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Use of amino amides derived from proline as chiral ligands in the ruthenium(II)-catalyzed transfer hydrogenation reaction of ketones

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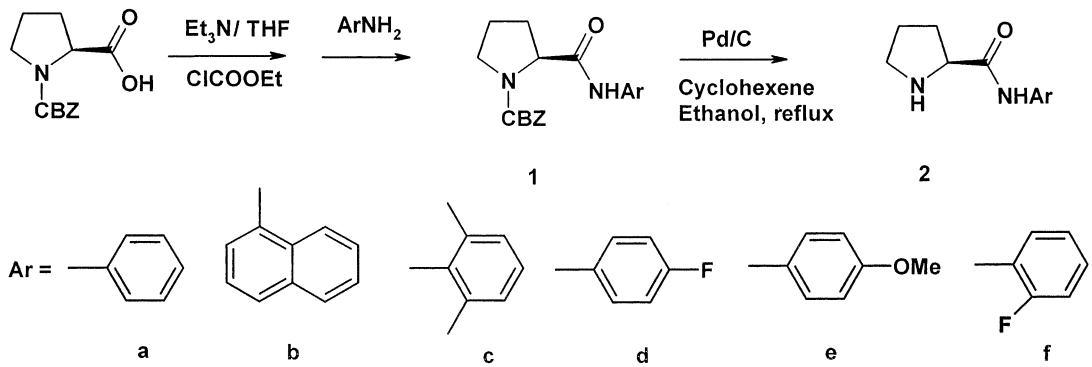
Abstract—We developed an efficient, easily available, and easy to use proline amide-based ruthenium(II) catalysts for the asymmetric hydride transfer reduction of prochiral ketones and e.e.s up to 98.8% have been measured.

The catalytic enantioselective reduction of ketones has been extensively studied during the last decade.[1] In view of the low cost of the reducing agent and operational simplicity, the transition-metal-catalyzed transfer hydrogenation reaction using *iso*-propanol (^{i}PrOH) or a HCO_2H/Et_3N mixture as a hydride source[2] appears to be an attractive supplement to catalytic hydrogenation with H_2. In particular, a ruthenium catalyst bearing a chiral ligand such as *N*-tosylated diphenylethylenediamine (DPEN-Ts, Noyori's ligand) has been well studied.[3] Recently, the use of amino acids[4] or their derivatives[5] as ligands in the ruthenium(II)-catalyzed enantioselective transfer hydrogenation of prochiral aromatic ketones has attracted attention because of their easy accessibility. However, when amino acids or their derivatives are used as chiral ligands, only ^{i}PrOH can be used as a hydrogen source. A HCO_2H/Et_3N mixture cannot be used as a hydride source. This limits the use of amino acids or their derivatives as chiral ligands and especially when imines are reduced, the use of HCO_2H/Et_3N mixture is a prerequisite for obtaining good results.[6] It seems that for catalytic systems bearing amino amides a HCO_2H/Et_3N mixture can be used as a hydride source. Another feature of catalytic systems bearing amino amide is their fine tuning capacity afforded by changing the functional group on the amide. Surprisingly, there have been no reports on the use of amino amides as chiral ligands in the asymmetric hydrogen transfer reaction.

Herein, we report efficient, easily obtainable, and easy to use proline amide-based ruthenium(II) catalysts for the asymmetric hydride transfer reduction of prochiral ketones.



Scheme 1. Synthesis of proline amide derivatives.

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Chiral proline amides were synthesized by Scheme 1. Treatment of *N*-carbobenzyloxy-L-proline with triethyl amine and ethyl chloroformate followed by aryl amine and subsequent deprotection by Pd/C and cyclohexene afforded proline amides.[7,†] The overall yields were 41–91%. We have screened ruthenium metal complexes using acetophenone and chiral ligand **2a** as the standard substrate and ligand, respectively (Table 1).[†]

The conversion and enantioselectivity were highly dependent upon the ruthenium complex, especially arene. The best conversion rate and enantioselectivity (92% and 78% e.e.) were obtained when cymene was used as an arene. The chiral Ru complexes were prepared *in situ* by heating a mixture of ruthenium complex ($[Ru(cymene)Cl_2]_2$) and a chiral ligand (1 equiv. versus Ru) in dichloromethane. Attempts to characterize the catalyst precursor were unsuccessful. We assumed that it would be a similar form as the Noyori's catalyst. Catalytic reactions were carried out by adding the substrate and a mixture of $HCOOH/Et_3N$ to the catalyst solution and allowed to react for the predetermined reaction time. The solution was quenched with excess water and diethyl ether or ethyl acetate. GC analysis of a sample aliquot then determined the conversion rate and enantioselectivity.

Next, we investigated the effect of solvent, the ratio of chiral ligand to metal ($[Ru(cymene)Cl_2]_2$), and the ratio of $HCOOH/Et_3N$ on the enantioselectivities and conversion yields. Dichloromethane, DMF, and acetonitrile were good solvents. However, dichloromethane was the solvent of choice owing to its easy purification and low boiling point. The enantioselectivities and conversion yields were rather insensitive to the ratio of chiral ligand to metal. Thus, a 1:1 ratio of ligand to metal was used for all the experiments. The best result was obtained when the ratio of $HCOOH/Et_3N$ was 5:2. We have also examined the hydrogen transfer reaction of other aromatic ketones (Fig. 1) with various chiral ligands (Table 2).

Table 1. Asymmetric reduction of acetophenone with various Ru(II) complexes[a]

Entry	Metal sources	Conv. (%)[b]	e.e. (%)[b]
1	$[RuCl_2(benzene)]_2$	49	3.7
2	$[RuCl_2(p\text{-cym})]_2$	92	78
3	$[RuCl_2(Me_6C_6)]_2$	33	54
4	$RuCl_2(PPh_3)_3$	0	

[a] Acetophenone 1 mmol, S/C = 50, $HCOOH/Et_3N$ (5/2) azeotrope (distilled, 0.5 ml), and CH_2Cl_2 (0.5 ml) at 30°C for 6 h. Absolute configuration (*R*) was determined by the sign of optical rotation.
[b] Conv. (%) and e.e. (%) were determined by chiral GC using a Chrompak Chirasil-Dex CB column.

For the transfer hydrogenation reaction of acetophenone **3a**, the conversion yields and enantioselectivities were highly dependent upon the chiral ligand **2**. When **2c** was used as a chiral ligand, no reaction was observed. Chiral ligand **2b** is not effective. Comparing the activities and enantioselectivities of **2d–f**, **2f** which is more electronegative and less sterically hindered, gave the best results. Thus, the reaction was highly dependent upon the steric bulkiness of alkyl group and electronegativities of aromatic groups in the amino amide ligand. However, the most active and selective ligand is **2a**, which has no substituents on the phenyl ring. When (1*S*,2*S*)-DPEN-Ts was used as a ligand to compare with ligand **2a**, it showed a much higher enantioselectivity than **2a**. For the hydrogenation transfer reaction of **3b–d**, the enantioselectivities decreased as the steric bulkiness increased. For the hydrogen transfer reaction of **4a**, conversion rates and enantioselectivities were obtained independently of the chiral ligand. When the S/C ratio was doubled, the reaction time for complete conversion was also twice as long without the loss of the e.e. value. For the transfer hydrogenation reaction of **3c**, the highest enantioselectivity (98.8%) was obtained when the chiral ligand **2a** was used. Chiral ligands **2d** and **2f** were also quite effective. For the hydrogen transfer reaction of **4c**, a poor conversion rate was observed and the enantioselectivities were ca. 89%. For the hydrogen transfer reaction of **4d**, the yield was quantitative and quite high enantioselectivities (94.8%) were obtained. In this case, the conversion rate and enantioselectivities were rather insensitive to chiral ligands. However, when (1*S*,2*S*)-DPEN-Ts was used as a ligand, quite low conversion (30.3%) and poor enantioselectivity (72.1%) were obtained. Thus, the proline amides can be used as a complement to the Noyori's ligand for the hydrogen transfer reaction of the *ortho*-substituted aromatic

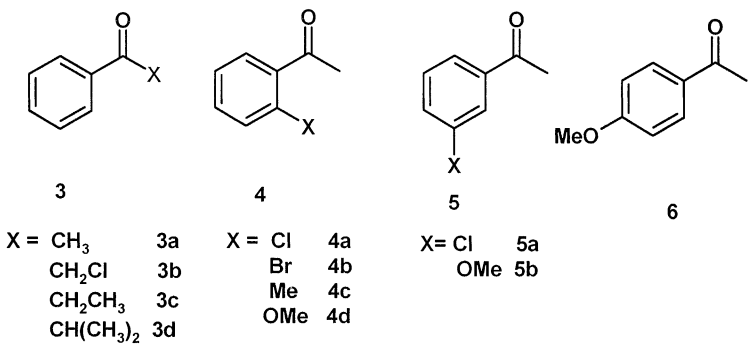

Figure 1. Prochiral aromatic acetophenone derivatives.

[†] See the Supporting Information.

Table 2. Asymmetric transfer hydrogenation of aromatic ketones[a]

Entry	Ligand	Substrate	Time (h)	Conv. (%)	E.e. (%)
1	**2a**	**3a**	7	96.5	79
2	**2b**	**3a**	15	29	50.8
3	**2c**	**3a**	24	0	
4	**2d**	**3a**	7	82	74.6
5	**2e**	**3a**	6	57	74.2
6	**2f**	**3a**	7	76	74.1
7[b]	(1*S*,2*S*)-DPEN-Ts	**3a**	7	90.5	96.2
8	**2a**	**3b**	7	93.4	69.8
9	**2a**	**3c**	6	100	70.8
10	**2a**	**3d**	7	11.6	33.9
11	**2a**	**4a**	6	99.4	90.9
12	**2d**	**4a**	6	100	90.2
13[c]	**2d**	**4a**	12	99.5	90
14	**2f**	**4a**	6	95	91.6
15	**2a**	**4b**	6	75	98.8
16	**2d**	**4b**	6	84	98.3
17	**2f**	**4b**	9	97	96.8
18	**2a**	**4c**	6	20	88.8
19	**2f**	**4c**	6	13	89
20	**2a**	**4d**	6	98.4	94.8
21	**2d**	**4d**	6	100	94.6
22	**2f**	**4d**	6	96.3	94.8
23[b]	(1*S*,2*S*)-DPEN-Ts	**4d**	6	30.3	72.1
24	**2a**	**5a**	7	99.3	74.6
25	**2a**	**5b**	7	89	74
26	**2a**	**6**	24	92	77.3

[a] Absolute configuration (*R*) was determined by the sign of optical rotation or retetion time of GC peak. The same reaction condition as in Table 1 was used. Conv. (%) and e.e. (%) were determined by GC using a Chrompak Chirasil-Dex CB 25 m×0.32 μm column. Conv. (%) and e.e. (%) of **4a** and **4b** were determined by GC using a Ultra2 50 m×0.32 μm column.
[b] The starting material of ligand was 98% e.e. and configuration was *R*.
[c] 1 mol% catalyst was used.

ketones. The order of enantioselectivities for acetophenone derivatives is **4b**>**4d**>**4a**>**4c**. For the hydrogenation transfer reaction of **5** and **6**, high yields were obtained for all the reactions, but the enantioselectivities were rather poor.

This work shows that proline amides are good ligands for the asymmetric hydride transfer reduction of prochiral ketones since e.e.s up to 98.8% have been measured. So, we have developed efficient, easily obtainable, and easy to use catalyst. The next challenge is recovery of the catalyst through the development of a heterogeneous version. This is currently under investigation.

Supporting information

A typical procedure for synthesis of 1

Synthesis of 1a: *N*-Carbobenzyloxy-L-proline (2.0 g, 8.0 mmol) and TEA (0.81 g, 8.0 mmol) were dissolved in 30 ml of THF. The solution was cooled to 0°C. To the solution was added dropwise ethylchloroformate (0.88 g, 8.0 mmol) for 15 min. After the solution was stirred for 30 min, aniline (8.0 mmol) was added for 15 min. The resulting solution was stirred at 0°C for 1 h and at rt for 16 h, and heated at reflux for 3 h. After the solution was cooled to rt, the solution was washed with ethyl acetate, filtered off any solids, evaporated to dryness, and chromatographed on a silica gel column eluting with hexane and ethyl acetate (v/v, 2:1). Removal of the solvent gave **1a** (2.40 g, 92.5%).

A typical procedure for synthesis of 2

Synthesis of 2a: Compounds **1a** (2.0 g), 5% Pd/C (0.1 g), cyclohexene (1.0 ml), and ethanol (30 ml) were put in a 100 ml Schlenk flask. The solution was heated at reflux until no reactant (**1**) was remained in the solution. The solution was cooled to rt, washed with ethanol, filtered on Celite to remove any solids, and evaporated to dryness. The residue was chromatographed on a silica gel column or recrystallized in *n*-hexane/CH_2Cl_2 to obtain pure **2a**. Compounds **2a–c** were known compounds.[8]

Compound **2d**: mp 66–67°C; $[\alpha]_D^{21} = -70$ (*c* 0.1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 9.74 (s, CONH), 7.55–7.59 (m, 2 H), 6.98–7.05 (m, 2 H), 3.86 (dd, 9.26, 5.16 Hz, 1 H), 2.96–3.11 (m, 2 H), 2.03–2.22 (m, 2 H), 1.74–1.79 (m, 2 H), 1.73–1.78 (br, NH) ppm; IR (KBr) *v*CO 1668 (s) cm^{-1}. Anal. calcd for $C_{11}H_{13}FN_2O$: C, 63.45; H, 6.29; N, 13.45. Found: C, 63.09; H, 6.32; N, 13.43.

Compound **2e**: mp 81–82°C; $[\alpha]_D^{17} = -63$ (*c* 0.1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 9.54 (s, NH), 7.44 (d, 12.24 Hz, 2 H), 6.78 (d, 12.26 Hz, 2 H), 3.78 (dd, 9.18, 5.23 Hz, 1

H), 3.72 (s, OCH_3), 2.87–3.05 (m, 2 H), 1.91–2.18 (m, 2 H), 1.83 (s, NH), 1.65–1.73 (m, 2 H) ppm; IR (KBr) νCO 1662 (s) cm^{-1}. Anal. calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.35; H, 7.40; N, 12.82.

Compound **2f**: mp 48°C; $[\alpha]_D^{17} = -54$ (c 0.1, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 10.08 (s, CONH), 8.40 (t, 10.23 Hz, 1 H), 7.03–7.12 (m, 3 H), 3.90 (dd, 9.24, 5.07 Hz, 1 H), 3.01–3.11 (m, 2 H), 2.05–2.22 (m, 2 H), 1.80–2.05 (br, NH), 1.24–1.80 (m, 2 H) ppm; IR (KBr) νCO 1672 (s) cm^{-1}. Anal. calcd for $C_{11}H_{13}FN_2O$: C, 63.45; H, 6.29; N, 13.45. Found: C, 63.24; H, 6.40; N, 13.51.

A typical procedure for catalytic reactions

Ruthenium metal complex (2 mol% [Ru]), chiral ligand (2 mol%), and solvent were dissolved in a 20 ml Schlenk flask. The solution was stirred for 30 min and allowed to warm to the temperature at which a catalytic reaction would be carried out. At the temperature, substrate (1 mmol) was added to the solution. Subsequently, a mixture of $HCOOH/Et_3N$ was added and allowed to react for the predetermined reaction time. The solution was quenched with excess water and diethyl ether or ethyl acetate. GC analysis of a sample aliquot then determined the conversion rate and enantioselectivity.

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