Asymmetric Catalysis

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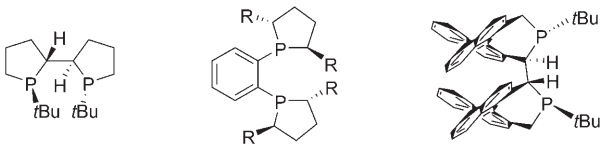
Rh-Catalyzed Asymmetric Hydrogenation of α-Aryl Imino Esters: An Efficient Enantioselective Synthesis of Aryl Glycine Derivatives**

*Gao Shang, Qin Yang, and Xumu Zhang**

Enantiomerically pure α-amino acids and their derivatives are of great importance in pharmaceutical, biological and synthetic chemistry. An interesting class of these compounds are the chiral aryl glycines, which are important building blocks for many bioactive molecules such as amoxicillins,[1] nocardicins,[2] cephalecins,[3] and glycopeptide antibiotics.[4] A number of methods have been applied to synthesize these intermediates,[5] such as the Sharpless asymmetric aminohydroxylation,[5b] the catalytic enantioselective amination of enolate intermediates,[5c] and the asymmetric Strecker reaction.[5d,e] However, achieving regioselectivity has been a challenge in the asymmetric aminohydroxylation reaction, and in the enantioselective amination of enolates, high catalyst loading has been used with only moderate success. These problems prompted us to seek for an alternative approach to synthesize chiral aryl glycines. Herein, we report a highly enantioselective synthesis of a series of chiral aryl glycine derivatives by using the asymmetric hydrogenation of α-aryl imino esters with a Rh–tangphos catalyst (tangphos = 1,1′-di-*tert*-butyl-(2,2′)-diphospholane, see Scheme 1).



A: (*S,S,R,R*)-tangphos **B**: R = Et, (*R,R*)-Et-duphos **C**: R = Me, (*R,R*)-Me-duphos **D**: (*S*)-binapine

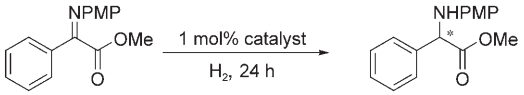
Scheme 1. Chiral ligands for asymmetric hydrogenation.

Asymmetric hydrogenation catalyzed by transition metals has been shown to be highly efficient in many syntheses.[6] A large number of α-alkyl amino acids and their derivatives have been prepared with high enantioselectivity from the asymmetric hydrogenation of α-dehydroamino acids or esters.[6] However, aryl glycines lacking the β-hydrogen atom cannot be synthesized in an analogous manner by hydrogenation of alkenes. Nevertheless, asymmetric hydrogenation of the C=N double bond in the corresponding α-imino acids or esters could be an alternative way to synthesize chiral aryl glycines. In fact, reduction of a C=N bond is the key step of transaminase in some biological transformations. Despite the great potential of this transformation, there have been very few reports of both good enantioselectivities and yields, because the imine substrates are difficult to prepare and also because the substrates show relatively poor reactivity toward hydrogenation.[7] Recently, Kadyrov et al. reported the synthesis of chiral α-*N*-benzylamino acids resulting from the reductive amination of keto acids, but the method proved less successful for aryl glycines.[7c] Amii and co-workers have also reported the asymmetric hydrogenation of α-fluorinated imino esters, but this method is successful for only a limited range of substrates.[7d]

We started our investigation using PMP-protected α-aryl imino esters **1** (Table 1) as the substrates, since they could be synthesized in one step and in high yield from the corresponding α-keto esters,[8] and the resulting products could be deprotected under mild conditions using cerium ammonium nitrate (CAN).[9] Moreover, the PMP-protected α-aryl imino esters are notably more stable than their corresponding imines. Key to achieving high enantioselectivity and turnover rates in the reduction of α-aryl imino esters is to find an effective catalyst. We initially examined the hydrogenation of **1a** using the Rh–tangphos catalyst, which was developed within our research group. Its electron-rich character and rigid, well-defined geometry offers both high activity and enantioselectivity in the asymmetric hydrogenation of a wide range of substrates.[6d,10]

Several commercially available chiral ligands were also screened for the hydrogenation of **1a** (Scheme 1). We achieved up to 93% *ee* with the Rh–tangphos catalyst,

Table 1: Asymmetric hydrogenation of α-imino ester **1a**.



1a **2a**

Entry	Catalyst[a]	H_2 pressure [atm]	*T* [°C]	Solvent	Conv. [%][b]	*ee* [%][c]
1	**E**	30	25	CH_2Cl_2	>95	93
2	**F**	30	25	CH_2Cl_2	>95	83
3	**G**	30	25	CH_2Cl_2	29	75
4	**H**	30	25	CH_2Cl_2	70	85
5	**E**	50	25	CH_2Cl_2	>95	93
6	**E**	70	25	CH_2Cl_2	>95	93
7	**E**	50	50	CH_2Cl_2	>99	95
8	**E**	50	80	CH_2Cl_2	>99	91

[a] **E**: Rh[(*S,S,R,R*)-tangphos](cod)]BF_4; **F**: [Rh{(*S*)-binapine}(cod)]BF_4; **G**: [Rh{(*R,R*)-Me-duphos}(cod)]BF_4; **H**: [Rh{(*R,R*)-Et-duphos}(cod)]BF_4. [b] % Conversions were determined by ^1H NMR spectroscopy. [c] *ee* values were determined by chiral HPLC. PMP = *para*-methoxyphenyl, cod = cycloocta-1,5-diene.

[*] G. Shang, Q. Yang, Prof. X. Zhang
Department of Chemistry
The Pennsylvania State University
104 Chemistry Building, University Park, PA 16802 (USA)
Fax: (+1) 814-863-8403
E-mail: xumu@chem.psu.edu

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(Table 1, entry 1), while 83% *ee* was obtained with the Rh–binapine catalyst (Table 1, entry 2). Hydrogenation with Me-duphos and Et-duphos offered moderate conversions and *ee* values (29% and 75% *ee* for **F**; 70% and 85% *ee* for **G**; Table 1, entries 3 and 4).

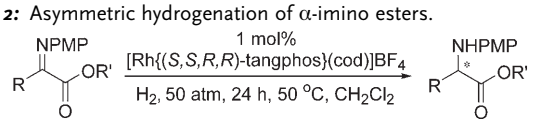
The effects of hydrogen pressure and reaction temperature on the hydrogenation were also studied. An increase in pressure from 30 to 70 atm had no apparent effect on the conversion or enantioselectivity of this transformation (Table 1, entries 1, 5, and 6). However, increasing the reaction temperature from 25 °C to 50 °C resulted in a slightly higher enantioselectivity (Table 1, entry 7), but the *ee* value dropped to 91% at 80 °C (Table 1, entry 8). An investigation into the effects of the solvent was also carried out. Common solvents such as THF, methanol, toluene, and acetone gave either poor conversion or low *ee* values. Only dichloromethane and trifluoroethanol resulted in both high conversion and enantioselectivity.

We examined the scope of the reaction using different α-imino esters under the optimized reaction conditions (Table 1, entry 7). Thus, we synthesized a number of α-imino esters **1a**–**1o** with various substituents on the aromatic ring or the ester group.[8] Asymmetric hydrogenation was performed using the [Rh{(*S*,*S*,*R*,*R*)-tangphos}(cod)]BF_4 complex as the catalyst precursor. Good conversions were observed for all substrates, with *ee* values ranging from 90% to 95%. Notably, 99% ee was achieved after one recrystallization when using **2a**. The electronic properties of the substituents had no apparent effect on the yields or the enantioselectivities. The presence of the sterically hindered naphthyl group resulted in slightly lower enantioselectivity (90% and 91% *ee*; Table 2, entries 11 and 12). A lower *ee* value was also observed with **1n** bearing an ethyl group at the R′ position (84% *ee*; Table 2, entry 14). To explore the efficiency of the catalyst for α-alkyl imino esters, **1o** was synthesized and hydrogenated under the optimized conditions. We were pleased to find that a high *ee* value was observed (94% *ee*; Table 2, entry 15).

To determine the potential of the asymmetric hydrogenation of α-aryl imino esters catalyzed by Rh–tangphos as a practical means to synthesize chiral α-aryl amino acid derivatives the hydrogenation of **1a** was carried out using a low catalyst loading (substrate/catalyst 1000:1) and a gram of the substrate (1.08 g, 4 mmol). Using catalyst made in situ and CH_2Cl_2 as the solvent, α-aryl amino ester **2a** was obtained in 82% yield (turnover number (TON) >820) and with 91% *ee*.[11] Moreover, the PMP group of **2a** could be easily removed by CAN in 86% yield, without affecting the *ee* value.[9]

In conclusion, a series of chiral aryl glycines were synthesized in high enantioselectivity in the first Rh-catalyzed asymmetric hydrogenation of the corresponding α-aryl imino esters using the tangphos ligand. This method is potentially useful for the preparation of a variety of chiral aryl glycines with high *ee* values and yields. However, the synthesis of the imine substrates and the relatively high catalytic loadings are limitations of this work. Further studies to improve the results and to expand the range of substrates that can be used will be reported in due course.

Table 2: Asymmetric hydrogenation of α-imino esters.



1a–o **2a–o**

Entry	R	R′	Product	Conv. [%][a]	*ee* [%][b]	Config.[c]
1	C_6H_5 (**1a**)	CH_3	**2a**	>99(99)	95(99)	*S*(−)
2	2-FC_6H_4 (**1b**)	CH_3	**2b**	>99	91	(−)
3	3-FC_6H_4 (**1c**)	CH_3	**2c**	>95	94	(−)
4	4-FC_6H_4 (**1d**)	CH_3	**2d**	>95	93	(−)
5	4-ClC_6H_5 (**1e**)	CH_3	**2e**	>99	92	(−)
6	4-BrC_6H_5 (**1f**)	CH_3	**2f**	>95	92	(−)
7	2-$CH_3OC_6H_4$ (**1g**)	CH_3	**2g**	>95	95	(−)
8	3-$CH_3OC_6H_4$ (**1h**)	CH_3	**2h**	>99	93	(−)
9	4-$CH_3OC_6H_5$ (**1i**)	CH_3	**2i**	>95	93	(−)
10	4-$CH_3C_6H_5$ (**1j**)	CH_3	**2j**	>99	93	(−)
11	*2*-naphthyl (**1k**)	CH_3	**2k**	>99	90	(−)
12	1-naphthyl (**1l**)	CH_3	**2l**	>95	91	(−)
13	3-nitro (**1m**)	CH_3	**2m**	>99	93	(−)
14	C_6H_5 (**1n**)	C_2H_5	**2n**	>95	84	(−)
15	cyclohexyl (**1o**)	CH_3	**2o**	84	94	(+)

[a] % Conversions were determined by ^{1}H NMR spectroscopy and the values in parentheses correspond to the yield of the isolated product. [b] *ee* values were determined by chiral HPLC and the value in parentheses corresponds to the *ee* value after one recrystallization. [c] Absolute configuration was determined by comparison of the sign of the optical rotation of the deprotected product (phenylglycine methyl ester) with (*S*)-phenylglycine methyl ester.

Experimental Section

General procedure for asymmetric hydrogenation of α-imino esters: $[Rh(cod)_2]BF_4$ (40.6 mg, 0.1 mmol) and (*S*,*S*,*R*,*R*)-tangphos (28.6 mg, 0.1 mmol) were dissolved in degassed dichloromethane (2 mL) in a Schlenk tube under N_2. After stirring the solution at room temperature for 1 h, degassed hexanes (10 mL) was added to precipitate the catalyst, which was filtered under nitrogen to give [Rh{(*S*,*S*,*R*,*R*)-tangphos}(cod)]BF_4 as an orange solid. The complex (52.0 mg, 88.9% yield) was stored in a nitrogen-filled glovebox until required. The complex (11.7 mg, 0.02 mmol) was dissolved in degassed dichloromethane (10 mL) in a glovebox and divided equally among 10 vials. To each of the vials was added **1** (0.2 mmol, substrate/catalyst 100:1) and the resulting mixture was transferred to an autoclave, which was then charged with H_2 (50 atm). The hydrogenation was performed at 50 °C for 24 h. After carefully releasing the hydrogen gas, the solvent was removed under reduced pressure. The crude product was purified through a plug of silica gel (eluting with a mixture of Hex/EtOAc, 10:1) to afford the aryl glycine **2**. The enantiomeric excess was determined by HPLC on a chiral stationary phase.

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[11] See supporting information for more results and experimental details.

