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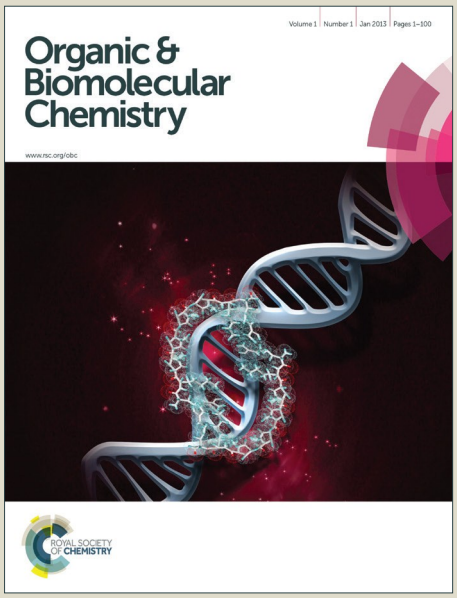

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ARTICLE

Synthesis of Chiral Lactams via Asymmetric Hydrogenation of α,β-Unsaturated Nitriles†

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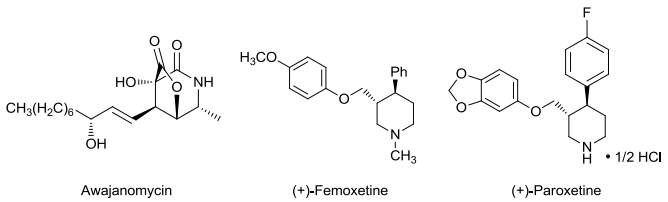
A highly efficient Rh-catalyzed enantioselective hydrogenation of α,β-unsaturated nitriles containing ester/amide groups has been developed. Under mild conditions, with a complex of rhodium and (*S*,*S*)-f-spiroPhos as the catalyst, a variety of α,β-unsaturated nitriles bearing an ester or amide group were successfully hydrogenated to the corresponding chiral nitriles with excellent enantioselectivities (up to 99.7% ee) and high turnover numbers (TON=10,000). Furthermore, this catalyst system was also successfully applied to the synthesis of important chiral pharmacophore fragments, lactams, Paroxetine and amino acids.

Introduction

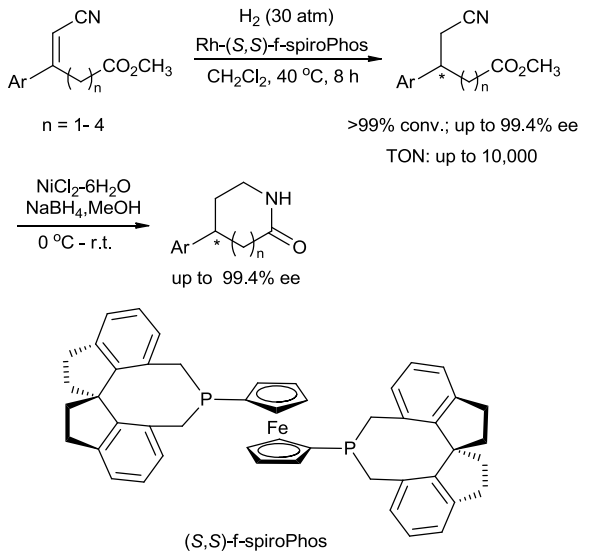
Chiral lactams are extremely important building blocks present in a broad range of biologically active molecules such as natural products and pharmaceuticals.[1] Typical examples include a number of widely employed medicinal antibiotics bearing chiral lactams.[2,3] Accordingly, various chiral lactams and structurally related derivatives have also attracted considerable attention from chemists because of biological properties of this kind of compounds, including anti-HIV agents, anti-tumour compounds, enzyme inhibitors, and anti-thrombotic agents.[1b,4] For example, enantiomerically pure δ-lactams, as key intermediates, are readily converted into pharmacologically important molecules, such as 3, 4-disubstituted piperidines represented by Paroxetine and Femoxetine (Figure 1).[5] Moreover, lactams can be easily hydrolyzed to the corresponding amino acids and their derivatives.[6] Accordingly, it is not surprising that considerable efforts have been directed towards a rapid access to optically active lactams.



Awajanomycin (+)-Femoxetine (+)-Paroxetine

Figure 1. Structures of biologically active compounds.

Although a number of prochiral compounds have been successfully hydrogenated with high enantioselectivity and activity,[7] the direct hydrogenation of α,β-unsaturated nitriles containing ester/amide groups to produce chiral nitriles is rarely reported. The resulting hydrogenation products can be readily converted into the corresponding lactams and amino acids.[6b,8] Recently using a chiral ferrocenyl diphosphine ligand f-spiroPhos bearing privileged spirobiindane skeleton,[9] we reported the asymmetric hydrogenation of γ-cyano acrylate esters and ketones, and similar excellent enantioselectivity and activity was revealed as in the asymmetric hydrogenation of other various substrates.[10] As an extension of this part of work, We herein wish to report the highly efficient and enantioselective hydrogenation of α,β-unsaturated nitriles containing ester/amide groups, which provides an efficient route to optically active lactams and amino acids (Scheme 1).[5a,11]



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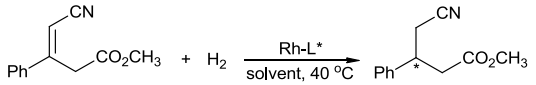
† Electronic Supplementary Information (ESI) available: NMR of substrates and hydrogenation products, GC and HPLC spectra of analysis of enantioselectivities of products. See DOI: 10.1039/x0xx00000x

Scheme 1. Rh-Catalyzed asymmetric hydrogenation of α,β-unsaturated nitriles containing ester/amide groups.

Results and discussion

Initially, (*E*)-methyl 4-cyano-3-phenylbut-3-enoate **1a** was chosen as a model substrate and hydrogenated under 80 atm of H_2 in CH_2Cl_2 at 40 °C using the complex of (*S,S*)-f-spiroPhos and $[Rh(COD)Cl]_2$. To our delight, a full conversion with excellent enantioselectivity was achieved in 8 hours (Table 1, entry 1). Some other phosphine ligands including Binap, DuanPhos, JosiPhos, f-Binaphane and MonoPhos (Table **1**) were also screened, but low conversions and poor enantioselectivities were observed (entries 2–6) except for JosiPhos-**1** and f-Binaphane providing a moderate conversion and ee value. The introduction of the rigid spirobiindane skeleton presumably resulted in higher activity and enantioselectivity of the ligand, (*S,S*)-f-spiroPhos. The solvent effect was subsequently investigated and showed that most of non-polar solvents such as toluene, THF and DME were suitable for this transformation albeit with slightly lower enantioselectivities (entries 7–10). However, polar solvent, MeOH, provided decreased conversion and enantioselectivity (entry 11). Even under lower hydrogen pressure, 30 atm, the hydrogenation could smoothly complete in 4 hours and the enantioselectivity was maintained (entries 12).

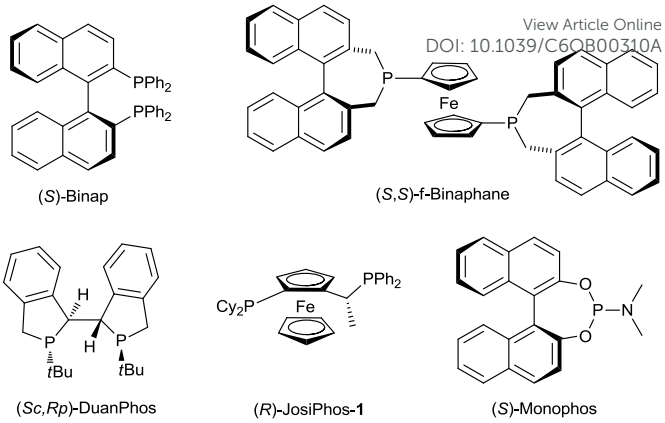
Table 1. Rh-Catalyzed asymmetric hydrogenation of (*E*)-methyl 4-cyano-3-phenylbut-3-enoate **1a**, optimizing reaction conditions.[a]



1a **2a**

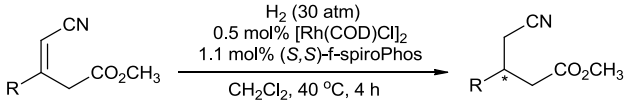
entry	ligand	solvent	conv. (%)[b]	ee. (%)[c]
1	(*S,S*)-f-spiroPhos	CH_2Cl_2	>99	98
2	(*S*)-Binap	CH_2Cl_2	6	12
3	(*S,R*)-DuanPhos	CH_2Cl_2	13	18
4	(*R*)-JosiPhos-1	CH_2Cl_2	78	34
5	(*S,S*)-f-Binaphane	CH_2Cl_2	60	80
6	(*S*)-MonoPhos	CH_2Cl_2	<5	ND
7	(*S,S*)-f-spiroPhos	Toluene	>99	93
8	(*S,S*)-f-spiroPhos	THF	>99	94
9	(*S,S*)-f-spiroPhos	dioxane	>99	95
10	(*S,S*)-f-spiroPhos	DME	>99	95
11	(*S,S*)-f-spiroPhos	MeOH	89	76
12[d]	(*S,S*)-f-spiroPhos	CH_2Cl_2	>99	98

[a] Unless otherwise mentioned, all reactions were carried out with a $[Rh(COD)Cl]_2$/diphosphine/substrate ratio of 0.5 : 1.1 : 100, 40 °C, 8 h. [b] Determined by ^1H NMR. [c] Determined by HPLC analysis using a chiral stationary phase. [d] 30 atm H_2, 4 h.



Under the optimized reaction conditions, a variety of α,β-unsaturated nitriles containing an ester group **1b–1j**, which were prepared as a single isomer from β-ketoesters, were then evaluated for the hydrogenation and results are illustrated in Table 2. All substrates bearing different substituents in the phenyl ring were successfully hydrogenated providing the corresponding products **2** with excellent enantioselectivities, 94% – 99.4% ee, regardless of the position or electronic property of substituents. For example, the substrates **1d** and **1e** with an electron-withdrawing *para*-chloro or bromo group and the substrate **1b** bearing an electron-donating *para*-methyl group gave similar enantioselectivities, 99% and 98% ee respectively (entries 4-5). The substrate **1c** with a fluoro group at the *para*-position of phenyl ring provided **2c** with the highest enantioselectivity, 99.4% ee (entry 3). The similar effect was also observed for the *meta*-substituted substrates (entries 6-8). The substrate **1j** with a 2-naphthyl group also afforded **2j** in full conversion with 99% ee (entry 10).

Table 2. Rh-Catalyzed asymmetric hydrogenation of α,β-unsaturated nitriles containing ester/amide groups **1**.[a]

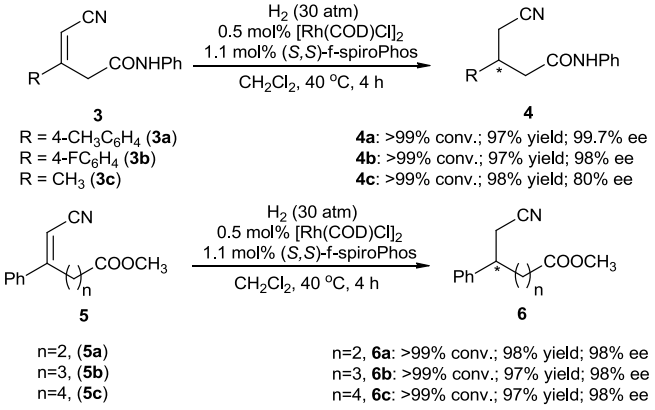


1 **2**

entry	R	product	conv. (%)[b]	ee (%)[c]
1	C_6H_5 (**1a**)	**2a**	>99(97)	98(*S*)
2	4-$CH_3C_6H_4$ (**1b**)	**2b**	>99(97)	98(+)
3	4-FC_6H_4 (**1c**)	**2c**	>99(98)	99.4(*S*)
4	4-ClC_6H_4 (**1d**)	**2d**	>99(98)	99(+)
5	4-BrC_6H_4 (**1e**)	**2e**	>99(98)	99(+)
6	3-$CH_3OC_6H_4$ (**1f**)	**2f**	>99(96)	96(+)
7	3-FC_6H_4 (**1g**)	**2g**	>99(97)	96(+)
8	3-ClC_6H_4 (**1h**)	**2h**	>99(98)	96(+)
9	2-ClC_6H_4 (**1i**)	**2i**	>99(96)	94(+)
10	2-naphthyl (**1j**)	**2j**	>99(98)	99(+)

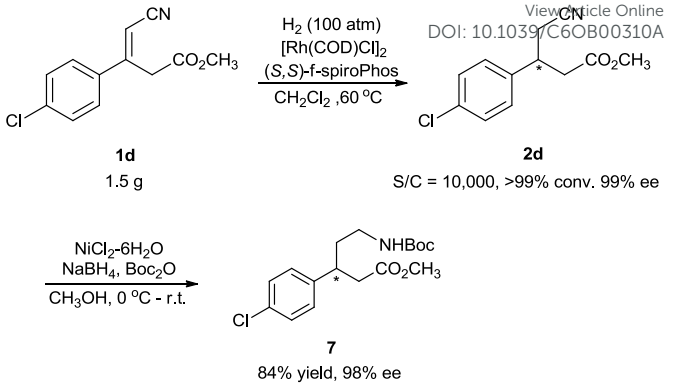
[a] Unless otherwise mentioned, all reactions were carried out with a $[Rh(COD)Cl]_2$/(*S,S*)-f-spiroPhos/substrate ratio of 0.5 : 1.1 : 100, CH_2Cl_2, 30 atm H_2, 40 °C, 4 h. [b] Determined by ^1H NMR spectroscopy or GC analysis; data in parentheses are isolated yields. [c] Determined by HPLC analysis using a chiral stationary phase or chiral GC analysis.

Furthermore, the Rh-(*S*,*S*)-f-spiroPhos catalyst was also applied to the asymmetric hydrogenation of α,β-unsaturated nitriles containing an amide group and exhibited comparable high efficiency and enantioselectivity. Under the optimized reaction conditions, substrates **3a** and **3b** were smoothly hydrogenated to the corresponding products **4a** and **4b** in full conversions and excellent enantioselectivities, 99.7% and 98% ee respectively (Scheme 2). However, a dramatically decreased ee value was observed when the alkyl substituted substrate **3c** was evaluated. Encouraged by the results of the hydrogenation of substrates **1** and **3**, some other α,β-unsaturated nitriles bearing a long chain ester group, substrates **5a-c**, were also evaluated to provide the corresponding hydrogenated products **6a-c** with high yields and excellent enantioselectivitis.



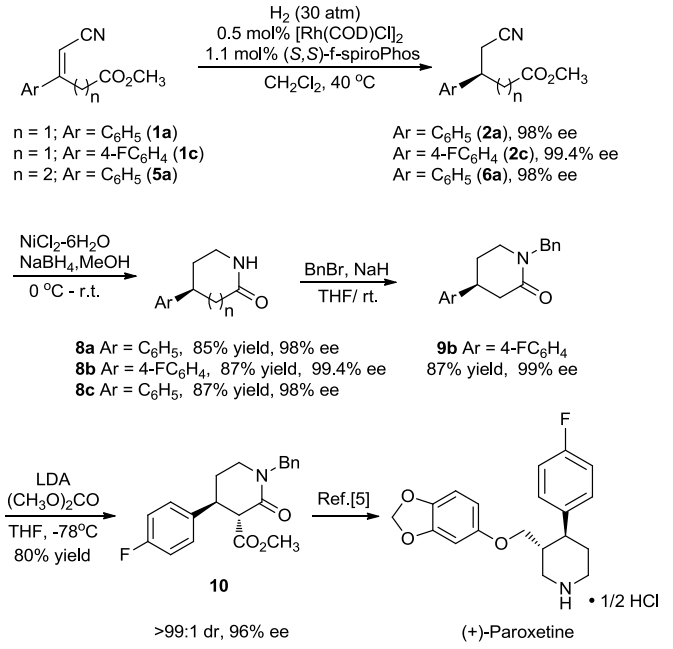
Scheme 2. Rh-Catalyzed asymmetric hydrogenation of α,β-unsaturated nitriles containing ester/amide groups.

To further evaluate the performance and application potency of this catalyst system, a gram scale hydrogenation with much lower catalyst loading was carried out. The result revealed that the high activity and excellent enantioselectivity could be maintained under even lower catalyst loading. With the Rh-(*S*,*S*)-f-spiroPhos catalyst, the substrate **1d** was hydrogenated on gram scale at a catalyst loading of 0.01 mol% under 100 atm of initial H_2 pressure, the desired product **2d** was obtained in full conversion without any erosion of enantioselectivity. The results indicated that this catalyst is exceptionally highly efficient for the asymmetric hydrogenation of these substrates and can achieve very high turnover numbers (TON) approaching 10,000 (Scheme 3). The product **2d** could be readily converted to the amino acid derivative **7** in good yield and almost unchanged ee value.



Scheme 3. Asymmetric hydrogenation of **1d** under lower catalyst loading and synthesis of chiral amino ester **7**.

Finally, this catalyst system can also be successfully applied to the synthesis of important chiral pharmacophore fragments, δ- and ε-lactams and amino acids (Scheme 4).[6b] The hydrogenation products were further reduced to amines followed by subsequent cyclization.[6a] δ- and ε-lactams were then obtained. By this route, the key intermediate, δ-lactam **8**, for the synthesis of the selective serotonin reuptake inhibitors Paroxetine and Femoxetine[11e,12] was accessed in high yield without any loss of enantioselectivity. Treatment of **8b** with BnBr followed by a nucleophilic substitution in the presence of LDA, gave the desired product **10** with > 99:1 dr and 96% ee,[5a,13] which could be easily transformed to Paroxetine and Femoxetine according to literature procedures.[5]



Scheme 4. Synthesis of δ-lactams and Paroxetine.

Experimental

General Information

All the air or moisture sensitive reactions and manipulations were performed by using standard Schlenk techniques and in a nitrogen-filled glovebox. DME, THF, dioxane and toluene were distilled from sodium benzophenone ketyl. CH_2Cl_2 was distilled from calcium hydride. Anhydrous MeOH was distilled from magnesium. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AV (400 MHz) spectrometers. $CDC1_3$ was the solvent used for the NMR analysis, with TMS as the internal standard. Chemical shifts were reported upfield to TMS (0.00 ppm) for ^{1}H NMR. Data is represented as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, dd = double of doublets, t = triplet, q = quartet, m = multiplet) and coupling constants (*J*) in Hertz (Hz). Optical rotation was determined using a Perkin Elmer 241 MC polarimeter. GC analysis was conducted on an Agilent 7890A series instrument. HPLC analysis was conducted on Agilent 1260 series instrument. HRMS were recorded on a Waters LCT Premier XE mass spectrometer with APCI or ESI.

General procedure for the preparation of compounds 1a-j and 3a-b:[8b] The appropriate β-keto esters and amides (0.02 mol) and 2-(triphenylphosphoranylidene)-acetonitrile (0.024 mol) were dissolved in toluene (30 ml) in a round bottle flask equipped with a reflux condenser. The solution was stirred at reflux temperature until no starting material was detected by TLC. After the solvent was removed in vacuo, the residue was purified by silica gel column chromatography using petroleum ether/AcOEt as an eluent to afford the compounds **1a-j** and **3a-b**.

(*E*)-methyl 4-cyano-3-phenylbut-3-enoate (1a): yellow liquid; Yield: 80%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.36-7.34 (m, 5H), 5.72 (s, 1H), 3.83 (s, 2H), 3.61 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 169.1, 155.6, 136.7, 130.6, 129.0, 126.1, 116.8, 99.2, 52.6, 39.0. APCI-HRMS Calcd. for $C_{12}H_{12}NO_2$ [M+H$^+$]: 202.0868, found 202.0864.

(*E*)-methyl 4-cyano-3-(*p*-tolyl)but-3-enoate (1b): yellow solid; MP: 68-70 ^{o}C; Yield: 67%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.27 (d, *J* = 8.2 Hz, 2H), 7.14 (d, *J* = 8.2 Hz, 2H), 5.70 (s, 1H), 3.82 (s, 2H), 3.61 (s, 3H), 2.30 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 169.2, 155.3, 141.1, 133.8, 129.8, 126.0, 117.1, 98.0, 52.5, 38.9, 21.3. APCI-HRMS Calcd. for $C_{13}H_{14}NO_2$ [M+H$^+$]: 216.1025, found 216.1023.

(*E*)-methyl 4-cyano-3-(4-fluorophenyl)but-3-enoate (1c): colorless crystal; MP: 60-62 ^{o}C; Yield: 70%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.39-7.36 (m, 2H), 7.05-7.01 (m, 2H), 5.68 (s, 1H), 3.82 (s, 2H), 3.62 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 169.0, 164.0 (d, *J* = 250.0 Hz), 154.4, 132.9 (d, *J* = 4.0 Hz), 128.3 (*J* = d, 2.0 Hz), 116.7, 116.1 (d, *J* = 22.0 Hz), 99.1 (d, *J* = 1.0 Hz), 52.6, 39.0. ^{19}F NMR ($CDCl_3$, 376 MHz) δ: -109.4. APCI-HRMS Calcd. for $C_{12}H_{11}NO_2F$ [M+H$^+$]: 220.0774, found 220.0777.

(*E*)-methyl 3-(4-chlorophenyl)-4-cyanobut-3-enoate (1d): colorless crystal; MP:76-78 ^{o}C; Yield: 85%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.38 (s, 4H), 5.77 (s, 1H), 3.89 (s, 2H), 3.69 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.9, 154.3, 136.7, 135.2, 129.3, 127.5, 116.5, 99.7, 52.6, 38.9. APCI-HRMS Calcd. for $C_{12}H_{11}NO_2Cl$ [M+H$^+$]: 236.0478, found 236.0472.

(*E*)-methyl 3-(4-bromophenyl)-4-cyanobut-3-enoate (1e): colorless crystal; MP: 92-94 ^{o}C; Yield: 80%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.49-7.46 (m, 2H), 7.26-7.19 (m, 2H), 5.71 (s, 1H), 3.81 (s, 2H), 3.62 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.8, 154.5, 135.7, 132.3, 127.6, 125.1, 116.4, 99.7, 52.6, 38.9. APCI-HRMS Calcd. for $C_{12}H_{11}NO_2Br$ [M+H$^+$]: 279.9973, found 279.9975.

(*E*)-methyl 4-cyano-3-(3-methoxyphenyl)but-3-enoate (1f): yellow liquid; Yield: 59%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.26-7.22 (m, 1H), 6.95-6.88 (m, 3H), 5.71 (s, 1H), 3.81 (s, 2H), 3.75 (s, 3H), 3.61 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 169.1, 159.9, 155.4, 138.1, 130.1, 118.5, 116.8, 115.8, 112.0, 99.4, 55.3, 52.5, 39.0. APCI-HRMS Calcd. for $C_{13}H_{14}NO_3$ [M+H$^+$]: 232.0974, found 232.0971.

(*E*)-methyl 4-cyano-3-(3-fluorophenyl)but-3-enoate (1g): yellow liquid; Yield: 62%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.16-7.14 (m, 1H), 7.09-7.03 (m, 3H), 5.73 (s, 1H), 3.81 (s, 2H), 3.62 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.8, 162.9 (d, *J* = 247.0 Hz), 154.3 (d, *J* = 3.0 Hz), 138.9 (d, *J* = 8.0 Hz), 130.7 (d, *J* = 9.0 Hz), 121.9 (d, *J* = 4.0 Hz), 117.5 (d, *J* = 21.0 Hz), 116.3, 113.3 (d, *J* = 22.0 Hz), 100.4, 52.6, 39.0. ^{19}F NMR ($CDCl_3$, 376 MHz) δ: -111.4. APCI-HRMS Calcd. for $C_{12}H_{11}NO_2F$ [M+H$^+$]: 220.0774, found 220.0777.

(*E*)-methyl 3-(3-chlorophenyl)-4-cyanobut-3-enoate (1h): yellow liquid; Yield: 75%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.35-7.23 (m, 4H), 5.71 (s, 1H), 3.80 (s, 2H), 3.62 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.7, 154.3, 138.7, 135.1, 130.5, 130.3, 126.3, 124.3, 116.3, 100.6, 52.6, 39.0. APCI-HRMS Calcd. for $C_{12}H_{11}NO_2Cl$ [M+H$^+$]: 236.0478, found 236.0472.

(*E*)-methyl 3-(2-chlorophenyl)-4-cyanobut-3-enoate (1i): yellow liquid; Yield: 52%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.36-7.26 (m, 4H), 5.57 (s, 1H), 3.92 (s, 2H), 3.66 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.5, 156.0, 137.2, 131.4, 130.5, 130.1, 130.0, 127.1, 115.6, 104.4, 52.3, 40.1. APCI-HRMS Calcd. for $C_{12}H_{11}NO_2Cl$ [M+H$^+$]: 236.0478, found 236.0472.

(*E*)-methyl 4-cyano-3-(naphthalen-2-yl)but-3-enoate (1j): colorless crystal; MP: 58-60 ^{o}C; Yield: 68%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.92-7.83 (m, 4H), 7.57-7.26 (m, 3H), 5.93 (s, 1H), 4.03 (s, 2H), 3.69 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 169.2, 155.3, 134.1, 133.9, 132.9, 129.0, 128.8, 127.7, 127.6, 127.0, 126.4, 122.9, 116.9, 99.4, 52.6, 39.1. APCI-HRMS Calcd. for $C_{16}H_{14}NO_2$ [M+H$^+$]: 252.1025, found 252.1019.

(*E*)-4-cyano-*N*-phenyl-3-(*p*-tolyl)but-3-enamide (3a): white solid; MP: 164-166 ^{o}C; Yield: 78%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.50-7.43 (m, 5H), 7.30-7.08 (m, 5H), 5.83 (s, 1H), 3.94 (s, 2H), 2.37 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.2, 156.9, 141.4, 137.5, 133.7, 129.8, 128.9, 126.3, 124.7, 120.3, 117.7, 97.5, 41.9, 21.3. TOF-HRMS Calcd. for $C_{18}H_{17}N_2O$ [M+H$^+$]: 277.1335, found 277.1334.

(*E*)-4-cyano-3-(4-fluorophenyl)-*N*-phenylbut-3-enamide (3b): white solid; MP: 162-164 ^{o}C; Yield: 85%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.50-7.44 (m, 3H), 7.31 (d, *J* = 7.9 Hz, 2H), 7.17-7.12 (m, 2H), 6.99-6.94 (m, 3H), 5.64 (s, 1H), 3.78 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 165.5, 165.4, 163.0, 156.2, 137.2, 132.9, 129.0, 128.7, 128.6, 124.9, 120.2, 117.4, 116.3, 116.1, 98.3, 42.5. ^{19}F NMR ($CDCl_3$, 376 MHz) δ: -108.9. TOF-HRMS Calcd. for $C_{17}H_{14}N_2OF$ [M+H$^+$]: 281.1084, found 281.1083.

(*Z*)-4-cyano-3-methyl-N-phenylbut-3-enamide (3c): white solid; MP: 110-112 ^{o}C; Yield: 78%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.51-7.49 (m, 3H), 7.35-7.30 (m, 2H), 7.15-7.11 (m, 1H), 5.35 (s,

1H), 3.48 (s, 2H), 2.13 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 166.5, 159.6, 138.1, 129.6, 125.3, 120.8, 117.4, 99.3, 44.9, 24.4. TOF-HRMS Calcd. for $C_{12}H_{13}N_2O$ [M+H$^+$]: 201.1022, found 201.1023.

General procedure for the preparation of compound 5: NaH (0.03 mol) and THF (50 mL) were placed in an oven-dried two-neck round bottom flask under nitrogen. The reaction mixture was cooled and diethyl cyanomethylphosphonate (0.024 mol) was added dropwise at 0 ^{o}C. The solution was stirred at room temperature until gas evolution had ceased. And then, the corresponding keto esters (0.02 mol) were added dropwise. The solution was stirred at room temperature until no starting material was detected by TLC. The reaction mixture was quenched with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4. After the solvent was removed in vacuo, the residue was purified by silica gel column chromatography using petroleum ether/AcOEt as an eluent.

(*E*)-methyl 5-cyano-4-phenylpent-4-enoate (5a): colorless liquid; Yield: 87%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.43-7.26 (m, 5H), 5.54 (s, 1H), 3.64 (s, 3H), 3.20 (t, *J* = 8.0 Hz, 2H), 2.45 (t, *J* = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 172.2, 162.8, 136.7, 130.4, 129.1, 126.4, 116.9, 97.0, 51.9, 32.5, 29.1.

(*E*)-methyl 6-cyano-5-phenylhex-5-enoate (5b): Yield: 81%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.43 (s, 5H), 5.56 (s, 1H), 3.68 (s, 3H), 2.95 (t, *J* = 8.0 Hz, 2H), 2.38 (t, *J* = 8.0 Hz, 2H), 1.85-1.78 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 173.2, 163.8, 137.0, 130.3, 129.0, 126.3, 117.2, 96.3, 51.7, 33.1, 32.9, 23.5. TOF-HRMS Calcd. for $C_{14}H_{16}NO_2$ [M+H$^+$]: 230.1175, found 230.1177.

(*E*)-methyl 7-cyano-6-phenylhept-6-enoate (5c): Yield: 89%; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.42-7.26 (m, 5H), 5.51 (s, 1H), 3.62 (s, 3H), 2.89 (t, *J* = 8.0 Hz, 2H), 2.30 (t, *J* = 8.0 Hz, 2H), 1.72-1.64 (m, 2H), 1.54-1.46 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 173.7, 164.5, 137.3, 130.2, 129.0, 126.3, 117.3, 96.0, 51,5, 33.6, 33.4, 27.8, 24.3. TOF-HRMS Calcd. for $C_{15}H_{18}NO_2$ [M+H$^+$]: 244.1332, found 244.1330.

General procedure for asymmetric hydrogenation of compounds 1, 3 and 5: A stock solution was made by mixing $[Rh(COD)Cl]_2$ with (*S*,*S*)-f- spiroPhos in a 1:1.1 molar ratio of Rh/(*S*,*S*)-f-spiroPhos in CH_2Cl_2 at room temperature for 20 min in a nitrogen-filled glovebox. An aliquot of the catalyst solution (1.0 mL, 0.001 mmol) was transferred by syringe into the vials charged with different substrates (0.1 mmol for each) in anhydrous CH_2Cl_2 (2.0 mL). The vials were then placed into a steel autoclave. The inert atmosphere was replaced by H_2 and the reaction mixture was stirred under H_2 (30 atm) at 40 ^{o}C. The hydrogen gas was released slowly and carefully. The solution was concentrated and passed through a short column of silica gel to remove the metal complex. The ee values of all products were determined by GC or HPLC analysis on a chiral stationary phase.

(*S*)-methyl 4-cyano-3-phenylbutanoate (2a): colorless liquid; Yield: 97%; 98% ee; $[\alpha]_D^{25}$ = +22.6 (c = 0.5, $CHCl_3$); HPLC condition: Lux 5u Cellulose-3 (250 × 4.60mm), ipa : hex = 40:60, 1.0 mL/min, 220 nm; t_R = 13.8 min (major), t_R = 24.2 min (minor).[1]H NMR ($CDCl_3$, 400 MHz) δ: 7.30-7.18 (m, 5H), 3.58 (s, 3H), 3.48-3.41 (m, 1H), 2.82-2.67 (m, 4H).[14]

methyl 4-cyano-3-(*p*-tolyl)butanoate (2b): colorless liquid; Yield: 97%; 98% ee; $[\alpha]_D^{25}$ = +19.4 (c = 0.5, $CHCl_3$); GC condition: Supelco gamma Dex^{TM} 225 column (30 m × 0.25 mm × 0.25 µm), N_2 1.0 mL/min, programmed 100 ^{o}C – 0.6 ^{o}C/min – 200 ^{o}C – 100 min; t_R = 108.4 min (major), t_R = 109.0 min (minor). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.26-7.13 (m, 4H), 3.65 (s, 3H), 3.51-3.44 (m, 1H), 2.87-2.71 (m, 4H), 2.33 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 171.5, 137.5, 137.4, 129.7, 126.8, 118.0, 51.9, 38.9, 37.7, 24.4, 21.0. APCI-HRMS Calcd. for $C_{13}H_{16}NO_2$ [M+H$^+$]: 218.1181, found 218.1175.

(*S*)-methyl 4-cyano-3-(4-fluorophenyl)butanoate (2c): colorless liquid; Yield: 98%; 99.4% ee; $[\alpha]_D^{25}$ = +20.2 (c = 0.5, CH_3CN); GC condition: Supelco gamma Dex^{TM} 225 column (30 m × 0.25 mm × 0.25 µm), N_2 1.0 mL/min, programmed 100 ^{o}C – 1 ^{o}C/min – 200 ^{o}C – 100 min; t_R = 71.7 min (major), t_R = 72.8 min (minor). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.19-7.15 (m, 2H), 6.99-6.95 (m, 2H), 3.57 (s, 3H), 3.46-3.42 (m, 1H), 2.80-2.64 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.2, 161.2 (d, *J* = 245.0 Hz), 135.1 (d, *J* = 4.0 Hz), 127.7 (d, *J* = 8.0 Hz), 116.7, 115.0 (d, *J* = 22.0 Hz), 51.0, 37.9, 36.4, 23.4. ^{19}F NMR ($CDCl_3$, 376 MHz) δ: -114.3.[15]

methyl 3-(4-chlorophenyl)-4-cyanobutanoate (2d): yellow liquid; Yield: 98%; 99% ee; $[\alpha]_D^{25}$ = +26.6 (c = 0.5, $CHCl_3$); GC condition: Supelco gamma Dex^{TM} 225 column (30 m × 0.25 mm × 0.25 µm), N_2 1.0 mL/min, programmed 100 ^{o}C – 1 ^{o}C/min – 200 ^{o}C – 100 min; t_R = 90.8 min (major), t_R = 91.9 min (minor). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.33-7.31 (m, 2H), 7.22-7.18 (m, 2H), 3.64 (s, 3H), 3.51-3.46 (m, 1H), 2.86-2.71 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 171.2, 138.8, 133.8, 129.2, 128.4, 117.6, 52.0, 38.6, 37.5, 24.3. APCI-HRMS Calcd. for $C_{12}H_{13}NO_2Cl$ [M+H$^+$]: 238.0635, found 238.0629.

methyl 3-(4-bromophenyl)-4-cyanobutanoate (2e): colorless liquid; Yield: 98%; 99% ee; $[\alpha]_D^{25}$ = +24.0 (c = 0.5, $CHCl_3$); GC condition: Supelco gamma Dex^{TM} 225 column (30 m × 0.25 mm × 0.25 µm), N_2 1.0 mL/min, programmed 100 ^{o}C – 1 ^{o}C/min – 200 ^{o}C – 100 min; t_R = 100.0 min (major), t_R = 100.9 min (minor). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.50-7.46 (m, 2H), 7.14 (d, *J* = 8.4 Hz, 2H), 3.64 (s, 3H), 3.52-3.45 (m, 1H), 2.86-2.71 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 171.1, 139.3, 132.2, 128.6, 121.8, 117.6, 52.0, 38.6, 37.6, 24.2. APCI-HRMS Calcd. for $C_{12}H_{13}NO_2Br$ [M+H$^+$]: 282.0130, found 282.0124.

methyl 4-cyano-3-(3-methoxyphenyl)butanoate (2f): colorless liquid; Yield: 96%; 96% ee; $[\alpha]_D^{25}$ = +18.4 (c = 0.5, $CHCl_3$); HPLC condition: Lux 5u Cellulose-3 (250 × 4.60mm), ipa : hex = 20:80, 1.0 mL/min, 225 nm; t_R = 19.1 min (major), t_R = 24.1 min (minor). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.19 (t, *J* = 8.0 Hz, 1H), 6.77-6.72 (m, 3H), 3.73 (s, 3H), 3.58 (s, 3H), 3.44-3.37 (m, 1H), 2.79-2.65 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.4, 159.0, 141.0, 129.1, 118.1, 116.9, 112.1, 112.0, 54.2, 50.9, 37.8, 37.1, 23.2. APCI-HRMS Calcd. for $C_{13}H_{16}NO_3$ [M+H$^+$]: 234.1130, found 234.1123.

methyl 4-cyano-3-(3-fluorophenyl)butanoate (2g): colorless liquid; Yield: 97%; 96% ee; $[\alpha]_D^{25}$ = +20.6 (c = 0.5, $CHCl_3$); GC condition: Supelco gamma Dex^{TM} 225 column (30 m × 0.25 mm × 0.25 µm), N_2 1.0 mL/min, programmed 100 ^{o}C – 1 ^{o}C/min – 200 ^{o}C – 100 min; t_R = 71.5 min (major), t_R = 72.7 min (minor). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.32-7.26 (m, 1H), 7.06-6.95 (m,

3H), 3.66 (s, 3H), 3.55-3.48 (m, 1H), 2.87-2.73 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 171.1, 163.0 (d, J = 246.0 Hz), 142.8 (d, J = 7.0 Hz), 130.6 (d, J = 8.0 Hz), 122.7 (d, J = 3.0 Hz), 117.5, 114.9 (d, J = 21.0 Hz), 114.1 (d, J = 22.0 Hz), 52.0, 38.6, 37.8 (d, J = 1.0 Hz), 24.2. ^{19}F NMR ($CDCl_3$, 376 MHz) δ: -112.7. APCI-HRMS Calcd. for $C_{12}H_{13}NO_2F$ [M+H$^+$]: 222.0930, found 222.0928.

methyl 3-(3-chlorophenyl)-4-cyanobutanoate (2h): yellow liquid; Yield: 98%; 96% ee; $[\alpha]_D^{25}$ = +25.6 (c = 0.5, $CHCl_3$); GC condition: Supelco gamma Dex^{TM} 225 column (30 m × 0.25 mm × 0.25 μm), N_2 1.0 mL/min, programmed 100 ^{o}C – 1 ^{o}C/min – 200 ^{o}C – 100 min; t_R = 88.1 min (major), t_R = 89.0 min (minor). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.21-7.08 (m, 4H), 3.59 (s, 3H), 3.46-3.39 (m, 1H), 2.80-2.66 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 170.1, 141.4, 133.8, 129.3, 127.1, 126.2, 124.3, 116.5, 51.0, 37.5, 36.8, 23.1. APCI-HRMS Calcd. for $C_{12}H_{13}NO_2Cl$ [M+H$^+$]: 238.0635, found 238.0629.

methyl 3-(2-chlorophenyl)-4-cyanobutanoate (2i): yellow liquid; Yield: 96%; 94% ee; $[\alpha]_D^{25}$ = +26.8 (c = 0.5, $CHCl_3$); GC condition: Supelco gamma Dex^{TM} 225 column (30 m × 0.25 mm × 0.25 μm), N_2 1.0 mL/min, programmed 100 ^{o}C – 1 ^{o}C/min – 200 ^{o}C – 100 min; t_R = 79.7 min (major), t_R = 80.0 min (minor). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.32-7.14 (m, 4H), 4.02-3.95 (m, 1H), 3.60 (s, 3H), 2.88-2.70 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 171.2, 137.4, 133.6, 130.2, 129.0, 127.6, 127.5, 117.5, 52.0, 37.0, 33.9, 22.5. APCI-HRMS Calcd. for $C_{12}H_{13}NO_2Cl$ [M+H$^+$]: 238.0635, found 238.0629.

methyl 4-cyano-3-(naphthalen-2-yl)butanoate (2j): white solid; MP: 68-70 ^{o}C; Yield: 98%; 99% ee; $[\alpha]_D^{25}$ = +24.4 (c = 0.5, $CHCl_3$); HPLC condition: Lux 5u Cellulose-3 (250 × 4.60mm), ipa : hex = 30:70, 1.0 mL/min, 254 nm; t_R = 18.5 min (major), t_R = 23.3 min (minor). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.83-7.73 (m, 4H), 7.53-7.36 (m, 3H), 3.73-3.65 (m, 4H), 2.99-2.86 (m, 2H), 2.83 (d, J = 6.7 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 171.4, 137.8, 133.4, 132.9, 129.0, 127.9, 127.7, 126.5, 126.2, 126.0, 124.8, 117.9, 52.0, 38.9, 38.2, 24.3. APCI-HRMS Calcd. for $C_{16}H_{16}NO_2$ [M+H$^+$]: 254.1181, found 254.1180.

4-cyano-*N*-phenyl-3-(*p*-tolyl)butanamide (4a): white solid; Yield: 97%; 99.7% ee; HPLC condition: Lux 5u Cellulose-3 (250 × 4.60mm), ipa : hex = 10:90, 1.0 mL/min, 254 nm; t_R = 23.1 min (major), t_R = 33.7 min (minor). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.70 (br, 1H), 7.42-7.08 (m, 9H), 3.59 (t, J = 6.7 Hz, 1H), 2.85-2.74 (m, 4H), 2.32 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.6, 137.6, 137.5, 129.8, 129.0, 126.9, 124.6, 120.1, 118.4, 41.8, 37.7, 24.3, 21.1.

4-cyano-3-(4-fluorophenyl)-*N*-phenylbutanamide (4b): colorless liquid; Yield: 97%; 98% ee; HPLC condition: Lux 5u Cellulose-3 (250 × 4.60mm), ipa : hex = 20:80, 1.0 mL/min, 254 nm; t_R = 13.5 min (major), t_R = 16.1 min (minor). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.68 (br, 1H), 7.42-7.22 (m, 6H), 7.12-6.99 (m, 3H), 3.66-3.59 (m, 1H), 2.85-2.70 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 168.1, 163.2, 160.8, 137.2, 136.2, 136.1, 128.8, 128.6, 128.5, 124.6, 119.9, 117.9, 115.9, 115.7, 41.4, 37.1, 24.2. ^{19}F NMR ($CDCl_3$, 376 MHz) δ: -114.2. TOF-HRMS Calcd. for $C_{17}H_{16}N_2OF$ [M+H$^+$]: 283.1241, found 283.1242.

4-cyano-3-methyl-N-phenylbutanamide (4c): colorless liquid; Yield: 98%; 80% ee; $[\alpha]_D^{25}$ = -15.2 (c = 0.5, $CHCl_3$); HPLC condition: Lux 5u Cellulose-1 (250 × 4.60mm), ipa : hex = 30:70, 1.0 mL/min, 254 nm; t_R = 5.7 min (major), t_R = 7.1 min (minor). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.87 (s, 1H), 7.51 (d, J = 8.0 Hz, 2H), 7.30 (t, J = 8.0 Hz, 2H), 7.12 (t, J = 8.0 Hz, 1H), 2.53-2.38 (m, 5H), 1.16 (d, J = 8.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 169.7, 138.2, 129.6, 125.1, 120.6, 119.0, 43.0, 28.0, 24.5, 19.9. TOF-HRMS Calcd. for $C_{12}H_{15}N_2O$ [M+H$^+$]: 203.1178, found 203.1180.

methyl 5-cyano-4-phenylpentanoate (6a): colorless liquid; Yield: 98%; 98% ee; HPLC condition: Lux 5u Cellulose-1 (250 × 4.60mm), ipa : hex = 10:90, 1.0 mL/min, 225 nm; t_R = 16.4 min (major), t_R = 18.2 min (minor). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.35-7.18 (m, 5H), 3.56 (s, 3H), 3.02-2.95 (m, 1H), 2.61 (d, J = 7.2 Hz, 2H), 2.20-2.05 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 173.1, 140.4, 129.1, 127.8, 127.3, 118.3, 51.7, 41.5, 31.6, 29.9, 25.1. TOF-HRMS Calcd. for $C_{13}H_{16}NO_2$ [M+H$^+$]: 218.1175, found 218.1178.

methyl 6-cyano-5-phenylhexanoate (6b): colorless liquid; Yield: 97%; 98% ee; HPLC condition: Lux 5u Cellulose-1 (250 × 4.60mm), ipa : hex = 20:80, 1.0 mL/min, 225 nm; t_R = 21.3 min (minor), t_R = 22.6 min (major). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.35-7.19 (m, 5H), 3.63 (s, 3H), 2.93-2.91 (m, 1H), 2.61-2.58 (m, 2H), 2.29-2.26 (m, 2H), 2.84-1.75 (m, 2H), 1.76-1.50 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 173.5, 141.2, 128.9, 127.6, 127.2, 118.5, 51.6, 42.0, 34.2, 33.6, 25.1, 22.6. TOF-HRMS Calcd. for $C_{14}H_{18}NO_2$ [M+H$^+$]: 232.1332, found 232.1330.

methyl 7-cyano-6-phenylheptanoate (6c): colorless liquid; Yield: 97%; 98% ee; HPLC condition: Lux 5u Cellulose-1 (250 × 4.60mm), ipa : hex = 10:90, 1.0 mL/min, 225 nm; t_R = 26.4 min (minor), t_R = 28.3 min (major). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.35-7.18 (m, 5H), 3.62 (s, 3H), 2.94-2.88 (m, 1H), 2.58 (d, J = 7.2 Hz, 2H), 2.26-2.22 (m, 2H), 1.87-1.70 (m, 2H), 1.66-1.55 (m, 2H), 1.27-1.16 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 173.9, 141.5, 128.9, 127.5, 127.2, 118.6, 51.5, 42.0, 34.5, 33.7, 26.7, 25.2, 24.6. TOF-HRMS Calcd. for $C_{15}H_{20}NO_2$ [M+H$^+$]: 246.1488, found 246.1486.

Procedure for the synthesis of compound 7:[8b] To a stirring solution of the hydrogenation product 2d (0.2 mmol) in MeOH (3.0 mL) Boc_2O (0.4 mmol) and $NiCl_2.6H_2O$ (0.4 mmol) were first added, then $NaBH_4$ (1.6 mmol) was added portionwise at 0 ^{o}C over 1 hour. The mixture was stirred at room temperature until no starting material was detected by TLC and carefully quenched with H_2O. The aqueous layer was extracted with ethyl acetate, dried over $MgSO_4$. After the solvent was removed in vacuo, the residue was purified by silica gel column chromatography using petroleum ether/AcOEt as an eluent. colorless liquid; Yield: 84%; 98% ee; $[\alpha]_D^{25}$ = -5.2 (c = 0.5, $CHCl_3$); HPLC condition: Lux 5u Cellulose-2 (250 × 4.60mm), ipa : hex = 5:95, 1.0 mL/min, 230 nm; t_R = 14.6 min (major), t_R = 16.3 min (minor). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.19-7.11 (m, 2H), 7.10-7.02 (m, 2H), 4.42 (s, 1H), 3.49 (s, 3H), 3.07-3.03 (m, 1H), 2.87 (s, 2H), 2.58-2.44 (m, 2H), 1.82-1.64 (m, 2H), 1.33 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 172.2, 155.8, 141.5, 132.5, 128.8, 128.7, 127.3, 126.8, 51.6, 41.2, 39.1, 36.1, 28.4. ESI-HRMS Calcd. for $C_{17}H_{24}NO_4ClNa$ [M+Na$^+$]: 364.1292, found 364.1286.

Procedure for the synthesis of compound 8-10:[16] To a stirring solution of the hydrogenation product 2(0.2 mmol) in MeOH (3.0 mL) $NiCl_2.6H_2O$ (0.4 mmol) was first added, then $NaBH_4$

(1.6 mmol) was added portionwise at 0 °C over 1 h. The mixture was stirred at room temperature for 2 h and carefully quenched with H_2O. The aqueous layer was extracted with ethyl acetate, dried over $MgSO_4$. After the solvent was removed in vacuo, the residue was purified by silica gel column chromatography using petroleum ether/ AcOEt as an eluent.

(*S*)-4-phenylpiperidin-2-one (8a): white solid; Yield: 85%; MP: 137-139 °C; 98% ee; $[\alpha]_D^{25}$ = -20.2 (c = 0.5, $CHCl_3$); GC condition: Supelco beta Dex™ 225 column (30 m × 0.25 mm × 0.25 μm), N_2 1.0 mL/min, programmed 100 °C – 1 °C/min – 200 °C – 100 min; t_R = 93.0 min (major), t_R = 93.4 min (minor). ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.29-7.14 (m, 5H), 6.24 (s, 1H), 3.35-3.32 (m, 2H), 3.04-3.02 (m, 1H), 2.65-2.59 (m, 1H), 2.46-2.39 (m, 1H), 2.04-2.00 (m, 1H), 1.91-1.85 (m, 1H).[7a]

(*S*)-4-(4-fluorophenyl)piperidin-2-one (8b): white solid; Yield: 87%; MP: 156-158 °C; 99.4% ee; $[\alpha]_D^{25}$ = -22.2 (c = 0.5, $CHCl_3$); GC condition: Supelco beta Dex™ 225 column (30 m × 0.25 mm × 0.25 μm), N_2 1.0 mL/min, programmed 100 °C – 1 °C/min – 200 °C – 50 min; t_R = 97.9 min (major), t_R = 98.9 min (minor). ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.19-7.15 (m, 2H), 7.04-7.00 (m, 2H), 6.17 (s, 1H), 3.42-3.38 (m, 2H), 3.10-3.08 (m, 1H), 2.70-2.64 (m, 1H), 2.48-2.40 (m, 1H), 2.08-2.05 (m, 1H), 1.95-1.67 (m, 1H). ^{19}F NMR ($CDCl_3$, 376 MHz) *δ*: -116.9.[17]

5-phenylazepan-2-one (8c): Same protocol as for 5a. The mixture was stirred at reflux temperature until no starting material was detected by TLC and carefully quenched with H_2O. colorless liquid; Yield: 87%; 98% ee; HPLC condition: Lux 5u Cellulose-1 (250 × 4.60mm), ipa : hex = 20:80, 1.0 mL/min, 225 nm; t_R = 13.8 min (major), t_R = 15.2 min (minor). ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.32-7.16 (m, 5H), 6.52 (s, 1H), 3.43-3.27 (m, 2H), 2.58 (t, *J* = 12.0 Hz, 1H), 2.66-2.53 (m, 2H), 2.02-1.99 (m, 2H), 1.84-1.68 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 178.0, 145.9, 128.2, 126.2, 126.1, 48.4, 41.7, 36.9, 35.4, 30.1. TOF-HRMS Calcd. for $C_{12}H_{16}NO$ [M+H$^+$]: 190.1226, found 190.1227.

(*S*)-1-benzyl-4-(4-fluorophenyl)piperidin-2-one (9b): To a solution of 8b (0.200 g, 1.04 mmol) in THF (4.0 mL) under an N_2 atmosphere at room temperature was added NaH (0.124 g, 3.12 mmol), followed by benzylbromide (0.62 mL, 5.2 mmol). The mixture was stirred until no starting material was detected by TLC and carefully quenched with H_2O. The aqueous layer was extracted with ether, dried over $MgSO_4$ and concentrated. Purification by column chromatography gave white solid. Yield: 87%; MP: 64-66 °C; 99% ee; $[\alpha]_D^{25}$ = -15.2 (c = 0.5, $CHCl_3$); HPLC condition: Lux 5u Cellulose-3 (250 × 4.60mm), ipa : hex = 10:90, 1.0 mL/min, 230 nm; t_R = 10.0 min (minor), t_R = 10.3 min (major). ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.33-7.26 (m, 5H), 7.16-7.12 (m, 2H), 7.02-6.98 (m, 2H), 4.73 (d, *J* = 14.5 Hz, 1H), 4.54 (d, *J* = 14.5 Hz, 1H), 3.30-3.25 (m, 2H), 3.09-3.08 (m, 1H), 2.82-2.76 (m, 1H), 2.57-2.50 (m, 1H), 2.04-2.03 (m, 1H), 1.94-1.84 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 169.5, 163.4, 160.9, 139.7, 139.6, 137.6, 129.2, 128.7, 128.5, 128.0, 116.7, 116.0, 50.6, 46.8, 40.2, 38.5, 30.9. ^{19}F NMR ($CDCl_3$, 376 MHz) *δ*: -116.1.[18]

(*3R,4S*)-methyl-1-benzyl-4-(4-fluorophenyl)-2-oxopiperidine-3-carboxylate (10): To a stirred solution of 9b (0.100 g, 0.35 mmol) in tetrahydrofuran (2.0 mL) at −78 °C was added dropwise a solution of lithium diisopropylamide in cyclohexane (2.0 M, 0.53 mL, 1.05 mmol). After 1 hour, dimethyl carbonate (0.158 g, 1.75 mmol) was added dropwise. The resultant solution was stirred at −78 °C for 4 hours and quenched at this temperature with aqueous ammonium chloride. The aqueous layer was extracted with ethyl acetate, dried over $MgSO_4$ and concentrated. Purification by column chromatography gave white solid. Yield: 80%; MP: 96-98 °C; 96% ee; $[\alpha]_D^{25}$ = +3.2 (c = 0.5, $CHCl_3$); HPLC condition: Lux 5u Cellulose-1 (250 × 4.60mm), ipa : hex = 10:90, 1.0 mL/min, 254 nm; t_R = 21.9 min (minor), t_R = 27.8 min (major). ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.34-7.25 (m, 5H), 7.16-7.12 (m, 2H), 7.01-6.97 (m, 2H), 4.80 (d, *J* = 14.5 Hz, 1H), 4.78 (d, *J* = 14.5 Hz, 1H), 3.64 (s, 3H), 3.59 (d, *J* = 11.0 Hz, 1H), 3.47-3.36 (m, 2H), 3.31-3.29 (m, 1H), 2.04-1.98 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 171.0, 166.2, 161.0, 137.1, 129.3, 129.2, 128.8, 128.7, 128.5, 128.2, 128.0, 116.4, 115.9, 57.2, 52.9, 50.9, 46.7, 42.3, 29.2. ^{19}F NMR ($CDCl_3$, 376 MHz) *δ*: -115.1.[19]

Conclusions

In conclusion, we have developed a highly efficient and enantioselective hydrogenation of α,β-unsaturated nitriles bearing an ester or amide group to produce chiral nitriles with excellent enantioselectivities (up to 99.7% ee) and high turnover numbers (TON up to 10,000). Moreover, this method is also successfully employed to the synthesis of the chiral lactams including pharmaceuticals, Paroxetine and Femoxetine in high yields with excellent enantioselectivities.

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