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Enantioselective Hydrogenation of β,β-Disubstituted Unsaturated Carboxylic Acids under Base-free Conditions

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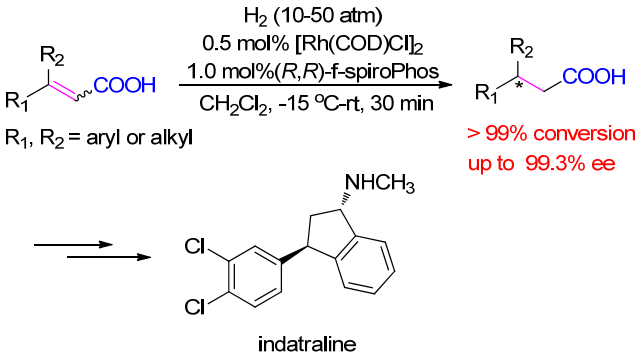


ABSTRACT: An additive-free enantioselective hydrogenation of β,β-disubstituted unsaturated carboxylic acids catalyzed by Rh-(*R*,*R*)-f-spiroPhos complex has been developed. Under mild conditions, a wide scope of β,β-disubstituted unsaturated carboxylic acids were hydrogenated to the corresponding chiral carboxylic acids with excellent enantioselectivities (up to 99.3% ee). This methodology was also successfully applied to the synthesis of the pharmaceutical molecule, indatraline.

INTRODUCTION

Optically active β,β-disubstituted propionic acids are important structural moieties which widely exist in many biologically active compounds and pharmaceuticals, including Lyrica,[1] baclofen,[2] ar-turmerone,[3] indatraline,[4] R-106578, and natural products, such as cherylline [5] and

Heliannuols [6] (Figure 1). Accordingly, the development of methodologies for the enantioselective synthesis of chiral β,β-disubstituted propionic acids is highly desirable and has attracted much attention from synthetic chemists.

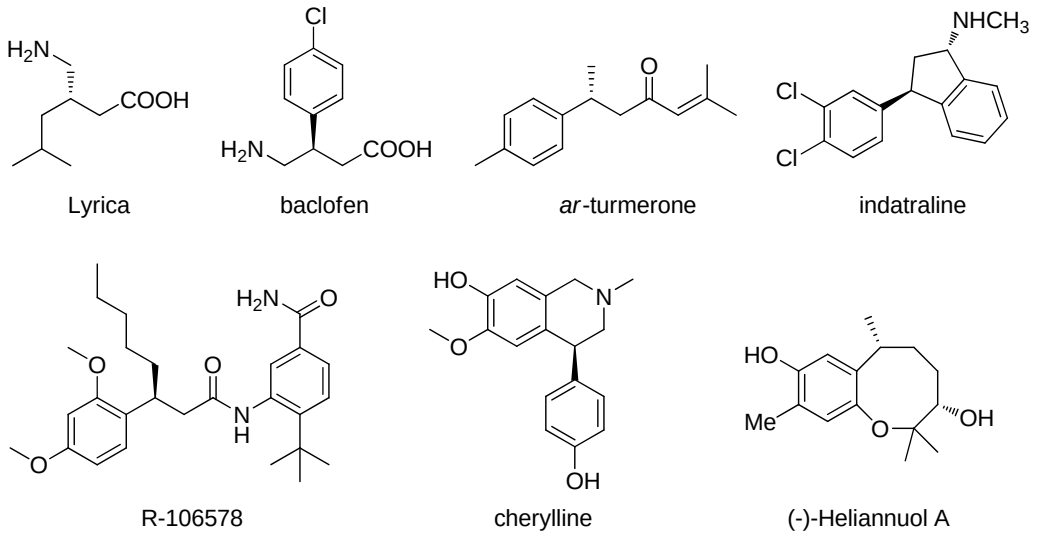
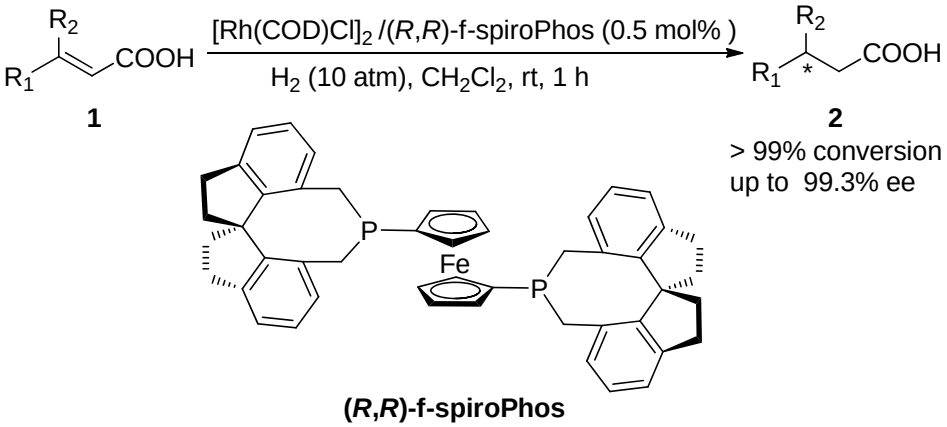


Figure 1. Key structural elements in chiral pharmaceuticals and natural products.

Up to now, there are many methods for approaching chiral β,β-disubstituted propionic acids,[7] such as Cu-, Co- or Rh-catalyzed asymmetric 1,4-reduction of β,β-disubstituted unsaturated acrylates or nitriles using moisture-sensitive hydrosilane derivatives or borohydride reagents,[8] and asymmetric 1,4-additions of nucleophilic reagents to α,β-unsaturated carbonyl compounds catalyzed by Pd, Rh or Cu complexes.[9] Among these, the direct enantioselective hydrogenation of β,β-disubstituted unsaturated acrylic acids is the most straightforward and efficient method for chiral β,β-disubstituted propionic acids in spite of the asymmetric hydrogenation of β-arylbut-3-enoic acids and β,β-disubstituted unsaturated acrylates.[10] However, contrasted with the asymmetric hydrogenation of α-substituted unsaturated acrylic acids,[10i,11] the enantioselective hydrogenation of β,β-disubstituted unsaturated acrylic acids still remains a challenge and is less explored. Rh catalysts with chiral phosphine ligands and the Ru-Binap complex were developed

for asymmetric hydrogenations β,β-disubstituted unsaturated acrylic acids with good enantioselectivity.[12] A Pd catalyst with cinchona alkaloid could also be used in the hydrogenation of β-CF_3-substituted acrylic acids, but poor enantioselectivities were obtained.[13] Recently, Ding and co-workers developed a Rh catalyst containing a chiral monodentate phosphine (SPO) ligand and an achiral Ph_3P ligand, which exhibited excellent enantioselectivity for the asymmetric hydrogenation of β,β-diarylacrylic acids and β-CF_3-substituted acrylic acids.[11f,14] Whereas in most of reported cases of the asymmetric hydrogenation of unsaturated acrylic acids, a base additive (NEt_3 or morpholine) was required to achieve high efficiency and enantioselectivity.[11-14] Accordingly, the development of more efficient catalysts for the asymmetric hydrogenation of β,β-disubstituted acrylic acids is highly desirable. Inspired by the excellent performance of the chiral diphosphine ligand f-spiroPhos in Rh- or Ir-catalyzed asymmetric hydrogenations of α,β-unsaturated nitriles and nitroolefins,[15] we evaluated this ligand for the hydrogenation of β,β-disubstituted unsaturated acrylic acids including sterically similar β,β-diaryl unsaturated acrylic acids and found that its Rh complex showing excellent enantioselectivities (up to 99.3% ee) under mild reaction conditions without any additive (Scheme 1).

Scheme 1



(*R*,*R*)-f-spiroPhos

RESULTS AND DISCUSSION

To optimize the reaction conditions, (*E*)-3-phenylbut-2-enoic acid **1a** was used as the model substrate, and the hydrogenation was initially performed without any additive using the complex of (*R*,*R*)-f-spiroPhos and $[Rh(COD)Cl]_2$ or $[Ir(COD)Cl]_2$ as the catalyst under 50 atm of H_2 in CH_2Cl_2 at room temperature for 6 h. To our delight, the Rh-(*R*,*R*)-f-spiroPhos catalyst provided a full conversion and high enantioselectivity, 93% ee (Table 1, entry 1), which was attributed to the electron-rich property and rigidity of the ligand. Whereas poor results, 26% conversion and 35% ee, were observed using $[Ir(COD)Cl]_2$ precursor. Subsequently, some other chiral phosphorus ligands illustrated in Figure 2 were investigated and the results revealed that most of them were not efficient for this transformation giving either low conversions or poor enantioselectivities (entries 2–5) except for (*S*,*S*)-f-Binaphane, which provided a good conversion and enantioselectivty (entry 6). Good enantioselectivities and almost full conversions could be achieved in most of solvents, such as THF, MeOH, toluene, and DME (entries 7–10). In addition to CH_2Cl_2, 1,4-dioxane could also afford a similar enantioselectivity despite incomplete conversion (entry 11). Moreover, decreasing the hydrogen pressure from 50 atm to 10 atm, this transformation could still complete in 1 h with a slight higher enantioselectivity (entry 12). Lower reaction temperature resulted in a much higher ee value, 97% ee, in spite of a little longer time required for the full conversion (entry 13). Finally, we evaluated the effect of added base (10 mol% NEt_3) on catalyst performance under the optimized conditions, a moderate enantioselectivity and incomplete conversion (72% ee, 27% conv.) was obtained. The asymmetric hydrogenation of the corresponding (*E*)-methyl 3-phenylbut-2-enoate was also investigated, but a very poor reactivity

(< 1% conv.) was observed. These results revealed that this catalyst should be more suitable for the free acids and has good tolerance for acidic condition.

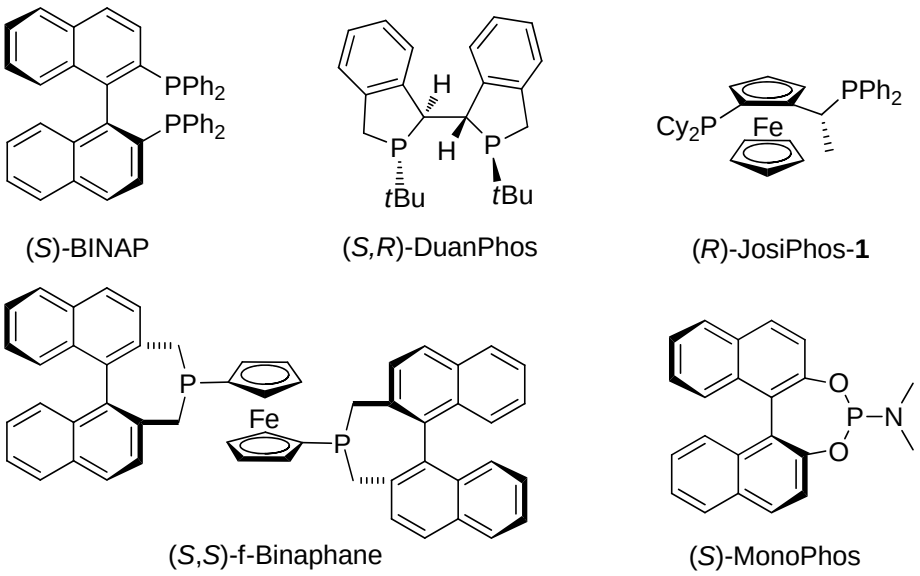
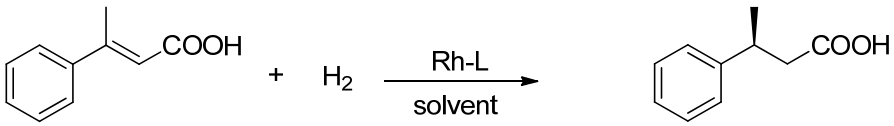


Figure 2. Phosphine ligands tested for the hydrogenation of (*E*)-3-phenylbut-2-enoic acid **1a**.

Table 1. Asymmetric Hydrogenation of (*E*)-3-Phenylbut-2-enoic Acid 1a, Optimizing Reaction Conditions.[a]



1a **2a**

entry	ligand	solvent	conversion (%)[b]	ee (%)[c]
1	(*R*,*R*)-f-spiroPhos	CH_2Cl_2	>99	93
2	(*S*)-Binap	CH_2Cl_2	2	42
3	(*S*,*R*)-DuanPhos	CH_2Cl_2	2	14
4	(*R*)-JosiPhos-1	CH_2Cl_2	37	15
5	(*S*)-MonoPhos	CH_2Cl_2	0.4	ND
6	(*S*,*S*)-f-Binaphane	CH_2Cl_2	79	86
7	(*R*,*R*)-f-spiroPhos	THF	98	60
8	(*R*,*R*)-f-spiroPhos	MeOH	>99	86
9	(*R*,*R*)-f-spiroPhos	Toluene	97	91

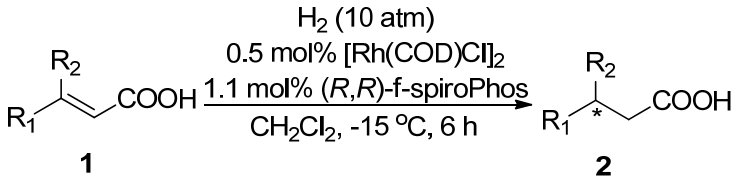
10	(*R*,*R*)-f-spiroPhos	DME	95	88
11	(*R*,*R*)-f-spiroPhos	dioxane	95	94
12[d]	(*R*,*R*)-f-spiroPhos	CH_2Cl_2	>99	94
13[e]	(*R*,*R*)-f-spiroPhos	CH_2Cl_2	>99	97

[a] reaction conditions: $[Rh(COD)Cl]_2$/diphosphine (monophosphine)/substrate ratio = 0.5 : 1.1 (2.1) : 100, 50 atm H_2, 6 h, r.t. [b] Determined by chiral GC. [c] Determined by chiral GC using a Supelco Gamma-Dex 225 column (30 m × 0.25 mm × 0.25 μm). [d] 10 atm H_2, 1 h. [e] 10 atm H_2, -15 ^oC, 6 h.

Encouraged by the promising results obtained in the hydrogenation of substrate **1a**, a series of β,β-disubstituted unsaturated carboxylic acids **1b**–**1t** were successfully hydrogenated under optimized reaction conditions to provide the corresponding chiral acids with excellent ee values, 91-99.3% ee, and complete conversions, regardless of the position or electronic property of substituents on the phenyl ring (Table 2). For example, Substrates bearing an electron-withdrawing substituent, F, Cl, Br, NO_2 group or an electron-donating substituent, Me, MeO group at the *para*- , *meta*- or *ortho*- position of the phenyl group were hydrogenated with excellent enatioselectivities, up to 99.3% ee (entries 1–11). The substrate **1j** with a methyl group at the *ortho*-position of phenyl ring provided **2j** with the highest enantioselectivity, 99.3% ee, presumably due to the steric hindrance. The similar effect was also observed for substrates **1k** with an *ortho*-nitro group and **1l** with a 1-naphthyl group, and excellent enantioselectivities were provided even at room temperature (entries 11–12). Gratifyingly, excellent ee values, 97 and 98% ee respectively, were also obtained for the substrates with a larger alkyl group, ^{i}Pr or cyclohexyl (entries 14–15). However, for the dialkyl substrates **1p** and **1q**, only moderate enantioselectivities were observed possibly attributed to the flexibility of the alkyl groups (entries 16–17). It is notable

that this catalyst system was also efficient for the asymmetric hydrogenation of challenging substrates β,β-diarylacrylic acids due to the difficult differentiation of a stereogenic center with two sterically similar aryl groups, providing the corresponding β,β-diarylpropionic acids with excellent enantioselectivities (entries 18–20). In addition, a large scale (1.5 g) hydrogenation of **1b** could be performed smoothly with a full conversion and maintained ee value (entry 21).

Table 2. Rh-Catalyzed Asymmetric Hydrogenation of β,β-Disubstituted Unsaturated Carboxylic Acids 1.[a]



1 **2**

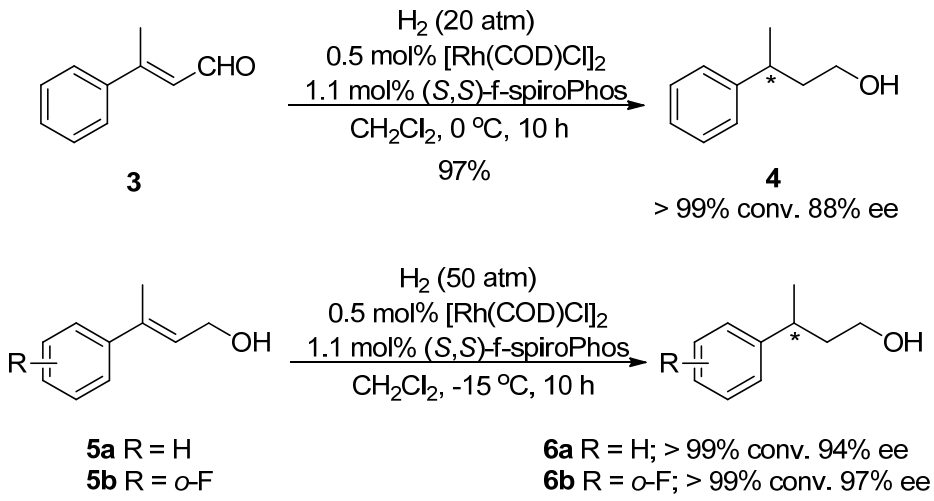
entry	R_1	R_2	product	Conversion (%)[b]	ee (%)[c]
1	(*E*)-C_6H_5(**1a**)	Me	**2a**	>99	97(*S*)
2	(*E*)-4-ClC_6H_4(**1b**)	Me	**2b**	>99	95(+)
3	(*E*)-4-$NO_2C_6H_4$(**1c**)	Me	**2c**	>99	97(+)
4	(*E*)-3-FC_6H_4(**1d**)	Me	**2d**	>99	96(+)
5	(*E*)-3-BrC_6H_4(**1e**)	Me	**2e**	>99	97(+)
6	(*E*)-3-$NO_2C_6H_4$(**1f**)	Me	**2f**	>99	97(+)
7	(*E*)-3-$MeOC_6H_4$(**1g**)	Me	**2g**	>99	91(+)
8	(*E*)-2-FC_6H_4(**1h**)	Me	**2h**	>99	96(+)
9	(*E*)-2-ClC_6H_4(**1i**)	Me	**2i**	>99	93(-)
10	(*E*)-2-MeC_6H_4(**1j**)	Me	**2j**	>99	99.3(+)
11[d]	(*E*)-2-$NO_2C_6H_4$(**1k**)	Me	**2k**	>99	97(-)
12[d]	(*E*)-1-naphthyl(**1l**)	Me	**2l**	>99	98(*S*)
13[d]	(*E*)-C_6H_5(**1m**)	Et	**2m**	>99	94(*S*)
14[d]	(*E*)-C_6H_5(**1n**)	^{i}Pr	**2n**	>99	97(*S*)
15[d]	(*E*)-C_6H_5(**1o**)	C_6H_{11}	**2o**	>99	98(*S*)
16[d]	(*E*)-$C_6H_5(CH_2)_2$(**1p**)	Me	**2p**	>99	66(*R*)
17[d]	(*E*)-C_6H_{11}(**1q**)	Me	**2q**	91	73(-)
18[e]	(*Z*)-3,4-ClC_6H_4(**1r**)	C_6H_5	**2r**	>99	97(*S*)

19[e]	(*Z*)-2-FC_6H_4(**1s**)	C_6H_5	**2s**	>99	94(*S*)
20[e]	(*Z*)-3-ClC_6H_4(**1t**)	C_6H_5	**2t**	>99	97(-)
21[f]	(*E*)-4-ClC_6H_4(**1b**)	Me	**2b**	>99	95(+)

[a] Unless otherwise mentioned, all reactions were carried out with a $[Rh(COD)Cl]_2$/(*R*,*R*)-f-spiroPhos/substrate ratio of 0.5 : 1.1 : 100, CH_2Cl_2, 50 atm H_2, -15 °C, 6 h. [b] Determined by ^1H NMR spectroscopy or GC analysis. [c] Determined by HPLC analysis using a chiral stationary phase or chiral GC analysis. [d] r.t., 10 atm H_2, 1 h. [e] 0 °C, 10 atm H_2, 4 h. [f] 1.5 g substrate.

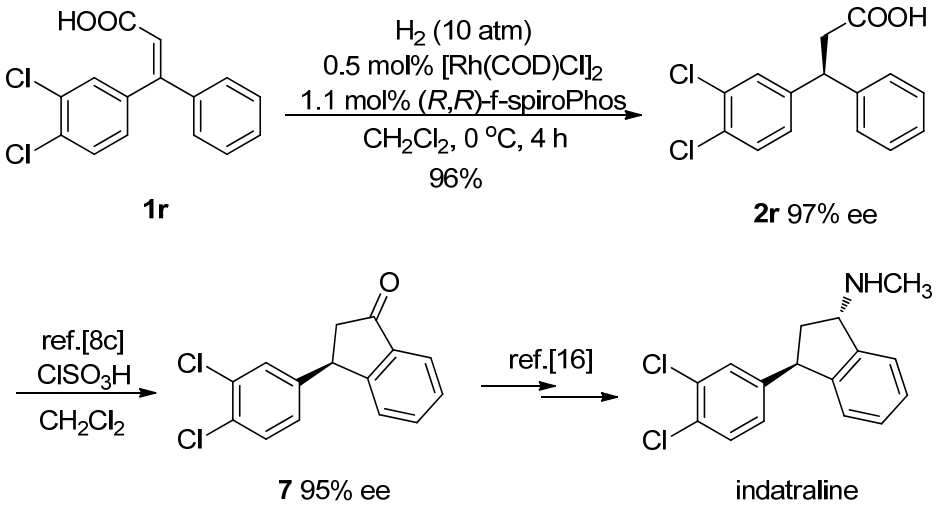
To our delight, in addition to β,β-disubstituted unsaturated carboxylic acids, this catalyst system exhibited excellent enantioselectivity for the asymmetric hydrogenation of β,β-disubstituted unsaturated aldehydes and γ,γ-disubstituted unsaturated alcohols. Under the mild reaction conditions, the unsaturated aldehyde **3** and γ,γ-disubstituted unsaturated alcohols **5a** and **5b** were successfully hydrogenated affording chiral alcohols **4** and **6** in full conversions and excellent enantioselectivities, up to 97% ee (scheme 2). But when this catalyst was applied to the substrates bearing a neighboring polar group, such as an ester ((*E*)-4-methoxy-4-oxo-3-phenylbut-2-enoic) or amide group ((*Z*)-4-oxo-3-phenyl-4-(phenylamino)but-2-enoic acid), very poor reactivities (< 10% conv.) were observed for both substrates presumably due to the effect on the electronic property of C=C bond by two polar groups.

Scheme 2



To demonstrate the application of this method, this catalyst system was applied to the preparation of the key intermediate **7** for the synthesis of indatraline, a non-selective monoamine reuptake inhibitor.[4] It could be readily afforded by this method from the hydrogenation product β,β-diarylacrylic acid **1r** in high yield and excellent enantioselectivity, 95% ee (Scheme 3).[8c, 16]

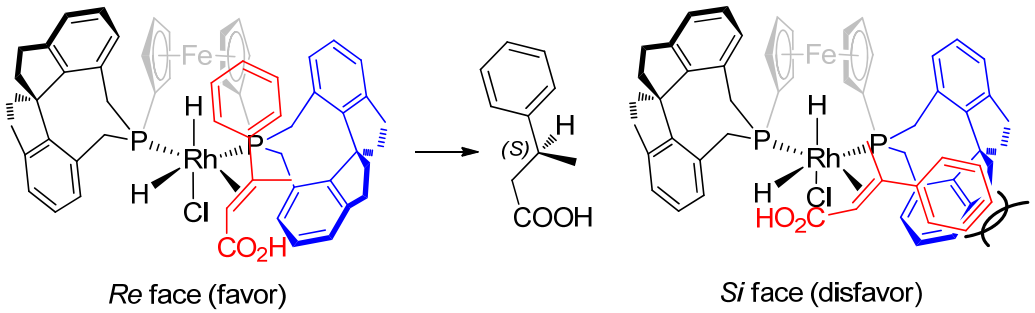
Scheme 3



According to the reported mechanism of rhodium catalyzed asymmetric hydrogenation of unsaturated nitriles,[15a] a possible enantio-determining transition model were also proposed (Scheme 4). The different bulk of two substituents at the beta carbon atom possibly had an

influence on the coordination of the substrate to rhodium. It was revealed that the coordination from the *Re*-face of the substrates was much more favorable resulting in the (*S*) products, which was in agreement with the absolute configuration outcome of the hydrogenation products. For 3,3-diaryl-substituted substrates, the primary recognition element responsible for enantioselection probably was the alpha C atom bearing a small H atom and a significantly larger carboxylic group. The enantioselectivity probably mainly depends on the steric bulk difference between the two substituents on the alpha C atom.[10h, 11g]

Scheme 4



CONCLUSIONS

In conclusion, we have developed a method for Rh-catalyzed asymmetric hydrogenation of β,β-disubstituted unsaturated carboxylic acids without any additive with high activities and excellent enantioselectivities. This catalyst system is tolerant towards steric hindrance and is also very efficient for the asymmetric hydrogenation of β,β-diarylacrylic acids, β,β-disubstituted unsaturated aldehyde and γ,γ-disubstituted unsaturated alcohols with excellent enantioselectives.

EXPERIMENTAL SECTION

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 spectra were recorded on 400 MHz spectrometers. ^{13}C NMR (proton-decoupled) spectra were obtained at 100 MHz. $CDC1_3$ or DMSO-d^6 was the solvent used for the NMR analysis, with tetramethylsilane as the internal standard. Chemical shifts were reported upfield to TMS (0.00 ppm) for ^{1}H NMR. Optical rotation was determined using a polarimeter. HRMS were recorded on a mass spectrometer with APCI.

General procedure for the synthesis and characterization data for compounds 1: To a suspension of sodium hydride (0.7-1.5 g, 20.9-43.7 mmol, 1.5 equiv, 70% in mineral oil) in THF (140 mL) was added dropwise the corresponding triethyl phosphonoacetate (4.7-9.8 g, 20.9-43.7 mmol, 1.5 equiv) at 0 ^{o}C. The resulting solution was stirred for 3.0 h until gas evolution had ceased. And the corresponding ketone (3.5 g, 13.9-29.1 mmol, 1.0 equiv) in THF (14 mL) was added via syringe. The solution was stirred at room temperature until no starting material was detected by TLC. Then the reaction mixture was quenched with saturated aqueous NH_4Cl solution. The layers were separated and the aqueous phase was extracted with diethyl ether. The combined organic layers were washed with saturated aqueous NaCl solution, dried over Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (PE : EA = 50:1-20:1) afforded the corresponding acrylate.

The corresponding acrylate (500.0 mg, 1.6-2.6 mmol) was placed in a 50 mL round bottom flask, then EtOH (5.4 mL) was added, the reaction mixture was stirred and NaOH (10%, 10.8 mL) was added. The reaction mixture was stirred at room temperature until no starting material was detected by TLC. Then adjust PH to 1.0 with HCl (1 N). The mixture was extracted with diethyl

ether. The combined organic layer was washed with saturated aqueous NaCl solution, dried over Na_2SO_4 and concentrated in vacuo. Purification by recrystallization provided the corresponding carboxylic acid **1**.[17]

(*E*)-3-phenylbut-2-enoic acid (**1a**): Purification by recrystallization (EA / PE) afforded the product as white solid; yield: 423 mg, > 99%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 12.01 (s, 1H), 7.53-7.50 (m, 2H), 7.44-7.39 (m, 3H), 6.20 (d, *J* = 0.9 Hz, 1H), 2.63 (d, *J* = 0.8 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ = 172.7, 158.5, 141.9, 129.3, 128.5, 126.3, 116.5, 18.2; MP: 90-92 ^{o}C. The analytical data are consistent with the literature.[14]

(*E*)-3-(4-chlorophenyl)but-2-enoic acid (**1b**): Purification by recrystallization (EA / PE) afforded the product as white solid; yield: 434 mg, > 99%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.44-7.42 (m, 2H), 7.38-7.35 (m, 2H), 6.15 (d, *J* = 1.2 Hz, 1H), 2.58 (d, *J* = 1.2 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ = 172.5, 157.2, 140.3, 135.4, 128.8, 127.8, 116.8, 18.2; MP: 130-132 ^{o}C. The analytical data are consistent with the literature.[18]

(*E*)-3-(4-nitrophenyl)but-2-enoic acid (**1c**): Purification by recrystallization (EA / PE) afforded the product as white solid; 437 mg, yield: > 99%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.27-8.25 (m, 2H), 7.65-7.63 (m, 2H), 6.22 (d, *J* = 1.3 Hz, 1H), 2.62 (d, *J* = 1.3 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ = 171.4, 155.9, 148.2, 148.1, 127.4, 123.9, 119.2, 18.4; MP: 164-166 ^{o}C. The analytical data are consistent with the literature.[19]

(*E*)-3-(3-fluorophenyl)but-2-enoic acid (**1d**): Purification by recrystallization (EA / PE) afforded the product as white solid; yield: 430 mg, > 99%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39-7.33 (m, 1H), 7.20-7.19 (m, 1H), 7.18-7.17 (m, 1H), 7.11-7.06 (m, 1H), 6.17 (d, *J* = 1.2 Hz, 1H), 2.58 (d, *J* = 1.2 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ = 172.3, 162.7 (d, $^1J_{C\text{-}F}$ = 245.0 Hz), 156.9,

144.1 (d, *J* = 7.2 Hz), 130.1 (d, *J* = 8.2 Hz), 122.1 (d, *J* = 2.6 Hz), 117.3, 116.1 (d, *J* = 21.1 Hz), 113.5 (d, *J* = 22.2 Hz), 18.2; MP: 129-131 °C. The analytical data are consistent with the literature.[20]

(*E*)-3-(3-bromophenyl)but-2-enoic acid (**1e**): Purification by recrystallization (EA / PE) afforded the product as white solid; yield: 446 mg, > 99%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.63-7.62 (m, 1H), 7.53-7.50 (m, 1H), 7.43-7.40 (m, 1H), 7.29-7.25 (m, 1H), 6.15 (d, *J* = 1.2 Hz, 1H), 2.57 (d, *J* = 1.2 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, DMSO-d^6) δ = 167.8, 152.4, 144.4, 132.2, 131.1, 129.3, 125.8, 122.5, 119.3, 17.6; MP: 156-158 °C. The analytical data are consistent with the literature.[21]

(*E*)-3-(3-nitrophenyl)but-2-enoic acid (**1f**): Purification by recrystallization (EA / PE) afforded the product as white solid; yield: 430 mg, 98%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.36 (m, 1H), 8.26-8.24 (m, 1H), 7.83-7.81 (m, 1H), 7.61-7.57 (m, 1H), 6.25 (s, 1H), 2.64 (d, *J* = 0.9 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d^6) δ = 167.8, 151.5, 148.5, 143.5, 133.2, 130.6, 124.0, 121.3, 120.2, 17.6; MP: 188-190 °C. The analytical data are consistent with the literature.[22]

(*E*)-3-(3-methoxyphenyl)but-2-enoic acid(**1g**): Purification by recrystallization (EA / PE) afforded the product as white solid; yield: 430 mg, 99%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.33-7.29 (m, 1H), 7.10-7.07 (m, 1H), 7.01-7.00 (m, 1H), 6.94-6.92 (m, 1H), 6.17 (d, *J* = 1.3 Hz, 1H), 3.84 (s, 3H), 2.59 (d, *J* = 1.3 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ = 172.5, 159.6, 158.4, 143.5, 129.5, 118.8, 116.6, 114.7, 112.1, 55.3, 18.4; MP: 94-96 °C. The analytical data are consistent with the literature.[23]

(*E*)-3-(2-fluorophenyl)but-2-enoic acid (**1h**): Purification by recrystallization (EA / PE) afforded the product as white solid; yield: 434 mg, > 99%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36-7.28 (m, 2H), 7.17-7.07 (m, 2H), 6.05 (d, *J* = 1.2 Hz, 1H), 2.56 (t, *J* = 1.6 Hz, 3H); ^{13}C{^{1}H}NMR (100

MHz, $CDCl_3$) δ = 172.2, 159.4 (d, $^1J_{C\text{-}F}$ = 248.4 Hz), 155.1, 130.7 (d, *J* = 13.1 Hz), 130.3 (d, *J* = 8.5 Hz), 129.1 (d, *J* = 3.5 Hz), 124.2 (d, *J* = 2.4 Hz), 119.8 (d, *J* = 2.4 Hz), 116.1 (d, *J* = 22.1 Hz), 19.8 (d, *J* = 3.6 Hz); MP: 90-92 °C. The analytical data are consistent with the literature.[20]

(*E*)-3-(2-chlorophenyl)but-2-enoic acid (**1i**): Purification by recrystallization (EA / PE) afforded the product as white solid; yield: 240 mg, 83%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41-7.39 (m, 1H), 7.28-7.25 (m, 2H), 7.20-7.17 (m, 2H), 5.88 (d, *J* = 1.4 Hz,1H), 2.52 (d, *J* = 1.4 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ = 172.2, 158.9, 142.4, 131.1, 129.9, 129.3, 128.8, 126.8, 120.1, 20.6; MP: 102-104 °C. The analytical data are consistent with the literature.[24]

(*E*)-3-(o-tolyl)but-2-enoic acid (**1j**): Purification by column chromatography (PE : EA = 2:1) afforded the product as light yellow solid; yield: 140 mg, 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.25-7.16 (m, 3H), 7.09-7.08 (m, 1H), 5.82 (d, *J* = 1.1 Hz, 1H), 2.47 (d, *J* = 1.3 Hz, 3H), 2.30 (s, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ = 172.4, 161.4, 143.7, 133.7, 130.5, 127.9, 126.9, 125.8, 118.9, 21.2, 19.7; MP: 83-85 °C. The analytical data are consistent with the literature.[25]

(*E*)-3-(2-nitrophenyl)but-2-enoic acid (**1k**): Purification by recrystallization (EA / PE) afforded the product as light orange solid; yield: 440 mg, > 99%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.08-8.05 (m, 1H), 7.66-7.62 (m, 1H), 7.54-7.50 (m, 1H), 7.33-7.31 (m, 1H), 5.84 (d, *J* = 1.4 Hz, 1H), 2.48 (d, *J* = 1.3 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ = 171.5, 158.0, 146.7, 139.3, 133.6, 129.8, 129.1, 124.8, 118.4, 20.8; MP: 122-124 °C. APCI-HRMS: Calcd. for $C_{10}H_{10}NO_4$ [M+H$^+$]: 208.0304, found 208.0308.

(*E*)-3-(naphthalen-1-yl)but-2-enoic acid (**1l**): Purification by recrystallization (EA / PE) afforded the product as light yellow solid; yield: 398 mg, 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.93-7.83 (m, 3H), 7.55-7.45 (m, 3H), 7.33-7.32 (m, 1H), 6.08-6.07 (m, 1H), 2.69-2.68 (m, 3H);

$^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$) δ = 172.5, 160.3, 141.8, 133.6, 129.8, 128.5, 128.4, 126.4, 126.0, 125.1, 124.1, 120.0, 22.0; MP: 90-92 °C. The analytical data are consistent with the literature.[26]

(*E*)-3-phenylpent-2-enoic acid (**1m**): Purification by recrystallization (EA / PE) afforded the product as white solid; yield: 410 mg, 95%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.48 -7.46 (m, 2H), 7.41-7.38 (m, 3H), 6.06 (s, 1H), 3.16-3.11 (m, 2H), 1.09 (t, *J* = 7.4 Hz, 3H); $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$) δ = 172.3, 165.0, 140.8, 129.2, 128.5, 126.7, 116.1, 24.5, 13.6; MP: 94-96 °C. The analytical data are consistent with the literature.[27]

(*E*)-4-methyl-3-phenylpent-2-enoic acid (**1n**): Purification by recrystallization (EA / PE) afforded the product as white solid; yield: 353 mg, 81%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36-7.32 (m, 3H), 7.22-7.20 (m, 2H), 5.75 (s, 1H), 4.18-4.09 (m, 1H), 1.10 (d, *J* = 7.0 Hz, 6H); $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$) δ = 172.0, 170.2, 140.5, 127.8, 127.7, 127.5, 117.9, 29.7, 21.3; MP: 96-98 °C. The analytical data are consistent with the literature.[25]

(*E*)-3-cyclohexyl-3-phenylacrylic acid (**1o**): Purification by recrystallization (EA / PE) afforded the product as white solid; yield: 160 mg, 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35 -7.29 (m, 3H), 7.10-7.07 (m, 2H), 5.82 (d, *J* = 0.9 Hz, 1H), 2.28-2.22 (m, 1H), 1.80-1.75 (m, 4H), 1.26-1.10 (m, 6H); $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$) δ = 171.6, 167.0, 139.9, 127.7, 127.4, 127.0, 115.2, 47.7, 31.6, 26.4, 26.0; MP: 140-142 °C. The analytical data are consistent with the literature.[28]

(*E*)-3-methyl-5-phenylpent-2-enoic acid (**1p**): Purification by recrystallization (EA / PE) afforded the product as white solid; yield: 427 mg, 98%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34-7.31 (m, 2H), 7.23-7.20 (m, 3H), 5.74 (s, 1H), 2.85-2.81 (m, 2H), 2.53-2.49 (m, 2H), 2.25 (s, 3H); $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$) δ = 172.6, 162.3, 140.9, 128.6, 128.3, 126.2, 115.7, 43.0, 33.9, 19.4; MP: 50-52 °C. The analytical data are consistent with the literature.[29]

(*E*)-3-cyclohexylbut-2-enoic acid (**1q**): Purification by recrystallization (EA / PE) afforded the product as white solid; yield: 427 mg, > 99%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.68 (t, *J* = 1.0 Hz, 1H), 2.15 (d, *J* = 1.2 Hz, 3H), 2.04-1.98 (m, 1H), 1.84-1.69 (m, 5H), 1.37-1.11 (m, 5H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ = 173.0, 168.1, 113.5, 49.0, 31.2, 26.3, 26.0, 17.7; MP: 74-76 ^{o}C. The analytical data are consistent with the literature.[30]

(*Z*)-3-(3,4-dichlorophenyl)-3-phenylacrylic acid (**1r**): Purification by recrystallization (EA / PE) afforded the product as white solid; yield: 447 mg, 98%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.47-7.07 (m, 8H), 6.38 (s, 1H); ^{13}C{^{1}H}NMR (100 MHz, DMSO- d^6) δ = 166.8, 152.0, 140.1, 139.7, 131.2, 131.1, 131.0, 130.6, 130.1, 129.8, 129.2, 128.3, 120.2; MP: 174-176 ^{o}C. The analytical data are consistent with the literature.[14]

(*Z*)-3-(2-fluorophenyl)-3-phenylacrylic acid (**1s**): Purification by recrystallization (EA / PE) afforded the product as white solid; yield: 358 mg, 80%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.40 -7.30 (m, 6H), 7.18-7.08 (m, 3H), 6.48 (s, 1H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ = 170.9, 159.4 (d, $^{1}J_{C\text{-}F}$ = 246.1 Hz), 152.2, 139.5, 130.7, 130.1 (d, *J* = 8.0 Hz), 129.9, 128.5, 127.8, 126.0 (d, *J* = 15.8 Hz), 123.7, 118.5, 115.4 (d, *J* = 21.8 Hz); MP: 156-158 ^{o}C. The analytical data are consistent with the literature.[14]

(*Z*)-3-(3-chlorophenyl)-3-phenylacrylic acid (**1t**): Purification by recrystallization (EA / PE) afforded the product as white solid; yield: 263 mg, > 99%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38-7.28 (m, 5H), 7.24-7.23 (m, 2H), 7.16 (s, 1H), 7.09-7.07 (m, 1H), 6.32 (s, 1H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ = 171.2, 157.5, 140.0, 139.9, 133.8, 130.0, 129.2, 129.0, 128.5, 128.4, 128.3, 127.4, 117.0; MP: 137-139 ^{o}C. APCI-HRMS: Calcd. For $C_{15}H_{12}ClO_2$ [M+H^{+}]: 259.0520, Found: 259.0523.

The procedure for the synthesis and characterization data for the compound 3: (*E*)-3-phenylbut-2-enenitrile (500.0 mg, 3.5 mmol, 1.0 eq)[15a] was placed in an oven-dried 50 mL, three-neck round bottom flask. THF (5 mL) was added under nitrogen. The reaction mixture was cooled and DibAl-H (5.2 ml, 1.0 M, 5.2 mmol, 1.5 eq) was added dropwise with stirring at -10 ^{o}C. The solution was stirred at rt for 2.0 h. Then, the reaction mixture was quenched with water and HCl (5%) slowly maintaining the temperature at -10 ^{o}C. The mixture extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purification by chromatography (PE : EA = 15:1) on silica gel to give **3** (yellow liquid, 240.3 mg, 47.1%).[31] ^{1}H NMR (400 MHz, $CDCl_3$) δ = 10.2 (d, *J* = 7.9 Hz, 1H), 7.55-7.53 (m, 2H), 7.42-7.41 (m, 3H), 6.39 (d, *J* = 7.9 Hz, 1H), 2.57 (s, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ = 191.1, 157.5, 140.3, 129.9, 128.5, 127.0, 126.1, 16.1; The analytical data are consistent with the literature.[32]

General procedure for the synthesis and characterization data for compounds 5: The corresponding acrylate (0.7 g, 3.7 mmol for **5a**; 0.9 g, 4.1 mmol for **5b**) was placed in an oven-dried 50 mL, three-neck round bottom flask. THF (20 mL) was added under nitrogen. The reaction mixture was cooled and $LiAlH_4$ (140 mg for **5a**; 150 mg for **5b**, 1.0 eq) was added dropwise with stirring at -78 ^{o}C. The solution was stirred at room temperature for 1 h. Then, the reaction mixture was quenched with water and HCl (5%) slowly maintaining the trmperature at -78 ^{o}C. The mixture extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purification by chromatography (PE : EA = 5:1) on silica gel to give **5a** (400 mg colourless liquid 73.4%) and **5b** (646 mg colourless liquid 95%).[17a, 31c]

(*E*)-3-phenylbut-2-en-1-ol (**5a**): Purification by recrystallization (EA / PE) afforded the product as yellow liquid; yield: 400 mg, 73%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29-7.27 (m, 2H), 7.21-7.18 (m, 2H), 7.15-7.11 (m, 1H), 5.84 (t, *J* = 6.6 Hz, 1H), 4.23 (d, *J* = 6.6 Hz, 2H), 1.95 (s, 3H), 1.42 (s, 1H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ = 142.6, 136.9, 128.0, 126.9, 126.5, 125.5, 59.4, 15.7; The analytical data are consistent with the literature.[33]

(*E*)-3-(2-fluorophenyl)but-2-en-1-ol (**5b**): Purification by recrystallization (EA / PE) afforded the product as yellow liquid; yield: 646 mg, 95%; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.12-7.07 (m, 2H), 6.97-6.93 (m, 1H), 6.91-6.86 (m, 1H), 5.67 (t, *J* = 6.3 Hz, 1H), 4.21 (d, *J* = 5.3 Hz, 2H), 1.91 (s, 3H), 1.60 (s, 1H); ^{13}C{^{1}H}NMR (400 MHz, $CDCl_3$) δ = 159.8 (d, $^{1}J_{C\text{-}F}$ = 245.5 Hz), 134.1, 131.7 (d, *J* = 14.0 Hz), 130.0, 129.6 (d, *J* = 4.1 Hz), 128.6 (d, *J* = 8.2 Hz), 124.0 (d, *J* = 3.2 Hz), 115.7 (d, *J* = 22.5 Hz), 59.3, 17.1 (d, *J* = 3.6 Hz); APCI-HRMS Calcd. for $C_{10}H_{12}FO$ [M+H^{+}]: 167.0872, found 167.0873.

General procedure for asymmetric hydrogenation and characterization data for products: A stock solution was made by mixing $[Rh(COD)Cl]_2$ (1.3 mg) with (*R*,*R*)-f-spirophos (4.3 mg) in a 1:2.2 molar ratio in CH_2Cl_2 (4.0 mL) at room temperature for 20 min in a nitrogen-filled glovebox. An aliquot of the catalyst solution (1.0 mL, 0.00132 mmol) was transferred by syringe into the vials charged with different substrates (0.125 mmol for each) in anhydrous CH_2Cl_2 (2.0 mL). The vials were subsequently transferred into an autoclave which hydrogen gas was charged. The reaction was then stirred under H_2 (10 atm) at -15 ^{o}C for 6 h. The hydrogen gas was released slowly and carefully. The solution was passed through a short column of silica gel to remove the metal complex then concentrated in vacuo. The residue dissolved in CH_2Cl_2, then aniline, EDC and DMAP were added at 0 ^{o}C. The solution stirred for 4-10h. The residue was purified by

chromatography. The ee values of amides were determined by HPLC analysis on a chiral stationary phase.

The procedure for the large scale asymmetric hydrogenation of 1b: The catalyst solution was made by mixing $[Rh(COD)Cl]_2$ (17.1 mg, 0.035 mmol) with (*R*,*R*)-f-spirophos (56.5 mg, 0.0765 mmol) in a 1:2.2 molar ratio in CH_2Cl_2 (2.0 mL) at room temperature for 20 min in a nitrogen-filled glovebox, and then transferred by syringe into the vials charged with **1b** (1.5 g, 7.65 mmol) in anhydrous CH_2Cl_2 (4.0 mL). The vials were subsequently placed into an autoclave which hydrogen gas was charged. The reaction was then stirred under H_2 (10 atm) at -15 ^oC for 6 h. The resulting solution was passed through a short column of silica gel to remove the metal complex then concentrated in vacuo. The residue dissolved in CH_2Cl_2, followed by addition of aniline, EDC and DMAP at 0 ^oC and stirred for 10 h. The corresponding amide was purified by chromatography and then subjected to determine the ee value by HPLC analysis on a chiral stationary phase.

(*S*)-3-phenylbutanoic acid (**2a**): Light yellow liquid; 20.1 mg, 98% yield; 97% ee; $[\alpha]_D^{20}$ = +12.2 (c = 0.7, CH_2Cl_2), GC condition: Supelco gamma Dex^{TM} 225 column (30 m × 0.25 mm × 0.25 μm), N_2 1.0 mL/min, programmed 100 ^oC – 1 ^oC /min - 200 ^oC - 50 min; t_R = 44.5 min (major), t_R = 45.2 min (minor). ^1H NMR (400 MHz, $CDCl_3$) δ = 11.37 (s, 1H), 7.23-7.20 (m, 2H), 7.14-7.10 (m, 3H), 3.22-3.14 (m, 1H), 2.60-2.45 (m, 2H), 1.23 (d, *J* = 6.9 Hz, 3H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ = 179.1, 145.3, 128.5, 126.6, 126.5, 42.6, 36.0, 21.8. The absolute configuration of (*S*)-**2a** was determined by comparison with optical rotation data for the reported literature.[10d]

(+)-3-(4-chlorophenyl)butanoic acid (**2b**): Light yellow solid; 24.1 mg, 97% yield; 95% ee; $[\alpha]_D^{20}$ = +44.94 (c = 1.07, CH_2Cl_2); HPLC condition: Lux 5u Cellulose-1 (250 × 4.60mm), ipa : hex =

20:80, 1mL/min, 254 nm; t_R = 7.5 min (minor), t_R = 9.1 min (major). ^{1}H NMR (400 MHz, CDCl3) δ = 10.19 (s, 1H), 7.21-7.19 (m, 2H), 7.09-7.07 (m, 2H), 3.22-3.13 (m, 1H), 2.59-2.47 (m, 2H), 1.22 (d, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ = 178.6, 143.8, 132.1, 128.7, 128.1, 42.4, 35.6, 21.9; MP: 60-62 °C. The analytical data are consistent with the literature.[10c]

(+)-3-(4-nitrophenyl)butanoic acid (**2c**): Light yellow solid; 25.1 mg, 96% yield; 97% ee; $[\alpha]_D^{20}$ = +45.8 (c = 1.3, CH_2Cl_2); HPLC condition: Lux 5u Cellulose-1 (250 × 4.60mm), ipa : hex = 20:80, 1mL/min, 254 nm; t_R = 12.6 min (minor), t_R = 19.3 min (major). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.17-8.15 (m, 2H), 7.40-7.37 (m, 2H), 3.43-3.34 (m, 1H), 2.72-2.61 (m, 2H), 1.34 (d, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ = 177.8, 152.8, 146.7, 127.7, 123.9, 41.8, 36.0, 21.7; MP: 120-122 °C. The analytical data are consistent with the literature.[34]

(+)-3-(3-fluorophenyl)butanoic acid (**2d**): Light yellow liquid; 22.1 mg, 97% yield; 96% ee; $[\alpha]_D^{20}$ = +25.5 (c = 1.1, CH_2Cl_2); HPLC condition: Lux 5u Cellulose-1 (250 × 4.60mm), ipa : hex = 20:80, 1mL/min, 254 nm; t_R = 7.6 min (minor), t_R = 9.0min (major). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.16-7.11 (m, 1H), 6.89-6.87 (m, 1H), 6.82-6.75 (m, 2H), 3.20-3.11 (m, 1H), 2.56-2.42 (m, 2H), 1.19 (d, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ = 178.6, 162.9 (d, $^1J_{C\text{-}F}$ = 243.8 Hz), 148.0 (d, *J* = 6.7 Hz), 130.0 (d, *J* = 8.2 Hz), 122.4, 113.6 (d, *J* = 21.2 Hz), 113.4 (d, *J* = 21.1 Hz), 42.3, 35.9, 21.7. The analytical data are consistent with the literature.[10c]

(+)-3-(3-bromophenyl)butanoic acid (**2e**): Light yellow liquid; 29.2 mg, 96% yield; 97% ee; $[\alpha]_D^{20}$ = +28.4 (c = 1.6, CH_2Cl_2); HPLC condition: Lux 5u Cellulose-1 (250 × 4.60mm), ipa : hex = 10:90, 0.5 mL/min, 254 nm; t_R = 40.6 min (minor), t_R = 42.4 min (major). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36-7.33 (m, 2H), 7.19-7.14 (m, 2H), 3.29-3.20 (m, 1H), 2.68-2.54 (m, 2H), 1.31 (d, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ = 178.5, 147.7, 130.1, 129.9, 129.6, 125.4,

122.6, 42.3, 35.8, 21.7. The analytical data are consistent with the literature.[35]

(+)-3-(3-nitrophenyl)butanoic acid (**2f**): Light yellow solid; 25.6 mg, 98% yield; 97% ee; $[\alpha]_D^{20}$ = +28.7 (c = 1.3, CH_2Cl_2); HPLC condition: Lux 5u Cellulose-1 (250 × 4.60mm), ipa : hex = 20:80, 1mL/min, 254 nm; t_R = 10.1 min (minor), t_R = 13.1 min (major). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.09-8.06 (m, 2H), 7.57-7.55 (m, 1H), 7.49-7.45 (m, 1H), 3.43-3.34 (m, 1H), 2.73-2.60 (m, 2H), 1.36 (d, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ = 178.3, 148.4, 147.4, 133.3, 129.6, 121.7, 42.1, 35.8, 21.7; MP: 164-166 ^{o}C. The analytical data are consistent with the literature.[36]

(+)-3-(3-methoxyphenyl)butanoic acid (**2g**): Light yellow liquid; 23.8 mg, 98% yield; 91% ee; $[\alpha]_D^{20}$ = +30.2 (c = 1.2, CH_2Cl_2); HPLC condition: Lux 5u Cellulose-1 (250 × 4.60mm), ipa : hex = 20:80, 1mL/min, 254 nm; t_R = 11.7 min (minor), t_R = 16.2 min (major). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.31 (s, 1H), 7.35-7.30 (m, 1H), 6.93-6.91 (m, 1H), 6.87-6.84 (m, 2H), 3.89 (s, 3H), 3.39-3.32 (m, 1H), 2.79-2.63 (m, 2H), 1.41 (d, *J* = 6.9 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ = 178.9, 159.6, 147.1, 129.5, 119.0, 112.7, 111.5, 55.1, 42.5, 36.1, 21.7. The analytical data are consistent with the literature.[10c]

(+)-3-(2-fluorophenyl)butanoic acid (**2h**): Light yellow liquid; 22.3 mg, 98% yield; 96% ee; $[\alpha]_D^{20}$ = +18.4 (c = 1.14, CH_2Cl_2); HPLC condition: Lux 5u Cellulose-1 (250 × 4.60mm), ipa : hex = 5:95, 1mL/min, 254 nm; t_R = 41.1 min (minor), t_R = 43.1 min (major). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.26-7.17 (m, 2H), 7.11-7.07 (m, 1H), 7.04-7.00 (m, 1H), 3.61-3.52 (m, 1H), 2.78-2.60 (m, 2H), 1.34 (d, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ = 178.7, 160.6 (d, $^1J_{C\text{-}F}$ = 244.2 Hz), 131.9 (d, *J* = 14.1 Hz), 128.0 (d, *J* = 1.8 Hz), 127.9 (d, *J* = 5.6 Hz), 124.2 (d, *J* = 3.4 Hz), 115.6 (d, *J* = 22.3 Hz), 40.8, 30.1, 20.4. The analytical data are consistent with the literature.[37]

(-)-3-(2-chlorophenyl)butanoic acid (**2i**): Light yellow liquid; 24.3 mg, 98% yield; 93% ee; $[\alpha]_D^{20}$

= -16.4 (c = 1.22, CH_2Cl_2); HPLC condition: Lux 5u Cellulose-1 (250 × 4.60mm), ipa : hex = 20:80, 1mL/min, 254 nm; t_R = 10.1 min (major), t_R = 11.6 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.38-7.27 (m, 1H), 7.25-7.22 (m, 2H), 7.18-7.14 (m, 1H), 3.85-3.76 (m, 1H), 2.79-2.53 (m, 2H), 1.33 (d, *J* = 6.9 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ = 178.6, 142.4, 133.5, 129.8, 127.6, 127.1, 126.9, 41.0, 32.1, 20.2. The analytical data are consistent with the literature.[38]

(+)-3-(o-tolyl)butanoic acid (**2j**): Light yellow solid; 21.8 mg, 98% yield; 99.3% ee; $[\alpha]_D^{20}$ = +16.2 (c = 1.11, CH_2Cl_2), [lit[13]: $[\alpha]_D^{20}$ = +8.8 (c = 1.00 $CHCl_3$) for 16% ee]; HPLC condition: Lux 5u Cellulose-1 (250 × 4.60mm), ipa : hex = 10:90, 1mL/min, 254 nm; t_R = 21.0 min (major), t_R = 22.9 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.52 (s, 1H), 7.21-7.117 (m, 4H), 3.60-3.51 (m, 1H), 2.73-2.55 (m, 2H), 2.39 (s, 3H), 1.30 (d, *J* = 6.9 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ =179.4, 143.7, 135.3, 130.6, 126.4, 126.2, 125.0, 42.1, 31.3, 21.3, 19.5; MP: 41-43 ^{o}C. The analytical data are consistent with the literature.[10d]

(-)-3-(2-nitrophenyl)butanoic acid (**2k**): Light yellow liquid; 25.4 mg, 97% yield; 97% ee; $[\alpha]_D^{20}$ = -93.5 (c = 1.0, CH_2Cl_2); HPLC condition: Lux 5u Cellulose-3 (250 × 4.60mm), ipa : hex = 8:92, 1mL/min, 254 nm; t_R = 39.6 min (minor), t_R = 43.6 min (major). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.68-7.66 (m, 1H), 7.50-7.46 (m, 1H), 7.36-7.34 (m, 1H), 7.29-7.25 (m, 1H), 3.77-3.68 (m, 1H), 2.72-2.52 (m, 2H), 1.30 (d, *J* = 6.9 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ = 177.9, 149.8, 139.4, 132.8, 127.7, 127.2, 124.2, 41.7, 30.3, 21.3. The analytical data are consistent with the literature.[10d]

(*S*)-3-(naphthalen-1-yl)butanoic acid (**2l**): Light yellow solid; 26.0 mg, 97% yield; 98% ee; $[\alpha]_D^{20}$ = +7.3 (c = 1.2, CH_2Cl_2), HPLC condition: Lux 5u Cellulose-1 (250 × 4.60mm), ipa : hex = 20:80,

1mL/min, 254 nm; t_R = 10.5 min (major), t_R = 14.4 min (minor); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.70 (s,1H), 8.20-7.19 (m, 1H), 7.91-7.89 (m, 1H), 7.77-7.75 (m, 1H), 7.59-7.52 (m, 3H), 7.50-7.41 (m, 1H), 4.24-4.16 (m, 1H), 2.96-2.91 (m, 1H), 2.72-2.66 (m, 1H), 1.50 (d, *J* = 6.8 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ = 179.5, 141.4, 134.1, 131.1, 129.1, 127.1, 126.2, 125.6, 123.0, 122.4, 42.3, 30.6, 21.2; MP: 82-84 ^{o}C. The analytical data are consistent with the literature.[10d]

(*S*)-3-phenylpentanoic acid (**2m**): Light yellow liquid; 21.8 mg, 98% yield; 94% ee; $[\alpha]_D^{20}$ = +22.5 (c = 1.1, CH_2Cl_2); HPLC condition: Lux 5u Cellulose-1 (250 × 4.60mm), ipa : hex = 20:80, 1mL/min, 254 nm; t_R = 8.5 min (major), t_R = 9.4 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.32-7.28 (m, 2H), 7.23-7.17 (m, 3H), 3.03-2.96 (m, 1H), 2.70-2.59 (m, 2H), 1.78-1.58 (m, 2H), 0.80 (t, *J* = 7.3 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ = 179.0, 143.7, 128.3, 127.4, 126.4, 43.5, 41.5, 29.0, 11.8. The analytical data are consistent with the literature.[39]

(*S*)-4-methyl-3-phenylpentanoic acid (**2n**): Light yellow liquid; 23.6 mg, 98% yield; 97% ee; $[\alpha]_D^{20}$ = -23.5 (c = 1.2, CH_2Cl_2); HPLC condition: Lux 5u Cellulose-1 (250 × 4.60mm), ipa : hex = 20:80, 1mL/min, 254 nm; t_R = 6.5 min (major), t_R = 9.0 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 9.30 (s, 1H), 7.05-7.01 (m, 2H), 6.97-6.95 (m, 1H), 6.93-6.89 (m, 2H), 2.66-2.52 (m, 2H), 2.39-2.33 (m, 1H), 1.66-1.58 (m, 1H), 0.70 (d, *J* = 6.7 Hz, 3H), 0.52 (d, *J* = 6.7 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ = 179.1, 142.5, 128.2, 128.1, 126.4, 48.3, 38.1, 33.0, 20.5, 20.1. The analytical data are consistent with the literature.[40]

(*S*)-3-cyclohexyl-3-phenylpropanoic acid (**2o**): Light yellow solid; 28.5 mg, 98% yield; 98% ee; $[\alpha]_D^{20}$ = -58.2(c = 1.3, CH_2Cl_2); HPLC condition: Lux 5u Cellulose-1 (250 × 4.60mm), ipa : hex = 20:80, 1mL/min, 254 nm; t_R = 6.9 min (minor), t_R = 9.7 min (major). ^{1}H NMR (400 MHz, $CDCl_3$)

δ = 7.29-7.25 (m, 2H), 7.21-7.17 (m, 1H), 7.13-7.12 (m, 2H), 2.91-2.80 (m, 2H), 2.62-2.55 (m, 1H), 1.82-1.72 (m, 2H), 1.62-1.59 (m, 2H), 1.52-1.43 (m, 2H), 1.27-1.16 (m, 1H), 1.13-1.05 (m, 2H), 1.02-0.89 (m, 1H), 0.87-0.75 (m, 1H); $^{13}C\{^{1}H\}$NMR (100 MHz, DMSO-d^6) δ = 174.3, 143.8, 128.7, 128.3, 126.4, 47.9, 42.7, 38.1, 30.9, 30.6, 26.4, 26.3; MP: 92-94 °C. The analytical data are consistent with the literature.[39]

(*R*)-(+)-3-methyl-5-phenylpentanoic acid (**2p**): Light yellow liquid; 23.6 mg, 98% yield; 66% ee; $[\alpha]_D^{20}$ = +1.2 (c = 1.3, CH_2Cl_2); HPLC condition: Lux 5u Cellulose-3 (250 × 4.60mm), ipa : hex = 20:80, 1mL/min, 254 nm; t_R = 7.2 min (minor), t_R = 8.7 min (major). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.32-7.28 (m, 2H), 7.21-7.19 (m, 3H), 2.74-2.58 (m, 2H), 2.46-2.41 (m, 1H), 2.26-2.21 (m, 1H), 2.10-2.01 (m, 1H), 1.77-1.68 (m, 1H), 1.62-1.52 (m, 1H), 1.07 (d, *J* = 6.6 Hz, 3H); $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$) δ = 179.7, 142.2, 128.3, 128.2, 125.7, 41.7, 38.4, 33.2, 29.9, 19.5. The analytical data are consistent with the literature.[41]

(-)-3-cyclohexylbutanoic acid (**2q**): Light yellow liquid; 20.9 mg, 98% yield; 73% ee; $[\alpha]_D^{20}$ = -22.8 (c = 1.1, CH_2Cl_2); HPLC condition: Lux 5u Cellulose-1 (250 × 4.60mm), ipa : hex = 20:80, 1mL/min, 254 nm; t_R = 6.6 min (minor), t_R = 8.1 min (major). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 11.1 (s, 1H), 2.44 (m, 1H), 2.16 (m, 1H), 1.85 (s, 1H), 1.73 (m, 2H), 1.63 (m, 3H), 1.25-1.08 (m, 4H), 1.00-0.94 (m, 2H), 0.92-0.90 (m, 3H); $^{13}C\{^{1}H\}$NMR (100 MHz, $CDCl_3$) δ = 180.5, 42.6, 39.7, 35.3, 30.2, 28.9, 26.7, 26.6, 26.6, 16.4. The analytical data are consistent with the literature.[42]

(*S*)-3-(3,4-dichlorophenyl)-3-phenylpropanoic acid (**2r**): Light yellow liquid; 36.2 mg, 98% yield; 97% ee; $[\alpha]_D^{20}$ = -1.0 (c = 1.4, CH_2Cl_2); HPLC condition: Lux 5u Cellulose-3 (250 × 4.60mm), ipa : hex = 20:80, 1mL/min, 254 nm ; t_R = 12.5 min (major), t_R = 15.8 min (minor). ^{1}H NMR (400

MHz, $CDCl_3$) δ = 7.29-7.22 (m, 4H), 7.19-7.11 (m, 3H), 7.02-7.00 (m, 1H), 4.41 (t, *J* = 7.9 Hz, 1H), 3.04-2.93 (m, 2H). $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ = 177.5, 143.4, 141.9, 132.6, 130.7, 130.5, 129.6, 128.9, 127.4, 127.1, 127.0, 45.7, 40.0. The analytical data are consistent with the literature.[14]

(*S*)-3-(2-fluorophenyl)-3-phenylpropanoic acid (**2s**): Light yellow solid; 29.3 mg, 96% yield; 94% ee; $[\alpha]_D^{25}$ = +5.2 (c = 1.36, CH_2Cl_2); HPLC condition: Lux 5u Cellulose-1 (250 × 4.60mm), ipa : hex = 20:80, 1mL/min, 254 nm; t_R = 12.1 min (major), t_R = 13.4 min (minor); ^1H NMR (400 MHz, $CDCl_3$) δ = 7.25-7.10 (m, 7H), 7.04-7.00 (m, 1H), 6.97-6.92 (m, 1H), 4.76 (t, *J* = 7.9 Hz, 1H), 3.06 (d, *J* = 8.0 Hz, 2H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ = 177.9, 160.4 (d, $^1J_{C\text{-}F}$ = 244.9 Hz), 141.9, 130.2 (d, *J* = 14.2 Hz), 128.6, 128.4 (d, *J* = 4.2 Hz), 128.3 (d, *J* = 8.4 Hz), 127.6, 126.8, 124.2 (d, *J* = 3.4 Hz), 115.7 (d, *J* = 22.4 Hz), 40.0, 39.2; MP: 120-122 °C. The analytical data are consistent with the literature.[14]

(-)-3-(3-chlorophenyl)-3-phenylpropanoic acid (**2t**): Light yellow solid; 31.6 mg, 97% yield; 97% ee; $[\alpha]_D^{20}$ = -12.3 (c = 1.62, CH_2Cl_2); HPLC condition: Lux 5u Cellulose-1 (250 × 4.60mm), ipa : hex = 10:90, 1mL/min, 254 nm ; t_R = 28.9 min (major), t_R = 31.9 min (minor); ^1H NMR (400 MHz, $CDCl_3$) δ = 7.32-7.29 (m, 2H), 7.24-7.17 (m, 6H), 7.14-7.12 (m, 1H), 4.50 (t, *J* = 7.9 Hz, 1H), 3.07 (d, *J* = 7.9 Hz, 2H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ = 177.8, 145.2, 142.4, 134.4, 129.9, 128.8, 127.8, 127.5, 126.9, 126.9, 125.8, 46.2, 40.1; MP: 112-114 °C. The analytical data are consistent with the literature.[4]

(*S*)-3-phenylbutan-1-ol (**4**): Light yellow liquid; 18.4 mg, 98% yield; 88% ee; $[\alpha]_D^{20}$ = -10.5 (c = 0.6, CH_2Cl_2); GC condition: Supelco alpha Dex™ 120 column (30 m × 0.25 mm × 0.25 μm), N_2 1.0 mL/min, programmed 90 °C– 0.5 °C /min - 200 °C - 50 min; t_R = 50.8 min (minor), t_R = 51.5

min (major). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.31-7.29 (m, 2H), 7.23-7.19 (m, 3H), 3.61-3.50 (m, 2H), 2.94-2.85 (m, 1H), 1.89-1.84 (m, 2H), 1.29 (d, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ = 146.8, 128.3, 126.8, 125.9, 60.7, 40.7, 36.2, 22.2. The analytical data are consistent with the literature.[43]

(*S*)-3-phenylbutan-1-ol (**6a**): Light yellow liquid; 18.4 mg, 98% yield; 94% ee; $[\alpha]_D^{20}$ = -11.5 (c = 0.6, CH_2Cl_2); GC condition: Supelco alpha Dex^{TM} 120 column (30 m × 0.25 mm × 0.25 μm), N_2 1.0 mL/min, programmed 90 ^{o}C– 0.5 ^{o}C /min – 200 ^{o}C - 50 min; t_R = 50.8 min (minor), t_R = 51.6 min (major). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.31-7.29 (m, 2H), 7.23-7.19 (m, 3H), 3.61-3.50 (m, 2H), 2.94-2.85 (m, 1H), 1.89-1.84 (m, 2H), 1.29 (d, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ = 146.8, 128.3, 126.8, 125.9, 60.7, 40.7, 36.2, 22.2. The analytical data are consistent with the literature.[43]

(-)-3-(2-fluorophenyl)butan-1-ol (**6b**): Light yellow liquid; 20.2 mg, 96% yield; 97% ee; $[\alpha]_D^{20}$ = -11.5 (c = 0.8, CH_2Cl_2), GC condition: Supelco gamma Dex^{TM} 120 column (30 m × 0.25 mm × 0.25 μm), N_2 1.0 mL/min, programmed 100 ^{o}C – 0.5 ^{o}C /min - 200 ^{o}C - 50 min; t_R = 43.9 min (minor), t_R = 44.4 min (major). ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.11-7.00 (m, 2H), 6.97-6.93 (m, 1H), 6.89-6.84 (m, 1H), 3.43-3.42 (m, 2H), 3.15-3.06 (m, 1H), 1.76-1.71 (m, 2H), 1.41 (d, *J* = 16.6 Hz, 1H), 1.15 (d, *J* = 6.9 Hz, 3H); ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ = 160.6 (d, $^1J_{C\text{-}F}$ = 242.7 Hz), 133.0 (d, *J* = 14.4 Hz), 127.9 (d, *J* = 5.2 Hz), 127.2 (d, *J* = 8.3 Hz), 124.1 (d, *J* = 3.4 Hz), 115.2 (d, *J* = 22.9 Hz), 60.9, 39.7, 29.1, 20.8. The analytical data are consistent with the literature.[44]

Synthesis of (-)-indatraline precursor 7: Chlorosulfonic acid (0.1 mL, 2.1 mmol) was slowly added by a syringe to a solution of the acid **2r** (54.0 mg, 0.18 mmol) in CH_2Cl_2 (2.0 mL) at room

temperature under nitrogen. After the start material was completely consumed, the resulted mixture was then quenched with water and extracted with CH_2Cl_2 for three times. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated by rotary evaporator. The residue was subsequently purified by column chromatography (PE/EtOAc = 10:1) to give compound **7** as a white solid (46.6 mg, 95%). MP: 107-109 ^oC; 95% ee; $[\alpha]_D^{20}$ = - 43.8 (c = 0.5, CH_2Cl_2); HPLC condition: Lux 5u Cellulose-1 (250 × 4.60mm), ipa : hex = 10:90, 1.0 mL/min, 230 nm ; t_R = 9.1 min (minor), t_R = 10.5 min (major); ^1H NMR (400 MHz, $CDCl_3$) δ = 7.83 (d, *J* = 7.7 Hz, 1H), 7.61 (m, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 7.38 (d, *J* = 8.3 Hz, 1H), 7.27-7.25 (m, 1H), 7.22 (d, *J* = 2.1 Hz, 1H), 6.95 (dd, J_1= 8.3 Hz, J_2= 2.1 Hz, 1H), 4.55 (dd, J_1= 8.1 Hz, J_2= 3.8 Hz, 1H), 3.23 (dd, J_1= 19.2 Hz, J_2= 8.2 Hz, 1H), 2.62 (dd, J_1= 19.2 Hz, J_2= 3.9 Hz, 1H); $^{13}C\{^1H\}$NMR (100 MHz, $CDCl_3$) δ = 204.5, 156.3, 143.8, 136.5, 135.1, 132.6, 130.8, 130.7, 129.4, 128.1, 126.9, 126.5, 123.4, 46.2, 43.3. The analytical data are consistent with the literature.[15a,16a]

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SUPPORTING INFORMATION

NMR, GC and HPLC spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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