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Highly enantioselective hydrogenation of enamides catalyzed by rhodium–monodentate phosphoramidite complex

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Abstract—The monodentate phosphoramidite ligand monophos was used in the Rh-catalyzed asymmetric hydrogenation of enamides to give high enantioselectivities (up to 96% ee). © 2002 Published by Elsevier Science Ltd.

Optically active amines and amides are useful resolving agents, chiral auxiliaries and intermediates for the synthesis of biologically active compounds.[1] Traditional methods for the synthesis of these valuable compounds include fermentation, optical resolution and the use of chiral starting materials. From a practical standpoint, the asymmetric catalytic hydrogenation of enamides is a convenient and economical route for the preparation of chiral amides or amine derivatives. However, compared with the great success made in the synthesis of chiral amino acids and their derivatives through asymmetric hydrogenation in the past three decades, successful examples of the asymmetric hydrogenation of enamides without the carboxyl functionality are much less abundant. For example, the well-known rhodium and ruthenium chiral diphosphine complexes, such as Rh(BINAP), Rh(chiraphos), Rh(DIOP) and Ru(BINAP) afforded poor enantioselectivities in the asymmetric hydrogenation of enamides. In 1996, Burk et al. reported an important advance in the enantioselective hydrogenation of arylenamides with Rh catalysts containing Duphos and BPE ligands.[2a] Recently, several reports of effective systems for the enantioselective hydrogenation of enamides have been published.[2b–d] In this paper, we report a highly active and enantioselective catalyst for this useful reaction.

Many phosphorus compounds are important ligands for the preparation of catalysts used in transition metal-catalyzed reactions.[2e–g] A large number of chiral phosphorus ligands with excellent enantioselectivity have been designed and applied in asymmetric hydrogenation.[3–16] Previous studies involved mostly chiral bidentate ligands because of the seemingly important chelating effect. Recently, Reetz[17] and Feringa[18] described a highly enantioselective Rh catalyst containing chiral monodentate phosphoramidite ligands for the asymmetric hydrogenation of dehydroamino acid and itaconic acid derivatives. Pringle[19] and co-workers applied a monodentate phosphonite ligand in the Rh-catalyzed hydrogenation of methyl 2-acetamidoacrylate. Herein, we report the application of the monodentate phoshoramidite ligand 2,2′-*O*,*O*′-(1,1′-binaphthyl) - *O*,*O*′ - dioxo - *N*,*N* - dimethylphospholidine (monophos)[18] in the Rh-catalyzed asymmetric hydrogenation of enamides.

N-(1-Phenylethenyl)acetamide **1**, an enamide easily prepared by the reduction of the corresponding oxime with iron powder in the presence of acetic anhydride,[20] was chosen as a model substrate in the initial study (Scheme 1). The preliminary results showed that the catalyst was highly effective and quantitative conversions were observed in all reactions.[21] Changes in hydrogen pressure had little effect on enantioselectivity (entries 6–8, Table 1). However, changing the solvent from CH_2Cl_2 to THF, MeOH, EtOAc and acetone reduced the ee value of the product from 87 to 75, 67, 70 and 72%, respectively (entries 1–5). Temperature was also an important factor. Using dichloromethane as solvent, a significant increase in enantioselectivity was observed when the reaction temperature was decreased. The ee

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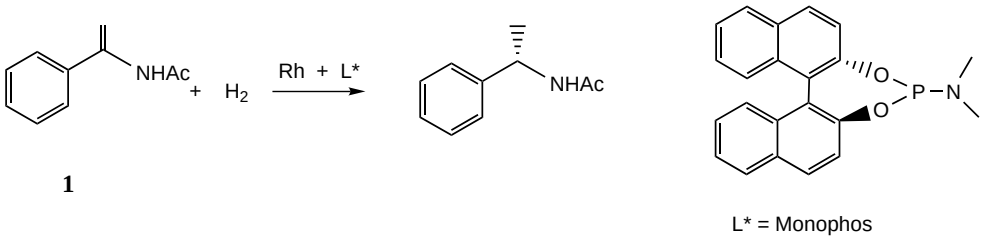
reached a plateau at a reaction temperature of –20°C. Further decrease in temperature did not give any further enhancement in enantioselectivity. Under optimum conditions, 95% ee was obtained (entry 10).

A variety of substrates were investigated (Scheme 2) and high enantioselectivities and good conversions were achieved in most cases (entries 1–4, 8, Table 2). However, the conversion rates for substrates **5** and **6** were



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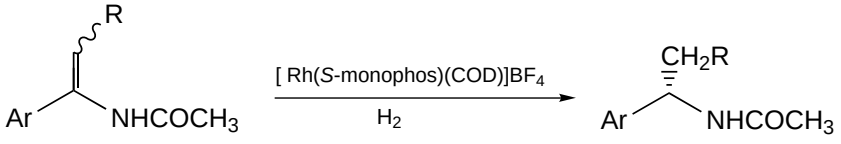
Scheme 1.

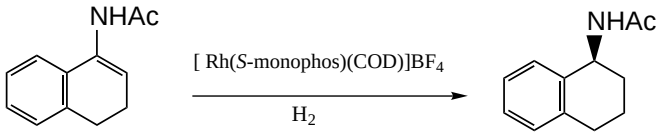
Table 1. Asymmetric hydrogenation of enamide **1** catalyzed by rhodium–monophos complex[a]

Entry	Solvent	H_2 (psi)	Temperature (°C)	t (h)	ee (%)[b]
1	THF	300	rt	1	75
2	CH_2Cl_2	300	rt	1	87
3	EtOAc	300	rt	1	70
4	MeOH	300	rt	1	67
5	Acetone	300	rt	1	72
6	CH_2Cl_2	200	rt	1	87
7	CH_2Cl_2	500	rt	1	85
8	CH_2Cl_2	700	rt	1	85
9	CH_2Cl_2	300	0	1.5	90
10	CH_2Cl_2	300	−20	3	95
11	CH_2Cl_2	300	−30	6	95
12	CH_2Cl_2	300	−40	6	95

[a] A typical procedure for the catalytic reaction is shown at the end of this paper;[21] quantitative yields were observed in all reactions.
[b] The ee's were determined by chiral GC analysis using a Chrompack chiral fused silical 50 m×0.25 mm chirasil-L-VAL column. The *S* configuration was assigned by comparing the experimental results with published data.



1: Ar = C_6H_5 R = H
2: Ar = *p*-CH_3-C_6H_4 R = H
3: Ar = *p*-CH_3O-C_6H_4 R = H
4: Ar = *p*-CF_3-C_6H_4 R = H
5: Ar = 1-naphthyl R = H
6: Ar = C_6H_5 R = CH_3
7: Ar = *p*-Br-C_6H_5 R = H
8: Ar = *m*-$CH_3OC_6H_5$ R = H
9: Ar = *m*-$CH_3C_6H_5$ R = H



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Scheme 2.

Table 2. Asymmetric hydrogenation of enamides catalyzed by rhodium–monophos[a]

Entry	Substrate	S/C (mol/mol)	Temperature (°C)	*t* (h)	Yield (%)	ee (%)[b]
1	**1**	100	−20	8	>99	95
2	**2**	100	−20	8	>99	92
3	**3**	100	−20	8	>99	90
4	**4**	100	−20	6	>99	96
5	**5**	50	rt	6	>99	55
6	**5**	50	−20	18	20	70
7	**6**	100	−20	18	25	89
8	**7**	100	−20	8	>99	96
9	**8**	100	−20	8	>99	96
10	**9**	100	−20	8	>99	93
11	**10**	100	−20	10	>99	84
12	**10**	100	rt	2	>99	57

[a] Hydrogen pressure was 300 psi in all reactions.
[b] The ee's were determined by chiral GC analysis using a Chrompack chiral fused silical 50 m×0.25 mm chirasil-L-VAL column.

low (entries 6–7), probably due to the steric hindrance effect of the substituents. The results demonstrated that by using this simple rhodium–monophos catalyst, α-aryl enamides can be easily hydrogenated to give the desired products in high ee's. Electron-withdrawing groups at the *para* position of the phenyl ring of the substrate enhanced the enantioselectivity (entry 4); while electron-donating groups gave a negative effect (entries 2–3). A naphthyl group on the substrate caused decreases in both the reaction rate and the enantioselectivity, probably due to its size (entry 5).

In conclusion, chiral monophos ligand (*S*)-2,2′-*O*,*O*′-(1,1′-binaphthyl)-*O*,*O*′-dioxo-*N*,*N*-dimethylphospholidine was found to be an effective ligand for the Rh-catalyzed asymmetric hydrogenation of enamides. The preparation of other effective monodentate ligands and their application in the asymmetric hydrogenation of enamides are in progress.

Acknowledgements

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21. A typical procedure for the hydrogenation of enamides: The catalyst was made in situ by mixing $[Rh(COD)_2]BF_4$ (2 mg) and monophos (4 mg) in a chosen solvent (1 mL). The mixture was stirred for 10 min. A small portion of the catalyst solution (0.2 mL) was transferred into a 50 mL stainless steel autoclave with a glass liner, which contained the enamide substrate and a magnetic stirring bar. H_2 gas was charged to the reactor at the required temperature and the solution was stirred for a predetermined period of time. After the reaction was complete, the hydrogen gas was released and the ee value of the product was measured directly using the reaction mixture without further purification.