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Asymmetric transfer hydrogenation of γ-aryl α,γ-dioxo-butyric acid esters†

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The asymmetric transfer hydrogenation (ATH) of a series of γ-aryl-α,γ-dioxo-butyric acid esters has been accomplished smoothly. Six ferrocene-based chiral ligands have been prepared and applied in the reactions respectively. Simultaneously, enantiopure Ts-DPEN's utilization in the ATH also has been investigated and the products were obtained in 30–85% chemical yields with 37–95.5% ee.

Introduction

Chiral α-hydroxy-γ-keto-butyric acid ethyl esters are key building blocks for some important bioactive compounds, such as Croomia,[1,2] Citrafungins[3] and other natural extracts.[4–10] The synthesis of the chiral pharmaceutical α-hydroxy-γ-keto intermediates is of great interest in organic chemistry. However, only a few methods have been reported on their preparation such as asymmetric reduction *via* enzymatic catalysis,[11–13] enantioselective aza-ene-type reactions[14,15] as well as Brønsted acid catalyzing asymmetric aldol reactions[16] and heterogeneous enantioselective hydrogenations.[17,18] Compared with the above reported methods, transition metal-catalyzed asymmetric transfer hydrogenation (ATH) should be a more facile access because of concise procedure and easy operation. As a kind of powerful method for asymmetric transformation,[19] ATH is widely used in both academics and industrials. Since it was reported in early 1980s,[20] many excellent chiral ligands have been found and various substrates have also been investigated.[21] Nowadays the pursuit for novel chiral ligands[22] and the new applications of the existed ligands[23–25] for ATH were still attractive. As far as the substrates in ATH were concerned, the class of chemicals with several carbonyl moieties in one molecule[26–29] were very interesting because multiple-carbonyl groups mean many synthetic applications. But there were limited papers on the ATH of multi-carbonyl compounds.[30] It was worthy of notice that the ATH of γ-aryl-α,γ-dioxo-butyric acid esters is seldom reported to date (Scheme 1).

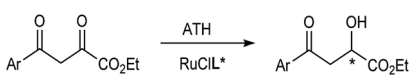
Ferrocene was an outstanding skeleton for ligand design.[31] There were lots of excellent ferrocene-based chiral ligands successfully used in many asymmetric transformations.[32] Our group have also developed a series of ferrocene-based chiral ligands. They possessed excellent enantioselectivities in many reactions.[33–36] Herein, we have chose two of them ($\mathbf{L_1}$, $\mathbf{L_2}$) as well as other four new prepared ligands ($\mathbf{L_3}$–$\mathbf{L_6}$) (Fig. 1) to carry out the research of the ATH of α,γ-dioxo-butyric acid esters. Simultaneously, the classical Noroyi's catalysts RuCl(*p*-cymene)[Ts-DPEN] (Fig. 2) have also been examined in this reaction to prepare chiral α-hydroxy-γ-keto-butyric acid ethyl esters in detail.

Results and discussion

The synthesis of ferrocene-based chiral ligands

The preparation of the six ferrocene-based chiral ligands (Fig. 1) was straightforward and as shown in Scheme 2. According to literature,[36] ortho-lithiation of (*R*)-Ugi's amine and subsequent treatment with $ClPAr_2$, Ac_2O and a large excess of ammonia, intermediate **1a** could be obtained. Then the reductive amination of **1a** with picolinaldehydes resulted in the formation of ligands $\mathbf{L_1}$–$\mathbf{L_3}$ in 30–54% isolated yields.[37] Similar process also could lead to $\mathbf{L_4}$ (50% yield). If (*R*)-Ugi's amine was stirred with Ac_2O at 100 °C under nitrogen conditions, acetate **2** was furnished and could be used in the next step without further purification.[36] After amination of **2** by (*S*,*S*) or (*R*,*R*)-1,2-diphenyl-1,2-ethanediamine in CH_3OH, $\mathbf{L_5}$ or $\mathbf{L_6}$ was produced directly.[36]

As to the structure of the above ligands, $\mathbf{L_1}$, $\mathbf{L_2}$ and $\mathbf{L_3}$ had both central chirality and planar chirality while $\mathbf{L_4}$, $\mathbf{L_5}$ and $\mathbf{L_6}$ only possessed stereogenic carbon. They were designed for



Scheme 1 Asymmetric transfer hydrogenation (ATH) of γ-aryl α,γ-dioxo-butyric acid ester.

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† Electronic supplementary information (ESI) available: ^1H, ^{13}C NMR of products **4a–g**, ^1H, ^{31}P, ^{13}C NMR and HRMS of compounds $\mathbf{L_1}$–$\mathbf{L_6}$, HPLC charts of products **4a–g**. X-ray crystal of **4b**, **4g**. See DOI: 10.1039/c6ra02500e

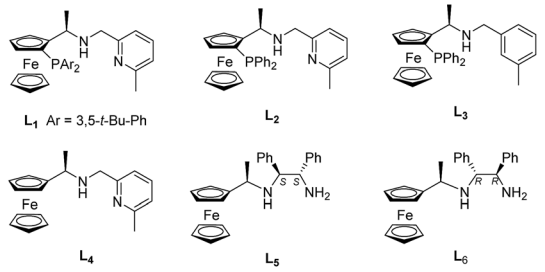


Fig. 1 The structure of ferrocene-based chiral ligands used in the ATH.

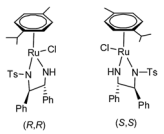
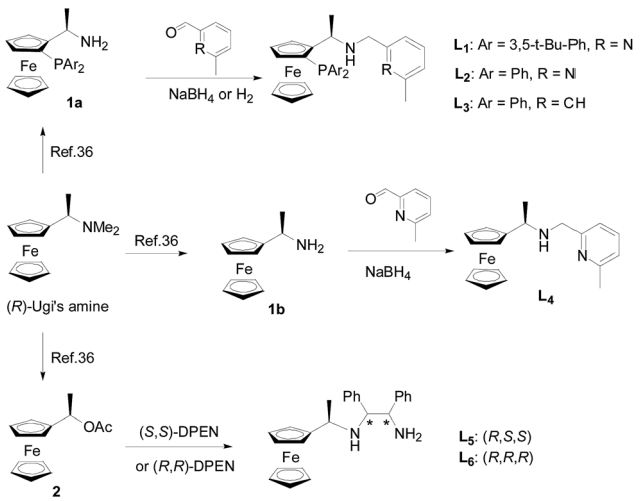


Fig. 2 The structure of RuCl(*p*-cymene)[Ts-DPEN].



Scheme 2 The route to ferrocene-based chiral ligands.

detection of the planer chirality and the match of multicentre chirality on the effect of the ATH reaction.

The ATH catalyzed by RuCl(*p*-cymene)(Ts-DPEN)

Noroyi's catalysts, RuCl(*p*-cymene)[(*S*,*S*)-Ts-DPEN] and its enantiomer have been star catalysts in ATH and they can be got in a commercial way. So their applications in ATH of γ-aryl-α,γ-dioxo-butyric acid esters (Scheme 1) have been carried out firstly.

A survey of reaction media was finished with γ-phenyl-α,γ-dioxo-butyric acid ester (**3a**)[38,39] as model substrate. Different hydrogen sources, various solvents and temperature were probed.

Initially, at room temperature (r.t.), two most common hydrogen source: both i-PrOH-KOH system and HCOOH/Et_3N (5 : 2) system have been tested. But after monitored by TLC, no transformation has happened in i-PrOH system. On the other hand, reaction in HCOOH/Et_3N (5 : 2) system have proceeded smoothly and afforded α-hydroxy ester with the yield of 85% and 84% ee (Table 1, entry 1). So HCOOH/Et_3N (5 : 2) was selected as hydrogen source for further experiments.

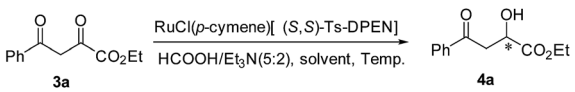
To optimize the reaction efficiency, several solvents have been examined. We have observed that the ee in proton solvent (MeOH) was moderate (73% ee), but the yield was low (30%) (Table 1, entry 2). Moreover, the results in nonproton solvents, such as DMF, dioxane, DCM, EtOAc and *t*-BuOMe, were better than that in proton solvent (Table 1, entry 2–8). Especially, polar nonproton solvent DMF gave the highest yield (85%) and the highest ee (84% ee). The solvent influence on the reaction may related to the formation of transition state. Bigger steric hindrance solvent corresponded to better enantioselectivity.

In order to investigate temperature effect on the reaction, we have decreased the temperature from r.t. to 0 °C. But the ees didn't change (Table 1, entry 1 *vs.* entry 10). At −20 °C, much higher optical yield (94% ee) accompanied with lower chemical yield (68%) was observed (Table 1, entry 11). However, at more lower temperature (−40 °C), the reaction only had trace conversion (Table 1, entry 12). Lastly, −20 °C was determined as the optimal temperature.

We have also found that the configuration of the product was controlled by the ligand. Switching the configuration of the Ts-DPEN from (*S*,*S*) to (*R*,*R*), the product configuration also changed to (*R*)-configuration (Table 1, entry 13).

Under the optimized conditions, a wide range of substrates have been put into the reaction and RuCl(*p*-cymene)[(*R*,*R*)-Ts-DPEN] has been employed (Table 2). Form these reaction, we noticed that substituent on the γ-phenyl had not effect on the

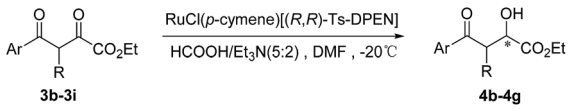
Table 1 The ATH reactions catalyzed by Ru-(*S*,*S*)-Ts-DPEN complex



Entry[a]	Temp.	Solvent	Yield (%)	ee[e] (%) (conf.)
1[b]	r.t.	DMF	85	84(*S*)
2[b]	r.t.	MeOH	30	73(*S*)
3[b]	r.t.	Et_2O	Trace	ND
4[b]	r.t.	DCM	Trace	ND
5[b]	r.t.	THF	73	50(*S*)
6[b]	r.t.	EtOAc	80	23(*S*)
7[b]	r.t.	Dioxane	77	60(*S*)
8[b]	r.t.	*t*-BuOMe	82	81(*S*)
9[c]	r.t.	—	75	79(*S*)
10[b]	0 °C	DMF	80	84(*S*)
11[b]	−20 °C	DMF	68	94(*S*)
12[b]	−40 °C	DMF	Trace	ND
13[b,d]	−20 °C	DMF	68	94(*R*)

[a] 1 mmol **3a** with 0.0025 mmol of Ru(*p*-cymene)Cl and 0.005 mmol of (*S*,*S*)-Ts-DPEN for each entry. [b] Dissolution in 4 mL HCOOH/Et_3N (5 : 2) and 1 mL solvent. [c] Using 5 mL of HCOOH/Et_3N (5 : 2) without solvent. [d] 0.005 mmol of (*R*,*R*)-Ts-DPEN instead of (*S*,*S*)-Ts-DPEN was employed. [e] The enantiomeric excess (ee) and configuration (conf.) of product were determined by chiral HPLC with Chiralpak OD-H column and according to literature or X-ray crystal.

Table 2 Different substrates of the ATH catalyzed by RuCl [(*R*,*R*)-TsDPEN](*p*-cymene)



Entry[a]	Substrate	Ar	R	Product	Yield (%)	ee[b] (%) (conf.)
1	**3b**	4-F-Ph	H	**4b**	61	91(*R*)
2	**3c**	4-Cl-Ph	H	**4c**	58	91(*R*)
3	**3d**	4-Br-Ph	H	**4d**	60	91(*R*)
4	**3e**	4-OMe-Ph	H	**4e**	58	94.5(*R*)
5	**3f**	2-Furyl	H	**4f**	55	96(*R*)
6	**3g**	2-Thienyl	H	**4g**	71	96(*R*)
7	**3h**	Ph	Me	—	—	ND
8	**3i**	Ph	Ph	—	—	ND

[a] 1 mmol of substrate with 0.0025 mmol of Ru(*p*-cymene)Cl and 0.005 mmol of (*R*,*R*)-Ts-DPEN in 4 mL HCOOH/Et_3N (5 : 2) and 1 mL DMF at −20 °C stir 4 days for each entry. [b] The ee and configuration of product were determined by chiral HPLC with Chiralpak OD-H, OJ-H or AD-H column and according to literature or X-ray crystal.

results. **3b–3d**, which separately possessed electron withdrawing group (F, Cl, Br), afforded almost the same results as **3e** did (Table 2, entry 1–4). They all provided products with the ee exceeded 91% and the chemical yields were moderate. Moreover, for all substrates, there only α-carbonyl group could transfer into hydroxyl and got corresponding chiral α-hydroxy-γ-keto-butyric acid ethyl esters. To our delight, furan and thiophene derivatives (**3f** or **3g**) also gave satisfactory optical selectivity results (Both ees were more than 96%). It's should known that this two kind of compounds were widely used in pharmacy. When more sterically crowded substrate **3h** or **3i** has been tested, no product was detected (Table 2, entry 7–8). This indicated that steric-hindrance on the β-site influenced coordination between substrate and metal. All the products' configurations were consistent with that of the ligand. They were (*R*)-configuration. Product **4b** and **4e** were also characterized by X-ray single crystal diffraction analysis. The structure of **4e** was shown in Fig. 3.

The ATH catalyzed by ferrocene-based chiral catalysts

With ferrocene-based chiral ligands at hand, our initial survey has focused on evaluating the possibility of using these ligands $\mathbf{L_1}$–$\mathbf{L_6}$ for the chiral induction in ATH of **3a**. Employing $\mathbf{L_2}$ as ligand, we have tested the solvent and temperature of the reaction. They were shown in Table 3. Lastly, DMF and −20 °C proved to be the optimized condition.

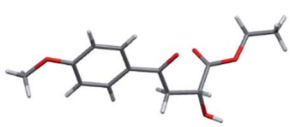
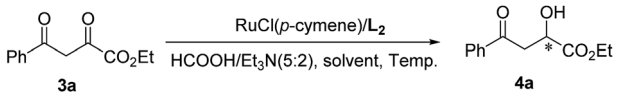


Fig. 3 X-ray crystal structure of (*R*)-**4e**.

Table 3 The ATH reactions catalyzed by $\mathbf{L_2}$

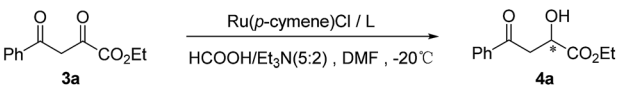


Entry[a]	Solvent	Temp.	Yield (%)	ee[b] (%) (conf.)
1	DMF	r.t.	72	5(*R*)
2	MeOH	r.t.	Trace	ND
3	THF	r.t.	Trace	ND
4	CH_2Cl_2	r.t.	Trace	ND
5	CH_3CN	r.t.	Trace	ND
6	DMF	−20 °C	60	65(*R*)

[a] 1 mmol of **3a** with 0.0025 mmol of Ru(*p*-cymene)Cl and 0.005 mmol of $\mathbf{L_2}$ in 4 mL HCOOH/Et_3N (5 : 2) and 1 mL DMF at −20 °C stir 4 days for each entry. [b] The ee and configuration of product were determined by chiral HPLC with Chiralpak OD-H column and according to literature or X-ray crystal.

Then screen of these chiral ligands was necessary. The results were described in Table 4. All the six chiral ligands induced moderate chemical yield while their optical results were much different. $\mathbf{L_1}$ had P, N, N three special elements and achieved the best optical yield (90% ee) (Table 4, entry 1). Comparing with $\mathbf{L_1}$, $\mathbf{L_2}$'s result was much worse though it had little structure difference with $\mathbf{L_1}$. The ee was only 65% (Table 4, entry 2). In order to check pyridine unit's impact on the reaction, $\mathbf{L_3}$ was prepared and the ee from $\mathbf{L_3}$ was a little lower than that of $\mathbf{L_2}$ (Table 4, entry 3). This implied that the N atom on pyridine of ligand influenced stereoselectivity and chemical yield but not too much. On the other hand, $\mathbf{L_4}$ only had one chiral element and the chiral centre was far from the metal center. Then its racemic result was not surprising (Table 4, entry 4). What' more, $\mathbf{L_5}$ and $\mathbf{L_6}$'s behaviours were almost the same. Their ees were 40% and 37%, but the configurations were

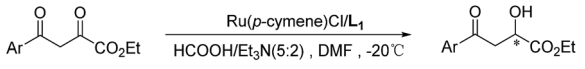
Table 4 The ATH reactions catalyzed by ferrocene-based chiral catalysts



Entry[a]	Ligand	Yield (%)	ee[b] (%) (conf.)
1	$\mathbf{L_1}$	57	90(*R*)
2	$\mathbf{L_2}$	60	65(*R*)
3	$\mathbf{L_3}$	55	50(*R*)
4	$\mathbf{L_4}$	47	Rac
5	$\mathbf{L_5}$	50	40(*S*)
6	$\mathbf{L_6}$	52	37(*R*)

[a] 1 mmol of **3a** with 0.0025 mmol of Ru(*p*-cymene)Cl and 0.005 mmol of ligand in 4 mL HCOOH/Et_3N (5 : 2) and 1 mL DMF at −20 °C stir 4 days for each entry. [b] The ee and configuration of product were determined by chiral HPLC with Chiralpak OD-H column and according to literature or X-ray crystal.

Table 5 Different substrates of the ATH reactions catalyzed by L_1



Entry[a]	Substrate	Ar	Product	Yield (%)	ee[b] (%) (conf.)
1	**3b**	4-F-Ph	**4b**	55	69(*R*)
2	**3c**	4-Cl-Ph	**4c**	58	67(*R*)
3	**3d**	4-Br-Ph	**4d**	53	75(*R*)
4	**3e**	4-OMe-Ph	**4e**	50	69(*R*)
5	**3f**	2-Furyl	**4f**	48	75(*R*)
6	**3g**	2-Thienyl	**4g**	50	87(*R*)

[a] 1 mmol of substrate with 0.0025 mmol of Ru(*p*-cymene)Cl and 0.005 mmol of $\mathbf{L_1}$ in 4 mL HCOOH/Et_3N (5 : 2) and 1 mL DMF at −20 °C stir 4 days for each entry. [b] The ee and configuration of product were determined by chiral HPLC with Chiralpak OD-H, OJ-H or AD-H column and according to literature or X-ray crystal.

different (Table 4, entry 5 and 6). So we can know that the chiral carbon centre of Ugi's amine almost had not attribution to the stereocontrol in the ATH. The planer chiral elements and the P unit on the ferrocene ring were essential for the high enantioselectivity. At the same time, the Ar groups on P provides bulkiness which caused better enantiocontrol in the reaction (Table 4 entry 1 *vs.* entry 2). N atom on pyridine also helped to improve this kind of selectivity (Table 4, entry 2 *vs.* entry 3). It's noteworthy that these six ligands' behavior were not as good as that of chiral RuCl(*p*-cymene)[Ts-DPEN]. Maybe it was due to the activity of H on N in these six ligands was lower than RuCl(*p*-cymene)[Ts-DPEN], which resulted in establishing Ru–H–C–O–H–N–Ru transition state ring harder.

Of course, $\mathbf{L_1}$ would applied to more substrates' ATH reactions. As Table 5 showed, at −20 °C and in HCOOH/Et_3N (5 : 2) system, $\mathbf{L_1}$ exhibited moderate to good inducing ability. The ees ranged from 67% to 87% with the yield of 50% or so. Like the results in Table 2, the substituent, F, Cl, Br or OMe on the γ-phenyl of the substrate had no influence on the ATH (Table 5, entry 1–4). Furthermore, furan derivative **3f** and thiophene derivative **3g** also gave corresponding α-hydroxy-γ-keto-butyric acid ethyl ester with 75% ee and 87% ee respectively (Table 5, entry 5 and 6).

Conclusion

This paper presented a convenient method toward chiral α-hydroxy-γ-keto-butyric acid ethyl esters. The preparation of six chiral ferrocene-based ligands and their utilization in ATH of multiple-carbonyl compounds were discussed. Several optical α-hydroxy-γ-keto-butyric acid ethyl esters were achieved with moderate to excellent ees and moderate chemical yields. Enantiopure RuCl(*p*-cymene)[Ts-DPEN] catalysts' application in the asymmetric transformation were also developed. Our six ferrocene-based ligands and the reaction for further utilization are both on going.

Experimental

General

All reactions involving air- or moisture-sensitive species were finished under N_2 atmosphere. High-resolution mass spectra were performed on a Bruker smartapex II CCD Mass Spectrometer with ES ionization (ESI). The ^1H and ^{13}C NMR spectra were recorded on a Bruker AV-400 spectrometer with TMS as an internal reference. Coupling constant (*J*) values were given in Hz. Multiplicities are designated by the following abbreviations/ s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, multiplet. Melting points were uncorrected and expressed in °C by MRS-2 melting point apparatus from Shanghai Apparatus Co., Ltd. An Agilent 1200 series apparatus and Chiralpak AD-H, OD-H and OJ-H columns, purchased from Daicel Chemical Industries, were used in Chiral High Performance Liquid Chromatography (HPLC) analyses. All commercially available reagents were used as received. Thin layer chromatography on silica (with GF254) was used to monitor all reactions. Products were purified by flash column chromatography on silica gel purchased from Qingdao Haiyang Chemical Co., Ltd. Optical rotations were measured on a Perkin Elmer 343 polarimeter. The configuration of the products had been assigned by comparison to the literature data or single crystal diffraction.

The synthesis of ferrocene-based chiral ligand

The synthesis of $\mathbf{L_1}$. Corresponding **1a** (1.284 g, 2 mmol), which could be prepared from (*R*)-Ugi's amine,[36] and 6-methyl-2-pyridylaldehyde (0.3025 g, 2.5 mmol) were dissolved in 10 mL MeOH. At r.t., the system was stirred for 6 hours under N_2 atmosphere. With $NaBH_4$ (0.19 g, 5 mmol) added, the reaction was proceeded overnight. After that, 10 mL H_2O was added and subsequently extracted with CH_2Cl_2 (10 mL) for three times. The organic layers were dried over Na_2SO_4. $\mathbf{L_1}$ can be purified by column chromatography (*n*-hexane/EtOAc/Et_3N = 8/1/0.03, v/v).

Yield 54%; yellow foam; $[\alpha]_D^{25} = -184.6°$ (c = 0.25, CH_2Cl_2); ^1H NMR (400 Hz, $CDCl_3$) δ 7.42–7.37 (m, 3H), 7.24 (s, 2H), 7.23–7.21 (m, 1H), 7.17–7.10 (m, 1H), 6.81 (d, J = 7.5 Hz, 1H), 5.89 (d, J = 8 Hz, 1H), 4.51 (s, 1H), 4.30–4.23 (m, 2H), 4.06 (s, 5H), 3.75 (s, 1H), 3.54 (d, J = 14.5 Hz, 1H), 3.48 (d, J = 14.5 Hz, 1H), 2.39 (s, 3H), 1.55 (d, J = 6.5 Hz, 3H), 1.29 (s, 18H), 1.13 (s, 18H); ^{31}P NMR (202 Hz, $CDCl_3$) δ −24.98 (s); ^{13}C NMR (101 Hz, $CDCl_3$) δ 159.4 (d, J = 5.9 Hz), 157.1, 150.5 (d, J = 6.6 Hz), 150.0 (d, J = 7.4 Hz), 138.5 (d, J = 7.7 Hz), 136.3, 135.6 (d, J = 7.3 Hz), 129.1 (d, J = 21.4 Hz), 127.4 (d, J = 20.7 Hz), 125.3, 122.7 (d, J = 20.5 Hz), 120.8, 117.8, 96.9, 75.1 (d, J = 14.1 Hz), 71.1 (d, J = 4.2 Hz), 69.6, 69.4 (d, J = 3.8 Hz), 68.6, 51.8, 51.1 (d, J = 10.1 Hz), 34.9, 34.8, 31.5, 31.3, 24.3, 19.2; HRMS (ESI) calcd for $C_{47}H_{63}FeN_2P$ $[M + H]^+$ = 743.4157, found/743.4148.

The synthesis $\mathbf{L_2}$. $\mathbf{L_2}$ is prepared from **1a** through the same procedure as described above for $\mathbf{L_1}$.

Yield 50%; red foam; $[\alpha]_D^{25} = -243.8°$ (c = 0.65, CH_2Cl_2); ^1H NMR (400 MHz, $CDCL_3$) δ 7.56–7.50 (m, 2H), 7.40–7.33 (m, 3H), 7.28–7.20 (m, 3H), 7.17–7.10 (m, 3H), 6.84 (d, J = 7.5 Hz, 1H), 6.33 (d, J = 7.5 Hz, 1H), 4.53 (s, 1H), 4.33–4.28 (m, 1H), 4.25–4.17 (m, 1H), 4.00 (s, 5H), 3.85–3.80 (m, 1H), 3.62 (s, 1H), 2.41 (s, 3H),

1.55 (d, J = 6.5 Hz, 3H); ^{31}P NMR (162 MHz, $CDCL_3$) δ −25.03 (s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 157.1, 140.1 (d, J = 9.8 Hz), 137.4 (d, J = 9.2 Hz), 136.3, 135.0 (d, J = 21.3 Hz), 132.6 (d, J = 18.6 Hz), 131.5 (d, J = 10 Hz), 129.1, 128.3 (d, J = 5.9 Hz), 128.3, 120.9, 118.3, 97.8 (d, J = 24.3 Hz), 75.1 (d, J = 8.2 Hz), 71.3 (d, J = 4 Hz), 69.6, 69.5 (d, J = 4.4 Hz), 69.1, 52.1, 51.3 (d, J = 9.2 Hz), 24.4, 19.4; HRMS (ESI) calcd for $C_{31}H_{31}FeN_2P$ $[M + H]^+$ = 519.1653, found/519.1645.

The synthesis of L_3. Corresponding **1a** (0.828 g, 2 mmol) and 6-methyl-2-benzaldehyde (0.3 g, 2.5 mmol) were dissolved in 10 mL MeOH. The system was stirred at r.t. for 6 hours under N_2 atmosphere. With 5 g Pd/C was added, the reaction was carried out under 20 atm of H_2 in autoclave overnight. Then filtered and the filtrate was dried over Na_2SO_4. L_3 can be purified by column chromatography (*n*-hexane/EtOAc/Et_3N = 8/1/0.03, v/v).

Yield 30%; red foam; $[\alpha]_D^{25} = -139^\circ$ (c = 0.1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89–7.75 (m, 2H), 7.73–7.60 (m, 2H), 7.59–7.47 (m, 3H), 7.42–7.30 (m, 3H), 6.99 (t, J = 7.5 Hz, 1H), 6.92 (d, J = 7.5 Hz, 1H), 6.67 (s, 1H), 6.59 (d, J = 7.1 Hz, 1H), 4.68 (d, J = 27.6 Hz, 1H), 4.39 (d, J = 2.3 Hz, 1H), 4.24 (s, 5H), 3.96 (s, 1H), 3.37 (s, 2H), 3.30 (dd, J = 7.1, 5.9 Hz, 1H), 2.23 (s, 3H), 1.53 (d, J = 6.6 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ −25.36 (s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.99 (s), 137.41 (s), 135.55 (s), 134.38 (d, J = 26.6 Hz), 133.19 (s), 131.61 (d, J = 2.7 Hz), 131.44 (d, J = 9.9 Hz), 131.19 (d, J = 9.9 Hz), 128.65 (s), 128.46 (d, J = 12.0 Hz), 128.31–127.84 (m), 127.19 (s), 126.97 (s), 125.04 (s), 98.53–94.93 (m), 73.54 (d, J = 15.2 Hz), 71.39 (s), 71.00 (d, J = 9.9 Hz), 70.30 (s), 70.04 (d, J = 11.5 Hz), 69.70–69.59 (m), 50.77 (s), 23.37 (s), 19.38 (s); HRMS (ESI) calcd for $C_{32}H_{32}FeNP$ $[M + H]^+$ = 518.1700, found/518.1739.

The synthesis of L_4. L_4 was prepared from **1b (0.458 g, 2 mmol)**, which was also obtained from (*R*)-Ugi's amine,[36] and 6-methyl-2-pyridylaldehyde through the same procedure as described above for L_1.

Yield 50%; red foam; $[\alpha]_D^{25} = -8^\circ$ (c = 0.25, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (t, J = 7.6 Hz, 1H), 7.11 (d, J = 7.6 Hz, 1H), 7.03 (d, J = 7.6 Hz, 1H), 4.26 (s, 1H), 4.20 (s, 6H), 4.13 (s, 2H), 3.92 (m, 2H), 3.57 (q, J = 6.4 Hz, 1H), 2.56 (s, 3H), 1.42 (d, J = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.94 (s), 158.01 (s), 136.60 (s), 121.42 (s), 119.26 (s), 94.06 (s), 68.55 (s), 68.51 (d, J = 6.8 Hz), 67.29 (s), 66.69 (s), 66.26 (s), 52.95 (s), 52.02 (s), 24.47 (s), 21.65 (d, J = 69.8 Hz); HRMS (ESI) calcd for $C_{19}H_{22}FeN_2$ $[M + H]^+$ = 335.1211, found/335.1224.

The synthesis of L_5. **2** (1.088 g, 4 mmol), which was prepared from (*R*)-Ugi's amine,[36] and (*S*,*S*)-DPEN (2.12 g, 10 mmol) were dissolved in the mixture of 30 mL MeOH, 30 mL THF and 3 mL H_2O. The reaction was stirred at 70 °C overnight under N_2 atmosphere. After vacuum distillation, the system was extracted with Et_2O (30 mL) three times and the organic layers were dried over Na_2SO_4. L_5 can be purified by column chromatography (*n*-hexane/EtOAc/Et_3N = 8/1/0.03, v/v).

Yield 40%; orange foam; $[\alpha]_D^{25} = -17.8^\circ$ (c = 0.5, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.15 (m, 10H), 4.24 (m, 1H), 4.14–4.06 (m, 4H), 4.01 (m, 5H), 3.34–3.20 (m, 2H), 1.23 (d, J = 6.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.18 (s), 143.20 (s), 141.45 (s), 128.20 (s), 127.92 (s), 127.14 (s), 127.11 (s), 127.05 (s), 94.93 (s), 68.27 (s), 67.29 (s), 66.44 (s), 66.06 (s), 61.53 (s), 47.71 (s), 23.29 (s); HRMS (ESI^+) calcd for $C_{26}H_{28}FeN_2$ $[M + H]^+$ = 425.1680, found/425.1686.

The synthesis of L_6. L_6 was prepared from (*R*,*R*)-DPEN through the same procedure as described above toward L_5.

Yield 40%; orange foam; $[\alpha]_D^{25} = 34.8^\circ$ (c = 1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.15 (m, 10H), 4.23 (s, 1H), 4.14–4.06 (m, 4H), 4.02 (s, 5H), 3.30 (m, 2H), 1.22 (d, J = 6.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.91 (s), 143.41 (s), 141.56 (s, J = 69.1 Hz), 128.13 (d, J = 1.6 Hz), 127.91 (s), 127.11 (s), 127.03 (s), 126.97 (s), 94.99 (s), 68.22 (s), 67.22 (s), 66.42 (s), 66.07 (d, J = 6.5 Hz), 61.60 (s), 47.73 (s), 23.35 (s); HRMS (ESI^+) calcd for $C_{26}H_{28}FeN_2$ $[M + H]^+$ = 425.1680, found/425.1679.

The general procedure for ATH in HCOOH/Et_3N (5 : 2)

1 mmol of substrate with 0.0025 mmol of Ru(*p*-cymene)Cl and 0.005 mmol of chiral ligand were dissolved in 1 mL solvent and stirred at r.t. for 4 hours under N_2 atmosphere. Then 4 mL HCOOH/Et_3N (5 : 2) was injected by syringe. The mixture was stirred at −20 °C for 4 days under N_2 atmosphere. Saturated $NaHCO_3$ (5 mL) and H_2O (5 mL) were added and then extracted with EtOAc (10 mL) for three times and dried over Na_2SO_4. The product was purified by column chromatography (*n*-hexane/EtOAc = 4/1, v/v).

Product 4a. Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 7.3 Hz, 2H), 7.64–7.57 (m, 1H), 7.49 (t, J = 7.7 Hz, 2H), 4.68 (m, 1H), 4.29 (q, J = 7.1 Hz, 2H), 3.52 (m, 2H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.57 (s), 173.83 (s), 136.42 (s), 133.63 (s), 128.70 (s), 128.18 (s), 67.20 (s), 61.85 (s), 42.19 (s), 14.11 (s).

Product 4b. Yellow solid; m.p. 71–72 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (m, 2H), 7.21–7.13 (m, 2H), 4.67 (t, J = 5.7, 3.9 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 3.49 (qd, J = 17.4, 4.9 Hz, 2H), 3.33 (d, J = 5.6 Hz, 1H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.90 (s), 173.72 (s), 130.94 (s), 130.84 (s), 115.99 (s), 115.77 (s), 67.18 (s), 61.96 (s), 42.06 (s), 14.13 (s).

Product 4c. Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95–7.88 (m, 2H), 7.51–7.44 (m, 2H), 4.67 (dd, J = 5.5, 1.6 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 3.48 (qd, J = 17.4, 4.9 Hz, 2H), 3.32 (d, J = 5.5 Hz, 1H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.26 (s), 173.69 (s), 140.15 (s), 134.80 (s), 129.86 (s), 129.51 (d, J = 18.2 Hz), 129.13 (d, J = 14.8 Hz), 67.13 (s), 61.98 (s), 42.13 (s), 14.13 (s).

Product 4d. Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (m, 2H), 7.61 (m, 2H), 4.70–4.61 (m, 1H), 4.26 (q, J = 7.1 Hz, 2H), 3.46 (dd, J = 17.2, 4.8 Hz, 2H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.47 (s), 173.76 (s), 135.20 (s), 132.02 (s), 129.68 (s), 128.85 (s), 67.05 (s), 61.91 (s), 42.16 (s), 14.12 (s).

Product 4e. Yellow solid; m.p. 65–66 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.8 Hz, 2H), 6.94 (d, J = 8.8 Hz, 2H), 4.65 (dd, J = 5.8, 4.1 Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H), 3.87 (s, 3H), 3.45 (qd, J = 17.3, 5.0 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 196.16 (s), 173.83 (s), 163.95 (s), 130.54 (s), 129.55 (s), 113.87 (s), 67.42 (s), 61.81 (s), 55.52 (s), 41.75 (s), 14.14 (s).

Product 4f. Black oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 1.0 Hz, 1H), 7.26 (s, 1H), 6.58 (dd, J = 3.6, 1.7 Hz, 1H), 4.66 (s

1H), 4.29 (q, $J = 7.1$ Hz, 2H), 3.45–3.31 (m, 2H), 1.30 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 186.16 (s), 173.65 (s), 152.40 (s), 146.84 (s), 117.85 (s), 112.50 (s), 67.06 (s), 61.98 (s), 42.02 (s), 14.09 (s).

Product 4g. Purple oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, $J = 3.8$ Hz, 1H), 7.71 (d, $J = 4.9$ Hz, 1H), 7.21–7.14 (m, 1H), 4.67 (dd, $J = 9.8$, 5.6 Hz, 1H), 4.30 (q, $J = 7.1$ Hz, 2H), 3.53–3.36 (m, 2H), 3.34 (d, $J = 5.6$ Hz, 1H), 1.31 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.14 (s), 173.57 (s), 143.67 (s), 134.47 (s), 132.66 (s), 128.24 (s), 67.34 (s), 61.99 (s), 42.81 (s), 14.10 (s).

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