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Highly Efficient Rhodium/Monodentate Phosphoramidite Catalyst and Its Application in the Enantioselective Hydrogenation of Enamides and α-Dehydroamino Acid Derivatives

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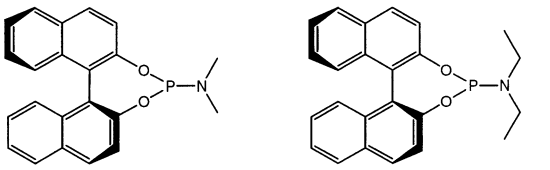
Abstract: An easily prepared and highly efficient monodentate phosphoramidite ligand derived from BINOL, (*S*)-2,2′-*O*,*O*-(1,1′-binaphthyl)-dioxo-*N*,*N*-diethylphospholidine, was examined in the hydrogenation of both enamides and α-dehydroamino acid derivatives. The catalyst provided remarkably high enantioselectivities (up to 99.6% ee for enamides and >99.9% ee for α-dehydroamino acid derivatives).

The enantioselective hydrogenation of prochiral olefins plays an important role in the application of homogeneous catalysts. Since the introduction of Kagan's DIOP ligand three decades ago,[1] most research work in this area has been focused on bidentate ligands,[2−5] which have been proved to be superior to monodentate ligands in most cases. An important breakthrough in the successful use of monodentate ligands was initiated by Pringle et al. in their use of monodentate phosphonites in asymmetric hydrogenation reaction.[6] Since then, the use of monodentate ligands has grown rapidly, especially in the area of enantioselective hydrogenation.[7−18] More recently, excellent results have been achieved by Feringa and co-workers using MonoPhos ligands.[9] From a practical standpoint, the development of easily prepared and highly efficient catalysts for asymmetric synthesis is an important challenge for organic chemists.

SCHEME 1



(*S*)-MonoPhos L*=(*S*)-2,2′-*O*,*O*- (1,1′-binaphthyl)-dioxo-*N*,*N*-diethylphospholidine

We have previously studied the use of MonoPhos ligand in the enantioselective hydrogenation of enamides and obtained up to 96% ee.[15] In this paper, we report a remarkably efficient Rh catalyst system containing a simple monodentate phosphoramidite ligand ((*S*)-2,2′-*O*,*O*-(1,1′-binaphthyl)-dioxo-*N*,*N*-diethylphospholidine) in the enantioselective hydrogenation of enamides and α-dehydroamino acid derivatives. On the basis of our previous study, we systematically optimized the structure of MonoPhos to study the relationship between the structures of the ligands and their related catalytic activities. A series of monodentate phosphoramidites were prepared, and their activities in the hydrogenation of enamides were examined. Interestingly, when a rhodium catalyst containing (*S*)-2,2′-*O*,*O*-(1,1′-binaphthyl)-dioxo-*N*,*N*-diethylphospholidine was used in the hydrogenation of substrate **1a** (Table 1, entry 1), a significant increase in the ee value of the product was obtained in comparison with the result from using MonoPhos.[15] When the reaction temperature was lowered to 5 °C, the ee value of the product was found to further increase to 99% (entry 2). When the catalyst was used in the hydrogenation of various enamides, most of the reactions gave extremely high ee values with full conversions (entries 2, 6, 7, and 9−12, 98−99.6% ee) except in the case of the hydrogenation of a highly hindered substrate (entry 13). The results also revealed that an electron-withdrawing group on the phenyl ring of the substrates enhanced the enatioselectivity, while an electron donor gave somewhat negative effects. The best ee value was obtained in the hydrogenation of *N*-α-*para*-trifluoromethyl-phenyl-acrylacetamide **1b** (entry 6, 99.6% ee).

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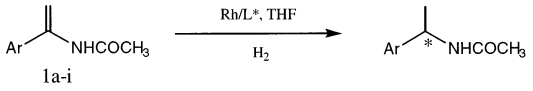
TABLE 1. Asymmetric Hydrogenation of Enamides Catalyzed by Rhodium−Monondentate Phosphoramidite Complex in THF[a]



entry	substrate	Ar	S/C [mol/mol]	*T* [°C]	*t* [h]	yield [%]	ee [%][b]
1	**1a**	C_6H_5	100	rt	4	>99	95 (87)
2	**1a**	C_6H_5	100	5	4	>99	99 (90)
3	**1a**	C_6H_5	200	5	8	>99	97
4	**1a**	C_6H_5	400	5	12	>99	96
5	**1b**	*p*-$F_3C-C_6H_5$	100	rt	4	>99	97 (89)
6	**1b**	*p*-$F_3C-C_6H_5$	100	5	4	>99	**99.6** (92)
7	**1c**	*p*-$Br-C_6H_5$	100	5	4	>99	99 (91)
8	**1d**	*p*-$CH_3O-C_6H_5$	100	rt	6	>99	93
9	**1e**	*p*-$CH_3O-C_6H_5$	100	5	6	>99	98
10	**1f**	*p*-$CH_3-C_6H_5$	100	5	6	>99	98
11	**1g**	*m*-$CH_3O-C_6H_5$	100	5	6	>99	98
12	**1h**	*m*-$CH_3-C_6H_5$	100	5	6	>99	98
13	**1i**	1-naphthyl	100	5	18	85	59

[a] Catalyst used in all reactions was prepared in situ. Hydrogen pressure was 300 psi in all reactions. [b] Ee values were determined by chiral GC analysis using a Chrompack chiral fused silical 50 m × 0.25 mm chirasil-L-VAL column. Numbers in parentheses were obtained by using MonoPhos under otherwise identical conditions. The (*R*)-configuration was assigned by comparing the experimental results with published data.

Further examination of this catalyst in the hydrogenation α-dehydroamino acid derivatives revealed that the catalyst was also excellent in this application (Table 2). Using **2a** as a model substrate in THF for the hydrogenation reaction at room temperature gave the desired product in 98% ee (entry 1). This result compared very favorably with MonoPhos (93% ee)[9] and H_8-MonoPhos (94% ee).[11] Expanding the scope of the catalyst system to 16 species of aromatic α-dehydroamino acid derivatives gave excellent results (>98% ee) in all cases, and 13 of the products were obtained in higher than 99% ee (entries 2−6 and 9−16). However, when the catalyst system was used with nonaromatic substrate, the ee dropped somewhat (entry 17). Essentially quantitative conversions were observed in most reactions.

To the best of our knowledge, this catalyst system is the best among rhodium/monodentate phosphoramidite systems for the enantioselective hydrogenation of enamides and α-dehydroamino acid derivatives. Its easy preparation and excellent performance makes it a good choice for practical applications.

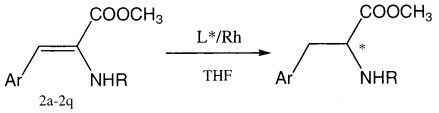
In conclusion, the rhodium catalyst containing monodentate phosphoramidite ligand (*S*)-2,2′-*O*,*O*- (1,1′-binaphthyl)-dioxo-*N*,*N*-diethylphospholidine has been established to be a highly efficient catalyst in the hydrogenation of enamides (up to 99.6% ee) and α-dehydroamino acid derivatives (up to >99.9% ee).

Experimental Section

General and Materials. All manipulations were carried out under a dry nitrogen atmosphere using standard Schlenk techniques or in a nitrogen atmosphere glovebox unless otherwise stated. Tetrahydrofuran (THF) was distilled from sodium benzophenone prior to use.

(*S*)-2,2′-*O*,*O*-(1,1′-Binaphthyl)-dioxo-*N*,*N*-diethylphospholidine. Phosphorus chloride (PCl_3, 0.3 mL) and triethylamine (Et_3N, 0.6 mL) were transferred with a syringe into a 100 mL round-bottomed flask containing BINOL (1 g, 3.5 mmol) in toluene (30 mL) at 0 °C under a nitrogen atmosphere. After the mixture was stirred for 6 h, the volatile materials were removed under reduced pressure. A solution of diethylamine (0.4 mL, 3.9 mmol) and triethylamine (0.6 mL) in toluene (30 mL) was added to the flask, and the mixture was stirred overnight. The resulting mixture was purified through an Al_2O_3 column. The solution was evaporated in vacuo to afford a white solid product (1.2 g, 86%). ^{1}H NMR (500 Hz, $CDCl_3$) δ: 1.03−1.06(t, J = 7.5 Hz, 6H), 2.35−3.01 (m, 2H), 3.02−3.08 (m, 2H), 7.22−7.51 (m, 8H), 7.88−7.96 (m, 4H). ^{13}C NMR (125 Hz, $CDCl_3$) δ: 14.93, 38.42, 122.22, 122.77, 124.27, 124.69, 124.95, 126.19, 127.20, 128.52, 130.08, 130.47, 130.92, 131.61, 132.89, 133.10, 149.93, 150.35, 150.39. ^{31}P NMR (200 Hz) δ: 150.3. HRMS calcd for $C_{24}H_{22}NO_2P$, 387.139; found, 387.139. The data were in agreement with those reported in the literature.[19]

TABLE 2. Enantioselective Hydrogenation of α-Dehydroamino Acid Derivatives by Rh−Monodentate Phosphoramidite/THF Catalyst[a]



entry	substrates	Ar	R	S/C [mol/mol]	*T* [h]	ee [%]
1	**2a**	Ph	Ac	100	4	98.0 (93.0)[c]
2	**2b**	*p*-F−Ph	Ac	100	4	**99.8**
3	**2c**	*p*-NO_2−Ph	Ac	100	4	**99.7** (96.0)
4	**2d**	*p*-Br−Ph	Ac	100	4	99.1
5	**2e**	*p*-Cl−Ph	Ac	100	4	99.1 (97.6)
6	**2f**	*o*-Cl−Ph	Ac	100	4	99.1 (92.1)
7	**2g**	*m*-Cl−Ph	Ac	100	4	98.6
8	**2h**	*p*-CH_3−Ph	Ac	100	4	98.1
9	**2i**	*p*-CH_3O−Ph	Ac	100	4	99.0 (94.0)
10	**2j**	*p*-AcO−Ph	Ac	100	4	99.4
11	**2k**	*p*-Br−Ph	PhCO	100	4	**99.7**
12[b]	**2l**	*p*-F−Ph	PhCO	100	4	>**99.9**
13	**2m**	*p*-Cl−Ph	PhCO	100	4	99.2
14	**2n**	*p*-CH_3−Ph	PhCO	100	4	99.0
15[b]	**2o**	*p*-CH_3O−Ph	PhCO	100	4	**99.7**
16	**2p**	*m*-Cl−Ph	PhCO	100	4	99.4
17	**2q**	H	Ac	100	4	96.5 (99.0)[c]
18	**2a**	Ph	Ac	200	8	97.7
19	**2a**	Ph	Ac	400	12	97.4

[a] Catalyst was prepared in situ. Hydrogen pressure was 300 psi in all reactions, and all reactions were performed at room temperature. Ee values were determined by chiral GC analysis using a Chrompack chiral fused silical 25m × 0.25 mm i.d. Coating CHIRASIL-L-VAL column unless otherwise noted. Numbers in parentheses were obtained by using MonoPhos under otherwise identical conditions. All products were assigned the (*R*)-configuration by comparison with data reported in the literature. [b] Ee values were determined by chiral HPLC analysis using a Chiralpak AD column. [c] See ref 9.

Typical Procedure for the Hydrogenation of Enamides. The catalyst was made in situ by mixing $[Rh(COD)_2]BF_4$ (2.0 mg) and (*S*)-2,2′-*O*,*O*-(1,1′-binaphthyl)-dioxo-*N*,*N*-diethylphospholidine (5.4 mg) in THF (1 mL) for 10 min. A small portion of the catalyst solution (0.2 mL) was transferred into a 50 mL stainless steel autoclave equipped with a glass liner, which contained an enamide substrate or a dehydroamino acid derivative (0.5 mmol) and a magnetic stirring bar. The reactor was charged with hydrogen gas, and the solution was stirred at the required temperature 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.

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Supporting Information Available: GC and HPLC analysis for the products of enantioselective hydrogenation. This material is available free of charge via the Internet at http://pubs.acs.org.

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