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Highly Stereoselective Asymmetric Hydrogenation of 2-Benzamidomethyl-3-oxobutanoate catalysed by Cationic binap–Ruthenium(II) Complexes†

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Highly diastereoselective hydrogenation of methyl 2-benzamidomethyl-3-oxobutanoate has been accomplished by using [RuI{(*R*)-binap}(*p*-cymene)]I and corresponding complexes of derivatives of binap as catalyst, giving methyl (2*S*,3*R*)-2-benzamidomethyl-3-hydroxybutanoate, a versatile intermediate for the synthesis of β-lactam antibiotics, in up to 98% diastereoisomeric excess and 99% enantiomeric excess.

Asymmetric hydrogenation of racemic 2-substituted β-keto ester derivatives catalysed by binap–Ru^{II} complexes proceeds smoothly accompanied by epimerization through enolization to afford mainly one of the diastereoisomeric products in high optical purity.[1,2] Hydrogenation of methyl 2-benzamidomethyl-3-oxobutanoate **1** in dichloromethane catalysed by $[Ru_2Cl_4\{(R)\text{-binap}\}_2(NEt_3)]$[3] (50 °C, H_2 100 kg cm^{-2}, 20 h) gave *syn*-(2*S*,3*R*)-**2** in 88% diastereoisomeric excess (d.e.) and 98% enantiomeric excess (e.e.).[2a] Because ruthenium-catalysed oxidation of the β-lactam **3** derived from *syn*-(2*S*,3*R*)-**2** affords **4** in >99% yield,[4] the product *syn*-(2*S*,3*R*)-**2** serves as an important starting material for the synthesis of β-lactam antibiotics, which led us to investigate various factors controlling the catalytic activity and stereoselectivity of this asymmetric hydrogenation by use of pure samples of cationic binap–Ru^{II}(arene) complexes **5** and **6** as catalysts.[5]‡ We have found that the diastereoselectivity of the hydrogenation depends strongly on the solvent and the halide anion in the binap–Ru^{II} complexes as well as the substituents on the four phenyl rings of the binap ligands, though the optical purities of the products are less sensitive to these factors.

When the hydrogenation of **1** was carried out in the presence of **5a** in anhydrous dichloromethane carefully dried over phosphorus pentoxide, the reaction proceeded rather slowly (substrate/catalyst 100, H_2 50 kg cm^{-2}, 50 °C, 40 h, 44% conv.). Addition of water (0.5% v/v) to the reaction mixture, however, accelerated the hydrogenation (40 h, 50 kg cm^{-2}, 98% conv.) to afford **2** in 88% d.e. and 97% e.e. (Table 1, run 5). The reaction in methanol or in methanol–dichloromethane proceeded smoothly, though under such conditions much lower stereoselectivities are inevitable (runs 6 and 7). The initial hydrogen pressure did not affect the diastereoselectivity. Thus, to complete the present catalysis as a practically useful process, we must develop more efficient catalysts which lead to almost complete diastereo- and enantio-selectivities even in the presence of methanol. For further investigations, we have carried out the hydrogenation using methanol, dichloromethane saturated with water at −20 °C, or a mixture of methanol and dichloromethane as solvent under 50 atm of hydrogen.

Effects of halogen anions bound to ruthenium have been examined in methanol. The results of runs 2, 4 and 6 in Table 1 show that the iodide complex gives the highest diastereoselectivity among the binap–Ru^{II} halide complexes. A similar tendency has also been observed for the reactions carried out in aqueous dichloromethane, though the diastereoselectivities are always relatively high (runs 1, 3 and 5). The beneficial effect of iodide on stereoselectivity has also been observed for Rh^{I} and Ir^{III} catalysed asymmetric hydrogenation of imines.[6]

In order to investigate the effects of substituents on the four phenyl rings of binap, we have prepared several new binap derivatives by standard procedures.[7]§ Plots of carbonyl stretching vibrations in IR spectra of RhCl(CO)(L) complexes (where L is *p*-MeO-binap,¶ 3,5-Bu$^t_2$-binap, *m*-Xy-binap, *m*-Tol-binap, *p*-Tol-binap,¶ binap, *p*-F-binap or *p*-Cl-binap) against Hammet σ_m and σ_p values showed a linear relationship between 2004 and 2020 cm^{-1}, which shows that the electronic properties of the phosphorus atoms of binap derivatives are subtly influenced by the substituents. The ruthenium complexes of these binap derivatives were used for the above reactions. Substituents such as methyl and methoxy in

† binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.

‡ The catalytic system prepared *in situ* by simply heating $[RuI_2(p\text{-cymene})]_2$ and binap in methanol–dichloromethane (3 : 1) at 50 °C for 1.5 h can be used directly for asymmetric hydrogenation of ketonic and unsaturated substrates without either isolation of the binap complex or further purification. Hydrogenation of methyl 3-oxobutanoate by use of the above catalytic system (30 °C, H_2 100 kg cm^{-2}, 40 h) gave methyl 3-hydroxybutanoate in 98% e.e.

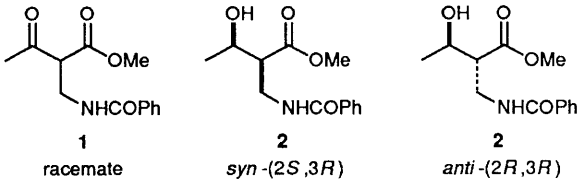
§ Physical and spectral data of new binap derivatives (^{31}P NMR data with respect to 85% H_3PO_4 as external standard): (*S*)-*p*-F-binap {2,2′-bis[bis(4-fluorophenyl)phosphino]-1,1′-binaphthyl}: m.p. 213 °C ^{31}P NMR ($CDCl_3$) δ −17.0 (s), $[\alpha]_D^{27}$ −90.6° (*c* 0.755, $CHCl_3$) (98.8% e.e); (*R*)-*p*-Cl-binap {2,2′-bis[bis(4-chlorophenyl)phosphino]-1,1′-binaphthyl}: m.p. 220 °C, ^{31}P NMR ($CDCl_3$) δ −16.8 (s), $[\alpha]_D^{27}$ +64.6° (*c* 0.245, $CHCl_3$) (98.8% e.e.); (*S*)-*m*-Tol-binap {2,2′-bis[bis(3-methylphenyl)phosphino]-1,1′-binaphthyl}: m.p. 179–182 °C, ^{31}P NMR ($CDCl_3$) δ −14.4 (s), $[\alpha]_D^{25}$ −232.4° (*c* 1.00, benzene) (99.9% e.e.); (*S*)-*m*-Xy-binap {2,2′-bis[bis(3,5-dimethylphenyl)phosphino]-1,1′-binaphthyl}: m.p. 255 °C, ^{31}P NMR ($CDCl_3$) δ −14.9 (s), $[\alpha]_D^{25}$ −220.8° (*c* 1.00, $CHCl_3$) (99.5% e.e.); (*R*)-3,5-Bu$^t_2$-binap {2,2′-bis[bis(3,5-di-*tert*-butylphenyl)phosphino]-1,1′-binaphthyl}: m.p. 211 °C, ^{31}P NMR ($CDCl_3$) δ −13.4 (s), $[\alpha]_D^{25}$ +63.6° (*c* 1.00, $CHCl_3$) (99.2 % e.e.).

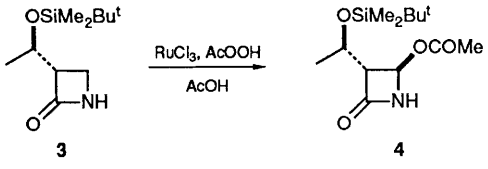
¶ *p*-MeO-binap: 2,2′-bis[bis(4-methoxyphenyl)phosphino]-1,1′-binaphthyl; *p*-Tol-binap: 2,2′-bis[bis(4-methylphenyl)phosphino]-1,1′-binaphthyl.

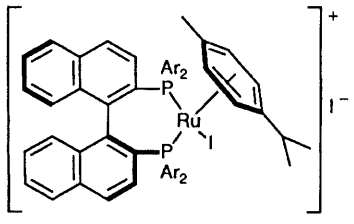
Table 1 Asymmetric hydrogenation of the ester **1**[a,b]

Run	Cat.	S/C[c]	Solvent	*t*/h	Conv. (%)	D.e.[d] (%)	E.e.[e] (%)	Config. of *syn*-**2**
1	(*R*)-**6a**	100	CH_2Cl_2[f]	40	91	74	90	(2*S*,3*R*)
2	(*R*)-**6a**	100	MeOH	40	100	0	77	(2*S*,3*R*)
3	(*R*)-**6b**	100	CH_2Cl_2[f]	40	91	79	98	(2*S*,3*R*)
4	(*R*)-**6b**	100	MeOH	40	95	9	80	(2*S*,3*R*)
5	(*S*)-**5a**	100	CH_2Cl_2[f]	40	98	88	97	(2*R*,3*S*)
6	(*S*)-**5a**	100	MeOH	40	100[g]	51	97	(2*R*,3*S*)
7	(*R*)-**5a**	1000	CH_2Cl_2–MeOH[h]	21	91	84	99	(2*S*,3*R*)
8	(*S*)-**5f**	1000	MeOH	20	94	67	91	(2*R*,3*S*)
9	(*S*)-**5g**	1000	MeOH	43	73	73	91	(2*R*,3*S*)
10	(*S*)-**5g**	1000	CH_2Cl_2–MeOH[h]	46	72	91	98	(2*R*,3*S*)
11	(*S*)-**5g**	100	CH_2Cl_2[f]	40	68	95	99	(2*R*,3*S*)
12	(*R*)-**7**[i]	1000	CH_2Cl_2–MeOH[h]	40	55	98	99	(2*S*,3*R*)
13	(*R*)-**7**[i]	500	MeOH	20	91	92	92	(2*S*,3*R*)

[a] Hydrogenation of **1** was carried out in an autoclave (50–60 °C) under an initial hydrogen pressure of 50 kg cm^{-2} unless otherwise stated. [b] The ratio of solvent to substrate was 4 (v/w). [c] Substrate to catalyst ratio. [d] Diastereoisomeric excess was determined by HPLC analysis [Cosmosil 5SL, with hexane–propan-2-ol (9:1) as eluent]. [e] Enantiomeric excess of *syn*-**2** was determined by HPLC analysis of the (+)-methoxy(trifluoromethyl)phenylacetyl ester of **2** [Nucleosil 100–3, with hexane–tetrahydrofuran–MeOH (400:100:1)] as eluent. [f] The solvent was saturated with water at −20 °C by addition of 0.5% v/v water to stirred dichloromethane (distilled from phosphorus pentoxide). [g] Initial pressure of hydrogen was 100 kg cm^{-2}. [h] The ratio of dichloromethane to methanol was 7:1. [i] See footnote ‖.

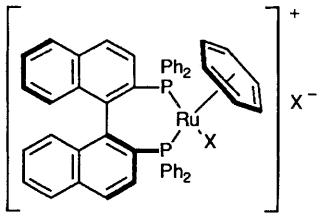






(*S*)-**5**

a : Ar = Ph
b : Ar = *p*-$MeOC_6H_4$
c : Ar = *p*-MeC_6H_4
d : Ar = *p*-FC_6H_4
e : Ar = *p*-ClC_6H_4
f : Ar = *m*-MeC_6H_4
g : Ar = *m*,*m*′-$Me_2C_6H_3$



(*S*)-**6**

a : X = Cl
b : X = Br

para-positions did not exert marked effects on the catalysis, while negative effects on catalytic activity and stereoselectivity were observed for electronegative substituents in *para*-positions. On the other hand, substituents in *meta*-positions are effective for high diastereoselectivity. Representative results are listed in Table 1. Since there are no substantial differences in an electronic sense between **5c**, **5f** and **5g**, the high efficiency of **5g** might be ascribable to the steric effect of methyl substituents in the *meta*-positions. Hydrogenation of the substrate **1** in the presence of (*R*)-3,5-Bu^t_2-binap–RuI_2 complex [(*R*)-**7**]§‖ in dichloromethane–methanol (7:1) afforded *syn*-(2*S*,3*R*)-**2** in 98 d.e. and 99% e.e.

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‖ The cationic iodoruthenium complex of (*R*)-3,5-Bu^t_2-binap similar to **5** could not be prepared by the standard procedure.[5] However heating a 2:1 mixture of the ligand and $[RuI_2(p\text{-cymene})]_2$ in ethanol–dichloromethane (1:1) at 80 °C for 18 h under hydrogen (50 kg cm^{-2}) afforded a 1:1 complex, (*R*)-3,5-Bu^t_2-binap–RuI_2 [(*R*)-**7**], whose ^{31}P NMR spectrum ($CDCl_3$) showed a singlet at δ 21.6. This complex was used for hydrogenation.