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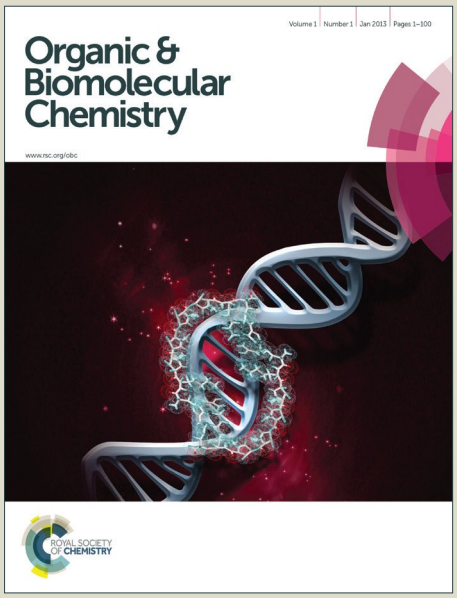

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ARTICLE

Ru-Catalyzed Asymmetric Hydrogenation of δ-Keto Weinreb Amides: Enantioselective Synthesis of (+)-Centrolobine

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An efficient asymmetric hydrogenation of δ-keto Weinreb amides catalyzed by Ru-Xyl-SunPhos-Daipen bifunctional catalyst has been achieved. This method afforded a series of enantioenriched δ-hydroxy Weinreb amides in good yields (up to 93%) and enantioselectivities (up to 99%). This protocol was successfully applied to the synthesis of the key intermediate of (+)-Centrolobine.

Introduction

Chiral δ-hydroxy acid derivatives are of particular interest to synthetic chemists as the key intermediates for natural products and pharmaceuticals, such as δ-lactones, Ezetimibe, and Centrolobine.[1-3] However, only a few methods are available for the synthesis of optically pure δ-hydroxy acid derivatives, including reduction of δ-ketoesters by chiral borane and asymmetric transfer hydrogenation, and kinetic resolution of racemic δ-hydroxy esters.[4] Furthermore, these synthetic routes suffered from either poor enantioselectivity or low efficiency. The development of highly enantioselective, atom-economic and concise strategies towards the synthesis of δ-hydroxy acid derivatives remains imperative.

Enantioselective hydrogenation of ketoacid derivatives provides an efficient and direct method for the synthesis of enantiomerically pure hydroxy acid derivatives. In the previous reports, the asymmetric hydrogenation of α-, β-, and γ-ketoesters catalyzed by Ru complexes has been well-studied.[5] However, the only example of asymmetric hydrogenation of δ-ketoesters was catalyzed by Ir complexes to give chiral 1-arylpentane-1,5-diols rather than δ-hydroxy esters.[6] We report herein the asymmetric hydrogenation of a serious of δ-keto Weinreb amides to afford chiral δ-hydroxy Weinreb amides with high yields and excellent enantioselectivities. Moreover, the efficient asymmetric hydrogenation was utilized to synthesize the key intermediate of (+)-Centrolobine.

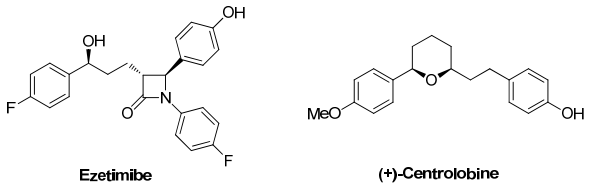

Figure 1 Ezetimibe and Centrolobine.

Results and discussion

Initially, the hydrogenation reaction of methyl 5-oxo-5-phenylpentanoate (**A**) was conducted by using $[RuCl_2(cymene)]_2$-(*S*)-SunPhos as catalyst in EtOH at 70 °C under 20 atm of H_2 based on the asymmetric hydrogenation of functionalized ketone,[5] but no product was detected after 15 h. Hydrochloric acid or $CeCl_3 \cdot 7H_2O$, which is usually as additive to enhance the conversion and enantioselectivity for hydrogenation reactions, did not improve the outcome (Scheme 1, Eq.1).[7] The result may be attributed to the unstable transition state in which the coordination of δ-ketoesters with the centre metal of catalyst formed an eight-membered ring transition state, while a stable six-membered ring transition state usually formed in the hydrogenation of β-ketoesters.[8] We envision that the introduction of a diamine ligand to the Ru catalytic system may shield the coordination of the ester

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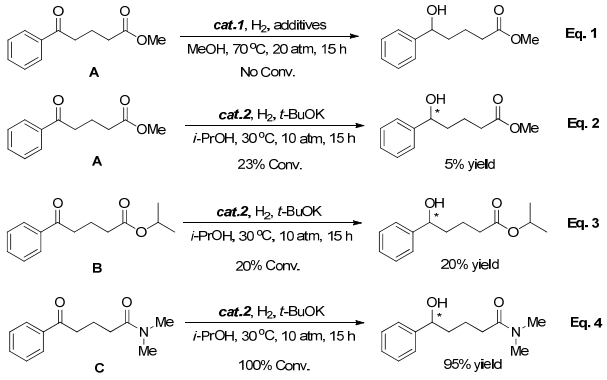
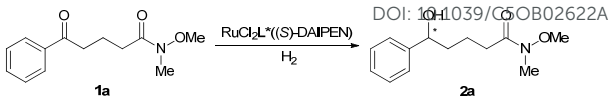
group of δ-ketoesters and result in the hydrogenation of the substrates as unfunctionalized ketones. The hydrogenation of **A** was then tested using $RuCl_2$[(*S*)-SunPhos][(*S*)-Daipen] in *i*-PrOH in the presence of *t*-BuOK based on the reaction conditions for the hydrogenation of simple ketones (Scheme 1, Eq. 1, 2).[9] Unfortunately, the reaction gave only a trace of the desired product (δ-hydroxy esters) and the corresponding lactone, accompanying with isopropyl 5-oxo-5-phenylpentanoate as the main product, while the hydrogenation did not occur in MeOH. Isopropyl 5-oxo-5-phenylpentanoate (**B**) was hydrogenated in *i*-PrOH to afford the δ-hydroxy product in only 20% yield (Scheme 1, Eq. 3). Then, a δ-ketoamide (**C**) was tested for the asymmetric hydrogenation because amide functional group is usually considered as the relatively resistant carboxylic acid derivatives and not easy to be alcoholyzed.[10] Pleasingly, when *N*,*N*-dimethyl-5-oxo-5-phenylpentanamide (**C**) was hydrogenated under the same conditions, it gave complete conversion of substrate and the hydrogenated product with 95% yield and 88% ee (Scheme 1, Eq. 4).

Therefore, the δ-keto Weinreb amide (**1a**), whose reduction product is the important acylation agent and can be easily transformed to other useful building blocks, was chosen as the model substrates to test the asymmetric hydrogenation. Under the above-mentioned asymmetric hydrogenation conditions, **1a** was hydrogenated completely to give the product (**2a**) with 88% ee (Table1, entry 1). Other commercially available chiral bidentate ligands, such as (*S*)-BINAP, (*S*)-SEGPhos, and (*S*)-*C*3-TunePhos were also tested, and similar results were achieved (Table 1,



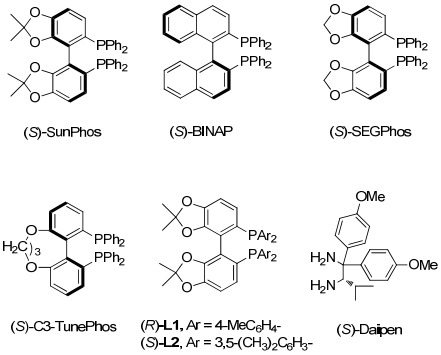
Scheme 1 Asymmetric hydrogenation of 5-oxo-5-phenylpentanoic acid derivatives.

Table 1 Ligand screening[a]



Entry	Ligand	Conv.[b] (%)	ee[c] (%)
1	(*S*)-SunPhos	100	88
2	(*S*)-BINAP	100	89
3	(*S*)-SEGPhos	73	87
4	(*S*)-*C*3-TunePhos	100	81
5	**L1**	100	−13
6	**L2**	100	99

[a]Unless otherwise stated,all reactions were carried out with a substrate (0.5 mmol) concentration of 0.25 M in *i*-PrOH for 15 h. Substrate/catalyst/*t*-BuOK = 100/1/5. [b]Determined by HPLC. [c]Determined by NMR analysis.



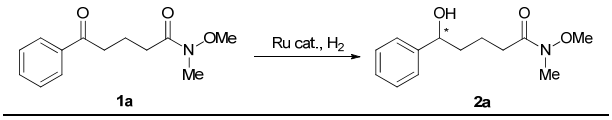
entries 2−4). The modifications of ligand on P atom always impose remarkable effects on enantioselectivity in the asymmetric hydrogenation.[11] The hydrogenation was then tested with (*R*)-4-Tol-SunPhos (**L1**, Table 1, entry 5) and (*S*)-Xyl-SunPhos (**L2**, Table 1, entry 6), and the best result was obtained by using **L2**, which provided the full conversion of **1a** to give the corresponding alcohol **2a** in 99% ee.

Further screening of solvents and bases for the hydrogenation was summarized in Table 2. Solvents were found to have an obvious influence on both reactivity and enantioselectivity. Switching the solvent to other protic solvents, poor results were observed: both low enantioselectivity and conversion were observed in methanol, high enantioselectivity but only moderate conversion were obtained in ethanol (Table 2, entries 1 and 2). Good results were achieved in dichloromethane, while hardly any reaction occurred in 1,2-dichloroethane (Table 2, entries 3 and 4). In addition, the hydrogenation was inefficient in toluene (Table 2, entry 5). Changing the base to KOH afforded the δ-hydroxy Weinreb amides with a comparable result to that with *t*-BuOK as

the base in terms of both conversion and enantioselectivity (Table 2, entry 6). However, when K_2CO_3 was used as the base, a 98%ee of **2a** with 27% of conversion of **1a** was obtained (Table 2, entry 7). Neither potassium bicarbonate nor NEt_3 works in this hydrogenation reaction (Table 2, entries 8 and 9). Potassium hydroxide was finally chosen as the base for this reaction because of the lower price and easier handling, and the optimized reaction conditions were therefore set as follows: $RuCl_2$[(*S*)-Xyl-SunPhos][(*S*)-Daipen] as the catalyst in *i*-PrOH and KOH as the base under 10 atm of H_2 at 30 °C for 15 h.

Under the optimized reaction conditions, the asymmetric hydrogenation of δ-keto Weinreb amides led to a variety of δ-hydroxy Weinreb amides in high yields with excellent enantioselectivities. Hydrogenation of substrates bearing either electron-withdrawing or electron-donating groups at *para*-or *meta*- positions on aryl group afforded the corresponding products in high ee with full conversion (Table 3, entries 2−7). Among them, 5-(4-Fluorophenyl)-5-hydroxy-*N*-methoxy-*N*-methylpentanamide (**2e**) was obtained with 93% yield and 99% ee, which is an intermediate for the synthesis of Ezetimibe.[2a-d] Absolute configuration of **2e** was assigned as (*R*) on the basis of the optical rotation of 1-(4-fluorophenyl)pentane-1,5-diol **2e'**.[6] In the cases of the substrates possessing *ortho*- substituents on the aromatic ring, the reaction time was prolonged to 30 h to achieve full conversions (Table 3, entries 8 and 9). These results stemmed from the steric hindrance which decreased the reaction reactivity. The naphthyl substituted compound **1j** was hydrogenated to the corresponding alcohol in 99% ee (Table 3, entry 10). Meanwhile, when the aryl group was changed from phenyl to hetero aromatic groups such as 2-thienyl, the reactions also showed excellent results and **2k** was attained in 90% yield with 99% ee (Table 3, entry 11). Unfortunately, the reaction of alkyl compound **1l** and **1m** gave low enantioselectivities, and even lower reactivity of **1m** was observed (Table 3, entries 12 and 13).

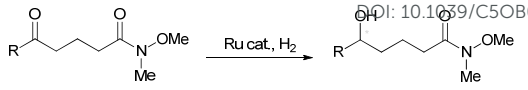
Table 2 Solvents and bases screening[a]



Entry	Solvent	Base	Conv.[b] (%)	ee[c] (%)
1	MeOH	*t*-BuOK	33	2
2	EtOH	*t*-BuOK	57	99
3	DCM	*t*-BuOK	100	97
4	DCE	*t*-BuOK	<5	--
5	Toluene	*t*-BuOK	25	89
6	*i*-PrOH	KOH	100	99
7	*i*-PrOH	K_2CO_3	27	98
8	*i*-PrOH	$KHCO_3$	<5	--
9	*i*-PrOH	NEt_3	<5	--

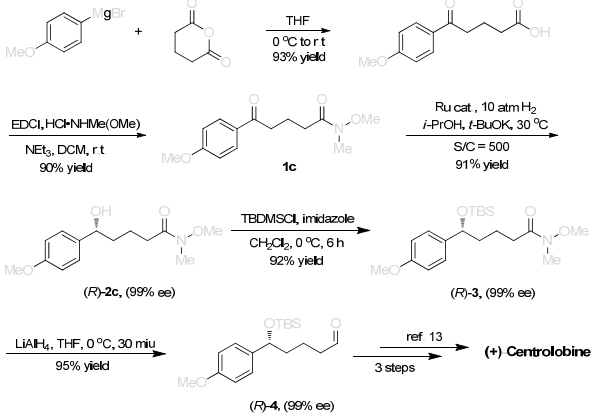
[a]All reactions were carried out under 10 atm of H_2 for 15 h at 30 °C using 0.5 mmol of the substrate **1** in *i*-PrOH (0.5 M) containing the $RuCl_2$[(*S*)-Xyl-SunPhos][(*S*)-Daipen] and base. Substrate/catalyst/base = 100/1/5. [b]Determined by NMR analysis. [c]Determined by HPLC on a ChiralPak column.

Table 3 Substrate scope [a]



Entry	**1**	R	Conv.[b](%)	Yield[c] (%)	ee[d] (%)
1	**1a**	C_6H_5	100	92	99
2	**1b**	4-MeC_6H_4	100	92	99
3	**1c**	4-$OMeC_6H_4$	100	91	99
4	**1d**	4-$CF_3C_6H_4$	100	93	99
5	**1e**	4-FC_6H_4	100	93	99
6	**1f**	4-ClC_6H_4	100	93	99
7	**1g**	3-MeC_6H_4	100	93	99
8[e]	**1h**	2-MeC_6H_4	100	91	99
9[e]	**1i**	2-$OMeC_6H_4$	100	91	98
10	**1j**	2-naphthyl	100	92	99
11	**1k**	2-thienyl	100	90	99
12	**1l**	Et	100	91	3
13[e]	**1m**	$C_6H_5CH_2$	62	57	9

[a]Unless otherwise stated, all reactions were carried out under10 atm of H_2 for 15 h at 30 °C using 0.5 mmol of the substrate **1** in *i*-PrOH(0.5 M) containing the catalyst $RuCl_2$[(*S*)-Xyl-SunPhos][(*S*)-Daipen] and KOH. Substrate/catalyst/base = 100/1/5. [b]Determined by NMR analysis. [c]Isolated yield by column chromatography.[d]Determined by HPLC on a ChiralPak column. [e]For 30 h.



Scheme 2 The synthesis of (+)-Centrolobine.

To probe the practical utility of this hydrogenation reaction, we utilized the reaction to synthesize (+)-Centrolobine which shows anti leishmanial activity against *Leishmaniaamazonensis* promastigotes, and many catalytic protocols have been reported for the total synthesis of this active drug.[2e-g,12] The δ-keto Weinreb amide **1c** was prepared in 83% yield via two steps (Scheme 2),[13] and then the compound **1c** was hydrogenated under the optimized conditions to give the δ-hydroxy Weinreb amide **2c** in 99% ee with S/C = 500. Protection of the hydroxy group of compound **2c** as the TBS ether gave compound **3** in 92% yield without loss of enantioselectivity.[14] Subsequently, the Weinreb amide **3** was allowed to be reduced with $LiAlH_4$ at 0 °C for 30 min to give δ-hydroxy aldehyde **4** in 95% yield.[15] Then (+)-Centrolobine could be obtained via three steps according to literature procedure.[14]

Conclusions

In conclusion, we have compared the hydrogenation reactivity of different δ-keto acid derivatives and confirmed that using stable amides as the functionalized group is essential for the asymmetric hydrogenation of δ-keto acid derivatives. The asymmetric hydrogenation of δ-keto Weinreb amides was achieved with excellent yields and enantioselectivities catalyzed by Ru-Xyl-SunPhos-Daipen catalyst system. The synthetic utility of this asymmetric method was demonstrated by the enantioselective synthesis of the key intermediate of (+)-Centrolobine.

Experimental

General methods

Commercially available reagents were used throughout without further purification beyond that detailed below: DMF and *i*-PrOH used in catalyst preparation and hydrogenation were distilled over calcium hydride. All reactions were carried out under an atmosphere of nitrogen using standard Schlenk techniques unless otherwise noted. ^{1}H NMR and ^{13}C NMR spectra were obtained on a 400 MHz NMR spectrometer. The chemical shifts of ^{1}H NMR were recorded in ppm downfield from tetramethylsilane (TMS) with the solvent resonance as the internal standard. The chemical shifts of ^{13}C NMR were recorded in ppm downfield using the central peak of $CDCl_3$ (77.00 ppm) as the internal standard. Coupling constants (*J*) are reported in hertz and refer to apparent peak multiplications. HRMS were performed under ESI ionization technique on ESI-TOF mass spectrometer. Flash column chromatography was performed on silica gel (300−400 mesh). $[\alpha]_D$ values were recorded at the D line of sodium (589 nm) in a 0.5 dm cell.

Preparation of 1a–m.

To the solution of glutaric anhydride (1.0 equiv.) in THF under N_2 atmosphere was added dropwise to the corresponding Grignard reagent (1.2 equiv.) at 0 °C. The solution was warmed to room temperature and stirred for a further 3 hours. The reaction was quenched with 10% HCl, and THF was removed in vacuum. The resulting aqueous solution was extracted with DCM. The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated in vacuum to give white solid as a crude product. The corresponding acid (1.0 equiv.) was added to *N,O*-dimethyl hydroxy amine hydrochloride (1.2 equiv.) in DCM. To this mixture was added 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide (1.2 equiv.) at 0 °C, and then Et_3N (2.0 equiv.) was added dropwise over 10 min. The ice bath was removed and the temperature maintained at room temperature overnight. The mixture was quenched by water, and the aqueous phase was extracted with DCM. The combined organic phase was washed with brine, dried (Na_2SO_4) and evaporated in vacuo and the crude product was purified by column chromatography to afford the desired compounds **1a**–**m**.

***N*-Methoxy-*N*-methyl-5-oxo-5-phenylpentanamide (1a).**[16] Colourless oil; 5.2 g, 85% yield;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97−7.95 (m, 2H), 7.57−7.50 (m, 1H), 7.48−7.39 (m, 2H), 3.65 (s, 3H), 3.16 (s, 3H), 3.07 (t, *J* = 7.2 Hz, 2H), 2.54 (t, *J* = 6.8 Hz, 2H), 2.07 (p, *J* = 7.2 Hz, 2H);^{13}C NMR (100 MHz, $CDCl_3$) δ 199.6, 173.7, 136.6, 132.7, 128.3, 127.8, 60.9, 37.5, 31.9, 30.7, 18.9.

***N*-Methoxy-*N*-methyl-5-oxo-5-(*p*-tolyl)pentanamide (1b).** Colourless oil; 3.1 g, 87% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89−7.83 (m, 2H), 7.26−7.21 (m, 2H), 3.66 (s, 3H), 3.17 (s, 3H), 3.04 (t, *J* = 7.2 Hz, 2H), 2.54 (t, *J* = 7.0 Hz, 2H), 2.39 (s, 3H), 2.07 (p, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.0, 173.6, 143.2, 134.0, 128.8, 127.7, 60.8, 37.2, 31.7, 30.6, 21.2, 18.8; HRMS calcd. for $C_{14}H_{19}NNaO_3[M + Na]^+$ 272.1263, found: 272.1277.

***N*-Methoxy-*N*-methyl-5-oxo-5-(4-methoxyphenyl)pentane-mide (1c).** Colourless oil; 4.8 g, 81% yield; ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.97−7.94 (m, 2H), 6.94−6.86 (m, 2H), 3.86 (s, 3H), 3.66 (s, 3H), 3.17 (s, 3H), 3.02 (t, *J* = 7.2 Hz, 2H), 2.54 (t, *J* = 6.6 Hz, 2H), 2.06 (p, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2, 173.8, 163.1, 130.0, 129.7, 113.4, 60.9, 55.2, 37.1, 31.8, 30.7, 19.1; HRMS calcd. for $C_{14}H_{19}NNaO_4$[M + Na]$^+$ 288.1212, found: 288.1221.

***N*-Methoxy-*N*-methyl-5-oxo-5-(4-(trifluoromethyl)phenyl)-pentanamide (1d).** Light yellow oil; 2.7 g, 79% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09−8.07 (m, 2H), 7.73−7.71 m, 2H), 3.67 (s, 3H), 3.18 (s, 3H), 3.11 (t, *J* = 7.2 Hz, 2H), 2.57 (t, *J* = 6.8 Hz, 2H), 2.09 (p, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 198.5, 173.6, 139.2, 133.7 (q, *J* = 32.2 Hz), 128.1, 125.3 (d, *J* = 2.5 Hz), 124.7 (q, *J* = 270.6 Hz), 60.8, 37.7, 31.7, 30.4, 18.6; HRMS calcd. for $C_{14}H_{16}F_3NNaO_3$[M + Na]$^+$: 326.0980, found: 326.0989.

***N*-Methoxy-*N*-methyl-5-oxo-5-(4-fluorophenyl)pentanamide (1e).** White solid; 2.9 g, 81% yield; mp 58.7−59.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05−7.96 (m, 2H), 7.15−7.07 (m, 2H), 3.67 (s, 3H), 3.18 (s, 3H), 3.05 (t, *J* = 7.2 Hz, 2H), 2.55 (t, *J* = 6.8 Hz, 2H), 2.07 (p, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 173.3, 164.9 (d, *J* = 252.5 Hz), 132.8, 130.1 (d, *J* = 8.7 Hz), 114.9 (d, *J* = 21.6 Hz), 60.5, 37.1, 31.4, 30.2, 18.5; HRMS calcd. for $C_{13}H_{16}FNNaO_3$[M + Na]$^+$: 276.1012, found: 276.1021.

***N*-Methoxy-*N*-methyl-5-oxo-5-(4-chlorophenyl)pentanamide (1f).** White solid; 3.0 g, 83% yield; mp 50.6−51.9; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96−7.89 (m, 2H), 7.46−7.39 (m, 2H), 3.67 (s, 3H), 3.18 (s, 3H), 3.05 (t, *J* = 7.2 Hz, 2H), 2.56 (t, *J* = 6.8 Hz, 2H), 2.07 (p, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.3, 173.6, 139.0, 134.9, 129.2, 128.6, 60.9, 37.5, 31.9, 30.5, 18.8; HRMS calcd. for $C_{13}H_{16}ClNNaO_3$[M + Na]$^+$: 292.0716, found: 292.0726.

***N*-Methoxy-*N*-methyl-5-oxo-5-(*m*-tolyl)pentanamide (1g).** Light yellow oil; 3.0 g, 83% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80−7.72 (m, 2H), 7.38−7.29 (m, 2H), 3.66 (s, 3H), 3.17 (s, 3H), 3.06 (t, *J* = 7.2 Hz, 2H), 2.54 (t, *J* = 6.6 Hz, 2H), 2.39 (s, 3H), 2.07 (p, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.3, 173.5, 137.7, 136.4, 133.2, 128.0, 127.9, 124.7, 60.6, 37.2, 31.5, 30.4, 20.8, 18.6; HRMS calcd. for $C_{14}H_{19}NNaO_3$[M + Na]$^+$: 272.1263, found: 272.1275.

***N*-Methoxy-*N*-methyl-5-oxo-5-(*o*-tolyl)pentanamide (1h).** Light yellow oil; 3.1 g, 85% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66−7.64 (m, 1H), 7.37−7.33 (m, 1H), 7.24−7.22 (m, 2H), 3.67 (s, 3H), 3.18 (s, 3H), 2.99 (t, *J* = 7.2 Hz, 2H), 2.54 (t, *J* = 7.2 Hz, 2H), 2.49 (s, 3H), 2.05 (p, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.6, 173.6, 137.5, 131.5, 130.8, 130.8, 128.2, 125.4, 60.8, 40.3, 31.7, 30.6, 20.9, 18.9; HRMS calcd. for $C_{14}H_{19}NNaO_3$[M + Na]$^+$: 272.1263, found: 272.1272.

***N*-Methoxy-*N*-methyl-5-(2-methoxyphenyl)-5-oxopentanamide (1i).** Light yellow oil; 1.8 g, 75% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67−7.64 (m, 1H), 7.45−7.40 (m, 1H), 7.00−6.92 (m, 2H), 3.88 (s, 3H), 3.65 (s, 3H), 3.16 (s, 3H), 3.05 (t, *J*= 7.2 Hz, 2H), 2.50 (t, *J* = 7.2 Hz, 2H), 2.02 (p, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.0, 173.2, 157.7, 132.5, 129.1, 127.4, 119.6, 110.9, 60.3, 54.6, 42.1, 31.2, 30.2, 18.5; HRMS calcd. for $C_{14}H_{19}NNaO_4$[M + Na]$^+$: 288.1212, found: 288.1223.

***N*-Methoxy-*N*-methyl-5-(naphthalen-2-yl)-5-oxopentanamide (1j).** White solid; 3.0 g, 83% yield; mp 42.9−44.1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.10−7.81 (m, 4H), 7.60−7.51 (m, 2H), 3.66 (s, 3H), 3.21 (t, *J* = 7.2 Hz, 2H), 3.18 (s, 3H), 2.60 (t, *J* = 6.8 Hz, 2H), 2.14 (p, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 173.1, 134.6, 133.3, 131.6, 128.8, 128.7, 127.5, 127.5, 126.9, 125.9, 122.9, 60.2, 36.9, 31.2, 30.1, 18.4; HRMS calcd. for $C_{17}H_{19}NNaO_3$[M + Na]$^+$: 308.1263, found: 308.1247.

***N*-Methoxy-*N*-methyl-5-oxo-5-(thiophen-2-yl)pentanamide (1k).** Light yellow oil; 2.6 g, 70% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 3.6, 1.2 Hz, 1H), 7.61 (dd,*J* = 4.8, 1.2 Hz, 1H), 7.12−7.10 (m, 1H), 3.66 (s, 3H), 3.17 (s, 3H), 3.01 (t, *J* = 7.2 Hz, 2H), 2.55 (t, *J* = 7.2 Hz, 2H), 2.08 (p,*J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.4, 173.3, 143.7, 133.1, 131.6, 127.7, 60.7, 37.9, 31.6, 30.3, 19.0; HRMS calcd. for $C_{11}H_{15}NNaO_3S$ [M + Na]$^+$: 264.0670, found: 264.0680.

***N*-Methoxy-*N*-methyl-5-oxoheptanamide (1l).** Light yellow oil; 4.4 g, 68% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (s, 3H), 3.15 (s, 3H), 2.50−2.34 (m, 6H), 1.89 (p, *J* = 7.2 Hz, 2H), 1.03 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.5, 173.5, 60.7, 40.8, 35.3, 31.6, 30.4, 18.2, 7.3; HRMS calcd. for $C_9H_{17}NNaO_3$[M + Na]$^+$: 210.1106, found: 210.1108.

***N*-Methoxy-*N*-methyl-5-oxo-6-phenylhexanamide (1m).** Yellow oil; 2.5 g, 70% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.29 (m, 2H), 7.28−7.22 (m, 1H), 7.21−7.18 (m, 2H), 3.68 (s, 2H), 3.62 (s, 3H), 3.14 (s, 3H), 2.56 (t, *J* = 7.2 Hz, 2H), 2.40 (t, *J* = 7.2 Hz, 2H), 1.89 (p, *J* = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.5, 173.6, 134.0, 129.1, 128.3, 126.6, 60.8, 49.7,

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40.7, 31.8, 30.4, 18.3; HRMS calcd. for $C_{14}H_{19}NNaO_3$[M + Na]$^+$: 272.1263, found: 272.1270.

Typical Procedure for the Asymmetric Hydrogenation

To a 25 mL Schlenk tube were added $[RuCl_2(benzene)]_2$ (5.0 mg, 0.01 mmol) and (*S*)-Xyl-SunPhos (17.2 mg, 0.022 mmol). The tube was vacuumed and purged with nitrogen for three times before addition of freshly distilled and freeze-and-thaw degassed DMF (3 mL). The resulting mixture was heated at 100 °C for 10 min. before it was cooled to room temperature, and then (*S*, *S*)-Daipen (6.8 mg, 0.022 mmol) was added under N_2. The tube was vacuumed and purged with nitrogen for three times before it was heated at 40 °C for 5 h. The solvent was removed under vacuum to give the catalyst as a yellow solid. The catalyst was dissolved in degassed *i*-PrOH (4 mL), and then the solution was equally charged into four vials which contained 0.5 mmol of substrates, base (0.025 mmol), and 1 mL of *i*-PrOH. The vials were then transferred into 300mL autoclave which is charged with 10 mL *i*-PrOH. The autoclaves were purged three times with H_2, and the required pressure of H_2 was set. The autoclaves were stirred under specified reaction conditions. After being cooled to ambient temperature and careful release of the hydrogen, the autoclaves were opened and the solvent was evaporated. The reaction solution was purified by a silica gel column to give the corresponding hydrogenation products, which was then directly analyzed by HPLC to determine the enantiomeric excess.

5-Hydroxy-*N*-methoxy-*N*-methyl-5-phenylpentanamide (2a). Colorless oil; 109.2 mg, 92% yield, 99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.30 (m, 4H), 7.27−7.22 (m, 1H), 4.69−4.66 (m, 1H), 3.65 (s, 3H), 3.16 (s, 3H), 2.58 (s, 1H), 2.46−2.45 (m, 2H), 1.87−1.73 (m, 4H);^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 144.7, 128.1, 127.1, 125.7, 73.7, 61.0, 38.6, 31.9, 31.3, 20.5; HPLC (Chiralcel OB-H column, hexane/*i*-PrOH = 80/20, 1.0 mL/min, 210 nm) t_1 = 12.4 min, t_2 = 15.1 min. $[\alpha]_D^{25}$ = +26.8 (c 0.54, CH_2Cl_2); IR (KBr): 3417, 2939, 1731, 1454, 1243, 993, 817, 761, 544 cm^{-1}; HRMS: calcd. for $C_{13}H_{19}NNaO_3$[M + Na]$^+$: 260.1263, found: 260.1275.

5-Hydroxy-*N*-methoxy-*N*-methyl-5-(*p*-tolyl)pentanamide (2b). Colourless oil; 115.5 mg, 92% yield, 99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.23 (m, 2H), 7.15−7.13 (m, 2H), 4.71−4.60 (m, 1H), 3.66 (s, 3H), 3.16 (s, 3H), 2.51−2.42 (m, 2H), 2.33 (s, 3H), 2.27 (s, 1H), 1.86−1.68 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 141.7, 136.7, 128.9, 125.7, 73.6, 61.0, 38.6, 32.0, 31.3, 21.0, 20.6; HPLC (Chiralcel OB-H column, hexane/*i*-PrOH = 88/12, 0.7 mL/min, 210 nm) t_1 = 26.2 min, t_2 = 31.4 min; $[\alpha]_D^{25}$ = +28.2 (c 0.58, CH_2Cl_2); IR (KBr): 3740, 2934, 1730, 1458, 1243, 993, 817, 766, 537 cm^{-1}; HRMS calcd. for $C_{14}H_{21}NNaO_3$[M + Na]$^+$: 274.1419, found: 274.1424.

5-Hydroxy-*N*-methoxy-*N*-methyl-5-(4-methoxyphenyl)pentanemide (2c). Colourless oil; 122.9 mg, 92% yield, 99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.26 (m, 2H), 6.89−6.85 (m, 2H), 4.67−4.60 (m, 1H), 3.80 (s, 3H), 3.66 (s, 3H), 3.16 (s, 3H), 2.48−2.43 (m, 2H), 2.26 (d, *J* = 3.6 Hz, 1H), 1.87−1.69 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 158.2, 136.9, 126.7, 113.2, 72.8, 60.7, 54.8, 38.3, 31.6, 31.1, 20.5; HPLC (Chiralcel OB-H column, hexane/*i*-PrOH = 80/20, 0.8 mL/min, 210 nm) t_1 = 28.4 min, t_2 = 34.9 min; $[\alpha]_D^{25}$ = +29.2 (c 0.80, CH_2Cl_2); IR (KBr): 3417, 2941, 1728, 1462, 1246, 996, 833, 765, 554 cm^{-1}; HRMS calcd. for $C_{14}H_{21}NNaO_4$[M + Na]$^+$: 290.1368, found: 290.1372.

5-Hydroxy-*N*-methoxy-*N*-methyl-5-(4-(trifluoromethyl)phenyl)pentanamide (2d). Light yellow oil; 142.5 mg, 93% yield, 99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58−7.56 (m, 2H), 7.47−7.45 (m, 2H), 4.74 (s, 1H), 3.65 (s, 3H), 3.19 (s, 1H), 3.16 (s, 3H), 2.47−2.46 (m, 2H), 1.82−1.70 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 149.1, 128.9 (q, *J* = 32.1 Hz), 128.1, 126.0, 124.9 (d, *J* = 3.1 Hz), 124.1 (q, *J* = 270.2 Hz), 72.8, 60.9, 38.6, 31.8, 31.08, 20.3; HPLC (Chiralcel OB-H column, hexane/*i*-PrOH = 88/12, 0.7 mL/min, 210 nm) t_1 = 11.8 min, t_2 = 13.1 min; $[\alpha]_D^{25}$ = +23.9 (c 0.50, CH_2Cl_2); IR (KBr): 3429, 2948, 1736, 1420, 1328, 1124, 843, 762, 527 cm^{-1}; HRMS calcd. for $C_{14}H_{18}F_3NNaO_3$[M + Na]$^+$: 328.1136, found: 328.1147.

5-Hydroxy-*N*-methoxy-*N*-methyl-5-(4-fluorophenyl)pentanamide (2e). Yellow oil; 119.4 mg, 94% yield, 99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.29 (m, 2H), 7.05−6.99 (m, 2H), 4.69−4.66 (m, 1H), 3.67 (s, 3H), 3.18 (s, 3H), 2.48−2.45 (m, 3H), 1.81−1.67 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 161.5 (d, *J* = 242.7 Hz), 140.6, 127.1 (d, *J* = 7.9 Hz), 114.6 (d, *J* = 21.0 Hz), 72.6, 60.8, 38.5, 31.7, 31.0, 20.3; HPLC (Chiralcel IA-H column, hexane/*i*-PrOH = 91/9, 0.5 mL/min, 210 nm) t_1 = 33.5 min, t_2 = 35.3 min; $[\alpha]_D^{25}$ = +29.2 (c 0.54, CH_2Cl_2); IR (KBr): 3409, 2940, 1731, 1423, 1222, 995, 838, 777, 544 cm^{-1}; HRMS calcd. for $C_{13}H_{18}FNNaO_3$[M + Na]$^+$: 278.1168, found: 278.1168.

1-(4-Fluorophenyl)pentane-1,5-diol(2e').[6] $LiAlH_4$ (76.2 mg, 2.0 mmol)was added to **2e** (128.0 mg, 0.5mmol) in THF at 25ºC.

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The reaction was stirred for 30 min at room temperature and quenched by addition of 10 ml 5% $KHSO_4$. After aqueous work-up, the pure product was obtained by purification with chromatography (80 mg, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.28 (m, 2H), 7.05–7.00 (m, 2H), 4.66 (t, *J* = 6.4, 1H), 3.62 (t, *J* = 6.4 Hz, 2H), 2.05 (s, 1H), 1.84–1.75 (m, 1H), 1.73–1.65 (m, 1H), 1.62–1.53 (m, 2H), 1.51–1.44 (m, 1H), 1.40–1.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 141.6, 127.6(d, *J* = 8.0 Hz), 115.5(d, *J* = 21.0 Hz), 73.98, 62.77, 38.9, 32.5, 22.1; HPLC (Chiralcel OD-H column, hexane/*i*-PrOH = 95/5, 0.8 mL/min, 210 nm) t_1 = 31.3 min, t_2 = 35.9 min; $[\alpha]_D^{20}$ = +16.3 (c 0.22, MeOH), 97% ee for *R* enantiomer [lit.[6] $[\alpha]_D^{20}$ = -24.2 (c 1.0, MeOH), 99% ee for *S* enantiomer].

5-Hydroxy-*N*-methoxy-*N*-methyl-5-(4-chlorophenyl)pentanamide (2f). Colourless oil; 126.6 mg, 93% yield, 99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (s, 4H), 4.69−4.64 (m, 1H), 3.66 (s, 3H), 3.17 (s, 3H), 2.47−2.45 (m, 3H), 1.80−1.67 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 143.4, 132.1, 127.8, 126.9, 72.5, 60.7, 38.3, 31.6, 30.9, 20.2; HPLC (Chiralcel OB-H column, hexane/*i*-PrOH = 88/12, 0.7 mL/min, 210 nm) t_1 = 28.1 min, t_2 = 31.8 min; $[\alpha]_D^{25}$ = +27.8 (c 0.66, CH_2Cl_2); IR (KBr): 3409, 2938, 1730, 1489, 1240, 995, 830, 720, 539 cm^{-1}; HRMS calcd. for $C_{13}H_{18}ClNNaO_3$[M + Na]$^+$: 294.0873, found: 294.0882.

5-Hydroxy-*N*-methoxy-*N*-methyl-5-(*m*-tolyl)pentanamide (2g). Colourless oil; 117.2 mg, 93% yield, 99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23−7.20 (m, 1H), 7.19−7.05 (m, 3H), 4.65−4.62 (m, 1H), 3.66 (s, 3H), 3.16 (s, 3H), 2.50−2.40 (m, 3H), 2.34 (s, 3H), 1.82−1.68 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3, 144.7, 137.6, 128.0, 127.8, 126.4, 122.7, 73.6, 61.0, 38.6, 31.9, 31.3, 21.3, 20.6; HPLC (Chiralcel OB-H column, hexane/*i*-PrOH = 88/12, 0.7 mL/min, 210 nm) t_1 = 21.5 min, t_2 = 28.9 min; $[\alpha]_D^{25}$ = +25.9 (c 0.71, CH_2Cl_2); IR (KBr): 3407, 2935, 1729, 1459, 1239, 995, 788, 704 cm^{-1}; HRMS calcd. for $C_{14}H_{21}NNaO_3$[M + Na]$^+$: 274.1419, found: 274.1431.

5-Hydroxy-*N*-methoxy-*N*-methyl-5-(*o*-tolyl)pentanamide (2h). Colourless oil; 114.8 mg, 91% yield, 99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49−7.47 (m, 1H), 7.23−7.08 (m, 3H), 4.93−4.90 (m, 1H), 3.65 (s, 3H), 3.16 (s, 3H), 2.52−2.46 (m, 3H), 2.32 (s, 3H), 1.87−1.71 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 142.9, 134.0, 130.0, 126.7, 125.9, 125.0, 69.9, 61.0, 37.6, 31.9, 31.3, 20.7, 18.9; HPLC (Chiralcel OB-H column, hexane/*i*-PrOH = 70/30, 0.8 mL/min, 210 nm) t_1 = 9.6 min, t_2 = 16.4 min; $[\alpha]_D^{25}$ = +44.5 (c 0.70, CH_2Cl_2); IR (KBr): 3417, 2939, 1730, 1461, 1181, 993, 758, 728, 503 cm^{-1}; HRMS calcd. for $C_{14}H_{21}NNaO_3$[M + Na]$^+$: 274.1419, found: 274.1422.

5-Hydroxy-N-methoxy-N-methyl-5-(2-methoxyphenyl)pentanamide (2i). Colourless oil; 121.7 mg, 91% yield, 98% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.32 (m, 1H), 7.25−7.20 (m, 1H), 7.00−6.83 (m, 2H), 4.92−4.87 (m, 1H), 3.84 (s, 3H), 3.67 (s, 3H), 3.17 (s, 3H), 2.78 (d, *J* = 4.0 Hz, 1H), 2.47 (t, *J* = 8.0 Hz, 2H), 1.87−1.69 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 156.0, 132.5, 127.8, 126.5, 120.4, 110.1, 69.3, 60.9, 55.0, 36.8, 31.9, 31.4, 20.7; HPLC (Chiralcel OB-H column, hexane/i-PrOH = 70/30, 0.8 mL/min, 210 nm) t_1 = 11.1 min, t_2 = 17.4 min; $[\alpha]_D^{25}$ = +21.1 (c 0.79, CH_2Cl_2); IR (KBr): 3425, 2942, 1730, 1647, 1440, 1240, 995, 757, 499 cm^{-1}; HRMS calcd. for $C_{14}H_{21}NNaO_4$[M + Na]$^+$: 290.1368, found: 290.1376.

5-Hydroxy-*N*-methoxy-*N*-methyl-5-(naphthalen-2-yl)pentanamide (2j). Light yellow oil; 132.0 mg, 92% yield, 99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85−7.77 (m, 4H), 7.49−7.42 (m, 3H), 4.85−4.82 (m, 1H), 3.61 (s, 3H), 3.14 (s, 3H), 2.45 (s, 2H), 1.93−1.68 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 142.3, 133.1, 132.6, 127.8, 127.7, 127.4, 125.8, 125.4, 124.3, 124.0, 73.7, 60.9, 38.4, 31.9, 31.2, 20.5; HPLC (Chiralcel OB-H column, hexane/*i*-PrOH = 80/20, 1.0 mL/min, 210 nm) t_1 = 17.9 min, t_2 = 23.1 min; $[\alpha]_D^{25}$ = +26.2 (c 0.86, CH_2Cl_2); IR (KBr): 3413, 2936, 1643, 1417, 1387, 1177, 993, 751, 479 cm^{-1}; HRMS calcd. for $C_{17}H_{21}NNaO_3$[M + Na]$^+$: 310.1419, found: 310.1426.

5-Hydroxy-*N*-methoxy-*N*-methyl-5-(thiophen-2-yl)pentanemide (2k). Yellow oil; 110.1 mg, 92% yield, 99% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21−7.20 (m, 1H), 6.97−6.92 (m, 2H), 4.93−4.89 (m, 1H), 3.65 (s, 3H), 3.15 (s, 3H), 3.00 (d, *J* = 4.0 Hz, 1H), 2.49−2.44 (m, 2H), 1.93−1.69 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 148.9, 126.0, 123.5, 122.9, 69.0, 60.7, 38.5, 31.6, 30.9, 20.3; HPLC (Chiralcel OB-H column, hexane/*i*-PrOH = 80/20, 1.0 mL/min, 210 nm) t_1 = 15.0 min, t_2 = 18.7 min; $[\alpha]_D^{25}$ = +11.8 (c 0.78, CH_2Cl_2); IR (KBr): 3393, 2938, 1727, 1440, 1180, 995, 850, 705 cm^{-1}; HRMS calcd. for $C_{11}H_{17}NNaO_3S$ [M + Na]$^+$: 266.0827, found: 266.0829.

5-Hydroxy-*N*-methoxy-*N*-methylheptanamide (2l).[17] Colourless oil; 86.5 mg, 92% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (s, 3H), 3.53−3.47 (m, 1H), 3.17 (s, 3H), 2.45 (t, *J* = 6.8 Hz, 2H), 2.07 (s, 1H), 1.80−1.67 (m, 2H), 1.55−1.40 (m, 4H), 0.92 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.5, 72.1, 60.9,

36.2, 31.9, 31.3, 29.8, 20.2, 9.7; $[\alpha]_D^{25}$ = -0.8 (c 0.71, CH_2Cl_2); IR (KBr): 3422, 2937, 1651, 1460, 1333, 1179, 993, 607, 500 cm^{-1}.

7-(Methoxy(methyl)amino)-7-oxoheptan-3-yl-4-nitrobenzoate (2l'). Yellow oil; 135.9 mg, 95% yield, 3% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 8.30−8.25 (m, 2H), 8.23−8.18 (m, 2H), 5.17−5.10 (m, 1H), 3.66 (s, 3H), 3.16 (s, 3H), 2.46−2.44 (m, 2H), 1.79−1.69 (m, 6H), 0.95 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 164.2, 150.2, 135.9, 130.5, 127.2, 123.6, 123.3, 76.7, 61.0, 32.9, 31.9, 31.2, 26.7, 20.0, 9.4; HPLC (Chiralcel OB-H column, hexane/*i*-PrOH = 80/20, 0.8 mL/min, 210 nm) t_1 = 15.4 min, t_2 = 26.4 min; IR (KBr): 3426, 2968, 1719, 1462, 1276, 1118, 995, 721, 507 cm^{-1}; HRMS calcd. for $C_{16}H_{21}N_2NaO_6$[M + Na]$^+$: 361.1376, found: 361.1377.

5-Hydroxy-*N*-methoxy-*N*-methyl-6-phenylhexanamide (2m). Colourless oil; 116.4 mg, 92% yield, 9% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.27 (m, 2H), 7.25−7.19 (m, 3H), 3.84−3.79 (m, 1H), 3.67 (s, 3H), 3.18 (s, 3H), 2.81 (dd, *J* = 13.6, 4.8 Hz, 1H), 2.69 (dd, *J* = 13.6, 8.0 Hz, 1H), 2.48−2.44 (m, 2H), 2.10 (d, *J* = 4.0 Hz, 1H), 1.87−1.70 (m, 2H), 1.63−1.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 138.5, 128.9, 127.7, 125.6, 71.5, 60.6, 43.5, 35.7, 31.5, 31.0, 20.1; HPLC (Chiralcel OJ-H column, hexane/*i*-PrOH = 88/12, 0.7 mL/min, 210 nm) t_1 = 16.8 min, t_2 = 18.1 min; $[\alpha]_D^{25}$ = +0.6 (c 0.70, CH_2Cl_2); IR (KBr): 3423, 2933, 1728, 1646, 1454, 1179, 992, 746, 504 cm^{-1}; HRMS calcd. for $C_{14}H_{21}NNaO_3$[M + Na]$^+$: 274.1419, found: 274.1423.

5-((*Tert*-butyldimethylsilyl)oxy)-*N*-methoxy-5-(4-methoxyphenyl)-*N*-methylpentanamide(3).[18] A solution of (*R*)-5-hydroxy-*N*-methoxy-N-methyl-5-(4-methoxyphenyl)pentanamide (99% ee, 500.0 mg, 1.9 mmol), imidazole (152.8 mg, 2.3 mmol), and TBSCl (338.3 mg, 2.3 mmol) in DCM (10 mL) was stirred at room temperature overnight and poured into saturated $NaHCO_3$. The mixture was stirred vigorously for 30 min. The layer was separated, and the aqueous layer was extracted with DCM twice. The combined extracts were dried and concentrated to give an oil, which was subjected to chromatography (PE/EA = 5/1) to furnish the compound **3** (646.6 mg, 92% yield, 99% ee). ^1H NMR (400 MHz, $CDCl_3$) δ 7.22−7.18 (m, 2H), 6.84−6.80 (m, 2H), 4.63−4.60 (m, 1H), 3.79 (s, 3H), 3.63 (s, 3H), 3.15 (s, 3H), 2.38 (t, *J* = 6.8 Hz, 2H), 1.74−1.68 (m, 2H), 1.64−1.58 (m, 2H), 0.86 (s, 9H), 0.01 (s, 3H), -0.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 158.4, 137.6, 126.8, 113.2, 74.4, 61.0, 55.0, 40.5, 32.0, 31.7, 25.8, 20.8, 18.1, -4.7, -5.0; HPLC (Chiralcel OB-H column, hexane/*i*-PrOH = 98/2, 0.3 mL/min, 210 nm) t_1 = 26.1 min, t_2 = 27.8 min; $[\alpha]_D^{25}$ = +47.5 (c 1.00, CH_2Cl_2); HRMS calcd. for $C_{20}H_{35}NNaO_4Si$ [M + Na]$^+$: 404.2233, found: 404.2225.

5-((*Tert*-butyldimethylsilyl)oxy)-5-(4-methoxyphenyl)-pentanal (4).[14, 15] $LiAlH_4$ (16.4 mg, 432.4 μmol)was added to 5-((*tert*-butyldimethylsilyl)oxy)-*N*-methoxy-5-(4-methoxyphenyl)-*N*-methylpentanamide **3** (150.0 mg, 393.1 μmol) in THF at 0 °C. The reaction was stirred for 20 min and quenched by addition of 10 ml 5% $KHSO_4$. After aqueous work-up, the pure product was obtained by purification with chromatography (120.4 mg, 95% yield, 99% ee). ^1H NMR (400 MHz, $CDCl_3$) δ 9.71 (t, *J* = 1.6 Hz, 1H), 7.21−7.18 (m, 2H), 6.87−6.79 (m, 2H), 4.63−4.60 (m, 1H), 3.79 (s, 3H), 2.42−2.36 (m, 2H), 1.75−1.67 (m, 2H), 1.65−1.57 (m, 2H), 0.87 (s, 9H), 0.01 (s, 3H), -0.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 158.5, 137.3, 126.9, 113.4, 74.2, 55.1, 43.7, 40.19, 25.8, 18.2, 1.0, -4.6, -5.0; HPLC (Chiralcel OJ-H column, hexane/*i*-PrOH = 98/2, 0.5 mL/min, 226 nm) t_1 = 12.7 min, t_2 = 14.0 min; $[\alpha]_D^{25}$ = +52.5 (c 1.00, CH_2Cl_2).

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