Tetrahedron Letters, Vol 32, No 33, pp 4163 4166, 1991
Printed in Great Britain

0040-4039/91 $3 00 + (
Pergamon Press plc

CONVENIENT PREPARATION OF BINAP—RUTHENIUM(II) COMPLEXES CATALYZING ASYMMETRIC HYDROGENATION OF FUNCTIONALIZED KETONES

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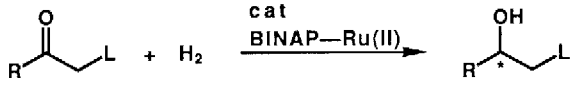
Summary: Ligand exchange between $[RuCl_2(benzene)]_2$ or $RuCl_2[Sb(C_6H_5)_3]_3$ and (*R*)- or (*S*)-BINAP produces BINAP—Ru(II) complexes which act as catalysts for the highly enantioselective hydrogenation of functionalized ketones.

Halogen-containing BINAP—Ru(II) complexes catalyze highly enantioselective hydrogenation of a wide variety of functionalized ketones including β-keto esters.[1,2] For example, reaction of methyl 3-oxobutanoate in methanol at room temperature under initial hydrogen pressure of 100 atm gives methyl (*R*)- or (*S*)-3-hydroxybutanoate in up to 99.4% ee and in nearly quantitative yield.[3] This high-pressure reaction can be conducted using a preformed BINAP—Ru complex catalyst[4] with substrate/catalyst (S/C) molar ratio of 1000—10000, employing up to 50% (v/v) substrate concentration, on any scale from <100 mg to 100 kg of the substrate In response to numerous inquiries about the possibility of using more readily accessible, or even crude, BINAP—Ru complexes and in addition the reaction conditions, particularly, hydrogen pressure and temperature, we here disclose additional information in this regard.



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A BINAP—Ru(II) complex that gives a high level of enantioselectivity is obtainable simply by heating a mixture of commercial $[RuCl_2(benzene)]_2$[5] and (*R*)- or (*S*)-BINAP (Ru:BINAP = 1:1.05) in *N*,*N*-dimethylformamide (DMF) at 100 °C for 10 min. The crude solid[6a] obtained by vacuum concentration of the reddish brown solution[6b] catalyzes asymmetric hydrogenation of methyl 3-oxobutanoate under the standard high-pressure, room temperature conditions to afford the corresponding alcohol in 99% ee.[7] As we noted earlier,[8] the hydrogenation at 100 °C was complete within 30 min giving the hydroxy ester with 98% ee. Hydrogen pressure appears to have little effect on the enantioselectivity, and reaction under 4 atm of hydrogen at 100 °C for 6 h afforded the product in 98% ee. However, satisfactory results were not obtained at atmospheric hydrogen pressure, with slow conversion even at 100 °C.

A BINAP—Ru(II) complex is also accessible by heating an equimolar mixture of $RuCl_2[Sb(C_6H_5)_3]_3$ and BINAP in *o*-dichlorobenzene at 160 °C for 10 min. This

Table I. Asymmetric Hydrogenation of Functionalized Ketones Catalyzed by BINAP–Ru Complexes[a]

substrate **1**	catalyst system[b] (S/C)	temp, °C	H_2, atm	time, h	product **2** % yield[c]	% ee[d]	abs[d]
$CH_3COCH_2COOCH_3$	1/2 $[RuCl_2(C_6H_6)]_2$[e] (*R*)-BINAP (1950)	25	100	40	97	99	*R*
$CH_3COCH_2COOCH_3$	1/2 $[RuCl_2(C_6H_6)]_2$[e] (*R*)-BINAP (1950)	100	100	0.5	97	98	*R*
$CH_3COCH_2COOCH_3$	1/2 $[RuCl_2(C_6H_6)]_2$[e] (*S*)-BINAP (1470)	100	4	6	95[f]	98	*S*
$CH_3COCH_2COOCH_3$	$RuCl_2[Sb(C_6H_5)_3]_3$[g] (*S*)-BINAP (1490)	25	100	40	94[f]	99	*S*
$CH_3COCH_2COOCH_3$	$RuCl_2[Sb(C_6H_5)_3]_3$[g] (*S*)-BINAP (1490)	100	100	0.5	93[f]	99	*S*
$CH_3COCH_2COOCH_3$	$RuCl_2[Sb(C_6H_5)_3]_3$[g] (*S*)-BINAP (1990)	100	4	6	96	98	*S*
$ClCH_2COCH_2COOC_2H_5$	1/2 $[RuCl_2(C_6H_6)]_2$[e] (*S*)-BINAP (2060)	100[h]	4	6	97	93	*R*
CH_3COCH_2OH	1/2 $[RuCl_2(C_6H_6)]_2$[e] (*R*)-BINAP (1720)	30[h]	100	40	97[i]	91	*R*
$CH_3COCH_2CH_2OH$	1/2 $[RuCl_2(C_6H_6)]_2$[e] (*R*)-BINAP (1140)	30[h]	100	40	96[f]	98	*R*
CH_3CO-*o*-BrC_6H_4	1/2 $[RuCl_2(C_6H_6)]_2$[e] (*S*)-BINAP (700)	100	100	3	83[f]	96	*S*

[a] Reactions were carried out in a 30–50% concentration of the substrate in methanol. [b] Ru:BINAP = 1:1.05. [c] Isolated yield in a 20-g scale reaction unless otherwise specified. [d] Determined by combination of HPLC analysis of the (*R*)-MTPA esters and rotation measurement. [e] Prepared by heating in DMF at 100 °C for 10 min and then removal of the volatiles. The S/C ratio was based on $RuCl_2$(binap). [f] A 2-g scale reaction. [g] Prepared by heating in *o*-dichlorobenzene at 160 °C for 10 min and then removal of the volatiles. The S/C ratio was based on $RuCl_2$(binap)/3 $Sb(C_6H_5)_3$. [h] Reaction in ethanol. [i] A 4-g scale reaction.

procedure may be preferable as the precursory Ru–stibine complex is air-stable and readily prepared from $RuCl_3 \cdot nH_2O$ and triphenylstibine;[9] completion of the ligand exchange with the diphosphine is clearly indicated by pink-to-reddish brown color change.

Some examples of the enantioselective hydrogenation using these in situ formed Ru complexes are given in Table I. The high-temperature ligand exchange between readily available Ru(II) complexes and BINAP allows facile preparation of chiral hydrogenation catalysts possessing reactivities comparable to those of the preformed complexes.[3] In laboratories, the large-scale reaction is performed conveniently and safely under high pressure by using a stainless steel autoclave, while one may conduct relatively small-scale reactions in a Parr apparatus or an ordinary thick-wall glass vessel equipped with Young's tap under pressure as low as 4 atm and at 80–100 °C. The low-pressure hydrogenation is obviously desirable for industrial production. Elevation of temperature may increase[8] or decrease the enantioselectivity depending on the

substrate. Although use of such crude catalysts tends to sometimes decrease the enantioselectivity, the results described here would be acceptable for most synthetic purposes. The high chemical yield, enantioselectivity, and reproducibility, combined with the ready availability of the catalyst, and operational simplicity of the reaction and workup, make the present catalytic system efficient for asymmetric catalysis.

The high efficiency displayed by the crude Ru catalysts relies on the ligand acceleration caused by BINAP ligation; the BINAP-coordinated Ru(II) complexes are both highly reactive and stereo-discriminating, whereas other Ru species lacking the BINAP ligand are virtually unreactive under such conditions. Formation of a singular catalytic species in the reaction cycle is a key feature in obtaining a high degree of stereoselection. Since the extent of adverse effects caused by impurities depends on the reaction system and reaction conditions, one should carefully choose the suitable experimental parameters to obtain satisfactory results.

The recommended procedures are follows. All solvents and substrates used here were degassed by freeze-thaw cycles.

Hydrogenation at 100 atm at 25 °C. A dry 20-mL Schlenk tube containing a Tefron-coated stirring bar was charged with $[RuCl_2(benzene)]_2$ (43.5 mg, 87.3 μmol), (*R*)-BINAP (113.7 mg, 0.183 mmol), and DMF (distilled from molecular sieves 4A immediately before use, 3 0 mL). The resulting reddish brown suspension was heated at 100 °C under argon for 10 min to give a clear reddish brown solution. The reaction mixture was cooled and concentrated at 1 mmHg at 50 °C with vigorous stirring and then at 0.1 mmHg for 1 h. The resulting reddish orange solid was used for hydrogenation. The (*R*)-BINAP—Ru complex (70.0 mg, weighed quickly in air; 88.1 μmol, calculated as $RuCl_2$[(*R*)-binap]) was added into a 100-mL dry Schlenk tube charged with methyl 3-oxobutanoate (20.0 g, 0.172 mol) and methanol (20 mL). The yellowish orange solution degassed by two freeze-thaw cycles. With use of cannula this solution was transferred under argon to a glass vessel placed in a 100-mL stainless steel autoclave. The gas inlet tube was then attached to a hydrogen source, and the air originally present in the tube was removed by flushing five times with 10 atm hydrogen. Hydrogen was introduced until pressure gauge indicates 50 atm. The pressure was carefully released to 10 atm. This procedure was repeated three times, and finally hydrogen was pressurized to 100 atm. The solution was stirred at 25 °C for 40 h during which time hydrogen cylinder was kept connected After the excess hydrogen had been carefully bled off, the apparatus was disassembled. The yellowish orange content was concentrated by a rotary evaporator to give a green colored residue. GC analysis indicated that the yield of methyl 3-hydroxybutanoate was 100%: column, PEG-20M on chromosorb WAW (Gasukuro Kogyo Inc.); column temperature, 120 °C; injector temperature, 160 °C; N_2 pressure, 1.2kg/cm^2; t_R of methyl 3-oxobutanoate and methyl 3-hydroxybutanoate are 36.0 and 47.2 min, respectively. Distillation (40 °C, 2 mmHg) afforded methyl (*R*)-3-hydroxybutanoate (19.7 g, 97% yield) in 99% ee assayed as the (*R*)-MTPA ester.[3]

Hydrogenation at 4 atm at 100 °C. A dry 20-mL Schlenk tube containing a Tefron-coated stirring bar was charged with $RuCl_2[Sb(C_6H_5)_3]_3$[9] (200.0 mg, 0.162 mmol), (*S*)-BINAP (105.9 mg, 0.170 mmol), and *o*-dichlorobenzene (distilled from calcium dihydride immediately before use, 3.0 mL). The resulting deep purplish red suspension was heated under argon for 10 min in a 160-°C oil bath. The reaction mixture was cooled and concentrated under vacuum at 50 °C with vigorous stirring. The residue was further evacuated at 0.1 mmHg and 50 °C for 1 h to give a mass of reddish brown solid, which was used for hydrogenation after crashing the mass with a spatula.[10] In a similar

manner to the above described hydrogenation, the methanol (20.0 mL) solution containing methyl 3-oxobutanoate (20.0 g) and the (S)-BINAP–Ru complex (160.0 mg, weighed quickly in air; 86.3 μmol calculated as $RuCl_2$[(S)-binap]/3 $Sb(C_6H_5)_3$) was prepared and transferred to a 300-mL glass autoclave equipped with the gas inlet tube, the stop valve, and the pressure gauge. After exchanging air and argon with hydrogen, hydrogen was pressurized until the gauge showed 3 atm. The yellowish orange solution was heated at 100 °C for 6 h during which time hydrogen cylinder was kept connected. After cooling, the excess hydrogen was removed and the apparatus disassembled. The yellowish orange content was concentrated by a rotary evaporator to give a green colored residue. GC analysis indicated production of methyl 3-hydroxybutanoate in 100% yield. Distillation (40 °C, 2 mmHg) afforded methyl (S)-3-hydroxybutanoate (19.4 g, 96% yield) in 98.2% ee assayed as the (*R*)-MTPA ester.[3]

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6. (a) Probably a crude mixture of $RuCl_2(binap)(dmf)_2$ and $[RuCl_2(binap)(dmf)]_n$. ^{31}P NMR ($CDCl_3$) δ 53.7 (d, *J* = 41 Hz), 54.5 (d, *J* = 42 Hz), 54.8 (d, *J* = 39 Hz), 57.4 (d, *J* = 41 Hz), 59.7 (d, *J* = 42 Hz), 61.5 (d, *J* = 39 Hz); conductivity 0.4 Scm^2/mol (CH_2Cl_2). (b) Possibly a crude mixture of $[RuCl(binap)(dmf)_3]Cl$ and $[Ru(binap)(dmf)_4]Cl_2$. ^{31}P NMR (4:1 DMF–$CDCl_3$) δ 60.6 (d, *J* = 46 Hz), 61.4 (d, *J* = 46 Hz), 61.8 (s); conductivity 27 Scm^2/mol (DMF). The DMF solution can be used directly for the hydrogenation although the reactivity is halved in comparison to those of the dried[6a] or preformed materials.[3]
7. *N*,*N*-Dimethylacetamide can be used in place of DMF. Use of commercial $[RuCl_2(1,5\text{-cyclooctadiene})]_n$ gave similar results but the ligand exchange required heating in DMF at 160 °C for 20 min.
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10. The fine powder which can be more easily handled is obtained by washing the solid with hexane under sonication.

(Received in Japan 10 April 1991)