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Rhodium-catalyzed asymmetric hydrogenation of β-acetylamino acrylonitriles

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ABSTRACT

The rhodium-catalyzed asymmetric hydrogenation of β-acetylamino acrylonitriles was investigated by using monophosphine and bisphosphine ligands. It was found that an Rh-QuinoxP* complex exhibited high enantioselectivities for β-aryl substituted β-acetylamino acrylonitriles and the Rh-JosiPhos CyPF-*t*-Bu complex was proven to be effective for the hydrogenation of tetrasubstituted olefins from cyclic β-acetylamino acrylonitriles.

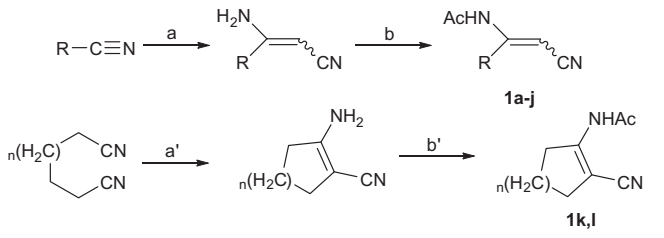
1. Introduction

Enantiopure β-amino nitriles are widely used as key intermediates or important building blocks in pharmaceuticals, for example, in the synthesis of alkylnitrile quinoline and isoindoline compounds.[1] Moreover, β-amino nitrile constitutes a versatile synthon that is readily transformed into β-amino carboxylic acids and 1,3-diamines, which are also valuable structural motifs for the synthesis of biologically active products.[2] Due to their significance in chemical synthesis, much effort has been devoted to the pursuit of practical asymmetric routes to produce chiral β-amino nitriles.[3]

Recently, we have reported a highly efficient Rh-TangPhos complex catalyst for the asymmetric hydrogenation of acyclic β-acetylamino acrylonitriles.[4] Although very good results have been achieved for these substrates, TangPhos is extremely sensitive to air and this drawback has prevented its widespread application in asymmetric catalysis. Furthermore, this catalyzed system provides very low conversion and enantioselectivity for the tetrasubstituted olefin of 2-acety1amino-1-cyclopentene-1-carbonitrile whose asymmetric hydrogenation is generally difficult and remains an unexplored area. These results suggested that new efficient catalysts were necessary for the development of the highly enantioselective hydrogenation of β-acetylamino acrylonitriles to give chiral β-acetylamino nitriles. We found that the enantioselectivities which were achieved in the hydrogenation of β-aryl substituted β-acetylamino acrylonitriles with a Rh-QuinoxP* complex were comparable to those with the Rh-TangPhos complex. However, this catalyzed system was also unsuccessfully applied to the asymmetric hydrogenation of 2-acety1amino-1-cyclopentene-1-carbonitrile. In further studies, Rh-JosiPhos CyPF-*t*-Bu was finally proven to be an effective catalyst for tetrasubstituted olefins of cyclic β-acetylamino acrylonitriles with good enantioselectivities, up to 83% ee being achieved. It is notable that both QuinoxP* and JosiPhos CyPF-*t*-Bu ligands are air-stable.

2. Results and discussion

The substrates for the asymmetric hydrogenation could be readily prepared in two steps via intermolecular dimerization of nitriles and intramolecular cyclization of dinitriles in the presence of potassium *tert*-butoxide[5] and then amino protection with acetic anhydride (Scheme 1).[6] We initially focused on the rhodium-catalyzed asymmetric hydrogenation of 3-acetylamino-3-phenyl acrylonitrile **1a** as a model substrate with a series of chiral ligands (Table 1). Hydrogenation proceeded smoothly with QuinoxP* and gave **2a** with 93% ee (entry 7) when the reactions were performed at 40 °C under 100 atm of hydrogen pressure in MeOH. Other types of ligand showed lower enantioselectivities or conversions (entries 1–6). Further studies indicated that changing the solvent (entries 8–12) led to poor results. The effect of the reaction hydrogen



Scheme 1. Synthesis of β-acetylamino acrylonitriles. Reagents and conditions: (a) CH_3CN, *t*-BuOK, toluene, ultrasound 4 h; (b) Ac_2O, Et_3N, toluene, reflux overnight; (a′) *t*-BuOK, overnight; (b′) Ac_2O, pyridine, reflux overnight; $n = 1, 2$.

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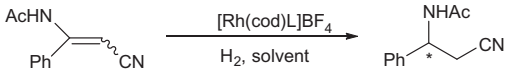
Table 1
Rhodium-catalyzed asymmetric hydrogenation of **1a** under various conditions[a]



1a **2a**

Entry	Ligand	Solvent	P_{H_2} (atm)	T (°C)	Conv.[b] (%)	ee[c] (%)
1	(*R*)-MonoPhos	MeOH	100	40	31	8
2	(*R*)-Mop	MeOH	100	40	0	/
3	(*R*)-SegPhos	MeOH	100	40	63	1
4	(*R,S*)-JosiPhos CyPF-*t*-Bu	MeOH	100	40	85	1
5	(S_c,R_p)-DuanPhos	MeOH	100	40	100	90
6	(*R,R*)-Et-DuPhos	MeOH	100	40	95	80
7	(*R,R*)-QuinoxP*	MeOH	100	40	100	93
8	(*R,R*)-QuinoxP*	THF	100	40	5	7
9	(*R,R*)-QuinoxP*	Toluene	100	40	9	8
10	(*R,R*)-QuinoxP*	Dioxane	100	40	5	35
11	(*R,R*)-QuinoxP*	CH_2Cl_2	100	40	6	75
12	(*R,R*)-QuinoxP*	CF_3CH_2OH	100	40	94	84
13	(*R,R*)-QuinoxP*	MeOH	50	40	90	93
14	(*R,R*)-QuinoxP*	MeOH	100	25	0	/

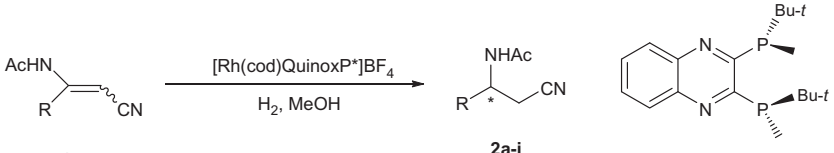
[a] All reactions were carried out with a substrate/catalyst ratio of 100:1, for 24 h.
[b] Determined by GC methods.
[c] The ee value of **2a** was determined by chiral phase GC.

pressure and temperature was also examined, however, we found that both the conversion and enantioselectivity decreased at a lower hydrogen pressure (entry 13), and that the reaction did not proceed at room temperature (entry 14).

Under the optimized reaction conditions, a variety of β-aryl substituted β-acetylamino acrylonitriles **1** were examined using an Rh-QuinoxP* catalyst system (Table 2). We studied the effect of the electronic properties of the substituents on the phenyl ring of the substrates with regard to the enantiomeric excess of the products. All substrates, except for **1f**, bearing electron-donating or electron-withdrawing substituents on the phenyl ring were smoothly hydrogenated to the corresponding products with good enantioselectivities (entries 2–6). Both the thiophen-2-yl and 2-naphthyl substrates afforded products in 92% and 84% ee values, respectively (entries 9 and 10). Compared with our previous studies, Rh-QuinoxP* catalyst is slightly sensitive to the ratios of *E/Z* isomers, and we found that substrates **1d–f, 1j** with lower ratios of *E/Z* isomers, which were hydrogenated by QuinoxP*, exhibited lower enantioselectivities than those hydrogenated by TangPhos.[4]

Since Rh-TangPhos and Rh-QuinoxP* catalysts have been proved to be very successful for the hydrogenation of β-aryl substituted β-acetylamino acrylonitriles, cyclic β-acetylamino acrylonitrile **1k** with **a** tetrasubstituted olefin was hydrogenated by both catalysts at 40 °C under 100 atm hydrogen pressure for 24 h (Table 3, entries 1 and 2). However, very poor enantioselectivities and conversions were achieved using either the TangPhos or QuinoxP* ligand. We thus turned our attention to other types of ligands. One particular ligand, JosiPhos CyPF-*t*-Bu, could make the

Table 2
Rhodium-catalyzed asymmetric hydrogenation of **1a–j** under the optimized reaction conditions[a]

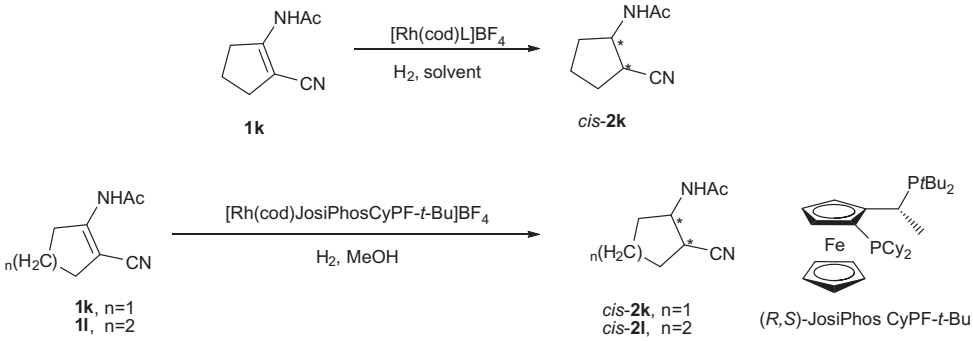


1a-j **2a-j** (*R,R*)-QuinoxP*

Entry	Substrate	*E:Z* [b]	R	Product	ee[c] (%) (config.) [d]
1	**1a**	2.3:1	C_6H_5	**2a**	93 (—)
2	**1b**	>99:1	*p*-MeC_6H_4	**2b**	89 (—)
3	**1c**	>99:1	*p*-$MeOC_6H_4$	**2c**	89 (—)
4	**1d**	2.2:1	*p*-ClC_6H_4	**2d**	82 (—)
5	**1e**	50:1	*p*-FC_6H_4	**2e**	84 (—)
6	**1f**	0.8:1	*p*-$CF_3C_6H_4$	**2f**	77 (—)
7	**1g**	>99:1	*m*-MeC_6H_4	**2g**	90 (—)
8	**1h**	>99:1	*m*-ClC_6H_4	**2h**	90 (—)
9	**1i**	>99:1	Thiophen-2-yl	**2i**	92 (—)
10	**1j**	50:1	2-Naphthyl	**2j**	84 (—)

[a] All reactions were carried out with a substrate/catalyst ratio of 100:1 in MeOH at 40 °C under 100 atm hydrogen pressure for 24 h, 100% conversion.
[b] Determined by ^{1}H NMR.
[c] The ee value was determined by GC or HPLC on a chiral phase.
[d] Sign of the specific rotation.

Table 3
Rhodium-catalyzed asymmetric hydrogenation of cyclic β-acety1amino acrylonitriles **1k–l**[a]



Entry	Ligand	Substrate	Solvent	P_{H_2} (atm)	T (°C)	Product	Conv.[b] (%)	ee[c] (%)
1	(*S*,*S*,*R*,*R*)-TangPhos	**1k**	MeOH	100	40	**2k**	73	26
2	(*R*,*R*)-QuinoxP*	**1k**	MeOH	100	40	**2k**	27	6
3	(*R*)-MonoPhos	**1k**	MeOH	100	40	**2k**	12	3
4	(*R*)-Mop	**1k**	MeOH	100	40	**2k**	5	6
5	(*R*)-SegPhos	**1k**	MeOH	100	40	**2k**	19	1
6	(*R*,*S*)-Josiphos CyPF-*t*-Bu	**1k**	MeOH	100	40	**2k**	100	62
7	(*R*,*S*)-JosiPhos	**1k**	MeOH	100	40	**2k**	92	24
8	(*R*,*R*)-Et-DuPhos	**1k**	MeOH	100	40	**2k**	81	49
9	(S_p,R_c)-DuanPhos	**1k**	MeOH	100	40	**2k**	50	44
10	(*S*)-PhanePhos	**1k**	MeOH	100	40	**2k**	57	16
11	(*R*,*S*)-JosiPhos CyPF-*t*-Bu	**1k**	THF	100	40	**2k**	49	0
12	(*R*,*S*)-JosiPhos CyPF-*t*-Bu	**1k**	Toluene	100	40	**2k**	13	3
13	(*R*,*S*)-JosiPhos CyPF-*t*-Bu	**1k**	Dioxane	100	40	**2k**	2	8
14	(*R*,*S*)-JosiPhos CyPF-*t*-Bu	**1k**	CH_2Cl_2	100	40	**2k**	2	51
15	(*R*,*S*)-Josiphos CyPF-*t*-Bu	**1k**	CF_3CH_2OH	100	40	**2k**	100	46
16	(*R*,*S*)-JosiPhos CyPF-*t*-Bu	**1k**	MeOH	100	25	**2k**	100	64
17	(*R*,*S*)-JosiPhos CyPF-*t*-Bu	**1k**	MeOH	70	25	**2k**	100	64
18	(*R*,*S*)-JosiPhos CyPF-*t*-Bu	**1k**	MeOH	50	25	**2k**	100	60
19	(*R*,*S*)-JosiPhos CyPF-*t*-Bu	**1l**	MeOH	70	25	**2m**	100	83

[a] All reactions were carried out with a substrate/catalyst ratio of 100:1, for 24 h.
[b] Determined by GC methods.
[c] The ee value was determined by chiral phase GC.

substrate completely convert to the desired product with moderate enantioselectivity (62% ee, entry 6). Further solvent screening (entries 11–14) revealed that the use of other solvents led to lower enantioselectivities and conversions. Although CF_3CH_2OH also gave complete conversion, the enantioselectivity decreased dramatically (entry 15). Subsequently, we investigated the effect of reaction temperature on the hydrogenation; it was found that the hydrogenation reaction proceeded completely and a slightly higher ee value was observed when the reaction temperature was decreased from 40 °C to 25 °C (64% ee; entry 16). Finally, when decreasing the hydrogen pressure to 70 atm (entry 17), we found no evident effect on the enantioselectivity. Decreasing the hydrogen pressure further caused a minor decrease in the ee value (entry 18).

The optimized reaction conditions were applied to the 6-membered analogue, 2-acety1amino-1-cyclohexene-1-carbonitrile **1l**. The substrate was found to give 83% ee (Table 3, entry 19), indicating that the hydrogenation was much better than that of **1k**.

3. Conclusion

We have studied Rh-catalyst systems with different ligands for the asymmetric hydrogenation of β-acety1amino acrylonitriles. The experimental results indicate that QuinoxP* exhibits high activities and enantioselectivities to β-aryl substituted β-acety1amino acrylonitriles, and JosiPhos CyPF-*t*-Bu was firstly proved to be effective for the hydrogenation of tetrasubstituted olefins of cyclic β-acety1amino acrylonitriles. Our future work will focus on investigating asymmetric hydrogenation of other olefins bearing an amine functionality to produce chiral amines which are useful synthetic intermediates for pharmaceutical products.

4. Experimental

4.1. General

Unless otherwise noted, all reagents and solvents were purchased from commercial suppliers and used without further purification. NMR spectra were recorded with a Varian spectrometer at 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR) in acetone-d_6 or $CDCl_3$. Chemical shifts are reported in ppm downfield from internal Me_4Si. Optical rotations were determined using a Perkin Elmer 341 MC polarimeter. HRMS were recorded on a quadrupole–hexapole–quadrupole (QHQ) mass spectrometer. GC analyses were performed using Hewlett Packard Model HP 7890 Series. HPLC analyses were conducted on an Agilent 1200 Series instrument. Column Chromatography was performed with silica gel Merck 60 (230–400 mesh).

4.2. General procedures for the synthesis of β-enaminonitriles

4.2.1. Acyclic-β-enaminonitriles

To a solution of aromatic nitrile (50 mmol) and acetonitrile (2.05 g, 50 mmol) in toluene (150 mL), powdered *t*-BuOK

(15.68 g, 140 mmol) was added. Then the mixture was ultrasounded with 35 kHz frequency at room temperature for 4 h. After completion, the reaction mixture was poured into water, extracted with diethyl ether, dried (anhydrous Na_2SO_4), and concentrated in vacuo to afford the crude product. Recrystallization of a series of the crude products from toluene gave acyclic-β-enaminonitriles in 75–92% yields.

4.2.2. Cyclic-β-enaminonitriles

A mixture of adiponitrile (5.40 g, 50 mmol) and powdered *t*-BuOK (6.72 g, 60 mmol) was kept at room temperature overnight. The crystalline solid that was formed by the addition of water to the reaction mixture was filtered off and recrystallized from MeOH to give 2-amino-1-cyclopentene-1-carbonitrile (4.26 g, 79%).

A mixture of pimelonitrile (6.10 g, 50 mmol) and powdered *t*-BuOK (6.72 g, 60 mmol) was kept at 80 °C for 3 h and then at room temperature overnight. Water was added to the reaction mixture and the product extracted with ether. The solvent was evaporated and the residual solid was recrystallized from MeOH to give 2-amino-1-cyclohexene-1-carbonitrile (5.23 g, 80%).

4.3. General procedures for the synthesis of compounds 1a–l

4.3.1. Compounds 1a–j

To a solution of acyclic-β-enaminonitriles (30 mmol) in toluene (180 mL), Ac_2O (15.30 g, 150 mmol) was added, after which Et_3N (6.06 g, 60 mmol) was dropped into the solution under stirring. The reaction mixture was then heated to reflux and stirred for 24 h. The reaction mixture was cooled to room temperature, washed with saturated sodium carbonate, water, and then dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Finally, the product mixture was purified by column chromatography using a mixture of hexane and ethyl acetate as eluent.

4.3.2. Compounds 1k and 1l

To a solution of cyclic-β-enaminonitriles (30 mmol) in dry pyridine (18 mL), Ac_2O (6.12 g, 60 mmol) was added. The reaction mixture was heated at reflux for 16 h and cooled to room temperature. It was then poured into a mixture of ice (about 50 g) and 60 mL of 6 molar hydrochloric acid and extracted with chloroform. After being washed with water, the extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Finally, the product mixture was purified by column chromatography using the mixture of hexane and ethyl acetate as eluent.

4.3.3. NMR and HRMS data of compounds 1a–l

4.3.3.1. 3-Acetylamino-3-phenyl acrylonitrile 1a. Yield: 55%, *E*/*Z* = 2.3:1. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46–7.42 (m, 5H, Ar-H), 7.02 (br, 1H, NH), 6.61 [s, 1H, =CH (*E*)], 5.22 [s, 1H, =CH(*Z*)], 2.06 (s, 3H, CH_3).

4.3.3.2. 3-Acetylamino-3-(*p*-methylphenyl)acrylonitrile 1b. Yield: 33%, *E*/*Z* >99:1. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.31 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.07 (br, 1H, NH), 6.72 (s, 1H, =CH), 2.43 (s, 3H, CH_3), 2.20 (s, 3H, CH_3).

4.3.3.3. 3-Acetylamino-3-(*p*-methoxyphenyl)acrylonitrile 1c. Yield: 26%, *E*/*Z* >99:1. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.07 (br, 1H, NH), 6.90 (d, *J* = 8.0 Hz, 2H, Ar-H), 6.55 (s, 1H, =CH), 3.78 (s, 3H, CH_3), 2.09 (s, 3H, CH_3).

4.3.3.4. 3-Acetylamino-3-(*p*-chlorophenyl)acrylonitrile 1d. Yield: 84%, *E*/*Z* = 2.2:1. ^{1}H NMR (acetone-d_6, 400 MHz) δ 9.20 (br, 1H, NH), 7.48 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.40 (d, *J* = 8.0 Hz, 2H, Ar-H), 6.57 [s, 1H, =CH (*E*)], 5.49 [s, 1H, =CH (*Z*)], 2.03 (s, 3H, CH_3).

4.3.3.5. 3-Acetylamino-3-(*p*-fluorophenyl)acrylonitrile 1e. Yield: 72%, *E*/*Z* = 50:1. ^{1}H NMR (acetone-d_6, 400 MHz) δ 9.17 (br, 1H, NH), 7.54–7.49 (m, 2H, Ar-H), 7.16–7.11 (m, 2H, Ar-H), 6.57 [s, 1H, =CH (*E*)], 5.49 [s, 1H, =CH (*Z*)], 2.04 (s, 3H, CH_3).

4.3.3.6. 3-Acetylamino-3-(*p*-trifluoromethylphenyl)acrylonitrile 1f. Yield: 26.8%, *E*/*Z* = 0.8:1. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.71–7.69 [m, 1.5H, Ar-H(*E*)], 7.60 [s, 2H, Ar-H(*Z*)], 7.58 [s, 2H, Ar-H(*Z*)], 7.45–7.43 [m, 1.9H, Ar-H(*E*)], 7.01 (br, 1H, NH), 6.74 [s, 1H, =CH(*E*)], 4.99 [s, 1H, =CH(*Z*)], 2.15 [s, 3H, CH_3 (*Z*)], 2.13 [s, 3H, CH_3 (*E*)].

4.3.3.7. 3-Acetylamino-3-(*m*-methylphenyl)acrylonitrile 1g. Yield: 31%, *E*/*Z* >99:1. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29–7.19 (m, 4H, Ar-H), 7.04 (br, 1H, NH), 6.63 (s, 1H, =CH), 2.34 (s, 3H, CH_3), 2.10 (s, 3H, CH_3).

4.3.3.8. 3-Acetylamino-3-(*m*-chlorophenyl)acrylonitrile 1h. Yield: 55%, *E*/*Z* >99:1. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.53–7.50 (m, 1H, Ar-H), 7.49–7.48 (m, 1H, Ar-H), 7.46–7.45 (m, 2H, Ar-H), 7.20 (br, 1H, NH), 6.76 (s, 1H, =CH), 2.20 (s, 3H, CH_3).

4.3.3.9. 3-Acetylamino-3-(thiophen-2-yl)acrylonitrile 1i. Yield: 24%, *E*/*Z* >99:1. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.54–7.52 (m, 1H, Ar-H), 7.44–7.43 (m, 1H, Ar-H), 7.08–7.06 (m, 2H, Ar-H), 6.60 (s, 1H, =CH), 2.13 (s, 3H, CH_3).

4.3.3.10. 3-Acetylamino-3-(2-naphthyl)acrylonitrile 1j. Yield: 35%, *E*/*Z* = 50:1. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04 (s, 1H, Ar-H), 7.98–7.96 (m, 1H, Ar-H), 7.94–7.90 (m, 2H, Ar-H), 7.62–7.61 (m, 1H, Ar-H), 7.60–7.57 (m, 2H, Ar-H), 7.27 (br, 1H, NH), 6.82 [s, 1H, =CH(*E*)], 5.23 [s, 1H, =CH(*Z*)], 2.22 (s, 3H, CH_3).

4.3.3.11. 2-Acety1amino-1-cyclopentene-1-carbonitrile 1k. Yield: 52%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (br, 1H, NH), 3.16–3.11 (m, 2H, CH_2), 2.55–2.51 (m, 2H, CH_2), 2.15 (s, 3H, CH_3), 2.05–1.97 (m, 2H, CH_2).

4.3.3.12. 2-Acety1amino-1-cyclohexene-1-carbonitrile 1l. Yield: 78%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32 (br, 1H, NH), 2.78–2.75 (m, 2H, CH_2), 2.22–2.20 (m, 2H, CH_2), 2.05 (s, 3H, CH_3), 1.63–1.55 (m, 4H, $2 \times CH_2$); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.16, 151.81, 118.01, 90.52, 27.66, 25.45, 24.70, 21.41, 20.98; MS (ESI): 165 (M^++1); HRMS Calcd for $C_9H_{13}N_2O$ 165.1028; Found 165.1023.

4.4. General procedures for the asymmetric hydrogenation of compounds 1a–l

4.4.1. Asymmetric hydrogenation of compounds 1a–j

A stock solution of $[Rh(COD)_2]BF_4$ (COD = cycloocta-1,5-diene) and QuinoxP* at a 1:1.1 molar ratio was stirred in MeOH at room temperature for 10 min in a nitrogen-filled glovebox. The required amount of catalyst solution (0.1 mL, 0.001 mmol) was then transferred by syringe into the vials charged with different substrates (0.1 mmol for each) in MeOH (2.9 mL). All of the vials were placed together in a steel autoclave into which hydrogen gas was charged. After the solution was stirred at 40 °C under 100 atm hydrogen pressure for 24 h, the hydrogen was released slowly. The solution was concentrated, and then the crude product was eluted by EtOAc through a plug of silica gel to remove the metal complex. The purified product mixture was analyzed by chiral GC or HPLC to determine the ee value.

4.4.2. Asymmetric hydrogenation of compounds 1k and 1l

A stock solution of $[Rh(COD)_2]BF_4$ and JosiPhos CyPF-*t*-Bu at a 1:1.1 molar ratio was stirred in MeOH at room temperature for 10 min in a nitrogen-filled glovebox. The required amount of catalyst solution (0.1 mL, 0.001 mmol) was then transferred by syringe

into the vials charged with different substrates (0.1 mmol for each) in MeOH (2.9 mL). All of the vials were placed together in a steel autoclave into which hydrogen gas was charged. After the solution was stirred at 25 °C under 70 atm hydrogen pressure for 24 h, hydrogen was released slowly, the solution was concentrated, and then the crude product was eluted by EtOAc through a plug of silica gel to remove the metal complex. The purified product mixture was analyzed by chiral GC to determine the ee value.

4.4.3. The NMR, specific rotation and HRMS data of compound 2

4.4.3.1. 3-Acetylamino-3-phenyl propionitrile 2a. $[\alpha]_D^{20} = -78.2$ (c 1.0, CH_2Cl_2), 93% ee. Enantiomeric excess was determined by GC, Supelco Gama Dex™ 225 column (30 m × 0.25 mm × 0.25 μm), He 1.0 mL/min, programmed from 130 °C to 180 °C at 2.0 °C/min, hold 40 min at 180 °C; t_R = 39.8 min (minor), t_R = 43.8 min (major). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36–7.34 (m, 1H, Ar-H), 7.33–7.31 (m, 3H, Ar-H), 7.30–7.28 (m, 1H, Ar-H), 6.13–6.11 (br, 1H, NH), 5.20–5.15 (m, 1H, CH), 2.98 (dd, J = 6.4 Hz, 16.8 Hz, 1H, CH), 2.82 (dd, J = 4.4 Hz, 16.8 Hz, 1H, CH), 1.97 (s, 3H, CH_3).

4.4.3.2. 3-Acetylamino-3-(*p*-methylphenyl)propionitrile 2b. $[\alpha]_D^{20} = -49.0$ (c 1.0, CH_2Cl_2), 89% ee. Enantiomeric excess was determined by GC, Supelco Gama Dex™ 225 column (30 m × 0.25 mm × 0.25 μm), He 1.0 mL/min, programmed from 130 °C to 180 °C at 2.0 °C/min, hold 40 min at 180 °C; t_R = 45.9 min (minor), t_R = 49.6 min (major). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.18 (d, J = 8.0 Hz, 2H, Ar-H), 7.13 (d, J = 8.0 Hz, 2H, Ar-H), 6.25–6.23 (br, 1H, NH), 5.14–5.09 (m, 1H, CH), 2.94 (dd, J = 6.4 Hz, 16.8 Hz, 1H, CH), 2.79 (dd, J = 4.8 Hz, 16.8 Hz, 1H, CH), 2.28 (s, 3H, CH_3), 1.94 (s, 3H, CH_3).

4.4.3.3. 3-Acetylamino-3-(*p*-methoxyphenyl)propionitrile 2c. $[\alpha]_D^{20} = -66.6$ (c 1.0, CH_2Cl_2), 89% ee. Enantiomeric excess was determined by GC, Supelco Gama Dex™ 225 column (30 m × 0.25 mm × 0.25 μm), He 1.0 mL/min, programmed from 130 °C to 180 °C at 2.0 °C/min, hold 100 min at 180 °C; t_R = 81.9 min (minor), t_R = 89.5 min (major). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24 (d, J = 8.8 Hz, 2H, Ar-H), 6.86 (d, J = 8.8 Hz, 2H, Ar-H), 5.94–5.93 (br, 1H, NH), 5.13–5.08 (m, 1H, CH), 3.75 (s, 3H, OCH_3), 2.97 (dd, J = 6.8 Hz, 16.4 Hz, 1H, CH), 2.82 (dd, J = 4.4 Hz, 16.8 Hz, 1H, CH), 1.97 (s, 3H, CH_3).

4.4.3.4. 3-Acetylamino-3-(*p*-chlorophenyl)propionitrile 2d. $[\alpha]_D^{20} = -55.8$ (c 1.0, CH_2Cl_2), 82% ee. Enantiomeric excess was determined by HPLC, Chiralpak AD column, n-hexane/2-propanol = 90:10, 1.0 mL/min, 222 nm UV detector, t_R = 10.2 min (minor), t_R = 14.3 min (major). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30 (d, J = 8.2 Hz, 2H, Ar-H), 7.24 (d, J = 8.4 Hz, 2H, Ar-H), 6.40–6.38 (br, 1H, NH), 5.20–5.15 (m, 1H, CH), 2.93 (dd, J = 6.4 Hz, 16.8 Hz, 1H, CH), 2.79 (dd, J = 5.2 Hz, 16.8 Hz, 1H, CH), 1.96 (s, 3H, CH_3).

4.4.3.5. 3-Acetylamino-3-(*p*-fluorophenyl)propionitrile 2e. $[\alpha]_D^{20} = -43.1$ (c 1.0, CH_2Cl_2), 84% ee. Enantiomeric excess was determined by HPLC, Chiralpak AD column, n-hexane/2-propanol = 90:10, 1.0 mL/min, 254 nm UV detector, t_R = 9.9 min (minor), t_R = 13.8 min (major). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32–7.29 (m, 2H, Ar-H), 7.06–7.02 (m, 2H, Ar-H), 5.92–5.90 (br, 1H, NH), 5.20–5.15 (m, 1H, CH), 3.99 (dd, J = 6.8 Hz, 16.8 Hz, 1H, CH), 2.83 (dd, J = 4.4 Hz, 16.8 Hz, 1H, CH), 1.99 (s, 3H, CH_3).

4.4.3.6. 3-Acetylamino-3-(*p*-trifluoromethylphenyl)propionitrile 2f. $[\alpha]_D^{20} = -33.9$ (c 1.0, CH_2Cl_2), 77% ee. Enantiomeric excess was determined by HPLC, Chiralpak AD column, n-hexane/2-propanol = 90:10, 1.0 mL/min, 222 nm UV detector, t_R = 9.2 min (minor), t_R = 13.6 min (major). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.58 (d, J = 8.0 Hz, 2H, Ar-H), 7.43 (d, J = 8.0 Hz, 2H, Ar-H), 6.58–6.56 (br, 1H, NH), 5.31–5.26 (m, 1H, CH), 2.95 (dd, J = 6.4 Hz, 16.8 Hz, 1H, CH), 2.82 (dd, J = 5.2 Hz, 16.8 Hz, 1H, CH), 1.96 (s, 3H, CH_3).

4.4.3.7. 3-Acetylamino-3-(*m*-methylphenyl)propionitrile 2g. $[\alpha]_D^{20} = -50.2$ (c 1.0, CH_2Cl_2), 90% ee. Enantiomeric excess was determined by GC, Supelco Gama Dex™ 225 column (30 m × 0.25 mm × 0.25 μm), He 1.0 mL/min, programmed from 130 °C to 180 °C at 2.0 °C/min, hold 40 min at 180 °C; t_R = 41.6 min (minor), t_R = 44.9 min (major). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25–7.19 (m, 1H, Ar-H), 7.12–7.10 (m, 3H, Ar-H), 6.01–6.00 (br, 1H, NH), 5.15–5.10 (m, 1H, CH), 2.98 (dd, J = 6.8 Hz, 16.4 Hz, 1H, CH), 2.82 (dd, J = 4.4 Hz, 16.8 Hz, 1H, CH), 2.31 (s, 3H, CH_3), 1.97 (s, 3H, CH_3).

4.4.3.8. 3-Acetylamino-3-(*m*-chlorophenyl)propionitrile 2h. $[\alpha]_D^{20} = -35.6$ (c 1.0, CH_2Cl_2), 90% ee. Enantiomeric excess was determined by HPLC, Chiralcel OD-H column, n-hexane/2-propanol = 85:15, 1.0 mL/min, 222 nm UV detector, t_R = 13.4 min (minor), t_R = 18.1 min (major). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.29–7.27 (m, 3H, Ar-H), 7.21–7.18 (m, 1H, Ar-H), 6.24–6.22 (br, 1H, NH), 5.21–5.16 (m, 1H, CH), 2.94 (dd, J = 4.8 Hz, 16.8 Hz, 1H, CH), 2.82 (dd, J = 4.8 Hz, 16.8 Hz, 1H, CH), 1.98 (s, 3H, CH_3).

4.4.3.9. 3-Acetylamino-3-(thiophen-2-yl)propionitrile 2i. $[\alpha]_D^{20} = -39.6$ (c 1.0, CH_2Cl_2), 92% ee. Enantiomeric excess was determined by HPLC, Chiralpak AS column, n-hexane/2-propanol = 60:40, 1.0 mL/min, 222 nm UV detector, t_R = 9.3 min (minor), t_R = 14.6 min (major). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25–7.23 (m, 1H, Ar-H), 7.07–7.06 (m, 1H, Ar-H), 6.96–6.94 (m, 1H, Ar-H), 6.08–6.07 (br, 1H, NH), 5.47–5.42 (m, 1H, CH), 3.04 (dd, J = 6.4 Hz, 16.8 Hz, 1H, CH), 2.89 (dd, J = 4.4 Hz, 16.8 Hz, 1H, CH), 1.98 (s, 3H, CH_3).

4.4.3.10. 3-Acetylamino-3-(2-naphthyl)propionitrile 2j. $[\alpha]_D^{20} = -46.5$ (c 1.0, CH_2Cl_2), 84% ee. Enantiomeric excess was determined by HPLC, Chiralpak AD column, n-hexane/2-propanol = 90:10, 1.0 mL/min, 254 nm UV detector, t_R = 12.2 min (minor), t_R = 17.1 min (major). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.83–7.81 (m, 1H, Ar-H), 7.79–7.77 (m, 3H, Ar-H), 7.47–7.44 (m, 2H, Ar-H), 7.39–7.36 (m, 2H, Ar-H), 6.10 (br, 1H, NH), 5.37–5.32 (m, 1H, CH), 3.08 (dd, J = 6.4 Hz, 16.8 Hz, 1H, CH), 2.93 (dd, J = 4.4 Hz, 16.8 Hz, 1H, CH), 2.00 (s, 3H, CH_3).

4.4.3.11. *cis*-2-Acety1amino-1-cyclopentane-1-carbonitrile 2k. $[\alpha]_D^{20} = -35.7$ (c 1.0, CH_2Cl_2), 64% ee. Enantiomeric excess was determined by GC, Supelco Gama Dex™ 225 column (30 m × 0.25 mm × 0.25 μm), He 1.0 mL/min, programmed from 130 °C to 180 °C at 2.0 °C/min, hold 20 min at 180 °C; t_R = 24.8 min (minor), t_R = 28.2 min (major). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.12 (br, 1H, NH), 4.34–4.26 (m, 1H, CH), 3.23–3.19 (m, 1H, CH), 2.04–1.99 (m, 2H, CH_2), 1.97 (s, 3H, CH_3), 1.95–1.92 (m, 1H, CH), 1.91–1.81 (m, 1H, CH), 1.69–1.60 (m, 1H, CH), 1.59–1.52 (m, 1H, CH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.46, 120.36, 52.13, 34.33, 29.98, 28.75, 23.05, 21.52; MS (ESI): 153 (M^++1); HRMS Calcd for $C_8H_{13}N_2O$ 153.1028, Found 153.1022.

4.4.3.12. *cis*-2-Acety1amino-1-cyclohexane-1-carbonitrile 2l. $[\alpha]_D^{20} = -109.7$ (c 1.0, CH_2Cl_2), 83% ee. Enantiomeric excess was determined by GC, Supelco Gama Dex™ 225 column (30 m × 0.25 mm × 0.25 μm), He 1.0 mL/min, programmed from 130 °C to 180 °C at 2.0 °C/min, hold 20 min at 180 °C; t_R = 21.8 min (minor), t_R = 24.4 min (major). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.81 (br, 1H, NH), 3.87–3.80 (m, 1H, CH), 3.29–3.28 (m, 1H, CH), 1.96 (m, 1H, CH), 1.94 (s, 3H, CH_3), 1.81–1.72 (m, 2H, CH_2), 1.64–1.53 (m, 2H, CH_2), 1.52–1.44 (m, 2H, CH_2), 1.36–1.26 (m, 1H, CH); ^{13}C

NMR ($CDCl_3$, 100 MHz) δ 169.75, 120.04, 48.35, 33.87, 28.49, 27.40, 24.55, 23.20, 21.21; MS (ESI): 167 (M^++1); HRMS Calcd for $C_9H_{15}N_2O$ 167.1184, Found 167.1179.

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