R*)-dicyclopentane.

(9) XylBINAP = 2,2-bis(di-3,5-xylylphosphino)-1,1′-binaphthyl. DAIPEN = 1,1-di(4-anisyl)-2-isopropyl-1,2-ethylenediamine.

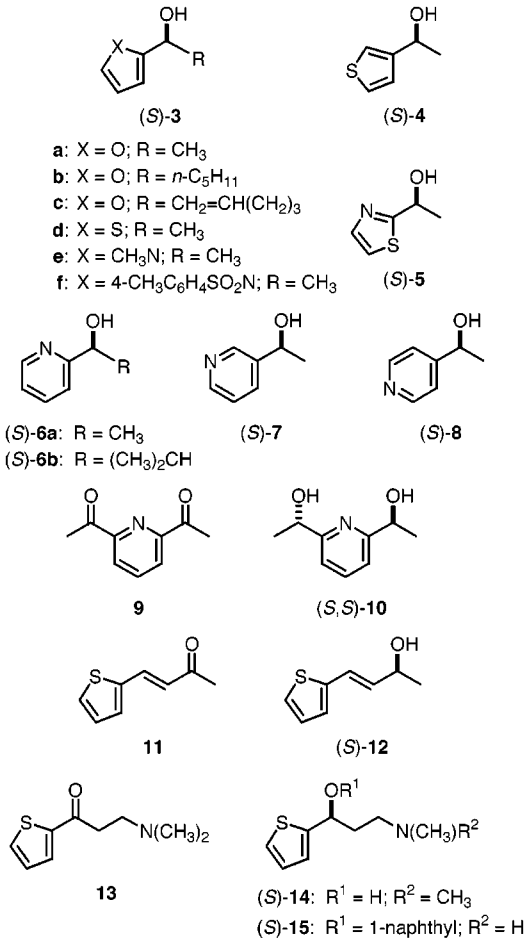
(10) Rh catalyzed asymmetric hydrogenation of **1a** (ketone/Rh/chiral phosphine = 100:1:1): Jiang, Q.; Jiang, Y.; Xiao, D.; Cao, P.; Zhang, X. *Angew. Chem., Int. Ed.* **1998**, *37*, 1100−1103.

(11) Experimental procedure: Solid (*R*,*R*)-**2** (30.5 mg, 0.025 mmol), **1a** (110.1 g, 1.00 mol), 2-propanol (100 mL), and a 1.0 M *t*-C_4H_9OK in *tert*-butyl alcohol (7.5 mL, 7.5 mmol) were placed in a 1.5-L stainless steel autoclave. This mixture was degassed, and hydrogen was introduced to a pressure of 50 atm. The reaction mixture was then vigorously stirred at 24 °C for 22 h. The yield and ee of (*S*)-**3a** determined by GC analysis were 96 and 99%, respectively. Chiral GC (column, Chirasil-DEX CB, df = 0.25 μm, 0.32 mm i.d. × 25 m, CHROMPACK.; carrier gas, helium (41 kPa); column temp, 75 °C); retention time (t_R) of (*R*)-**3a**, 31.9 min (0.7%); t_R of *S* isomer, 32.4 min (99.3%). After the hydrogen gas was carefully vented, the solvent was removed under reduced pressure. Distillation of the residue gave (*S*)-**3a** (92.8 g, 83% yield, 99% ee): bp 76 °C/18 mmHg; $[\alpha]^{24}_D$ −20.1° (*c* 1.00, $CHCl_3$) (lit.[12] $[\alpha]^{25}_D$ +20.8° (*c* 1.27, $CHCl_3$), *R* alcohol).

(12) Kobayashi, Y.; Kusakabe, M.; Kitano, Y.; Sato, F. *J. Org. Chem.* **1988**, *53*, 1586−1587.

(13) Suzuki, T.; Sugita, N.; Asai, M. *Chem. Lett.* **1973**, 789−792.

facilitated the reaction, giving (*S*)-**5** in 96% ee and 100% yield (94% after distillation).[15] This product is a synthetic equivalent of chiral 2-hydroxypropanal.[16]



In a similar manner, hydrogenation of the 2-pyridyl ketone **1i** in 2-propanol containing (*R*,*R*)-**2**, *t*-C_4H_9OK, and $B[OCH(CH_3)_2]_3$ at 8 atm afforded (*S*)-**6a** in 96% ee and 100% yield (96% after isolation). The higher analogue **1j** was hydrogenated smoothly without addition of the borate. The 3- and 4-pyridyl ketones, **1k** and **1l**, were hydrogenated equally with an S/C of 5000 to give (*S*)-**7** and (*S*)-**8**, respectively, with >99.5% ee and in high yield. Double hydrogenation of the diketone **9** catalyzed by (*R*,*R*)-**2** (S/C = 10000) gave only (*S*,*S*)-**10** among the three possible stereoisomers. This diol is useful for the synthesis of a chiral P,N,P ligand as well as pyridino-18-crown-6.[6b−d]

The synthetic utility of this method has further been manifested by the hydrogenation of structurally more elaborate ketones. The vinylogous 2-thienyl ketone **11** was hydrogenated in the presence of (*R*,*R*)-**2** and K_2CO_3[4d] to give the *S* allylic alcohol **12** in 91% ee without saturation of the olefinic bond. The absolute configuration of **12** was determined by the CD spectrum of its 4-bromobenzoate (λ_{max} (CH_3OH) 252 nm, $\Delta\epsilon$ +2.59).[17] When the 2-thienyl ketone **13** possessing a β-dimethylamino group was hydrogenated with the *R*,*R* catalyst,[18] (*S*)-**14** was obtained in 92% ee and 100% yield (91% after distillation). The amino alcohol serves as an intermediate for the synthesis of (*S*)-duloxetine [(*S*)-**15**], a potent inhibitor of serotonin and norepinephrine uptake carriers.[5f,g]

This method thus allows the asymmetric hydrogenation of an expansive array of heteroaromatic ketones. The hydrogenation is selective for the carbonyl functionality. The reaction proceeds with consistently high enantioselectivity and predictable stereochemistry regardless of the nature of the hetero-aromatic rings. The electronic properties, Lewis basic tendency, and steric size have little effect on the facial selectivity. The uniform pattern of asymmetric sense[19] eliminates the possibility of chelate mechanism involving heteroatom/Ru coordination even with the 2-acylated heterocyclic substrates. The reaction can be achieved with low catalyst loading (S/C = 1000−40000) and a high substrate concentration (up to 5 M) in an environmentally favorable solvent and at relatively low pressure (normally 8 atm or even 1 atm) and room temperature, thus providing a very practical tool for stereocontrolled organic synthesis.

Acknowledgment. We would like to thank Dr. Chizuko Kabuto, Tohoku University, for the X-ray determination of the structures of (*S*)-1-(3-thienyl)ethyl (1*S*)-camphanoate and (*S*)-1-(2-pyridyl)-2-methylpropyl (1*S*)-camphanoate. M.K. thanks the JSPS Research Fellowships for Young Scientists. This work was financially supported by grants-in-aid from the Ministry of Education, Science, Sports and Culture of Japan (Nos. 07CE2004 and 11440188).

Supporting Information Available: Procedure for the hydrogenation of heteroaromatic ketones, GC and HPLC behavior of products, and $[\alpha]_D$ values and absolute-configuration determination procedure for chiral alcohols. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) The absolute configuration was deduced by the Hoerau method: Zhou, W.-S.; Wei, D. *Tetrahedron*: *Asymmetry* **1991**, *2*, 767−770.

(15) In the reaction forming certain β-amino alcohols (not other alcohols), particularly those with a high S/C ratio, the Ru complex loses catalytic activity as hydrogenation proceeds. A *substoichiometric* amount of the borate (ketone/borate = 100:1) effectively avoids this retardation. The borate might catalytically remove the β-amino alcohol from the possible Ru aminoalkoxide product that lacks hydrogenation activity.

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(18) The catalyst is prepared by mixing (*R*,*R*)-**2** and *t*-C_4H_9OK in 2-propanol at 25 °C for 40 min prior to hydrogenation. This process is necessary to obtain a high yield in this reaction.

(19) The asymmetric direction is identical with that observed with simple aromatic ketones such as acetophenone.[4d]