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Practical Asymmetric Hydrogenation of 3-Quinuclidinone Catalyzed by the XylSkewphos/PICA−Ruthenium(II) Complex

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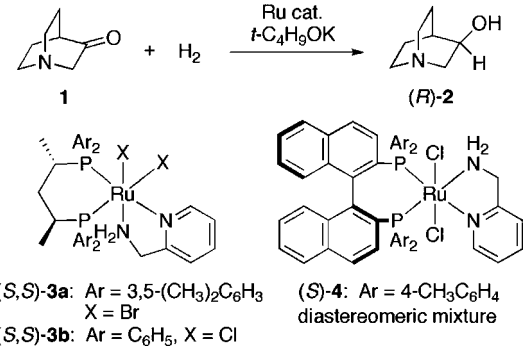
Abstract:

Asymmetric hydrogenation of 3-quinuclidinone with $RuBr_2$[(*S*,*S*)-xylskewphos](pica) in a base containing ethanol affords (*R*)-3-quinuclidinol in 88−90% ee (XylSkewphos = 2,4-bis(di-3,5-xylylphosphino)pentane, PICA = α-picolylamine). The optical purity of the product is readily increased to >99% by recrystallization. The hydrogenation of a 4.3-kg scale with a substrate-to-catalyst molar ratio of 100 000 under 15 atm of H_2 at 30−45 °C completes in 4 h. Use of methanol or 2-propanol as a solvent decreases the catalyst efficiency. $RuCl_2$(skewphos)(pica), and $RuCl_2$(tolbinap)(pica) which have similar structures, are less effective for this reaction.

Introduction

(*R*)-3-Quinuclidinol [(*R*)-**2**] (Scheme 1) is a key building block for the syntheses of muscarinic receptor ligands, including solifenacin (M_3 receptor antagonist),[1] revatropate (M_3 receptor antagonist),[2] and talsaclidine (M_1 receptor agonist).[3] Many synthetic procedures of (*R*)-**2** have been reported due to their clinical importance. Enzymatic resolution of the racemic ester of **2** by hydrolysis is a reliable procedure to obtain (*R*)-**2** in high optical purity, but this procedure has drawbacks of low yield and/or efficiency except when mediated by *Aspergillus melleus* protease.[4,5] Enzymatic reduction of 3-quinuclidinone (**1**) requires high dilution conditions,[6,7] although >99.9% optical yield is available in the best cases.[6h]

Scheme 1. **Asymmetric hydrogenation of 3-quinuclidinone (1) catalyzed by chiral Ru(II) complexes 3 and 4**



Asymmetric hydrogenation of **1** to (*R*)-**2** catalyzed by chiral metal complexes is a straightforward chemical procedure.[8] The reaction with an (*R*)-DM-SEGPHOS/(*S*)-DM-DAIPEN−Ru(II) catalyst afforded (*R*)-**2** in 97% ee (substrate-to-catalyst molar ratio (S/C) = 1000, 30 atm H_2, room temperature, 16 h, 97.5% conversion),[9,10] but the catalytic activity was not sufficient for

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practical use.[11] Since 1995, we have reported that chiral $RuCl_2$(diphosphine)(diamine)[12−15] and $RuCl_2$(diphosphine)-(pica)[16,17] (PICA = α-picolylamine) complexes act as excellent catalysts for asymmetric hydrogenation of ketones in base-containing alcoholic solvents. The latter diphosphine/PICA−Ru(II) catalysts show remarkably high activity in hydrogenation of sterically hindered *tert*-alkyl ketones[16a] and acylsilanes.[16b] The flat structure of the PICA ligand is supposed to allow bulky substrates to approach the reaction site of the catalysts. Therefore, we expected that the diphosphine/PICA−Ru(II) catalysts are appropriate for hydrogenation of 3-quinuclidinone (**1**) with a congested and rigid [2.2.2] cyclooctane skeleton. We here describe a practical procedure for the synthesis of (*R*)-**2** by asymmetric hydrogenation of **1** with a XylSkewphos/PICA−Ru(II) complex (XylSkewphos = 2,4-bis(di-3,5-xylylphosphino)pentane). The reaction was conducted with an S/C of 100 000 at a 4.3-kg scale.

Results and Discussion

The chiral diphosphine Xylskewphos was prepared as described in the literature.[18] The catalyst precursor $RuBr_2$[(*S*,*S*)-xylskewphos](pica) [(*S*,*S*)-**3a**] was prepared according to the methods described in the literature with some modifications (see the Experimental Section).[16,19] (*S*,*S*)-XylSkewphos and 1 equiv of commercial Ru(metallyl)$_2$(cod) were reacted in a degassed hexane at 70 °C for 6 h to give Ru(metallyl)$_2$[(*S*,*S*)-xylskewphos] in 76% yield. This complex was treated with a 48% aqueous solution of HBr (2 equiv) in a degassed acetone at 25 °C for 30 min to afford $RuBr_2$[(*S*,*S*)-xylskewphos] (104%) as a crude product. This crude complex was reacted with 1 equiv of PICA in a degassed DMF at 25 °C for 22 h to give (*S*,*S*)-**3a** in 80% yield. The $^{31}P\{^1H\}$ NMR measurement in $CDCl_3$ showed a set of doublet signals at δ 42.9 and 62.2 ppm with J_{P-P} = 43.6 Hz, indicating that (*S*,*S*)-**3a** exists as a sole diastereomer in the solution phase. These data are well correlated with the reported ^{31}P NMR signals of *cis*-$RuCl_2$(skewphos)(pica) (**3b**) (δ = 45.3 and 64.8 ppm, J_{P-P} = 44.7 Hz),[17] suggesting that **3a** also has the *cis*-$RuBr_2$ configuration. Catalyst precursors (*S*,*S*)-**3b** and (*S*)-**4** were prepared according to the methods described in the literature.[16,17]

The hydrogenation experiments were conducted in stainless-steel or glass autoclaves using the ketone **1**, which was prepared by neutralization of commercial **1** hydrochloride before use. The differences in the apparatus and source of substrate did not significantly affect the reactivity and stereoselectivity of the hydrogenation.

The XylSkewphos/PICA−Ru(II) complex (*S*,*S*)-**3a** with an alkaline base exhibited high catalytic activity and enantioselectivity in hydrogenation of ketone **1**. When **1** (3.40 g, 27.2 mmol) was hydrogenated with (*S*,*S*)-**3a** (0.50 mg, 0.54 μmol, S/C = 50 000) in a *t*-C_4H_9OK-containing ethanol (16 mM, 11 mL) at 30 °C under 10 atm of H_2 for 19 h, (*R*)-3-quinuclidinol [(*R*)-**2**] was obtained in 90% ee quantitatively (Table 1, entry 1). Ethanol was the solvent of choice. The reactivity and enantioselectivity were decreased in methanol or 2-propanol (entries 2 and 3). Addition of a small amount of water little affected the reaction (entry 4), suggesting that this reaction does not require absolutely dried solvents and substrates. When the hydrogenation was conducted with $RuCl_2$[(*S*,*S*)-skewphos]-(pica) [(*S*,*S*)-**3b**][17] or $RuCl_2$[(*S*)-tolbinap](pica) [(*S*)-**4**][16,20] instead of (*S*,*S*)-**3a**, the catalyst efficiency was seriously decreased, although both complexes also have the PICA ligand (entries 5 and 6). Thus, the XylSkewphos effectively increased the catalytic activity and controlled the chiral environment of the catalyst, although the actual reaction mechanism is unclear.

The hydrogenation of **1** (6.80 g, 3.4 M) with (*S*,*S*)-**3a** was conducted under 15 atm of H_2 to achieve a higher turnover number of 100 000, because the concentration of H_2 in solution phase is increased under the higher pressure of H_2. Interestingly, the catalyst efficiency was notably dependent on the reaction temperature. The hydrogenation at 40 °C was completed in 2.5 h affording (*R*)-**2** in 87% ee (Table 1, entry 10). The chemical

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(20) Complex **4** was obtained as a mixture of five diastereomers (see ref 16 for details), while the catalytic activity and enantioselectivity were independent of the initial diastereomeric ratio.

Table 1. **Asymmetric hydrogenation of 3-quinuclidinone (1)[a]**

entry	apparatus[b]	**1** (g)	[**1**] (M)	Ru cat.	S/C[c]	solvent	H_2 (atm)	temp (°C)	time (h)	(*R*)-**2** yield (%)[d]	(*R*)-**2** ee (%)[d]
1	A	3.4	2.1	(*S*,*S*)-**3a**	50000	C_2H_5OH	10	30	19	>99	90
2	A	3.4	2.1	(*S*,*S*)-**3a**	50000	CH_3OH	10	30	19	76	86
3	B	0.25	0.5	(*S*,*S*)-**3a**	1000	$(CH_3)_2CHOH$	10	30	19	96	78
4	A	3.4	2.1	(*S*,*S*)-**3a**	50000	C_2H_5OH:H_2O = 99:1	10	30	19	>99	88
5	B	0.25	0.5	(*S*,*S*)-**3b**	1000	C_2H_5OH	10	30	19	92	72
6	B	0.25	0.5	(*S*)-**4**	1000	C_2H_5OH	10	30	19	92	47[e]
7	B	6.8	3.4	(*S*,*S*)-**3a**	100000	C_2H_5OH	15	15	19	17	80
8	B	6.8	3.4	(*S*,*S*)-**3a**	100000	C_2H_5OH	15	20	19	92	85
9	B	6.8	3.4	(*S*,*S*)-**3a**	100000	C_2H_5OH	15	30	18	99	85
10	B	6.8	3.4	(*S*,*S*)-**3a**	100000	C_2H_5OH	15	40	2.5	>99	87
11	B	6.8	3.4	(*S*,*S*)-**3a**	100000	C_2H_5OH	15	50	2.5	82	85
12	C	660	3.5	(*S*,*S*)-**3a**	100000	C_2H_5OH	15	30−40	2	>99	88
13	D	4300	3.5	(*S*,*S*)-**3a**	100000	C_2H_5OH	15	30−45	4	>99 (82)[f]	88 (>99)[g]

[a] Reactions were conducted using ketone **1** in solvent containing a Ru catalyst **3** or **4** and *t*-C_4H_9OK (14−18 mM). [b] A: 100-mL stainless-steel autoclave. B: 100-mL glass autoclave. C: 3-L stainless-steel autoclave. D: 20-L stainless-steel autoclave. [c] Substrate/catalyst molar ratio. [d] Determined by chiral GC analysis. [e] (*S*)-**2** was obtained. [f] Isolated yield after recrystallization. [g] Data after recrystallization.

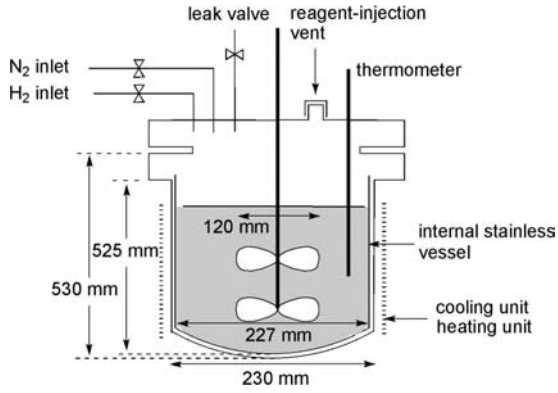

Figure 1. **Illustration of a 20-L stainless-steel autoclave.**

yield and enantioselectivity were slightly decreased at 50 °C, possibly due to the instability of the active catalytic species (entry 11). The reaction at 20−30 °C required more than 18 h for completion to give the alcohol in 85% ee (entries 8 and 9). The reaction rate was significantly decreased at 15 °C (entry 7). The enantioselectivity was little affected by the hydrogen pressure.

The hydrogenation could be scaled up without problem. The 660-g scale reaction ([**1**] = 3.5 M) in a 3-L stainless-steel autoclave was conducted at 30−40 °C under 15 atm of H_2 to give (*R*)-**2** in 88% ee quantitatively (Table 1, entry 12). Consequently, a pilot-scale reaction using 4.30 kg of **1** (3.5 M) with (*S*,*S*)-**3a** (317 mg, S/C = 100 000) and *t*-C_4H_9OK (14 mM) in ethanol (6.9 L) under 15 atm of H_2 in a 20-L stainless-steel autoclave equipped with a stirring blade (Figure 1) was completed in 4 h, affording the intended product in 88% ee (entry 13; see the Experimental Section). The reaction rate and temperature could be controlled by the stirring rate of the blade, which correlates with the concentration of H_2 in the reaction mixture. Careful release of H_2 followed by concentration of the reaction mixture under reduced pressure gave the crude product (4.4 kg). After the contaminating *t*-C_4H_9OK was neutralized with conc. HCl (11.7 mL), the crude alcohol was purified by recrystallization from a mixture of $CH_3CO_2C_2H_5$ and ethanol to give (*R*)-**2** in >99% ee (3.62 kg, 82% yield based on 4.30 kg of **1**).

In summary, the newly devised complex $RuBr_2$(xylskewphos)(pica) (**3a)** effectively catalyzes asymmetric hydrogenation of 3-quinuclidinone (**1**) in a base containing ethanol to afford 3-quinuclidinol (**2**) in 88% ee. The Skewphos/PICA−Ru (**3b**) and TolBINAP/PICA−Ru (**4**) complexes are much less effective for this purpose. The 4.3-kg-scale reaction with **3a** at an S/C of 100 000 under 15 atm of H_2 in a 20-L stainless-steel autoclave is completed in 4 h. The reaction rate and temperature are controlled by the rate of the stirring blade included with the autoclave. 3-Quinuclidinol in >99% ee (82% isolated yield) is readily obtained by recrystallization. Thus, this asymmetric hydrogenation provides a practical and simple method to produce optically active 3-quinuclidinol.

Experimental Section

$RuBr_2$[(*S*,*S*)-xylskewphos](pica) [(*S*,*S*)-3a]. Ru[η^3-$CH_2C(CH_3)CH_2]_2$(cod)[19] (1.79 g, 5.43 mmol) and (*S*,*S*)-XylSkewphos (3.00 g, 5.43 mmol) were placed in a 200-mL Schlenk flask under an argon atmosphere. A degassed hexane (140 mL) was added to the flask, and the mixture was degassed by ten cycles of vacuum filling with argon. The reaction mixture was stirred at 70 °C for 6 h. After the mixture was cooled to room temperature, it was transferred into a 1-L Schlenk flask through a glass filter under an argon atmosphere to give a brown solution. The solvent was removed under reduced pressure, and the residue was dried at 75 °C in vacuo for 15 h to afford crude Ru[η^3-$CH_2C(CH_3)CH_2]_2$[(*S*,*S*)-xylskewphos] (4.42 g, 106%). The crude complex was washed with a mixture of acetone (6.3 mL) and methanol (31.5 mL), and the solid was collected by filtration with a glass filter under an argon atmosphere. This treatment was repeated once more, and the resulting powder was dried in vacuo to give Ru[η^3-$CH_2C(CH_3)CH_2]_2$[(*S*,*S*)-xylskewphos] (3.16 g, 76%). ^{1}H NMR (400 MHz, C_6D_6, at 50 °C) δ 1.02 (br dd, 6H), 1.46 (br s, 2H), 1.59 (br d, 2H), 2.06 (s, 24H), 2.21 (br s, 6H), 2.88 (br s, 2H), 3.06 (br s, 2H), 6.75 (d, 4H, $^3J_{H-P}$ = 30 Hz), 6.99 (br d, 4H), 7.38 (br s, 4H). ^{31}P NMR (162 MHz, C_6D_6, at 50 °C) δ 48.6 (s).

Ru[η^3-$CH_2C(CH_3)CH_2]_2$[(*S*,*S*)-xylskewphos] (2.70 g, 3.53 mmol) was placed in a 200-mL Schlenk flask under an argon atmosphere. A degassed acetone (128 mL) was added to the flask, and the mixture was degassed by ten cycles of vacuum

filling with argon. To the dark-yellow solution was dropwise added hydrobromic acid (48 wt %, 798 μL) at 25 °C, resulting in a reddish brown solution, which was stirred for 30 min. The solvent was removed under reduced pressure, and the residue was dried at 25 °C in vacuo for 15 h to give crude $RuBr_2$[(*S*,*S*)-xylskewphos] (2.98 g, 104%). This crude complex was used for the next transformation.

The crude $RuBr_2$[(*S*,*S*)-xylskewphos] (2.44 g, estimated as 2.91 mmol) was placed in a 200-mL Schlenk flask under an argon atmosphere. A degassed DMF (78 mL) was added to the flask, and the mixture was degassed by ten cycles of vacuum filling with argon. To the reddish brown solution was added α-picolylamine (317 mg, 2.91 mmol) at 25 °C, and the solution was stirred for 22 h. The solvent was removed at 50 °C under reduced pressure, and the residue was dried in vacuo, resulting in the crude (*S*,*S*)-**3a** (2.90 g, 108%). The crude complex was dissolved with a degassed CH_2Cl_2 (59 mL), and insoluble materials were removed by filtration with a glass filter. The solvent of the filtrate was removed under reduced pressure, and the solid was washed with a mixture of CH_2Cl_2 (11.3 mL) and hexane (20.6 mL), then with hexane alone (16.9 mL). The resulting powder was dried at 50 °C in vacuo for 13 h to give (*S*,*S*)-**3a** (2.15 g, 80% yield). Decomposing point (dec) 334.6 °C. IR (KBr-disk) 3448, 3338, 2919, 2868, 1598, 1582, 1446, 1129, 852, 724, 695, 637, 565, 499 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.79 (dd, 3H, J = 6.9 and 11.9 Hz), 1.16 (dd, 3H, J = 7.3 and 13.7 Hz), 1.54−1.61 (m, 1H), 1.74−2.35 (m, 2H), 2.04 (s, 18H), 2.26 (br s, 3H), 2.52 (br s, 3H), 3.02−3.07 (m, 2H), 3.34−3.39 (m, 1H), 3.69 (br d, 1H, J = 14.7 Hz), 4.09 (br s, 1H), 6.68−7.11 (m, 8H), 7.40−7.44 (m, 2H), 7.58 (br d, 1H, J = 9.1 Hz), 9.11 (br d, 1H, J = 5.5 Hz).[21] ^{31}P NMR (162 MHz, $CDCl_3$) δ 42.9 (d, J_{P-P} = 43.6 Hz), 62.2 (d, J_{P-P} = 43.6 Hz). HRMS (EI^+) *m*/*z* 920.1156 (M^+), calcd for $C_{43}H_{54}{}^{79}Br^{81}BrN_2P_2{}^{100}Ru$: 920.1151. Anal. Calcd for $C_{43}H_{54}Br_2N_2P_2Ru\cdot 1.64CH_2Cl_2\cdot 0.03(C_3H_7NO)$: C, 50.54; H, 5.45; N, 2.67. Found: C, 50.95; H, 5.49; N, 2.76.

Hydrogenation of 3-Quinuclidinone (1). The air present in a 20-L stainless-steel autoclave equipped with a mechanical stirring blade, a pressure gauge, and a gas inlet tube attached to a hydrogen source was replaced by nitrogen (Figure 1). 3-Quinuclidinone (**1**) (>99% purity; 4.30 kg, 34.4 mol) in ethanol (4 L) which had been degassed by five cycles of vacuum filling with nitrogen was added to the autoclave under a stream of nitrogen. The Ru complex (*S*,*S*)-**3a** (317 mg, 0.344 mmol) and ethanol (500 mL) were placed in a 1-L three-necked flask under a nitrogen atmosphere, and then the resulting solution was degassed by five cycles of vacuum filling with nitrogen. Solid *t*-C_4H_9OK (15.5 g, 138 mmol) and ethanol (1 L) were placed in a 2-L three-necked flask under a nitrogen atmosphere, and the solution was degassed by five cycles of vacuum filling with nitrogen. The ethanol solutions of (*S*,*S*)-**3a** and *t*-C_4H_9OK, described above, and then ethanol (1.4 L) were transferred into the autoclave under a stream of nitrogen by cannula. The air present in the gas inlet tube was removed by flushing with a stream of hydrogen. Hydrogen was initially introduced into the autoclave at a pressure of 15 atm, before being reduced to 5 atm by carefully releasing the stop valve. After this procedure was repeated five times, the vessel was pressurized to 15 atm. The reaction mixture was stirred while maintaining a temperature range of 30−45 °C. After stirring for 4 h, hydrogen gas was carefully vented and completely replaced by nitrogen, and then the mixture was treated with conc. HCl (11.7 mL). The solvent was removed under reduced pressure to give crude (*R*)-3-quinuclidinol [(*R*)-**2**] (4.40 kg, 100% yield, 88% ee). Column, BETA DEX 120, df = 0.25 μm, 0.25 mm i.d. × 30 m, SUPELCO; carrier gas, helium (2.4 mL/min); column temp, 120 °C; detection, FID; retention time (t_R) of (*R*)-**2**, 33.2 min (94.0%); t_R of (*S*)-**2**, 32.7 min (6.0%).

The crude product was dissolved in a hot 20:1 mixture of $CH_3CO_2C_2H_5$ and ethanol (about 12 L), and then was cooled to ambient temperature, precipitating a white crystalline compound. The crystal was collected by the usual filtration method, and the collected compound was dried under reduced pressure (0.3 mmHg) to give (*R*)-**2** (3.62 kg, 82% yield) in >99% ee. Mp 223−224 °C. $[\alpha]_D^{22}$ −46.1 (*c* 2.90, 1.0 M HCl) (lit.[7b] $[\alpha]_D^{22}$ −45.7 (*c* 2.9, 1 M HCl), *R*). IR (KBr-disk) 3399, 3099, 2941, 2924, 2871, 1456, 1346, 1317, 1128, 1116, 1045, 988, 817, 795, 774 cm^{-1}. ^1H NMR (400 MHz, CD_3OD) δ 1.38−1.45 (m, 1H), 1.49−1.58 (m, 1H), 1.69−1.77 (m, 1H), 1.79−1.82 (m, 1H), 1.93−2.01 (m, 1H), 2.55 (dt, 1H, J = 14, 3 Hz), 2.61−2.69 (m, 1H), 2.71−2.90 (m, 3H), 3.07−3.13 (ddd, 1H, J = 2.3, 8.6, 14.0 Hz), 3.83−3.87 (m, 1H). ^{13}C NMR (100 MHz, CD_3OD) δ 20.4 (CH_2), 26.1 (CH_2), 29.9 (CH), 47.9 (CH_2), 48.9 (CH_2), 58.9 (CH_2), 69.0 (CH). Anal. Calcd for $C_7H_{13}NO$: C, 66.10%; H, 10.30%; N, 11.01%. Found: C, 66.17; H, 10.43; N, 10.99.

(21) The integration number of aromatic protons was less than the actual one. This may have been caused by their slow relaxation.

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Supporting Information Available

NMR charts of the Ru complex (*S*,*S*)-**3a** and the alcoholic product (*R*)-**2** and pictures of autoclaves, Figures A−C. This material is available free of charge via the Internet at http://pubs.acs.org.

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