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PII: S0040-4020(16)30696-2

DOI: 10.1016/j.tet.2016.07.046

Reference: TET 27942

To appear in: *Tetrahedron*

Received Date: 8 May 2016

Revised Date: 13 July 2016

Accepted Date: 15 July 2016

Please cite this article as: Fan D, Lu J, Liu Y, Zhang Z, Liu Y, Zhang W, Rh-catalyzed asymmetric hydrogenation of racemic aldimines via dynamic kinetic resolution, *Tetrahedron* (2016), doi: 10.1016/j.tet.2016.07.046.

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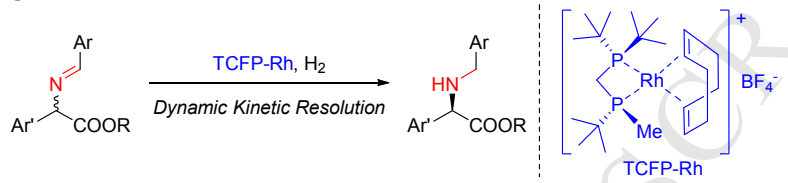

Tetrahedron
journal homepage: www.elsevier.com

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Asymmetric hydrogenation
Dynamic kinetic resolution
Chiral arylglycines
Racemic aldimines
Rhodium complex

ABSTRACT

Catalyzed by a rhodium complex of P-stereogenic diphosphine ligand trichickenfootphos (TCFP), asymmetric hydrogenation of racemic aldimines via dynamic kinetic resolution has been realized for the preparation of chiral arylglycines with good yields and enantioselectivities.

1. Introduction

As the key building blocks of important pharmaceuticals and bioactive compounds such as clopidogrel, prasugrel, vicagrel and aprepitant, the asymmetric synthesis of chiral arylglycines has attracted much attention.[1] Various methodologies have already been developed, such as those relying on hydrolysis or esterification via (dynamic) kinetic resolution,[2] the addition of aldimines with aryl or carbonyl reagents,[3] N-H insertion[4] and the reduction of ketimines.[5] However, a practical method which can be utilized in industry is still highly desired. Recently, asymmetric hydrogenation, a practical technology for large scale production,[6] has garnered considerable interest for the synthesis of chiral arylglycines.[7] However, the commonly utilized aryl-acyl ketimines require separation of the *Z*/*E* isomers and have the problem of low activity. It is envisaged that the asymmetric hydrogenation of racemic aldimines via dynamic kinetic resolution (DKR) can overcome these drawbacks.[8] Previously, racemic ketones and aldehydes have been studied in asymmetric hydrogenation via dynamic kinetic resolution.[9] A similar transformation of cyclic ketimines has also been mentioned as a key mechanistic step involved in the asymmetric hydrogenation of certain enamines and related precursors.[10] To the best of our knowledge, the dynamic kinetic resolution of aldimines has only been reported using a transfer hydrogenation strategy[11] and no methodologies concerning hydrogenation have been developed (Figure 1).

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† D. Fan and J. Lu contributed equally.

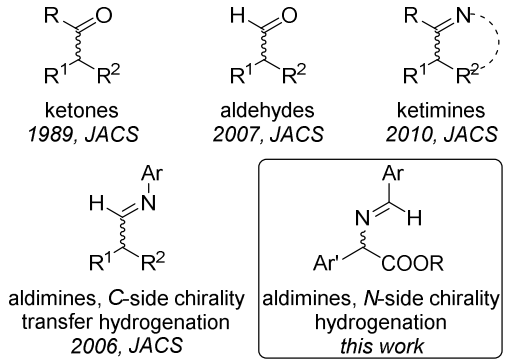


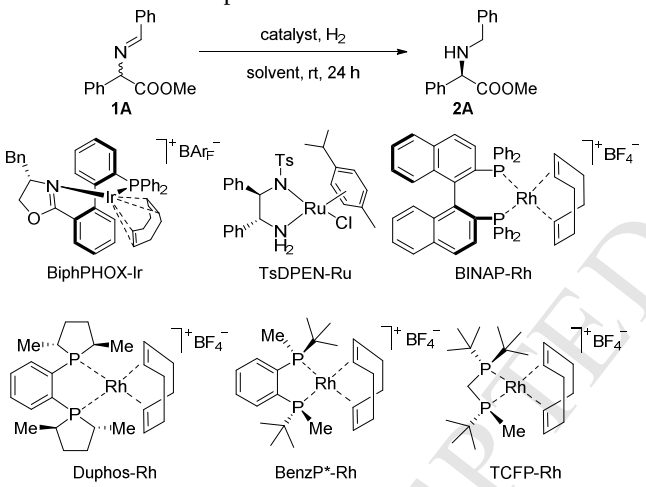
Figure 1. Substrates used in asymmetric hydrogenation via dynamic kinetic resolution.

2. Results and discussion

In contrast to previously reported racemic aldimines bearing a chiral center at the *C*-side of the C=N bond, a new type of substrates with a chiral center at the *N*-side of the C=N bond have been studied in this paper (Figure 1). Initially, a model substrate of methyl (*E*)-2-(benzylideneamino)-2-phenylacetate (**1A**), which can be simply synthesized from methyl 2-amino-2-phenylacetate and benzaldehyde, was tested in the hydrogenation (Table 1). Several commonly used transition metal catalysts such as BiphPHOX-Ir,[12] TsDPEN-Ru, BINAP-Rh were screened with the Rh catalyst giving the best result (entries 1-4). Further screening of other ligands led to the use of a P-stereogenic diphosphine ligand trichickenfootphos (TCFP)[13] which gave the reduced product **2A** in 44% conversion and 57% ee with the recovered

imine **1A** being obtained with 41% ee (entries 5-7). The solvent effect showed that the more bulky (or less polar) protic alcohols gave higher enantioselectivity but lower activity (entries 7-10). Another linear alcohol *n*-BuOH provided a similar result to that of using EtOH (entry 11). The highest conversion of 63% was obtained using the more polar solvent 2,2,2-trifluoroethanol (TFE) with an acceptable enantioselectivity (61% for product and 22% for recovered starting material) (entry 12). Other less polar solvents gave similar enantioselectivities with lower activities (entries 13-17). It is worth noting that obvious racemization of the starting material was only found when the solvent TFE was used because the ee value of recovered **1A** does not obey the rule of kinetic resolution.[14] To balance the enantioselectivity and activity, the mixed solvent system, hydrogen pressure and temperature were optimized to give more suitable conditions. Increasing the ratio of *i*PrOH/TFE from 1/2 to 2/1 increased ee but led to a decrease in conversion (entries 18-20). Further reducing the hydrogen pressure and reaction temperature showed a similar trend (entries 21-23). Finally, optimized reaction conditions consisted of TCFP-Rh as catalyst and conducting the reaction in a mixed solvent system of *i*PrOH/TFE (2/1), 10 atm hydrogen pressure and room temperature (entry 21). The absolute configuration of major enantiomer was assigned by comparison of the HPLC spectra with that of compound **2A** which was synthesized from the natural (*S*)-phenylglycine and benzyl bromide.

Table 1. Conditions optimization[a]

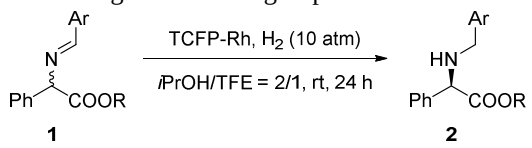


entry	catalyst	solvent	2A conversion [%][b]	2A ee [%][c]	1A recovery [%][b]	1A ee [%][c]
1	BiphPHOX-Ir	MeOH	7	14	92	0
2	TsDPEN-Ru	MeOH	100	0	0	-
3[d]	TsDPEN-Ru	MeOH	31	11	69	6
4	BINAP-Rh	MeOH	15	19	84	3
5	Duphos-Rh	MeOH	10	0	88	0
6	BenzP*-Rh	MeOH	4	17	96	0
7	TCFP-Rh	MeOH	44	57	50	41
8	TCFP-Rh	EtOH	16	70	78	17
9	TCFP-Rh	*i*PrOH	15	80	81	14
10	TCFP-Rh	*t*BuOH	6	84	88	5
11	TCFP-Rh	*n*BuOH	17	70	75	20
12	TCFP-Rh	TFE	63	61	31	22
13	TCFP-Rh	EtOAc	22	71	76	21
14	TCFP-Rh	THF	6	76	91	7
15	TCFP-Rh	dioxane	15	76	83	14
16	TCFP-Rh	DCM	29	78	70	29
17	TCFP-Rh	toluene	5	57	93	4
18	TCFP-Rh	*i*PrOH/TFE (1/2)	62	63	20	59
19	TCFP-Rh	*i*PrOH/TFE (1/1)	59	70	34	65
20	TCFP-Rh	*i*PrOH/TFE (2/1)	56	72	34	69
21[e]	TCFP-Rh	*i*PrOH/TFE (2/1)	47	75	47	59
22[f]	TCFP-Rh	*i*PrOH/TFE (2/1)	40	80	50	48
23[g]	TCFP-Rh	*i*PrOH/TFE (2/1)	37	83	57	46

[a] Conditions: **1A** (0.1 mmol), catalyst (1 mol %), H_2 (20 atm), solvent (2 mL), rt (20-25 °C), 24 h. [b] The conversions and recoveries were calculated from ^{1}H NMR spectra. [c] The ee values were determined by HPLC using chiral column. [d] 3 h. [e] H_2 (10 atm). [f] H_2 (5 atm). [g] 0 °C.

For the previously reported dynamic kinetic resolution of imines with a chiral center on the *C*-side of the C=N bond, racemization occurred through an intermediate of enamine under simple acidic conditions.[10,11] However, in our case with a chiral center on the *N*-side, addition of acetic acid resulted in a complete conversion to the product in racemic form. Use of a basic additive in a neutral solvent also failed without any conversion. Considering the different racemic pattern for the above mentioned two imines, we turned our attention to the racemization of the starting material by changing the substituents of Ar and R groups (Table 2). A by-product of **3** was detected in about 10% conversion for most of the entries.[15] Dramatic differences can be seen in the hydrogenation of both Me- and MeO-substituted imines (entries 2-10). 2-MeO-substituted imines provided the reduced product in 65% conversion and 67% ee with the recovered imine being obtained with 2% ee (entry 9). The substrate bearing an electron-withdrawing F atom at the 2-position was reduced to the product in 71% conversion and 58% ee. However, 87% ee was detected for the recovered starting material which means that almost no dynamic kinetic effect was observed (entry 11). The more bulky substituents Cl and Br at the 2-position prevented any product obtaining (entries 12-13). Other substrates with different Ar groups such as 1-naphthyl, 2-thienyl and 2-furyl showed comparatively worse result than that of a 2-methoxyphenyl substituted species (entries 14-16 vs 9). Increasing the loading of catalyst to 2 mol % promoted the conversion (entry 17). Changing the R group to more bulky alkyl groups had no obvious effect on the reaction (entries 18-20). Extending the reaction time to 48 h resulted in a complete transformation of **1a**. The desired product **2a** was obtained in 82% conversion and a satisfactory ee of 60% (entry 21).

Table 2. Screening of Ar and R groups[a]



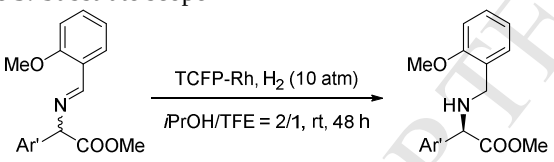
entry	Ar	R	2 conversion [%][b]	2 ee [%][c]	1 recovery [%][b]	1 ee [%][c]
1	C_6H_5	Me	47	75	47	59
2	4-MeC_6H_4	Me	34	79	60	35
3	3-MeC_6H_4	Me	48	71	40	12
4	2-MeC_6H_4	Me	39	84	46	41
5	2,4-$Me_2C_6H_3$	Me	28	77	58	5

6	2,6-$Me_2C_6H_3$	Me	0	-	100	-
7	4-$OMeC_6H_4$	Me	15	39	63	7
8	3-$OMeC_6H_4$	Me	48	78	40	61
9	2-$OMeC_6H_4$	Me	65	67	24	2
10	2,4-$(OMe)_2C_6H_3$	Me	15	20	37	5
11	2-FC_6H_4	Me	71	58	23	87
12	2-ClC_6H_4	Me	0	-	85	-
13	2-BrC_6H_4	Me	0	-	81	-
14	1-naphthyl	Me	59	45	30	67
15	2-thienyl	Me	52	67	40	18
16	2-furyl	Me	53	70	37	55
17[d]	2-$OMeC_6H_4$	Me	77	67	7	11
18[d]	2-$OMeC_6H_4$	Et	72	65	10	5
19[d]	2-$OMeC_6H_4$	*i*Pr	78	66	5	13
20[d]	2-$OMeC_6H_4$	*t*Bu	75	65	8	-
21[d,e]	2-$OMeC_6H_4$	Me	82	60	0	-

[a] Conditions: **1** (0.1 mmol), TCFP-Rh (1 mol %), H_2 (10 atm), *i*PrOH/TFE = 2/1 (2 mL), rt (20-25 °C), 24 h. [b] The conversions and recoveries were calculated from ^{1}H NMR spectra. [c] The ee values were determined by HPLC using chiral column. [d] TCFP-Rh (2 mol %). [e] 48 h.

With the optimized conditions in hand, the substrate scope of the hydrogenation reaction was investigated (Table 3). The substrates **1b-e** with electron-donating methyl substituents showed improved results compared to **1a** (entries 1-5). Substrates **1f** and **1g** possessing methoxy groups showed a slightly decrease in enantioselectivity, while a dimethoxy substituted substrate, **1h,** gave higher enantioselectivity (entries 6-8). A similar substrate **1i** bearing 3,4-(OCH_2O) substituent also gave the same level of enantioselectivity (entry 9). Substrate **1j** bearing a 4-substituted phenyl group was converted to its related product with slightly reduced enantioselectivity (entry 10). A low enantioselectivity was obtained for substrate **1k** bearing a 2-naphthyl substituent (entry 11). For the substrates **1l-n** bearing fluoro substituents, the enantioselectivity decreased according to the position of the fluoro substituent (entries 12-14).

Table 3. Substrate scope[a]

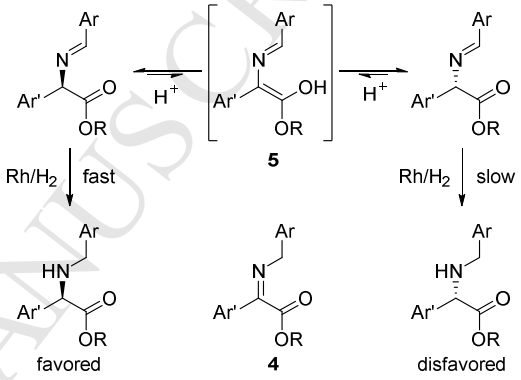


1 **2**

entry	**1**	Ar'	yield [%][b]	ee [%][c]
1	**1a**	C_6H_5	79	60
2	**1b**	4-MeC_6H_4	77	61
3	**1c**	3-MeC_6H_4	67	62
4	**1d**	2-MeC_6H_4	76	69
5	**1e**	2,4-$Me_2C_6H_3$	72	67
6	**1f**	4-$OMeC_6H_4$	69	58
7	**1g**	3-$OMeC_6H_4$	83	55
8	**1h**	3,4-$(OMe)_2C_6H_3$	79	66
9	**1i**	3,4-$(OCH_2O)C_6H_3$	70	56
10	**1j**	4-PhC_6H_4	82	57
11	**1k**	2-naphthyl	83	37
12	**1l**	4-FC_6H_4	79	55
13	**1m**	3-FC_6H_4	77	36
14	**1n**	2-FC_6H_4	53	19

[a] Conditions: **1** (0.2 mmol), TCFP-Rh (2 mol %), H_2 (10 atm), *i*PrOH/TFE = 2/1 (2 mL), rt (20-25 °C), 24 h. [b] Isolated yields. [c] The ee values were determined by HPLC using chiral column.

A substrate replacing COOMe group with Me group was tested to give the reduced product and recovered starting material both in racemic form. This result signifies that the carbonyl group is probably involved in the transition state during the reaction. In addition, the *N*-benzyl aryl-acyl imines **4**, which were reported as stable compounds,[16] were not detected during our reactions. A deuteration experiment of substrate **1c** was performed using D_2 under the same reaction conditions. Compared to the hydrogenated product, almost no change for the C*H* signal (δ = 4.34, s, 1H) is observed, whereas the CH_2 peak (δ = 3.72, dd, 2H) was replaced by a single C*H*D peak (δ = 3.78, s, 1H). Based on the above results, a mechanism has been proposed for the dynamic kinetic resolution of racemic aldimines bearing a chiral center at the *N*-side of the C=N bond (Scheme 1). As described in the literature which also ruled out the mechanism via intermediate **4**,[17] it can be proposed that the substrates are racemized via an unstable intermediate **5** with the aid of an acidic medium. One of the enantiomers is reduced at a faster rate to give the main product in the favored configuration.[18]



Scheme 1. Proposed mechanism.

3. Conclusions

In summary, asymmetric hydrogenation of racemic aldimines via dynamic kinetic resolution was realized for the first time. After careful screening and optimization, a series of chiral arylglycines were synthesized with good yields and enantioselectivities.

4. Experimetal section

All air sensitive reactions were performed in dried glassware under an atmosphere of dry nitrogen, and the workup was carried out in air, unless otherwise noted. Solvents were dried and distilled by standard procedures. Commercially available reagents were used without further purification. Column chromatography was performed using 100-200 mesh silica gel. ^{1}H NMR (400 MHz) and ^{13}C NMR (101 MHz) spectra were recorded on a Varian MERCURY plus-400 spectrometer. HRMS was performed on a Waters Micromass Q-TOF Premier Mass Spectrometer at the Instrumental Analysis Center of Shanghai Jiao Tong University. The ee values were determined by HPLC using Daicel Chiralpak columns. Melting points were measured with SGW X-4 micro melting point apparatus. IR was measured with PerkinElmer Spectrum 100 FT-IR Spectrometer. Optical rotations were measured on a Rudolph Research Analytical Autopol VI automatic polarimeter using a 50 mm path-length cell at 589 nm.

4.1. General procedure for the synthesis of substrates

Substrate **1a** were synthesized from commercially available racemic phenylglycine methyl ester, while other substrates **1b-j** were synthesized from related acetophenone derivatives according to the reported procedures.[19]

A mixture of acetophenone derivative (30 mmol) and selenium dioxide (5.0 g, 45 mmol) in pyridine (15 mL) was stirred at 110 °C under nitrogen atmosphere overnight. After cooling to room temperature, 4 Å molecular sieves (1.8 g) and methanol (20 mL) were added and the mixture was stirred for additional 10 min. Then thionyl chloride (11.3 mL, 150 mmol) was added dropwise over 1 h in an ice-water bath and stirred at room temperature for 12 h. Perchloric acid (12 mL, 150 mmol) in acetonitrile (240 mL) and deionized water (24 mL) (1:20:2 in volume ratio) were added into the flask, and the mixture was stirred for at least 0.5 h. Excess acid was neutralized by saturated sodium bicarbonate, then the mixture was filtrated. After removing the organic solvent by evaporation, the aqueous phase was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuum. The crude product was purified by flash chromatography (silica gel, petrol ether/ethyl acetate = 10/1) to obtain arylglyoxylate.[19a]

A mixture of above obtained arylglyoxylate (20 mmol), anhydrous sodium acetate (2.0 g, 24 mmol), hydroxylamine hydrochloride (2.2 g, 32 mmol) and methanol (70 mL) was heated to 60 °C for 3 h. After evaporating the organic solvent under vacuum, ethyl acetate was added to the resulting residue and the mixture was washed with water. The organic layer was then washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuum to afford oxime. To a solution of oxime (20 mmol) and formic acid (24 mL) in methanol (40 mL) and water (24 mL) at 0 °C was added Zn dust (3.8 g, 60 mmol) portion-wise over 1 h. The suspension was stirred for 3 h at 0 °C and an additional 4 h at room temperature. The mixture was filtered through celite and washed with methanol. The filtrate was concentrated and the resulting residue was purified by flash chromatography (silica gel, dichloromethane/methanol = 10/1) to afford the racemic arylglycine ester.[19b]

The above obtained arylglycine ester (10 mmol) and anhydrous magnesium sulfate (1.2 g) were stirred together in dichloromethane (50 mL) at room temperature for 20 min. Then the aldehyde (10 mmol) and triethylamine (8 mL) were added sequentially and dropwise. After stirred for 12 h at the same temperature, the resulting mixture was filtered and the organic solvent was evaporated in vacuum. The residue was dissolved in ethyl acetate (20 mL) and water (20 mL), and the separated aqueous layer was extracted with ether (2 × 20 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuum. The residue was purified by flash chromatography (silica gel, petrol ether/triethylamine = 50/1 to 20/1) to afford the substrate for hydrogenation as a white solid.[19c]

*4.1.1. Methyl (E)-2-((2-methoxybenzylidene)amino)-2-phenylacetate (**1a**).* White solid, mp 77–79 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.81 (s, 1H), 8.14 (d, J = 7.7 Hz, 1H), 7.53 (d, J = 7.7 Hz, 2H), 7.43–7.33 (m, 3H), 7.33–7.27 (m, 1H), 6.99 (t, J = 7.5 Hz, 1H), 6.89 (d, J = 8.3 Hz, 1H), 5.20 (s, 1H), 3.85 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.76, 159.81, 159.03, 138.57, 132.55, 128.58, 127.94, 127.91, 127.77, 124.14, 120.74, 110.91, 77.14, 55.47, 52.42; IR (KBr): v 3029, 2950, 1600, 1257, 1161, 1025, 757 cm^{-1}; HRMS (ESI): m/z calculated for $C_{17}H_{18}NO_3^+$ $[M+H]^+$ 284.1281, found 284.1281.

*4.1.2. Methyl (E)-2-((2-methoxybenzylidene)amino)-2-(p-tolyl)acetate (**1b**).* White solid, mp 63–65 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.79 (s, 1H), 8.12 (d, J = 7.7 Hz, 1H), 7.46–7.32 (m, 3H), 7.17 (d, J = 7.9 Hz, 2H), 6.98 (t, J = 7.6 Hz, 1H), 6.89 (d, J = 8.3 Hz, 1H), 5.17 (s, 1H), 3.85 (s, 3H), 3.73 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.95, 159.63, 158.98, 137.66, 135.62, 132.46, 129.28, 127.91, 127.63, 124.19, 120.72, 110.86, 76.90, 55.46, 52.40, 21.15; IR (KBr): v 3005, 2950, 1747, 1488, 1248, 1161, 751 cm^{-1}; HRMS (ESI): m/z calculated for $C_{18}H_{20}NO_3^+$ $[M+H]^+$ 298.1438, found 298.1435.

*4.1.3 Methyl (E)-2-((2-methoxybenzylidene)amino)-2-(m-tolyl)acetate (**1c**).* White solid, mp 57–59 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.80 (s, 1H), 8.14 (d, J = 6.9 Hz, 1H), 7.40 (t, J = 7.2 Hz, 1H), 7.37–7.28 (m, 2H), 7.28–7.23 (m, 1H), 7.11 (d, J = 7.3 Hz, 1H), 6.99 (t, J = 7.4 Hz, 1H), 6.89 (d, J = 8.2 Hz, 1H), 5.16 (s, 1H), 3.85 (s, 3H), 3.74 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.91, 159.74, 158.97, 138.40, 138.29, 132.51, 128.73, 128.47, 128.32, 127.91, 124.77, 124.10, 120.71, 110.84, 77.23, 55.45, 52.45, 21.45; IR (KBr): v 3004, 2950, 2840, 1909, 757 cm^{-1}; HRMS (ESI): m/z calculated for $C_{18}H_{20}NO_3^+$ $[M+H]^+$ 298.1438, found 298.1438.

*4.1.4. Methyl (E)-2-((2-methoxybenzylidene)amino)-2-(o-tolyl)acetate (**1d**).* White solid, mp 48–49 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.79 (s, 1H), 8.12 (dd, J = 7.7, 1.6 Hz, 1H), 7.64–7.57 (m, 1H), 7.42–7.36 (m, 1H), 7.25–7.15 (m, 3H), 6.98 (t, J = 7.5 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 5.39 (s, 1H), 3.84 (s, 3H), 3.73 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.87, 159.76, 159.02, 137.12, 135.91, 132.49, 130.58, 128.54, 127.87, 127.78, 126.29, 124.28, 120.75, 110.92, 74.05, 55.48, 52.41, 19.69; IR (KBr): v 3648, 3005, 2360, 1747, 1260, 750 cm^{-1}; HRMS (ESI): m/z calculated for $C_{18}H_{20}NO_3^+$ $[M+H]^+$ 298.1438, found 298.1439.

*4.1.5. Methyl (E)-2-(2,4-dimethylphenyl)-2-((2-methoxybenzylidene)amino)acetate (**1e**).* White solid, mp 60–61 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.77 (s, 1H), 8.11 (d, J = 7.7 Hz, 1H), 7.48 (d, J = 7.8 Hz, 1H), 7.38 (t, J = 7.9 Hz, 1H), 7.09–6.92 (m, 3H), 6.88 (d, J = 8.4 Hz, 1H), 5.36 (s, 1H), 3.84 (s, 3H), 3.73 (s, 3H), 2.40 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.04, 159.55, 158.96, 137.39, 135.71, 134.15, 132.37, 131.38, 128.46, 127.89, 126.96, 124.33, 120.71, 110.86, 73.80, 55.46, 52.36, 21.03, 19.58; IR (KBr): v 3689, 2360, 1747, 1488, 1249, 752 cm^{-1}; HRMS (ESI): m/z calculated for $C_{19}H_{22}NO_3^+$ $[M+H]^+$ 312.1594, found 312.1589.

*4.1.6. Methyl (E)-2-((2-methoxybenzylidene)amino)-2-(4-methoxyphenyl)acetate (**1f**).* White solid, mp 61–63 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.77 (s, 1H), 8.11 (d, J = 6.7 Hz, 1H), 7.46–7.34 (m, 3H), 6.97 (t, J = 7.4 Hz, 1H), 6.88 (d, J = 8.7 Hz, 3H), 5.14 (s, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 3.72 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.01, 159.51, 159.30, 158.99, 132.44, 130.75, 128.89, 127.88, 124.20, 120.72, 113.98, 110.88, 76.45, 55.46, 55.25, 52.35; IR (KBr): v 3649, 3005, 1744, 1508, 1259, 750 cm^{-1}; HRMS (ESI): m/z calculated for $C_{18}H_{20}NO_4^+$ $[M+H]^+$ 314.1387, found 314.1387.

*4.1.7. Methyl (E)-2-((2-methoxybenzylidene)amino)-2-(3-methoxyphenyl)acetate (**1g**).* White solid, mp 60–61 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.80 (s, 1H), 8.14 (d, J = 7.8 Hz, 1H), 7.40 (t, J = 7.7 Hz, 1H), 7.32–7.27 (m, 1H), 7.15–7.06 (m, 2H), 6.99 (t, J = 7.5 Hz, 1H), 6.92–6.81 (m, 2H), 5.17 (s, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.67, 159.89, 159.75, 159.04, 140.01, 132.55, 129.52, 127.90, 124.14, 120.73, 120.08, 113.62, 113.26, 110.91, 77.03, 55.47, 55.25, 52.42; IR (KBr): v 3003, 2950, 1744, 1600, 1541, 1249, 1161, 758 cm^{-1}; HRMS (ESI): m/z calculated for $C_{18}H_{20}NO_4^+$ $[M+H]^+$ 314,1387, found 314.1388.

*4.1.8. Methyl (E)-2-(3,4-dimethoxyphenyl)-2-((2-methoxybenzylidene)amino)acetate (**1h**).* White solid, mp 81–83 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.79 (s, 1H), 8.13 (dd, J = 7.7, 1.6 Hz, 1H), 7.43–7.37 (m, 1H), 7.10 (d, J = 1.8 Hz, 1H), 7.06–6.96 (m, 2H), 6.92–6.83 (m, 2H), 5.14 (s, 1H), 3.91 (s, 3H), 3.87 (s, 3H), 3.85 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.95, 159.66, 158.99, 149.03, 148.78, 132.52, 131.09,

127.83, 124.13, 120.71, 120.09, 111.03, 110.89, 110.79, 76.69, 55.93, 55.87, 55.45, 52.41; IR (KBr): *v* 3002, 2951, 2838, 1743, 1514, 1261, 1026, 758 cm^{-1}; HRMS (ESI): m/z calculated for $C_{19}H_{22}NO_5^+$ $[M+H]^+$ 344,1492, found 344.1487.

*4.1.9 Methyl (E)-2-(benzo[d][1,3]dioxol-5-yl)-2-((2-methoxybenzylidene)amino)acetate (**1i**).* White solid, mp 60–61 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.78 (s, 1H), 8.12 (d, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.08 (s, 1H), 6.97 (dd, *J* = 18.3, 8.2 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 5.95 (s, 2H), 5.10 (s, 1H), 3.85 (s, 3H), 3.74 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$): δ 171.82, 159.71, 158.97, 147.79, 147.29, 132.57, 132.36, 127.84, 124.01, 121.10, 120.73, 110.85, 108.32, 108.20, 101.08, 76.68, 55.45, 52.47; IR (KBr): *v* 2951, 2894, 1909, 1039, 728 cm^{-1}; HRMS (ESI): m/z calculated for $C_{18}H_{18}NO_5^+$ $[M+H]^+$ 328.1179, found 328.1179.

*4.1.10. Methyl (E)-2-([1,1'-biphenyl]-4-yl)-2-((2-methoxybenzylidene)amino)acetate (**1j**).* White solid, mp 85–86 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.84 (s, 1H), 8.16 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.63–7.54 (m, 6H), 7.46–7.38 (m, 3H), 7.34 (t, *J* = 7.4 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H), 6.90 (d, *J* = 8.3 Hz, 1H), 5.24 (s, 1H), 3.86 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.76, 159.93, 159.04, 140.87, 140.77, 137.58, 132.57, 128.73, 128.18, 127.92, 127.35, 127.30, 127.11, 124.13, 120.77, 110.90, 76.89, 55.48, 52.51; IR (KBr): *v* 3675, 3587, 2949, 1717, 1600, 1465, 757 cm^{-1}; HRMS (ESI): m/z calculated for $C_{23}H_{22}NO_3^+$ $[M+H]^+$ 360.1594, found 360.1598.

*4.1.11. Methyl (E)-2-((2-methoxybenzylidene)amino)-2-(naphthalen-2-yl)acetate (**1k**).* White solid, mp 91–92 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.87 (s, 1H), 8.18 (d, *J* = 6.1 Hz, 1H), 7.97 (s, 1H), 7.88–7.80 (m, 3H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.51–7.37 (m, 3H), 7.01 (t, *J* = 7.5 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 5.37 (s, 1H), 3.85 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.79, 160.05, 159.04, 136.03, 133.34, 133.05, 132.59, 128.31, 128.09, 127.94, 127.65, 126.75, 126.13, 126.07, 125.65, 124.15, 120.76, 110.90, 77.23, 55.46, 52.50; IR (KBr): *v* 3735, 3005, 2950, 2840, 1745, 1507, 1249, 751 cm^{-1}; HRMS (ESI): m/z calculated for $C_{21}H_{20}NO_3^+$ $[M+H]^+$ 334.1438, found 334.1433.

*4.1.12. Methyl (E)-2-(4-fluorophenyl)-2-((2-methoxybenzylidene)amino)acetate (**1l**).* White solid, mp 52–53 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.80 (s, 1H), 8.12 (d, *J* = 7.7 Hz, 1H), 7.57–7.46 (m, 2H), 7.40 (t, *J* = 7.8 Hz, 1H), 7.10–6.94 (m, 3H), 6.90 (d, *J* = 8.4 Hz, 1H), 5.17 (s, 1H), 3.86 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.57, 163.66, 161.21, 159.94, 159.05, 134.38, 134.35, 132.64, 129.45, 129.37, 127.83, 124.02, 120.76, 115.51, 115.30, 110.93, 76.29, 55.47, 52.47; IR (KBr): *v* 3649, 2952, 1747, 1508, 1248, 757 cm^{-1}; HRMS (ESI): m/z calculated for $C_{17}H_{17}FNO_3^+$ $[M+H]^+$ 302.1187, found 302.1180.

*4.1.13 Methyl (E-)-2-(3-fluorophenyl)-2-((2-methoxybenzylidene)amino)acetate (**1m**).* White solid, mp 66–67 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.82 (s, 1H), 8.14 (d, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.38–7.27 (m, 3H), 7.05–6.96 (m, 2H), 6.91 (d, *J* = 8.4 Hz, 1H), 5.18 (s, 1H), 3.86 (s, 3H), 3.75 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.25, 164.04, 161.59, 160.31, 159.05, 140.90, 140.83, 132.77, 130.02, 129.94, 127.83, 123.86, 123.33, 120.76, 114.96, 114.75, 110.91, 76.50, 55.45, 52.60; IR (KBr): *v* 2952, 2360, 1748, 1395, 783 cm^{-1}; HRMS (ESI): m/z calculated for $C_{17}H_{17}FNO_3^+$ $[M+H]^+$ 302.1187, found 302.1188.

*4.1.14 Methyl (E)-2-(2-fluorophenyl)-2-((2-methoxybenzylidene)amino)acetate (**1n**).* White solid, mp 94–95 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 8.82 (s, 1H), 8.14 (d, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.31 (t, *J* = 10.2 Hz, 3H), 7.01 (d, *J* = 7.4 Hz, 2H), 6.91 (d, *J* = 8.4 Hz, 1H), 5.18 (s, 1H), 3.86 (s, 3H), 3.75 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.00 (s), 161.29 (s), 160.92 (s), 159.08 (s), 158.84 (s), 132.73 (s), 129.61 (s), 129.57 (s), 129.48 (s), 129.40 (s), 127.78 (s), 125.95 (s), 125.81 (s), 124.36 (s), 124.32 (s), 123.96 (s), 120.70 (s), 115.39 (s), 115.17 (s), 110.92 (s), 69.78 (s), 55.47 (s), 52.63 (s).; IR (KBr): *v* 2952, 2360, 1748, 1653, 1395, 690 cm^{-1}; HRMS (ESI): m/z calculated for $C_{17}H_{17}FNO_3^+$ $[M+H]^+$ 302.1187, found 302.1186.

4.2. General procedure for the asymmetric hydrogenation

Substrate **1** (0.2 mmol) and [Rh((*S*)-TCFP)(cod)]BF_4 (2 mol %) were charged in an autoclave. And the system was evacuated and filled with hydrogen. After repeating this operation 3 times, degassed *i*PrOH/TFE (2/1, 2 mL) was added and the hydrogen pressure was adjusted to 10 atm. After vigorous stirring at room temperature for 48 h, the reaction mixture was evaporated under reduced pressure. After purification by flash chromatography (silica gel, petra ether/ethyl acetate = 5/1), the yield was calculated and the ee value was determined by HPLC using chiral column.

*4.2.1. Methyl 2-((2-methoxybenzyl)amino)-2-phenylacetate (**2a**).* Colorless oil, 47.7 mg, 79% yield, 60% ee; ^1H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, *J* = 7.1 Hz, 2H), 7.36–7.17 (m, 5H), 6.89 (t, *J* = 7.3 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 4.37 (s, 1H), 3.79 (s, 3H), 3.74 (dd, *J* = 54.8, 13.2 Hz, 2H), 3.61 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.40, 157.76, 138.33, 129.98, 128.62, 128.46, 128.05, 127.79, 127.57, 120.41, 110.29, 64.61, 55.24, 52.16, 46.93; IR (KBr): *v* 3029, 2951, 1737, 1493, 1243, 1028, 755 cm^{-1}; HRMS (ESI): m/z calculated for $C_{17}H_{20}NO_3^+$ $[M+H]^+$ 286.1438, found 286.1436; HPLC conditions: DAICEL Chiralpak OD column, Hexane/*i*-PrOH = 95/5, 220 nm, 1.0 mL/min, 25 °C, t_{major} = 14.6 min, t_{minor} = 9.4 min; $[\alpha]^{20}_D$ = -43 (*c* 0.52, DCM).

*4.2.2. Methyl 2-((2-methoxybenzyl)amino)-2-(p-tolyl)acetate (**2b**).* Colorless oil, 48.6 mg, 77% yield, 61% ee; ^1H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, *J* = 8.0 Hz, 2H), 7.25–7.18 (m, 2H), 7.14 (d, *J* = 7.9 Hz, 2H), 6.89 (t, *J* = 7.4 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 4.34 (s, 1H), 3.79 (s, 3H), 3.73 (dd, *J* = 54.7, 13.5 Hz, 2H), 3.61 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.54, 157.76, 137.76, 135.31, 129.99, 129.33, 128.42, 127.68, 127.62, 120.39, 110.26, 64.30, 55.24, 52.14, 46.86, 21.18; IR (KBr): *v* 3003, 2950, 1736, 1541, 1464, 1243, 1029, 754 cm^{-1}; HRMS (ESI): m/z calculated for $C_{18}H_{22}NO_3^+$ $[M+H]^+$ 300.1594, found 300.1602; HPLC conditions: DAICEL Chiralpak OJ column, Hexane/*i*-PrOH = 95/5, 220 nm, 1.0 mL/min, 25 °C, t_{major} = 19.1 min, t_{minor} = 22.8 min; $[\alpha]^{20}_D$ = -48 (*c* 0.43, DCM).

*4.2.3 Methyl 2-((2-methoxybenzyl)amino)-2-(m-tolyl)acetate (**2c**).* Colorless oil, 40.2 mg, 67% yield, 62% ee; ^1H NMR (400 MHz, $CDCl_3$): δ 7.26–7.15 (m, 5H), 7.10 (d, *J* = 7.1 Hz, 1H), 6.89 (t, *J* = 7.4 Hz, 1H), 6.84 (d, *J* = 8.1 Hz, 1H), 4.33 (s, 1H), 3.81 (s, 3H), 3.72 (dd, *J* = 64.0, 12.0 Hz, 2H), 3.63 (s, 3H), 2.34 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$): δ 173.46, 157.69, 138.28, 138.10, 129.97, 128.80, 128.44, 128.40, 128.29, 127.49, 124.82, 120.33, 110.17, 64.52, 55.20, 52.16, 46.93, 21.42.; IR (KBr): *v* 3003, 2951, 2837, 1734, 1363, 754 cm^{-1}; HRMS (ESI): m/z calculated for $C_{18}H_{22}NO_3^+$ $[M+H]^+$ 300.1594, found 300.1593; HPLC conditions: DAICEL Chiralpak OD column, Hexane/*i*-PrOH = 95/5, 220 nm, 1.0 mL/min, 25 °C, t_{major} = 13.6 min, t_{minor} = 9.0 min; $[\alpha]^{20}_D$ = -40 (*c* 0.44, DCM).

*4.2.4. Methyl 2-((2-methoxybenzyl)amino)-2-(o-tolyl)acetate (**2d**).* Colorless oil, 48.3 mg, 76% yield, 69% ee; ^1H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, *J* = 8.0 Hz, 2H), 7.25–7.18 (m, 2H), 7.14 (d, *J* = 7.9 Hz, 2H), 6.89 (t, *J* = 7.4 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 4.34 (s, 1H), 3.79 (s, 3H), 3.73 (dd, *J* = 54.7, 13.5 Hz, 2H), 3.61 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.76, 157.80, 136.82, 136.69, 130.70, 130.12, 128.49, 127.82, 127.68,

127.02, 126.29, 120.42, 110.28, 60.75, 55.23, 52.08, 47.06, 19.28; IR (KBr): *v* 3019, 2951, 1736, 1493, 1464, 1243, 1029, 754 cm^{-1}; HRMS (ESI): m/z calculated for $C_{18}H_{22}NO_3^+$ $[M+H]^+$ 300.1594, found 300.1594; HPLC conditions: DAICEL Chiralpak OD column, Hexane/*i*-PrOH = 95/5, 220 nm, 1.0 mL/min, 25 °C, t_{major} = 11.8 min, t_{minor} = 8.5 min; $[\alpha]^{20}_D$ = -38 (*c* 0.57, DCM).

*4.2.5. Methyl 2-(2,4-dimethylphenyl)-2-((2-methoxybenzyl)amino)acetate (**2e**).* Colorless oil, 48.4 mg, 72% yield, 67% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.13 (m, 3H), 7.02–6.94 (m, 2H), 6.88 (t, *J* = 7.4 Hz, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 4.54 (s, 1H), 3.79 (s, 3H), 3.74(dd, *J* = 34.0, 13.2 Hz, 2H) 3.63 (s, 3H), 2.28 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.85, 157.75, 137.38, 136.57, 133.65, 131.45, 130.06, 128.38, 127.72, 126.95, 126.93, 120.35, 110.20, 60.47, 55.19, 52.01, 46.94, 21.00, 19.13; IR (KBr): *v* 3003, 2950, 1735, 1491, 1243, 755 cm^{-1}; HRMS (ESI): m/z calculated for $C_{19}H_{24}NO_3^+$ $[M+H]^+$ 314.1751, found 314.1751; HPLC conditions: DAICEL Chiralpak OD column, Hexane/*i*-PrOH = 95/5, 220 nm, 1.0 mL/min, 25 °C, t_{major} = 10.9 min, t_{minor} = 7.7 min; $[\alpha]^{20}_D$ = -45 (*c* 0.71, DCM).

*4.2.6. Methyl 2-((2-methoxybenzyl)amino)-2-(4-methoxyphenyl)acetate (**2f**).* Colorless oil, 46.2 mg, 69% yield, 58% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, *J* = 8.3 Hz, 2H), 7.25–7.16 (m, 2H), 6.95–6.83 (m, 4H), 4.33 (s, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.73 (dd, *J* = 53.6, 13.4 Hz, 2H), 3.64 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.57, 159.34, 157.70, 130.36, 129.93, 128.85, 128.34, 127.59, 120.33, 113.95, 110.20, 63.88, 55.23, 55.20, 52.07, 46.77; IR (KBr): *v* 3335, 3001, 2931, 1736, 1587, 1247, 757 cm^{-1}; HRMS (ESI): m/z calculated for $C_{18}H_{22}NO_4^+$ $[M+H]^+$ 316.1543, found 316.1548; HPLC conditions: DAICEL Chiralpak OD column, Hexane/*i*-PrOH = 90/10, 220 nm, 1.0 mL/min, 25 °C, t_{major} = 13.6 min, t_{minor} = 10.2 min; $[\alpha]^{20}_D$ = -40 (*c* 0.21, DCM).

*4.2.7. Methyl 2-((2-methoxybenzyl)amino)-2-(3-methoxyphenyl)acetate (**2g**).* Colorless oil, 55.4 mg, 83% yield, 55% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.17 (m, 3H), 7.02–6.97 (m, 2H), 6.91 (t, *J* = 7.4 Hz, 1H), 6.85 (d, *J* = 8.1 Hz, 2H), 4.37 (s, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 3.75(dd, *J*= 56.8, 13.4 Hz, 2H), 3.64 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.26, 159.84, 157.75, 139.80, 130.00, 129.57, 128.46, 127.52, 120.38, 120.20, 113.70, 113.13, 110.27, 64.53, 55.25, 55.23, 52.19, 46.89; IR (KBr): *v* 3002, 2951, 1736, 1587, 1199, 1047, 755 cm^{-1}; HRMS (ESI): m/z calculated for $C_{18}H_{22}NO_4^+$ $[M+H]^+$ 316.1543, found 316.1543; HPLC conditions: DAICEL Chiralpak OJ column, Hexane/*i*-PrOH = 90/10, 220 nm, 1.0 mL/min, 25 °C, t_{major} = 21.1 min, t_{minor} = 25.7 min; $[\alpha]^{20}_D$ = -29 (*c* 0.43, DCM).

*4.2.8. Methyl 2-(3,4-dimethoxyphenyl)-2-((2-methoxybenzyl)amino)acetate (**2h**).* Colorless oil, 56.7 mg, 79% yield, 66% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (m, 2H), 6.97–6.78 (m, 5H), 4.30 (s, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.79 (s, 3H), 3.72 (dd, *J* = 54.8, 13.5 Hz, 2H), 3.62 (s, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.45, 157.72, 149.11, 148.81, 130.73, 129.98, 128.40, 127.51, 120.31, 120.27, 110.99, 110.49, 110.23, 64.15, 55.90, 55.86, 55.21, 52.12, 46.79; IR (KBr): *v* 3001, 2952, 2836, 1736, 1514, 1242, 1028, 757 cm^{-1}; HRMS (ESI): m/z calculated for $C_{19}H_{24}NO_5^+$ $[M+H]^+$ 346.1649, found 346.1646; HPLC conditions: DAICEL Chiralpak OJ column, Hexane/*i*-PrOH = 80/20, 220 nm, 1.0 mL/min, 25 °C, t_{major} = 17.3 min, t_{minor} = 22.1 min; $[\alpha]^{20}_D$ = -31 (*c* 0.47, DCM)

*4.2.9 Methyl 2-(benzo[d][1,3]dioxol-5-yl)-2-((2-methoxybenzyl)amino)acetate (**2i**).* Colorless oil, 46.1 mg, 70% yield, 56% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26–7.17 (m, 2H), 6.94–6.82 (m, 4H), 6.79–6.75 (m, 1H), 5.95 (s, 2H), 4.28 (s, 1H), 3.82 (s, 3H), 3.73 (dd, *J* = 48.0, 13.5 Hz, 2H), 3.64 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.31, 157.68, 147.86, 147.35, 132.04, 129.96, 128.42, 127.40, 121.38, 120.33, 110.19, 108.19, 107.95, 101.08, 64.10, 55.20, 52.20, 46.72; IR (KBr): *v* 2360, 1801, 1698, 1260, 1029, 803 cm^{-1}; HRMS (ESI): m/z calculated for $C_{18}H_{20}NO_5^+$ $[M+H]^+$ 330.1336, found 330.1337; HPLC conditions: DAICEL Chiralpak OD column, Hexane/*i*-PrOH = 90/10, 220 nm, 1.0 mL/min, 25 °C, t_{major} = 15.2 min, t_{minor} = 11.7 min; $[\alpha]^{20}_D$ = -40 (*c* 0.46, DCM).

*4.2.10. Methyl 2-([1,1'-biphenyl]-4-yl)-2-((2-methoxybenzyl)amino)acetate (**2j**).* Colorless oil, 61.1 mg, 82% yield, 57% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63–7.56 (m, 4H), 7.50 (d, *J* = 8.1 Hz, 2H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.3 Hz, 1H), 7.25 (dd, *J* = 10.2, 5.7 Hz, 2H), 6.93 (t, *J* = 7.4 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 1H), 4.45 (s, 1H), 3.83 (s, 3H), 3.80 (dd, *J* = 55.1, 13.5 Hz, 2H), 3.67 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.39, 157.78, 140.97, 140.75, 137.35, 130.03, 128.81, 128.50, 128.22, 127.56, 127.38, 127.12, 120.44, 110.30, 64.32, 55.27, 52.26, 46.99; IR (KBr): *v* 3029, 2950, 2836, 1464, 1490, 1029, 757, 699 cm^{-1}; HRMS (ESI): m/z calculated for $C_{23}H_{24}NO_3^+$ $[M+H]^+$ 362.1751, found 362.1755; HPLC conditions: DAICEL Chiralpak OJ column, Hexane/*i*-PrOH = 75/25, 220 nm, 1.0 mL/min, 25 °C, t_{major} = 14.6 min, t_{minor} = 27.5 min; $[\alpha]^{20}_D$ = -55 (*c* 0.70, DCM).

*4.2.11. Methyl 2-((2-methoxybenzyl)amino)-2-(naphthalen-2-yl)acetate (**2k**).* Colorless oil, 58.6 mg, 83% yield, 37% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (s, 1H), 7.84–7.76 (m, 3H), 7.53 (d, *J* = 8.5 Hz, 1H), 7.49–7.40 (m, 2H), 7.26–7.17 (m, 2H), 6.89 (t, *J* = 7.4 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 4.55 (s, 1H), 3.77 (dd, *J* = 61.9, 13.5 Hz, 2H), 3.76 (s, 3H), 3.60 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.30, 157.77, 135.69, 133.32, 133.18, 130.01, 128.46, 128.38, 128.00, 127.67, 127.53, 127.01, 126.16, 126.07, 125.52, 120.40, 110.28, 64.65, 55.23, 52.21, 46.87; IR (KBr): *v* 2951, 1541, 1507, 1464, 1244, 1028, 754 cm^{-1}; HRMS (ESI): m/z calculated for $C_{21}H_{22}NO_3^+$ $[M+H]^+$ 336.1594, found 336.1598; HPLC conditions: DAICEL Chiralpak OD column, Hexane/*i*-PrOH = 95/5, 220 nm, 1.0 mL/min, 25 °C, t_{major} = 18.6 min, t_{minor} = 14.0 min; $[\alpha]^{20}_D$ = -36 (*c* 0.53, DCM).

*4.2.12 Methyl 2-(4-fluorophenyl)-2-((2-methoxybenzyl)amino)acetate (**2l**).* Colorless oil, 50.4 mg, 79% yield, 55% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–7.35 (m, 2H), 7.23 (t, *J* = 7.7 Hz, 1H), 7.18 (d, *J* = 7.2 Hz, 1H), 7.02 (t, *J* = 8.6 Hz, 2H), 6.94–6.82 (m, 2H), 4.36 (s, 1H), 3.80 (s, 3H), 3.73 (dd, *J* = 62.7, 13.5 Hz, 2H), 3.62 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.18, 163.7, 161.25, 157.71, 134.06, 136.03, 129.93, 129.44, 129.36, 128.48, 127.36, 120.37, 115.52, 115.30, 110.27, 63.75, 55.20, 52.18, 46.84; IR (KBr): *v* 3004, 2952, 1740, 1540, 1493, 1243, 1029, 755 cm^{-1}; HRMS (ESI): m/z calculated for $C_{17}H_{18}FNO_3^+$ $[M+H]^+$ 304.1343, found 304.1344; HPLC conditions: DAICEL Chiralpak OJ column, Hexane/*i*-PrOH = 95/5, 220 nm, 1.0 mL/min, 25 °C, t_{major} = 18.7 min, t_{minor} = 20.1 min; $[\alpha]^{20}_D$ = -36 (*c* 0.51, DCM).

*4.2.13 Methyl 2-(3-fluorophenyl)-2-((2-methoxybenzyl)amino)acetate (**2m**).* Colorless oil, 46.8 mg, 77% yield, 36% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.22 (m, 2H), 7.22–7.13 (m, 3H), 7.04–6.96 (m, 1H), 6.94–6.84 (m, 2H), 4.37 (s, 1H), 3.83 (s, 3H), 3.73 (dd, *J* = 72.0, 16.0 Hz, 2H) 3.64 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.83, 164.13, 161.68, 157.68, 140.76, 140,69, 130.02, 129.97, 129.94, 128.54, 127.21, 123.48, 123.45, 120.36, 115.05, 114.84, 114.79, 114.57, 110.21, 63.99, 63.97, 55.19, 52.32, 46.88.; IR (KBr): *v* 2360, 1749, 1362, 1260, 1029, 750 cm^{-1}; HRMS (ESI): m/z calculated for $C_{17}H_{18}FNO_3^+$ $[M+H]^+$ 304.1343, found 304.1345; HPLC conditions: DAICEL Chiralpak OD column, Hexane/*i*-PrOH = 95/5, 220 nm, 1.0 mL/min, 25 °C, t_{major} = 13.0 min, t_{minor} = 9.0 min; $[\alpha]^{20}_D$ = -12 (*c* 0.35, DCM).

*4.2.14 Methyl 2-(2-fluorophenyl)-2-((2-methoxybenzyl)amino)acetate (**2n**).* Colorless oil, 32.2 mg, 53% yield, 19% ee; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (td, J = 7.5, 1.6 Hz, 1H), 7.29–7.16 (m, 3H), 7.12 (td, J = 7.5, 1.0 Hz, 1H), 7.08–7.00 (m, 1H), 6.92–6.79 (m, 2H), 4.70 (s, 1H), 3.80 (s, 3H), 3.74 (dd, J = 56.0, 12.0 Hz, 2H), 3.63 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 172.73, 162.07, 159.61, 157.68, 129.97, 129.56, 129.48, 128.96, 128.92, 128.48, 127.30, 125.73, 125.59, 124.33, 124.29, 120.41, 120.37, 115.68, 115.46, 110.16, 57.58, 57.55, 55.17, 52.33, 46.98; IR (KBr): ν 3004, 2952, 1740, 1363, 1030, 755 cm^{-1}; HRMS (ESI): m/z calculated for $C_{17}H_{18}FNO_3^+$ $[M+H]^+$ 304.1343, found 304.1342; HPLC conditions: DAICEL Chiralpak OD column, Hexane/*i*-PrOH = 95/5, 220 nm, 1.0 mL/min, 25 °C, t_{major} = 13.0 min, t_{minor} = 9.7 min; $[\alpha]^{20}_D$ = -27 (*c* 0.22, DCM).

Supplementary Data

Supplementary data (copies of NMR and HPLC spectra) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2016.XX.XXX.

Acknowledgments

This work was partially supported by the National Natural Science Foundation of China (No. 21572131) and Science and Technology Commission of Shanghai Municipality (No. 14XD1402300 and 15Z111220016). We thank the Instrumental Analysis Center of Shanghai Jiao Tong University (SJTU) for characterization.

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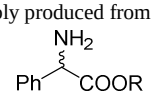
15. A control experiment of converting the product **2** to by-product **3** in the same hydrogenative conditions was failed, so it was presumed that compound **3** was probably produced from hydrolysis of substrate **1**.



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