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Rh(I)/DpenPhos catalyzed asymmetric hydrogenation of enol esters and potassium (*E*)-3-cyano-5-methylhex-3-enoate

Yan Liu, Zheng Wang, Kuiling Ding *

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, PR China

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ABSTRACT

Rh(I) complexes of a class of modular chiral monodentate phosphoramidites were highly efficient for the asymmetric hydrogenation of enol esters bearing α-aryl or α-alkyl groups, to afford the corresponding hydrogenation products in high enantioselectivities (87–95% ee) and reactivities (turnover number up to 10,000). These ligands were also shown to be effective in Rh(I)-catalyzed asymmetric hydrogenation of the potassium salt of (*E*)-3-cyano-5-methylhex-3-enoate, to give the corresponding product (a precursor to CI-1008) with up to 95% ee and complete conversion of substrate.

1. Introduction

Since the pioneering work on Rh(I)-catalyzed asymmetric hydrogenation (AH) by Knowles in 1968,[1] chemists have taken tremendous efforts in generating new asymmetric catalytic hydrogenation systems for synthetic organic chemistry.[2] Today, AH has become one of the most powerful methodologies for the construction of chiral amino acids, chiral amines, chiral alcohols, and many other important chiral compounds.[3] Undoubtedly, chiral phosphorus ligands, which are regarded as reaction speed accelerators and chirality inducers in the AH, play a central role.[4] Bidentate phosphine ligands have been considered to be essential for high reactivities and enantioselectivities for more than three decades in the asymmetric hydrogenation of prochiral olefins.[2–4] However, triggered by the pioneering works of Reetz, Ferringa, de Vries, Pringle, and others in 2000,[5] the development of monodentate phosphorus ligands for asymmetric hydrogenation has been a research topic of increasing interest due to their excellent catalytic performances, simplicity of synthesis, and ease of structural variation.[6] We have recently developed a new series of tunable chiral monodentate ligands, DpenPhos (Fig. 1), which has been successfully applied in Rh-catalyzed asymmetric hydrogenation of α- or β-(acylamino)acrylates, α-arylenamides, (*Z*)-methyl α-(acetoxy)acrylates, β-aryl substituted itaconates, α- or β-enamido phosphonates and α- or β-acyloxy α,β-unsaturated phosphonates.[7] As an ongoing effort to further explore the potential of this type of ligand, herein we report the application of DpenPhos in Rh(I)-catalyzed AH of enol esters and potassium (*E*)-3-cyano-5-methylhex-3-enoate. High reactivities (turnover number up to 10,000) and enantioselectivities (up to 95% ee) were achieved for acyclic enol esters bearing aromatic or aliphatic substituents. The hydrogenation of potassium (*E*)-3-cyano-5-methylhex-3-enoate in the presence of Rh(I)/DpenPhos afforded the corresponding product with 95% ee, a key precursor for the synthesis of CI-1008 (pregabalin).

2. Results and discussions

2.1. Rh-catalyzed asymmetric hydrogenation of enol esters

Rh-catalyzed asymmetric hydrogenation of enol esters provides a straightforward approach to chiral esters, which can be regarded as an attractive alternative to the enantioselective reduction of the corresponding prochiral ketones. Several efficient catalytic systems have been reported for the AH of enol esters.[8] However, in most cases the acceptable enantioselectivities (ee >90%) were only attained for the hydrogenation of aryl, vinyl or trifluoromethyl substituted substrates. The AH of enol esters bearing alkyl group at the olefinic function has been less explored despite the wide utility of the hydrogenation products. The only example of high enantioselectivity for AH of this type of substrates was reported by Reetz and co-workers using a catalytic system based on Rh-monophosphite complexes.[9] Unfortunately, no results for the AH of enol esters bearing an aromatic group at the vinyl position were

* Corresponding author. E-mail address: kding@mail.sioc.ac.cn (K. Ding).

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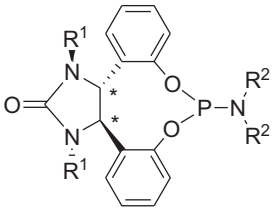
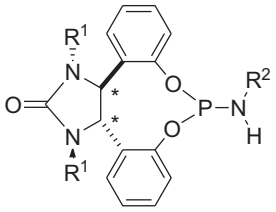


DpenPhos

(*R*,*R*)-**1a**: $R^1 = C_6H_5CH_2$, $R^2 = CH_3$
(*R*,*R*)-**1b**: $R^1 = 3,5\text{-}(CH_3)_2C_6H_3CH_2$, $R^2 = CH_3$
(*R*,*R*)-**1c**: $R^1 = 3,5\text{-}(t\text{-}C_4H_9)_2C_6H_3CH_2$, $R^2 = CH_3$



DpenPhos

(*S*,*S*)-**1d**: R^1 = Et, R^2= n-Pr
(*S*,*S*)-**1e**: R^1 = Et, R^2 = Bn
(*R*,*R*)-**1f**: R^1 = Bn, R^2 = n-Pr
(*R*,*R*)-**1g** R^1 = Bn, R^2 = Bn
(*S*,*S*,*R*)-**1h**: R^1 = Bn, R^2 = (*R*)-1-phenylethyl
(*S*,*S*,*S*)-**1i**: R^1= Bn, R^2 = (*S*)-1-phenylethyl
(*R*,*R*)-**1j**: R^1 = 3,5-diMeBn, R^2 = n-Pr
(*R*,*R*,*S*)-**1k**: R^1 = Et, R^2 = (*S*)-α-phenylethyl
(*R*,*R*,*S*)-**1l**: R^1 = 3,5-diMeBn, R^2 = (*S*)-α-phenylethyl

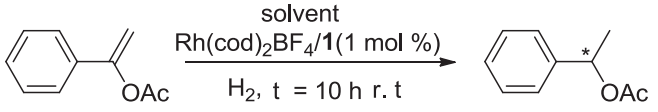
Fig. 1. DpenPhos ligands **1a**–**l** employed in this study.

reported in this protocol. Accordingly, the development of chiral catalysts for AH of both aromatic and aliphatic enol esters is still highly desirable.

We began our study on AH of enol esters using **2a** as the model substrate and the Rh(I) complex generated in situ from [Rh(cod)BF_4] (1 mol %) and DpenPhos (2 mol %) as the catalyst, and the results are summarized in Table 1. With dichloromethane as the solvent under 40 bar of H_2, an initial survey of the monophosphoramidite ligands (DpenPhos class and MonoPhos) indicated that **1h** having a P–N–H moiety, is an effective ligand for this reaction (entry 5). Complete conversion of **2a** to **3a** with a good enantiomeric excess value (70%) has been attained in this case (entry 5), whereas the use of MonoPhos or **1a**–**c** under the otherwise identical conditions only resulted in no reactivity or modest enantioselectivities (Table 1, entries 1–4). A dramatic solvent effect was observed in the AH of **2a** using the Rh/**1h** catalyst. While the reaction in 1,2-dichloroethane afforded the product with an enhanced enantiomeric excess value (83%, entry 8), no reaction occurred in toluene, methanol or isopropanol (entries 7, 10–11). Enlightened by the initial ligand screening results (entries 1–5), a series of DpenPhos ligands (**1d**–**l**) carrying the P–N–H moiety and different R^1 and R^2 groups in their structures were subsequently investigated in the Rh-catalyzed AH of **2a** under a lower pressure (5 bar) of H_2. The identities of groups R^1 and R^2 on the ligands were found to have a remarkable influence on the outcome of AH of **2a**, enantiomeric excess values of **3a** ranging from moderate to high were obtained under the tested conditions (entries 12–20). Intriguingly, for the AH of **2a** catalyzed by Rh complex of **1h** and **1i**, which are diastereomeric to each other in that they contain a 1-phenylethylamine moiety with reversed chiralities, only a slight difference in their chiral inductions was observed (entry 16 vs 17). Though the Rh complexes of DpenPhos **1d**–**l** can afford full conversions in the catalytic AH of **2a**, those of **1h**, **1i**, and **1l** are superior in terms of chiral inductions to give **3a** in good to high enantiomeric excess values (entries 16, 17, and 20). Further screening of the different concentrations of substrate **2a** revealed that a relatively dilute substrate solution seems to favor the enantioselectivity (entries 21–24). Thus, ligand screening and condition optimizations in the AH of **2a** indicated that **1h** and **1l** could afford high enantioselectivity with an opposite sense of chiral induction at room temperature (entries 20 vs 24). Finally, lowering the reaction temperature from room temperature to −20 °C resulted in a slight enhancement of enantiomeric excess values to 92% and 93%, respectively, for the Rh/**1h** or Rh/**1l** catalyzed AH of **2a** (entries 26 and 27).

Having established the optimal conditions for the model reaction, the AH of various enol esters was examined with Rh(I)/DpenPhos complexes as the catalysts. The reactions were typically performed in dichloroethane at −20 °C for 10 h, and the results are summarized in Table 2. Gratifyingly, high efficiency of Rh/**1h** and Rh/**1l** was achieved for AH of enol acetates with different aromatic groups on the α-vinyl positions, to afford the corresponding chiral acetates in full conversions with excellent enantioselectivity (entries 1–5). To demonstrate the efficiency of the catalyst Rh/**1l**, the

Table 1
Asymmetric hydrogenation of **2a** catalyzed by DpenPhos(**1**)/Rh

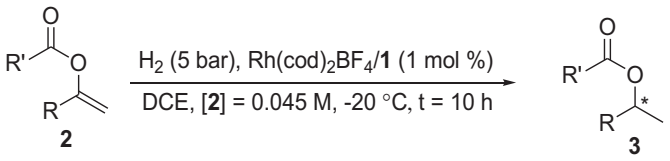


2a **3a**

Entry	Ligand	Solvent	P_{H2} (bar)	[**2a**] (M)	Conv[a] (%)	ee[b] (%)
1	MonoPhos	CH_2Cl_2	40	0.18	>99	−29
2	(*R*,*R*)-**1a**	CH_2Cl_2	40	0.18	>99	−10
3	(*R*,*R*)-**1b**	CH_2Cl_2	40	0.18	Trace	N.D.
4	(*R*,*R*)-**1c**	CH_2Cl_2	40	0.18	Trace	N.D.
5	(*S*,*S*,*R*)-**1h**	CH_2Cl_2	40	0.18	>99	70
6	(*S*,*S*,*R*)-**1h**	THF	40	0.18	>99	13
7	(*S*,*S*,*R*)-**1h**	Toluene	40	0.18	N.R.	N.D.
8	(*S*,*S*,*R*)-**1h**	DCE	40	0.18	>99	83
9	(*S*,*S*,*R*)-**1h**	$CHCl_3$	40	0.18	>99	70
10	(*S*,*S*,*R*)-**1h**	*i*-PrOH	40	0.18	N.R.	N.D.
11	(*S*,*S*,*R*)-**1h**	MeOH	40	0.18	N.R.	N.D.
12	(*S*,*S*)-**1d**	DCE	5	0.18	>99	48
13	(*S*,*S*)-**1e**	DCE	5	0.18	>99	50
14	(*R*,*R*)-**1f**	DCE	5	0.18	>99	−37
15	(*R*,*R*)-**1g**	DCE	5	0.18	>99	−54
16	(*S*,*S*,*R*)-**1h**	DCE	5	0.18	>99	85
17	(*S*,*S*,*S*)-**1i**	DCE	5	0.18	>99	82
18	(*R*,*R*)-**1j**	DCE	5	0.18	>99	−46
19	(*R*,*R*,*S*)-**1k**	DCE	5	0.045	>99	−67
20	(*R*,*R*,*S*)-**1l**	DCE	5	0.045	>99	−91
21	(*S*,*S*,*R*)-**1h**	DCE	5	0.36	>99	83
22	(*S*,*S*,*R*)-**1h**	DCE	5	0.09	>99	88
23	(*S*,*S*,*R*)-**1h**	DCE	5	0.06	>99	88
24	(*S*,*S*,*R*)-**1h**	DCE	5	0.045	>99	90
25	(*S*,*S*,*R*)-**1h**	DCE	1	0.045	>99	88
26[c]	(*S*,*S*,*R*)-**1h**	DCE	5	0.045	>99	92
27[c]	(*R*,*R*,*S*)-**1l**	DCE	5	0.045	>99	−93

[a] Determined by ^1H NMR.
[b] Determined by chiral GC.
[c] Reaction was carried out under −20 °C.

Table 2
Asymmetric hydrogenation of **2** catalyzed by DpenPhos(**1**)/Rh(I)



2 **3**

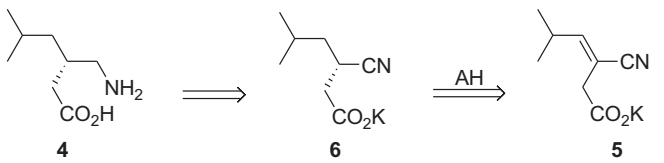
Entry	Sub.	R	R′	Ligand	Conv[a] (%)	ee[b] (%)	Config.[c]
1	**2a**	C_6H_5	Me	(*R*,*R*,*S*)-**1l**	>99	93	*R*
2	**2b**	2-Naphthyl	Me	(*S*,*S*,*R*)-**1h**	>99	91	*S*
3	**2c**	4-ClC_6H_4	Me	(*R*,*R*,*S*)-**1l**	>99	88	*R*
4	**2d**	3-ClC_6H_4	Me	(*R*,*R*,*S*)-**1l**	>99	92	*R*
5	**2e**	3-MeC_6H_4	Me	(*R*,*R*,*S*)-**1l**	>99	95	*R*
6[d]	**2e**	3-MeC_6H_4	Me	(*R*,*R*,*S*)-**1l**	>99	91	*R*
7[e]	**2f**	*n*-Bu	Ph	(*S*,*S*,*R*)-**1h**	>99	90	*R*
8[e]	**2g**	*n*-Pr	Ph	(*S*,*S*,*R*)-**1h**	>99	87	*R*
9[e]	**2h**	*n*-Pentyl	Ph	(*S*,*S*,*R*)-**1h**	>99	88	*R*
10[e]	**2i**	*n*-Hexyl	Ph	(*S*,*S*,*R*)-**1h**	>99	87	*R*

[a] Determined by ^{1}H NMR.
[b] Determined by HPLC on Chiralcel column or GC.
[c] Absolute configurations were assigned by comparison of $[\alpha]_D$ values with those of literature data.
[d] Substrate/[Rh]=10,000:1, rt, 20 bar H_2.
[e] $CHCl_3$ as solvent, and P_{H2}=40 bar.

hydrogenation of **2e** was carried out in the presence of a reduced catalyst loading (0.01 mol %) under a higher pressure of H_2 (20 bar), affording the corresponding ester **3e** in complete conversion without significant loss of enantioselectivity (entry 6 vs 5). To our delight, AH of enolate esters with aliphatic substituents on the vinyl positions, a class of particularly difficult substrates, also proceeded smoothly to full conversion under 40 bar of H_2 with Rh/**1h** as the catalyst, to afford the corresponding benzoyl esters with high enantiomeric excess values (entries 7–10).

2.2. Rh/DpenPhos catalyzed asymmetric hydrogenation of (*E*)-3-cyano-5-methylhex-3-enoate for the synthesis of CI-1008 precursor

(*S*)-(+)-3-Aminomethyl-5-methylhexanoic acid (**4**, pregabalin) is a pharmaceutical used to treat psychotic disorders, seizure disorders, and pain.[10] A resolution process was employed in the classic method to obtain the optical pure **4**.[11] Asymmetric catalytic hydrogenation of a suitable olefinic precursor, such as **5** represents a concise way to chiral pregabalin via intermediate **6** (Fig. 2). Several bidentate phosphines, such as DIPAMP,[12] DuPhos,[13] and others[14] have been identified as efficient ligands in the Rh(I)-catalyzed AH of **5**. However, to the best of our knowledge, there was still no reported example of a successful use of monodentate ligands in the Rh-catalyzed AH of **5**.

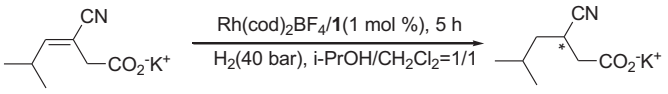


4 **6** **5**

Fig. 2. Asymmetric hydrogenation pathway to pregabalin (**4**).

We have examined the AH of **5** using the in situ generated Rh(I) complex of DpenPhos as the catalyst. The reactions were carried out in a CH_2Cl_2/*i*-PrOH (v/v=1:1) solvent mixture, and the results were shown in the Table 3. Remarkably, it was found that the presence of the N–H moiety in the structure of DpenPhos is critically important for achieving high activity and selectivity in the AH of **5** (Table 3, entry 1 vs 2–8). Similar behaviors have also been found in our previous studies on the AH of α-(acylamino) acrylates, (*Z*)-methyl *R*-(acetoxy)acrylates, itaconate derivatives, α(β)-enamido phosphonates, β-(acylamino)-acrylates, and enol esters catalyzed by the same type of Rh/DpenPhos complexes.[7] The chiral induction varies widely from modest to excellent depending on the *N*-substituents (R^1, R^2) on the ligands (entries 2–4, 7–8). The reactions took a prolonged time for full conversion when the temperature was decreased from 45 to 20 °C (entries 6–8). Among the ligands tested for this Rh(I) catalyzed reaction, **1l** turned out to be best in terms of the enantioselectivity, giving the chiral product **6** (a precursor to CI-1008) in complete conversion with 95% ee (entry 8).

Table 3
Asymmetric hydrogenation of **5** catalyzed by Rh(I)/DpenPhos(**1**)



5 **6**

Entry	Ligand	*T* (°C)	Conv[a] (%)	ee[b] (%)
1	(*R*,*R*)-**1a**	45	59	−23
2	(*R*,*R*)-**1g**	45	>99	−47
3	(*S*,*S*,*R*)-**1h**	45	>99	69
4	(*S*,*S*,*S*)-**1i**	45	>99	77
5	(*S*,*S*,*S*)-**1i**	35	>99	89
6[c]	(*S*,*S*,*S*)-**1i**	20	>99	90
7[c]	(*R*,*R*,*R*)-**1k**	20	>99	−33
8[c]	(*R*,*R*,*R*)-**1l**	20	>99	−95

[a] Determined by ^{1}H NMR spectroscopy.
[b] Determined by HPLC on Chiralcel column. Absolute configuration of **6** catalyzed by Rh/(*R*,*R*,*R*)-**1l** was determined to be *R* by comparison of $[\alpha]_D$ value with those of literature data.
[c] Reaction time: 24 h.

3. Conclusions

In summary, chiral monodentate phosphoramidite ligands DpenPhos have been successfully applied in the Rh(I)-catalyzed asymmetric hydrogenation of enol esters with α-aryl or α-alkyl groups, to afford the corresponding hydrogenation products in high enantioselectivities (87–95% ee) and reactivities (turnover number up to 10,000). These ligands were also demonstrated to be efficient in the Rh(I)-catalyzed AH of the potassium salt of (*E*)-3-cyano-5-methylhex-3-enoate, to give the corresponding product (a precursor to CI-1008) in complete conversion with up to 95% ee. Further work on the extension of these ligands in transition metal catalyzed asymmetric hydrogenation reactions are underway.

4. Experimental

4.1. General experimental

NMR spectra were recorded on a Varian Mercury 300 (^{1}H 300 MHz; ^{13}C 75 MHz) spectrometer in $CDCl_3$. Chemical shifts were expressed in parts per million with TMS as an internal standard (δ=0 ppm) for ^{1}H NMR. Coupling constants, *J*, are listed in Hertz. Optical rotations were measured on a Perkin–Elmer 341 automatic polarimeter. HPLC analyses were carried out on a JASCO 1580 liquid chromatograph with a JASCO CD-1595 detector and AS-1555 autosampler. GC analyses were measured on an Agilent 6890N network system. Dichloromethane, chloroform, and tetrachloromethane were freshly distilled from calcium hydride, THF, diethyl ether, and toluene from sodium benzophenone ketyl. All manipulations involving air- and moisture-sensitive organometallic compounds were carried out using standard Schlenk techniques under

an argon atmosphere. DpenPhos Ligands **1a**–**l** were synthesized by following our previously reported procedures.[7a–c]

4.2. General procedure for catalytic asymmetric hydrogenation of 2a–e

$[Rh(cod)_2]BF_4$ (2.0 mg, 0.005 mmol), **1** (0.011 mmol) were dissolved in $ClCH_2CH_2Cl$ (5 mL) under nitrogen and the solution was stirred at room temperature for 10 min. The substrate (0.5 mmol) in $ClCH_2CH_2Cl$ (6 mL) was added to the above catalyst solution. The mixture was then transferred to a stainless steel autoclave under a nitrogen atmosphere, and then sealed. After purging six times with hydrogen, the final H_2 pressure was adjusted to 5 bar. After stirring at −20 °C for 10 h, H_2 was released and the solvent was removed under the reduced pressure. The substrate conversion was assessed by ^1H NMR spectroscopic analysis of the mixture, and the residue was filtered through a short pad of Celite with ethyl acetate as the eluent. The enantiomeric excess of the product was determined by chiral HPLC or GC.

*4.2.1. (S)-(1-Phenyl)ethyl acetate (S)-**3a**.* Conversion: >99%, 93% ee, $[\alpha]_D^{20}$ −105.7 (*c* 2.2 in $CHCl_3$), [lit.[15] $[\alpha]_D^{20}$ +86.7 (*c* 1.00 in $CHCl_3$) for (*R*)]; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29–7.40 (m, 5H), 5.88 (q, *J*=6.6 Hz, 1H), 2.07 (s, 3H), 1.54 (d, *J*=6.6 Hz, 3H) ppm. The enantiomeric excess was determined by GC on Chiralcel Supelco BATA-DEX 120 column, 120 °C, t_R=16.0 min (major), 17.0 min (minor).

*4.2.2. (S)-1-(2-Naphthyl)ethyl acetate (S)-**3b**.* Conversion: >99%, 88% ee, $[\alpha]_D^{20}$ −108.6 (*c* 2.5 in $CHCl_3$), [lit.[16] $[\alpha]_D^{20}$ +109 (*c* 1.00 in $CHCl_3$) for (*R*)]; ^1H NMR (300 MHz, $CDCl_3$) δ 7.81–7.86 (m, 4H), 7.46–7.50 (m, 3H), 6.05 (q, *J*=6.6 Hz, 1H), 2.11 (s, 3H), 1.62 (d, *J*=6.6 Hz, 3H) ppm. The enantiomeric excess was determined by HPLC on Chiralcel AD column, hexane/isopropanol=95:5; flow rate=0.6 mL/min; UV detection at λ=230 nm; t_R=8.3 min (minor), 10.0 min (major), respectively.

*4.2.3. (S)-1-(4-Chlorophenyl)ethyl acetate (S)-**3c**.* Conversion: >99%, 88% ee, $[\alpha]_D^{20}$ −104.8 (*c* 2.0 in $CHCl_3$), [lit.[17] $[\alpha]_D^{20}$ +88.25 (*c* 1.00 in $CHCl_3$) for (*R*)]; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27–7.34 (m, 4H), 5.84 (q, *J*=6.6 Hz, 1H), 2.09 (s, 3H), 1.51 (d, *J*=6.6 Hz, 3H) ppm. The enantiomeric excess was determined by GC on Chiralcel Supelco BATA-DEX 120 column, 150 °C, t_R=13.6 min (major), 14.0 min (minor).

*4.2.4. (S)-1-(3-Chlorophenyl)ethyl acetate[8i] (S)-**3d**.* Conversion: >99%, 92% ee, $[\alpha]_D^{20}$ −65.0 (*c* 2.0 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.20–7.35 (m, 4H), 5.83 (q, *J*=6.6 Hz, 1H), 2.10 (s, 3H), 1.52 (d, *J*=6.6 Hz, 3H) ppm. The enantiomeric excess was determined by GC on Chiralcel Supelco BATA-DEX 120 column, 150 °C, t_R=15.0 min (major), 15.6 min (minor).

*4.2.5. (S)-1-(3-Methylphenyl)ethyl acetate[8i] (S)-**3e**.* Conversion: >99%, 95% ee, $[\alpha]_D^{20}$ −64.6 (*c* 2.2 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.22–7.27 (m, 1H), 7.10–7.16 (m, 3H), 5.85 (q, *J*=6.9 Hz, 1H), 2.36 (s, 3H), 2.08 (s, 3H), 1.53 (d, *J*=6.6 Hz, 3H) ppm. The enantiomeric excess was determined by GC on Chiralcel Supelco BATA-DEX 120 column, 140 °C, t_R=12.4 min (major), 12.8 min (minor).

4.3. Procedure for catalytic asymmetric hydrogenation of 2e using 0.01 mol % catalyst

$[Rh(cod)_2]BF_4$ (2.0 mg, 0.005 mmol) and (*R*,*R*,*S*)-**1l** 6.7 mg (0.011 mmol) were dissolved in $ClCH_2CH_2Cl$ (10 mL) under nitrogen and the solution was stirred at room temperature for 10 min. A 1 mL portion of the above solution was transferred to the solution of **2e** (880 mg, 5 mmol) in $ClCH_2CH_2Cl$ (3 mL). The resulting mixture was then transferred to a stainless steel autoclave under a nitrogen atmosphere, and then sealed. After purging six times with hydrogen, the final H_2 pressure was adjusted to 20 bar. After stirring at room temperature for 10 h, H_2 was released and the solvent was removed under the reduced pressure. The substrate conversion was assessed by ^1H NMR spectroscopic analysis of the mixture, and the residue was filtered through a short pad of Celite with ethyl acetate as the eluent. The enantiomeric excess of the product was determined by chiral GC.

4.4. General procedure for catalytic asymmetric hydrogenation of 2f–i

$[Rh(cod)_2]BF_4$ (2.0 mg, 0.005 mmol) and (*S*,*S*,*R*)-**1h** 5.9 mg (0.011 mmol) were dissolved in $CHCl_3$ (5 mL) under nitrogen, and the solution was stirred at room temperature for 10 min. A solution of the substrate (0.5 mmol) in $ClCH_2CH_2Cl$ (6 mL) was added to the above catalyst solution. The resulting mixture was then transferred to a stainless steel autoclave under nitrogen atmosphere, and then sealed. After purging six times with hydrogen, the final H_2 pressure was adjusted to 40 bar. After stirring at −20 °C for 10 h, H_2 was released and the solvent was removed under the reduced pressure. The substrate conversion was assessed by ^1H NMR spectroscopic analysis of the mixture, and the residue was filtered through a short pad of Celite with ethyl acetate as the eluent. The enantiomeric excess of the product was determined by chiral HPLC.

*4.4.1. (R)-Benzoic acid 1-methylpentyl ester,[9] (R)-**3f**.* Conversion: >99%, 90% ee, $[\alpha]_D^{20}$ +92.8 (*c* 1.0 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.04–8.07 (m, 2H), 7.52–7.58 (m, 1H), 7.41–7.46 (m, 2H), 5.10–5.19 (m, 1H), 1.56–1.78 (m, 2H), 1.28–1.44 (m, 7H), 0.83–0.87 (m, 3H) ppm. The enantiomeric excess was determined by HPLC on Chiralcel OB-H column, hexane/isopropanol=100:0; flow rate=0.2 mL/min; UV detection at λ=230 nm; t_R=32.1 min (minor), 34.2 min (major).

*4.4.2. (R)-Benzoic acid 1-methylbutyl ester, (R)-**3g**.* Conversion: >99%, 87% ee, $[\alpha]_D^{20}$ +180.0 (*c* 2.2 in $CHCl_3$), [lit.[18] $[\alpha]_D^{20}$ −23 (*c* 1.00 in C_2H_5OH) for (*R*)]; ^1H NMR (300 MHz, $CDCl_3$) δ 8.03–8.06 (m, 2H), 7.52–7.57 (m, 1H), 7.41–7.46 (m, 2H), 5.14–5.20 (m, 1H), 0.94–1.76 (m, 7H), 0.94 (t, *J*=6.9 Hz, 3H) ppm. The enantiomeric excess was determined by HPLC on Chiralcel OB-H column, hexane/isopropanol=100:0; flow rate=0.8 mL/min; UV detection at λ=230 nm; t_R=8.1 min (minor), 9.4 min (major).

*4.4.3. (R)-Benzoic acid 1-methylhexyl ester,[19] (R)-**3h**.* Conversion: >99%, 88% ee, $[\alpha]_D^{20}$ +87.3 (*c* 1.0 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.03–8.06 (m, 2H), 7.53–7.58 (m, 1H), 7.41–7.46 (m, 2H), 5.13–5.19 (m, 1H), 1.55–1.76 (m, 1H), 1.26–1.43 (m, 10H), 0.88 (t, *J*=6.6 Hz, 3H) ppm. The enantiomeric excess was determined by HPLC on Chiralcel OB-H column, hexane/isopropanol=100:0; flow rate=0.2 mL/min; UV detection at λ=230 nm; t_R=38.0 min (minor), 40.4 min (major).

*4.4.4. (R)-Benzoic acid 1-methylheptyl ester, (R)-**3i**.* Conversion: >99%, 87% ee, $[\alpha]_D^{20}$ −13.0 (*c* 1.0 in $CHCl_3$), [lit.[20] $[\alpha]_D^{20}$ +33.3 (*c* 1.00 in CH_2Cl_2) for (*R*)]; ^1H NMR (300 MHz, $CDCl_3$) δ 8.03–8.06 (m, 2H), 7.52–7.58 (m, 1H), 7.41–7.46 (m, 2H), 5.12–5.19 (m, 1H), 1.55–1.76 (m, 1H), 1.25–1.42 (m, 12H), 0.87 (t, *J*=6.6 Hz, 3H) ppm. The enantiomeric excess was determined by HPLC on Chiralcel OB-H column, hexane/isopropanol=100:0; flow rate=0.2 mL/min; UV detection at λ=230 nm; t_R=29.2 min (minor), 31.4 min (major).

4.5. General procedure for catalytic asymmetric hydrogenation of 5

$[Rh(cod)_2]BF_4$ (2.0 mg, 0.005 mmol) and (*R*,*R*,*R*)-**1l** (6.7 mg, 0.011 mmol) were dissolved in CH_2Cl_2 (2 mL) under nitrogen and

the solution was stirred at room temperature for 10 min. A solution of **5** (0.5 mmol) in *i*-PrOH (2 mL) was added to the above catalyst solution. The resulting mixture was then transferred to a stainless steel autoclave under nitrogen atmosphere, and then sealed. After purging six times with hydrogen, the final H_2 pressure was adjusted to 40 bar. After stirring at room temperature for 10 h, H_2 was released. After removal of the solvent under the reduced pressure, white solid was obtained and submitted to ^{1}H NMR spectroscopic analysis to assess the conversion of the substrate. Conversion: >99%, $[\alpha]_D^{20}$ +18.9 (*c* 1.0 in MeOH), [lit.[13] $[\alpha]_D^{20}$ −20.6 (*c* 1.00 in CH_3OH) for (*S*)]; ^{1}H NMR (300 MHz, D_2O) δ 3.05–3.10 (m, 1H), 2.49–2.51 (m, 2H), 1.59–1.69 (m, 2H), 1.34–1.43 (m, 1H), 0.93–0.96 (m, 6H) ppm. The enantiomeric excess value was determined after transformation into the corresponding methyl ester via the following procedure: the crude product was dissolved in the acetone (3 mL). The solution was acidified to pH=1 by 2 M HCl, followed by treated with diazomethane in Et_2O. The mixture was extracted with ethyl acetate (3×3 mL), dried over Na_2SO_4, and concentrated in vacuo. The enantiomeric excess of the product was determined by chiral GC 95% ee. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.75 (s, 3H), 3.04–3.09 (m, 1H), 2.51–2.76 (m, 2H), 1.82–1.90 (m, 1H), 1.59–1.71 (m, 2H), 0.95–0.99 (m, 6H) ppm. The enantiomeric excess was determined by GC on Chiralcel Supelco GAMA-DEX 225 column, 120 °C, t_R=18.5 min (major), 19.2 min (minor).

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