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Catalytic asymmetric hydrogenation of 1-aza-2-cycloalkene-2-carboxylates catalyzed by a *trans*-chelating chiral diphosphine PhTRAP–rhodium complex

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Abstract

A rhodium complex coordinated with a *trans*-chelating chiral diphosphine (*S,S*)-(*R,R*)-PhTRAP was an effective catalyst for asymmetric hydrogenation of *N*-acyl-1-aza-2-cycloalkene-2-carboxylates, which gave the corresponding protected cyclic α-amino acids with 73–97% ee.

Keywords: asymmetric reactions; rhodium; hydrogenation; amino acid derivaties.

Not only L-proline but also various optically active cyclic α-amino acids are important as biologically active compounds and peptide mimetics.[1] However, unlike optically active acyclic α-amino acids, which are most conveniently prepared by catalytic asymmetric hydrogenation of the corresponding α,β-dehydro α-amino acids,[2,3] catalytic asymmetric synthesis of cyclic α-amino acids has been limited.[4–6]

Recently, we reported that chiral rhodium complexes coordinated with *trans*-chelating peralkyldiphosphines, 2,2′′-bis[1-(dialkylphosphino)ethyl]-1,1′′-biferrocenes (**1**,† Fig. 1)[7,8] were effective for asymmetric hydrogenation of 1,4,5,6-tetrahydropyrazine-2-carboxamides.[9] Of particular interest is that the highly enantioselective hydrogenation of *N,N′*-protected 1,4,5,6-tetrahydropyrazine-2-carboxamides was catalyzed by the (*R,R*)-(*S,S*)-*i*-BuTRAP as well as (*R,R*)-(*S,S*)-MeTRAP–rhodium complex, affording the corresponding piperazine-2-carboxamides, however, with opposite absolute configuration, respectively. The results prompted us to examine asymmetric hydrogenation of 1-aza-2-cycloalkene-2-carboxylates by use of the *trans*-chelating chiral diphosphines **1**.

Initial attempts at asymmetric hydrogenation of 1,4,5,6-tetrahydropyridine-2-carboxylate **2a**‡ in the presence of rhodium(I) coordinated with alkylTRAP (**1a–c**) have not been successful, e.g., MeTRAP (**1a**)–rhodium complex did not promote the hydrogenation reaction at all (Table 1, entry 1), and use

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† Abbreviated to: TRAP=*trans*-chelating chiral diphosphine.

‡ *N*-Acyl-1-aza-2-cyclohexene-2-carboxylates **2** and **4–7** were prepared by similar procedure reported by Nicolaou et al.[4a]

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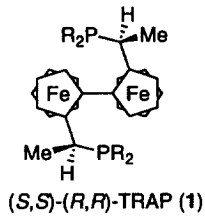
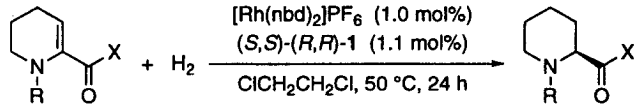


(*S*,*S*)-(*R*,*R*)-TRAP (**1**)

1a: R = Me (MeTRAP)
1b: R = Et (EtTRAP)
1c: R = *i*-Bu (*i*-BuTRAP)
1d: R = Ph (PhTRAP)
1e: R = *p*-$MeOC_6H_4$
1f: R = *p*-ClC_6H_4
1g: R = 2-Furyl

Figure 1. Structure of TRAP ligands

of EtTRAP (**1b**) and *i*-BuTRAP (**1c**) provided isobutyl (*R*)-*N*-acetylpipecolinate (**3a**), but with low enantiomeric excesses (entries 2 and 3). To our surprise, a TRAP ligand with aromatic *P*-substituents (PhTRAP, **1d**), which was not effective for asymmetric hydrogenation of 1,4,5,6-tetrahydropyrazine-2-carboxamides (27% conversion for 24 h with 2 mol% catalyst, 43% ee (*R*)),[9] gave **3a** of 90% ee with *S*-configuration in quantitative yield (entry 4).[§ ¶] Electron-donating and -withdrawing substituents on the phenyl rings of **1d** did not affect the enantioselectivity (entries 5 and 6), but TRAP ligand **1g** bearing furan substituents on the phosphorus significantly decreased the selectivity (entry 7).



2 **3**

2a: R = Boc, X = O(*i*-Bu)
2b: R = Boc, X = OMe
2c: R = Boc, X = NH(*t*-Bu)
2d: R = Cbz, X = O(*i*-Bu)
2e: R = Bz, X = O(*i*-Bu)

Dependency of the enantioselectivity upon the solvent employed is remarkable. 1,2-Dichloroethane gave the best result for the asymmetric hydrogenation. The reactions in THF and EtOH gave (*S*)-**3a** with 64% and 74% ee, respectively. However, use of *i*-PrOH produced a comparable result to that of 1,2-dichloroethane (94% conversion for 24 h, 89% ee). Higher hydrogen pressure diminished not only the enantioselectivity but also the catalytic activity of PhTRAP–rhodium catalyst (100 kg/cm^2: 62% conversion for 24 h, 59% ee).

Ester group of **2** did not influence enantioselectivity significantly (entries 4 and 8). Even *N*-*tert*-butyl amide **2c** gave the corresponding pipecolinamide (*S*)-**3c** with 93% ee (entry 9). On the other hand, the *N*-protection on **2** is much important, e.g., the reaction of *N*-benzoyl **2e** yielded (*S*)-**3e** with lower enantiomeric excess, suggesting that the effect of the *N*-protective group on the stereoselectivity would be greater than that of the 2-carbonyl group (entry 11).

§ Typical procedure for the catalytic asymmetric hydrogenation of 1-aza-2-cycloalkene-2-carboxylates **2** and **4**–**7** was as follows: A solution of $[Rh(nbd)_2]PF_6$ (2.2 mg, 5.0 μmol) and (*S*,*S*)-(*R*,*R*)-PhTRAP (**1d**) (4.4 mg, 5.5 μmol) in 1,2-dichloroethane (1.0 ml) was stirred at room temperature under argon atmosphere for 10 min. The solution was transferred by a cannula to an argon-filled glass vessel, in which **2** or **4**–**7** (0.5 mmol) was placed beforehand. Immediately, the vessel was cooled at −78°C and repeatedly evacuated and filled with hydrogen. The reaction mixture was stirred at 50°C for 24 h. After the solvent was evaporated, the residue was purified by flash column chromatography on silica gel to give **3** or **8**–**11**.

¶ Specific rotations of protected cyclic α-amino acids obtained here are as follows: (*S*)-**3a** (90% ee); $[\alpha]_D^{20}$=−46.5 (*c* 0.99, $CHCl_3$). (*S*)-**3b** (85% ee); $[\alpha]_D^{20}$=−48.1 (*c* 1.11, $CHCl_3$). (*S*)-**3c** (93% ee); $[\alpha]_D^{20}$=−108.5 (*c* 1.02, $CHCl_3$). (*S*)-**3d** (92% ee); $[\alpha]_D^{20}$=−48.8 (*c* 1.13, $CHCl_3$). (*S*)-**3e** (73% ee); $[\alpha]_D^{20}$=−51.1 (*c* 1.44, $CHCl_3$). (*S*)-**8a** (87% ee); $[\alpha]_D^{20}$=−20.4 (*c* 1.02, $CHCl_3$). (*S*)-**8b** (83% ee); $[\alpha]_D^{20}$=−109.2 (*c* 0.57, $CHCl_3$). (*S*)-**10** (97% ee); $[\alpha]_D^{20}$=−14.5 (*c* 1.15, $CHCl_3$). (*S*)-**11** (73% ee); $[\alpha]_D^{20}$=−78.8 (*c* 0.97, $CHCl_3$).

Table 1
Asymmetric hydrogenation of **2** with TRAP (**1**)–rhodium catalyst[a]

entry	2	TRAP (1)[b]	product (3)	convn, %[c]	ee, %	config[d]
1	**2a**	**1a**		0		
2	**2a**	**1b**	**3a**	63	29[e]	*R*
3	**2a**	**1c**	**3a**	100	50[e]	*R*
4	**2a**	**1d**	**3a**	100	90[e]	*S*
5	**2a**	**1e**	**3a**	100	89[e]	*S*
6	**2a**	**1f**	**3a**	98	89[e]	*S*
7	**2a**	**1g**	**3a**	100	35[e]	*S*
8	**2b**	**1d**	**3b**	100	85[f]	*S*
9	**2c**	**1d**	**3c**	100	93[g]	*S*
10	**2d**	**1d**	**3d**	100	92[g]	*S*
11	**2e**	**1d**	**3e**	100	73[h]	*S*

[a] All reactions were carried out at 50 °C in 1,2-dichloroethane under 1 kg/cm^2 of hydrogen for 24 h. The ratio of **2**/[Rh(nbd)$_2$]PF$_6$/**1** was 100/1.0/1.1. [b] (*S*,*S*)-(*R*,*R*)-**1** was used. [c] Determined by ^{1}H NMR analysis of crude product. [d] Assigned by comparison with the retention time of authentic (*S*)-**3** in HPLC analysis. [e] Determined by chiral HPLC analysis with CHIRALCEL OD-H. [f] Determined by chiral HPLC analysis with CHIRALCEL OB-H. [g] Determined by chiral HPLC analysis with CHIRALPAK AD. [h] Determined by chiral HPLC analysis with CHIRALCEL OA.

Based upon the enantioselective hydrogenation of **2** described above, substrates **4**–**7** were subjected to asymmetric hydrogenation catalyzed by the PhTRAP–rhodium complex (Table 2). The asymmetric hydrogenation of the seven-membered ring substrate **4a** proceeded well, giving (*S*)-**8a** with 87% ee (entry 1). It is notable that the *N*-protective group significantly influenced enantiomeric excesses of **8** more than the substituent on the 2-acyl carbon (entries 1–3). Dehydroproline **5** and bicyclic enamide **6** also underwent the hydrogenation with high enantioselectivity in the presence of **1d**–rhodium catalyst (entries 4 and 5). Especially, the hydrogenation of **6** afforded an α-amino acid derivative (*S*)-**10** with 97% ee, which is useful as a building block for HIV protease inhibitors[10] or a novel class of antifungal agents.[11] However, 4-*tert*-butoxycarbonyl-2,3-dehydromorpholine-3-carboxamide **7** gave morpholinecarboxamide **11** in moderate enantioselectivity (entry 6).[‖]

In conclusion, we succeeded in highly enantioselective hydrogenation of 1-aza-2-cycloalkene-2-carboxylates by a rhodium complex with *trans*-chelating chiral diphosphine PhTRAP (**1d**). The present asymmetric hydrogenation may provide a general and useful method for preparation of optically active cyclic α-amino acids. Further studies to improve the catalyst efficiency and the applicability are now in progress.

Acknowledgements

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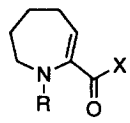
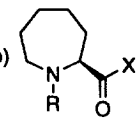
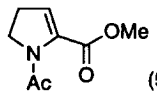
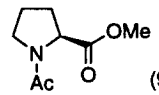
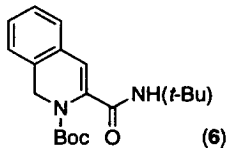
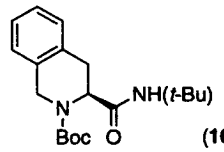
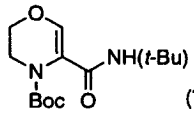
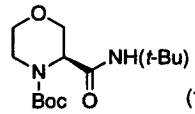
[‖] EtTRAP (**1b**) as well as PhTRAP (**1d**) induced a comparable enantioselectivity (71% ee) in the asymmetric hydrogenation of **7**, but with the opposite absolute configuration. Ligand **1a** and **1c**, which were effective for 1,4,5,6-tetrahydropyrazine-2-carboxamides (see Kuwano et al.[9]), gave (*R*)-**11** with 29% and 52% ee, respectively.

Table 2
Asymmetric hydrogenation of **4–7** with (*S,S*)-(*R,R*)-PhTRAP (**1d**)–rhodium catalyst[a]

entry	substrate	product	convn, %[b]	ee, %	confign
1	 R = Boc, X = O(*i*-Bu) (**4a**)	 R = Boc, X = O(*i*-Bu) (**8a**)	86	87[c]	–[d]
2	R = Boc, X = NH(*t*-Bu) (**4b**)	R = Boc, X = NH(*t*-Bu) (**8b**)	100	83[e]	–[f]
3	R = Cbz, X = O(*i*-Bu) (**4c**)	R = Cbz, X = O(*i*-Bu) (**8c**)	100	11[c]	–
4[g]	 (**5**)	 (**9**)	96	86[h]	*S*[i]
5	 (**6**)	 (**10**)	100	97[e]	*S*[i]
6	 (**7**)	 (**11**)	100	73[e]	–[f]

[a] All reactions were carried out at 50 °C in 1,2-dichloroethane under 1 kg/cm^2 of hydrogen for 24 h unless otherwise noted. The ratio of substrate/[Rh(nbd)$_2$]PF$_6$/**1d** was 100/1.0/1.1. [b] Determined by ^{1}H NMR analysis of crude product. [c] Determined by chiral HPLC analysis with CHIRALCEL OD-H. [d] The order of retention time of the major and minor enantiomers in the HPLC analysis was the same as those of **3a**. [e] Determined by chiral HPLC analysis with CHIRALPAK AD. [f] The order of retention time of the major and minor enantiomers in the HPLC analysis was the same as those of **3c** and **10**. [g] The reaction was carried out at 60 °C. [h] Determined by chiral GLC analysis with Chiraldex G-TA. [i] Assigned by comparison with the retention time of authentic (*S*)-**9** or (*S*)-**10** in HPLC analysis.

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