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Highly enantioselective Ir-catalyzed hydrogenation of exocyclic enamines

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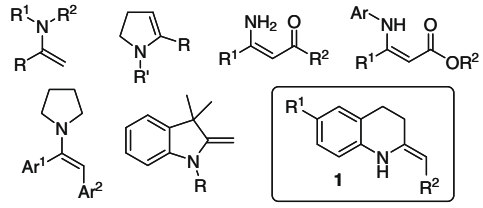
ABSTRACT

[Ir(COD)Cl]$_2$/MeO-BiPhep/I$_2$ catalyst system is highly effective for the asymmetric hydrogenation of exocyclic enamines with high enantioselectivities (up to 96% ee).

1. Introduction

Optically active amines are very important for the synthesis of biologically active natural products and pharmaceuticals.[1] Transition metal-catalyzed asymmetric hydrogenation of functionalized enamines is a well-known and important method for preparing them.[2] To date, a broad range of catalysts are available, which provide the desired *N*-acylamino acid with excellent enantioselectivities. It is widely accepted that *N*-acyl groups are important for high reactivity and selectivity for the chelation requirement between the substrate and metal.[3] However, tedious modification of the substrate and removal of the acyl groups under strongly acidic or basic conditions have seriously limited its application. Developing new catalysts that allow the asymmetric hydrogenation of simple enamines is still in great demand. Recently, some progress has been made in this area (Scheme 1). The pioneering work in asymmetric hydrogenation of simple enamines involved the utilization of [(*S*,*S*,*S*)-(EBTHI)TiO$_2$-binaphthol] as the catalyst (up to 98% ee).[4] In 2000, Börner et al. reported an asymmetric hydrogenation of simple enamines with up to 72% ee using Rh(I)-bisphosphine.[5] Scientists at Merck reported that the asymmetric hydrogenation of unprotected enamine esters and amides using Rh/Josiphos led to the chiral amines with high ee.[6] Zhang employed Rh/TangPhos for the asymmetric hydrogenation of *N*-aryl β-enamino esters with excellent ee's.[7] In 2006, Zhou et al. developed a highly enantioselective hydrogenation of simple N-unprotected enamines with Rh(I) complexes of chiral spiro phosphonite ligands, in which iodine and HOAc are crucial for the activity and enantioselectivity.[8a] Very recently, Zhou et al. described the iridium-catalyzed asymmetric hydrogenation of cyclic enamines with up to 97% ee.[8b] Despite the progresses that has been made for asymmetric hydrogenation of enamines, the suitable catalytic system and substrate scope are still rather limited.

Recently, some significant progress on the asymmetric hydrogenation of heteroaromatic compounds[9d,10] and Pd-catalyzed asymmetric hydrogenation of ketones and imines have been made by our group.[11,12] As a part of our continuing efforts in asymmetric hydrogenation, herein, we report our initial findings on the asymmetric hydrogenation of simple exocyclic enamines **1** using the [Ir(COD)Cl]$_2$/MeO-BiPhep/I$_2$ as a catalyst with up to 96% enantioselectivity.



Scheme 1. The structures of some typical simple enamines.

2. Results and discussion

Asymmetric hydrogenation of exocyclic enamines **1** provides a convenient route to synthesize chiral tetrahydroquinoline derivatives, which are important synthetic intermediates, structural units of natural products and biologically active compounds. Enamine (*Z*)-2-(3,4-dihydroquinolin-2(1*H*)-ylidene)-1-phenylethanone **1a**, which can be conveniently synthesized by partial hydrogenation of the corresponding quinoline derivatives, was selected as the model substrate. Considering that iridium has been successfully applied to asymmetric hydrogenation of imines, olefins, and quinolines,[2a,11] we firstly examined [Ir(COD)Cl]$_2$/(*S*)-MeO-Biphep/I$_2$ for hydrogenation of **1a**. To our delight, the reaction proceeded smoothly to give hydrogenation product with 96% ee. Then the solvent effect was investigated, and the results are summarized in Table 1 (entries 1–4). The conversions and ees of the products are highly solvent dependent. Benzene and toluene were found to be the optimal solvents. Iodine also plays a crucial role for enantioselectivity and reactivity, and the reaction did not occur in the absence of iodine (entry 5).

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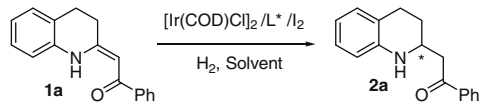
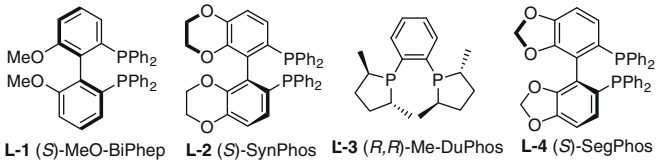
Table 1
Condition optimization for Ir-catalyzed asymmetric hydrogenation of exocyclic enamines **1a**[a]



Entry	Solvent	Ligand	Covn[b] (%)	ee[c] (%)
1	Toluene	**L-1**	>95	96
2	CH_2Cl_2	**L-1**	58	62
3	THF	**L-1**	>95	85
4	Benzene	**L-1**	>95	96
5[d]	Benzene	**L-1**	<5	—
6[e]	Benzene	**L-1**	>95	94
7[f]	Benzene	**L-1**	>95	96
8[g]	Benzene	**L-1**	>95	96
9[h]	Benzene	**L-1**	68	75
10	Benzene	**L-2**	>95	96
11	Benzene	**L-3**	15	2
12	Benzene	**L-4**	>95	96
13[i]	CF_3CH_2OH	**L-1**	>95	30
14[j]	Benzene	**L-1**	>95	16

[a] Reaction conditions: $[Ir(COD)Cl]_2$ (1 mol %), ligand (2.2 mol %), I_2 (10 mol %), 2 mL solvent, 16 h.
[b] Conversions were determined by ^1H NMR analysis of the crude products.
[c] Determined by HPLC analysis with OD-H column.
[d] Without I_2.
[e] Run at 50 °C.
[f] Run at 1200 psi of H_2.
[g] Run at 300 psi of H_2.
[h] $[Ir(COD)Cl]_2$ (0.10 mol %), ligand (0.22 mol %), I_2 (1.0 mol %).
[i] $Rh(COD)_2BF_4$/MeO-Biphep/H_2(6 atm)/TFA/50 °C.
[j] Enamine (*Z*)-CH_3(PMPNH)C=$CHCO_2Et$ was used



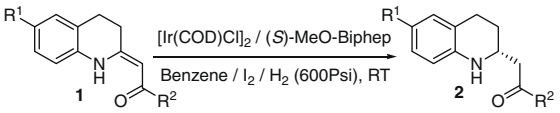
L-1 (*S*)-MeO-BiPhep **L-2** (*S*)-SynPhos **L-3** (*R,R*)-Me-DuPhos **L-4** (*S*)-SegPhos

The pressure and temperature effects on the reaction were also screened. The results showed that there is no obvious effect for the reaction. Slightly lower enantioselectivity was observed under a higher temperature (entry 6). The enantioselectivities of the reaction can be retained at lower or higher pressure of hydrogen (entries 7 and 8). However, when the catalyst loading was reduced to 0.1 mol %, only 68% conversion with 75% ee was obtained (entry 9). Next, the effect of various chiral ligands on the asymmetric hydrogenation of **1a** was also studied. The results showed that the axial chiral bisphosphine ligands exhibited excellent enantioselectivities with full conversions (entries 4, 10–12), whereas a lower conversion and poor enantioselectivity were achieved with electron-rich Me-DuPhos (**L-3**, entry 11). It is noteworthy that low enantioselectivity was observed using the Rh/(*S*)-MeO-Biphep/TFA[7] for hydrogenation of **1a**. Thus, the optimized conditions are: $[Ir(COD)Cl]_2$/(*S*)-MeO-BiPhep/Benzene/I_2.

Hydrogenation of the simple acyclic enamine ester (*Z*)-CH_3(PMPNH)C=$CHCO_2Et$ was carried out smoothly under the above optimized condition. However, the enantioselectivity is rather low (only 16% ee, entry 14).

A variety of exocyclic enamines **1** could be successfully hydrogenated using $[Ir(COD)Cl]_2$/(*S*)-MeO-BiPhep/I_2 catalyst system with high to excellent ee values (Table 2). Firstly, a series of exocyclic enamine ketone derivatives were screened. When the R^2 substituent is methyl, 94% ee and 99% yield are obtained. When the R^2 was changed to *n*-C_3H_7, the ee value was dropped to 85%. When the R^2 substituent is an aryl group, excellent enantioselectivities were

Table 2
Ir-Catalyzed hydrogenation of exocyclic enamines **1**[a]

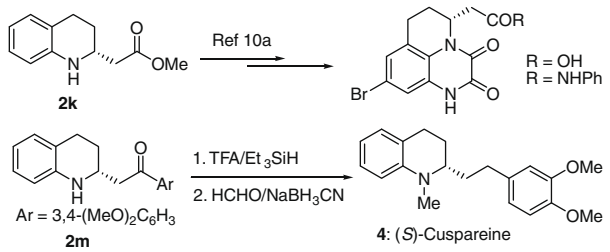


Entry	R^1/R^2	Yield[b] (%)	ee[c] (%)
1	H/Ph **1a**	97 **2a**	96 (*R*)
2	H/Me **1b**	99 **2b**	94 (*R*)
3	H/*n*-C_3H_7 **1c**	93 **2c**	85 (*R*)
4	H/4-CF_3–C_6H_4 **1d**	95 **2d**	94 (*R*)
5	H/4-^{i}Pr-C_6H_4 **1e**	94 **2e**	95 (*R*)
6	H/2-CH_3–C_6H_4 **1f**	91 **2f**	96 (*R*)
7	H/1-Naphthyl **1g**	94 **2g**	96 (*R*)
8	H/Phenethyl **1h**	99 **2h**	90 (*R*)
9	F/Ph **1i**	91 **2i**	96 (*R*)
10	Me/Ph **1j**	94 **2j**	90 (*R*)
11	H/Ome **1k**	96 **2k**	89 (*R*)
12	H/NEt_2 **1l**	97 **2l**	78 (*R*)
13	H/3,4-$(MeO)_2C_6H_4$ **1m**	97 **2m**	94 (*R*)

[a] Conditions: $[Ir(COD)Cl]_2$ (1 mol %), (*S*)-MeO-Biphep (2.2 mol %), I_2 (10 mol %), benzene, rt, 16 h.
[b] Isolated yields.
[c] Determined by HPLC analysis with chiral column.

obtained regardless of the electronic and steric effects of the aryl group (entries 4–6, and 13). The substrate with 1-naphthyl substituent can also give 96% ee value. However, when R^2 was changed to phenethyl, a slightly lower enantioselectivity was obtained (90% ee, entry 8). The substrate with a 6-substituted heteroaromatic ring could also be hydrogenated. Both electro-donating group such as Me and the electron-withdrawing group such as F, gave excellent enantioselectivities (entries 9–10). For the exocyclic enamine ester **11** and amide **12**, 89% ee and 78% ee can be obtained, respectively (entries 11 and 12).

Iridium-catalyzed asymmetric hydrogenation of exocyclic enamines provides a convenient route to synthesize optically active alkaloids and chiral drugs (Scheme 2). For example, **2k** is the key intermediate for the synthesis of NMDA-glycine antagonists.[13a] The naturally occurring tetrahydroquinoline alkaloid (*S*)-cuspareine can also be conveniently synthesized starting from the hydrogenation product **2m** in two steps.[13b]



Scheme 2. Formal synthesis of NMDA-glycine antagonists and synthesis of (*S*)-cuspareine.

3. Conclusions

In summary, the first highly enantioselective Ir-catalyzed asymmetric hydrogenation of unprotected exocyclic enamines has been developed using the $[Ir(COD)Cl]_2$/MeO-BiPhep/I_2 catalyst system with good reactivity and excellent enantioselectivities. This methodology has been successfully applied to the synthesis of natural products and chiral drugs. Further work will focus on the extension of the catalyst system to a broader range of unprotected enamines.

4. Experimental

4.1. General

Unless otherwise noted, all experiments were carried out under an inert atmosphere of dry nitrogen by using standard Schlenk-type techniques, or performed in a nitrogen-filled glovebox. Commercial reagents were used as received, unless otherwise stated. All the reactions were monitored by TLC with silica gel coated plates. Flash column chromatography was performed according to standard technique. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 spectrometers with $CDCl_3$ as the solvent and tetramethylsilane (TMS) as a reference. Optical rotations were measured with a JASCOP-1010 polarimeter.

4.2. Experimental procedures

4.2.1. General procedure for the synthesis of exocyclic enamines 1

Exocyclic enamines **1** can be prepared according to the known literature.[14a] Exocyclic enamines **1** can also be prepared according to the procedure as below: a mixture of $[Ir(COD)Cl]_2$ (3.4 mg, 0.005 mmol) and (*rac*)-MeO-BiPhep (6.4 mg, 0.011 mmol) in CH_2Cl_2 (4 mL) was stirred at room temperature for 10 min in a glovebox, then the mixture was transferred by a syringe to stainless steel autoclave, in which I_2 (12.8 mg, 0.05 mmol) and substrate (1.0 mmol) were placed beforehand. The hydrogenation was performed at room temperature under H_2 (400 psi) for 14 h. After carefully releasing the hydrogen, the reaction mixture was purified by a silica gel column eluted with ethyl acetate/petroleum to give pure products **1** (17–43%) and the corresponding tetrahydroquinoline side products (which can be used as racemic compounds of **2**).

4.2.1.1. (*Z*)-2-(3,4-Dihydroquinolin-2(1*H*)-ylidene)-1-phenylethanone 1a. Known compound.[14a] Yield 43%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.72 (t, *J* = 6.4 Hz, 2H), 2.87 (t, *J* = 7.6 Hz, 2H), 5.87 (s, 1H), 6.95 (q, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 7.6 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.41–7.47 (m, 3H), 7.91 (d, *J* = 6.8 Hz, 2H), 12.84 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 24.4, 28.8, 92.6, 116.8, 123.3, 125.3, 127.3, 127.9, 128.4, 128.5, 131.3, 136.8, 139.9, 159.0, 189.7.

4.2.1.2. (*Z*)-1-(3,4-Dihydroquinolin-2(1*H*)-ylidene)propan-2-one 1b. Yield 18%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.11 (s, 3H), 2.56 (t, *J* = 6.8 Hz, 2H), 2.79 (t, *J* = 7.2 Hz, 2H), 5.15 (s, 1H), 6.84 (d, *J* = 7.6 Hz, 1H), 6.92 (t, *J* = 7.6 Hz, 1H), 7.05 (d, *J* = 7.6 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 12.25 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 24.4, 28.2, 29.6, 96.0, 116.5, 122.8, 125.0, 127.8, 128.2, 136.9, 157.0, 197.4; HRMS Calcd for $C_{12}H_{14}NO$ $[M+H]^+$ 188.1075, found: 188.1082.

4.2.1.3. (*Z*)-1-(3,4-Dihydroquinolin-2(1*H*)-ylidene)pentan-2-one 1c. Yield 19%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.6 Hz, 3H), 1.62–1.69 (m, 2H), 2.32 (t, *J* = 7.6 Hz, 2H), 2.55–2.59 (m, 2H), 2.80 (t, *J* = 8.0 Hz, 2H), 5.15 (s, 1H), 6.83 (d, *J* = 7.6 Hz, 1H), 6.92 (t, *J* = 7.2 Hz, 1H), 7.05 (d, *J* = 7.6 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 12.31 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 14.2, 19.3, 24.5, 28.3, 44.6, 95.6, 116.5, 122.8, 125.0, 127.8, 128.3, 137.0, 157.0, 200.6; HRMS Calcd for $C_{14}H_{18}NO$ $[M+H]^+$ 216.1388, found: 216.1380.

4.2.1.4. (*Z*)-1-(4-(Trifluoromethyl)phenyl)-2-(3,4-dihydroquinolin-2(1*H*)-ylidene)ethanone 1d. Yield 24%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.74 (t, *J* = 6.8 Hz, 2H), 2.88 (t, *J* = 7.6 Hz, 2H), 5.85 (s, 1H), 6.95–7.02 (m, 2H), 7.11 (d, *J* = 7.6 Hz, 1H), 7.18–7.25 (m, 1H), 7.68 (d, *J* = 8.0 Hz, 2H), 7.99 (d, *J* = 8.0 Hz, 2H), 12.89 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 24.2, 28.8, 92.6, 117.0, 123.7, 125.4, 125.5, 127.6, 128.0, 128.4, 132.5, 136.4, 143.1, 160.0, 187.9; HRMS Calcd for $C_{18}H_{15}F_3NO$ $[M+H]^+$ 318.1106, found: 318.1111.

4.2.1.5. (*Z*)-2-(3,4-Dihydroquinolin-2(1*H*)-ylidene)-1-(4-iso propylphenyl)ethanone 1e. Yield 19%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (s, 3H), 1.28 (s, 3H), 2.71 (t, *J* = 6.4 Hz, 2H), 2.86 (t, *J* = 8.0 Hz, 2H), 2.94–2.97 (m, 1H), 5.86 (s, 1H), 6.92–6.97 (m, 2H), 7.08 (d, *J* = 7.6 Hz, 1H), 7.17 (t, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.85 (d, *J* = 8.0 Hz, 2H), 12.81 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 23.8, 24.0, 24.5, 28.8, 34.3, 92.5, 116.8, 123.1, 125.2, 126.6, 127.4, 127.9, 128.3, 136.9, 137.6, 152.6, 158.6, 189.6; HRMS Calcd for $C_{20}H_{22}NO$ $[M+H]^+$ 292.1701, found: 292.1702.

4.2.1.6. (*Z*)-2-(3,4-Dihydroquinolin-2(1*H*)-ylidene)-1-*o*-tolyl ethanone 1f. Yield 31%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.50 (s, 3H), 2.66 (t, *J* = 6.8 Hz, 2H), 2.85 (t, *J* = 8.0 Hz, 2H), 5.48 (s, 1H), 6.96 (t, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 7.2 Hz, 1H), 7.16–7.21 (m, 3H), 7.24–7.29 (m, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 12.64 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 20.4, 24.4, 28.6, 96.6, 116.8, 123.2, 125.2, 125.6, 127.5, 127.9, 128.3, 129.4, 131.2, 136.1, 136.8, 141.7, 158.4, 194.9; HRMS Calcd for $C_{18}H_{18}NO$ $[M+H]^+$ 264.1388, found: 264.1395.

4.2.1.7. (*Z*)-2-(3,4-Dihydroquinolin-2(1*H*)-ylidene)-1-(naphthalen-1-yl)ethanone 1g. Yield 20%.^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.69 (t, *J* = 6.8 Hz, 2H), 2.87 (t, *J* = 7.6 Hz,2H), 5.65 (s, 1H), 6.98 (d, *J* = 7.2 Hz, 2H), 7.10 (d, *J* = 7.2 Hz, 1H), 7.18–7.20 (m, 1H), 7.45–7.53 (m, 3H), 7.68 (d, *J* = 7.2 Hz, 1H), 7.87 (t, *J* = 8.8 Hz, 2H), 8.48 (d, *J* = 8.4 Hz, 1H), 12.83 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 24.4, 28.6, 97.3, 116.9, 123.3, 124.9, 125.3, 125.6, 126.1, 126.8, 127.9, 128.4, 130.3, 130.4, 134.0, 136.7, 139.9, 158.7, 194.1; HRMS Calcd for $C_{21}H_{18}NO$ $[M+H]^+$ 300.1388, found: 300.1390.

4.2.1.8. (*Z*)-1-(3,4-Dihydroquinolin-2(1*H*)-ylidene)-4-phenylbutan-2-one 1h. Yield 18%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.56 (t, *J* = 6.8 Hz, 2H), 2.67 (t, *J* = 7.2 Hz, 2H), 2.80 (t, *J* = 7.6 Hz, 2H), 2.97 (t, *J* = 8.4 Hz, 2H), 5.15 (s, 1H), 6.84 (d, *J* = 7.6 Hz, 1H), 6.93–6.95 (m, 1H), 7.05 (d, *J* = 7.2 Hz, 1H) 7.13–7.30 (m, 6H), 12.30 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 24.4, 28.3, 31.6, 44.0, 95.5, 116.5, 122.9, 125.0, 126.0, 127.8, 128.3, 128.5, 128.6, 136.9, 141.9, 157.3, 198.9; HRMS Calcd for $C_{19}H_{20}NO$ $[M+H]^+$ 278.1545, found: 278.1534.

4.2.1.9. (*Z*)-2-(6-Fluoro-3,4-dihydroquinolin-2(1*H*)-ylidene)-1-phenylethanone 1i. Yield 22%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.71 (t, *J* = 6.4 Hz, 2H), 2.86 (t, *J* = 7.6 Hz,2H), 5.87 (s, 1H), 6.83 (d, *J* = 6.4 Hz, 1H), 6.88 (d, *J* = 6.4 Hz, 2H), 7.42–7.50 (m, 3H), 7.90 (d, *J* = 6.8 Hz, 2H), 12.89 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 24.6, 28.4, 92.5, 114.3 (d, *J* = 90.8 Hz), 115.1 (d, *J* = 91.2 Hz), 117.1 (d, *J* = 32.8 Hz), 127.0 (d, *J* = 30.8 Hz), 127.2, 128.5, 131.3, 132.9, 139.8, 157.6, 158.6, 160.0, 189.7; HRMS Calcd for $C_{17}H_{15}NOF$ $[M+H]^+$ 268.1138, found: 268.1132.

4.2.1.10. (*Z*)-2-(3,4-Dihydro-6-methylquinolin-2(1*H*)-ylidene)-1-phenylethanone 1j. Yield 17%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.29 (s, 3H), 2.70 (t, *J* = 6.4 Hz, 2H), 2.83 (t, *J* = 7.6 Hz, 2H), 5.58 (s, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.92 (s, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 7.41–7.46 (m, 3H), 7.90 (d, *J* = 6.8 Hz, 2H), 12.85 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 21.0, 24.4, 28.9, 92.3, 116.7, 125.2, 127.2, 128.4, 128.5, 129.0, 131.2, 132.9, 134.3, 140.0, 159.1, 189.4; HRMS Calcd for $C_{18}H_{18}NO$ $[M+H]^+$ 264.1388, found: 264.1395.

4.2.1.11. (*Z*)-Methyl 2-(3,4-dihydroquinolin-2(1*H*)-ylidene) acetate (1k). Yield 19%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.56 (t, J = 6.8 Hz, 2H), 2.76 (t, J = 7.6 Hz, 2H), 3.68 (s, 3H), 4.67 (s, 1H), 6.67 (d, J = 8.0 Hz, 1H), 6.87 (t, J = 7.2 Hz, 1H), 7.03 (d, J = 7.2 Hz, 1H), 7.12 (t, J = 7.6 Hz, 1H), 10.40 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 24.7, 28.7. 50.5, 84.2, 115.7, 121.9, 124.2, 127.7, 128.2, 137.3, 156.5, 170.7; HRMS Calcd for $C_{12}H_{14}NO_2$ $[M+H]^+$ 204.1025, found: 204.1027.

4.2.1.12. (*Z*)-*N*,*N*-Diethyl-2-(3,4-dihydroquinolin-2(1*H*)-ylidene) acetamide 1l. Yield 25%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18–1.25 (m, 6H), 2.58 (t, J = 6.4 Hz, 2H), 2.78 (t, J = 7.6 Hz, 2H), 3.37 (br s, 4H), 4.78 (s, 1H), 6.67–6.83 (m, 2H), 7.01 (d, J = 7.2 Hz, 1H), 7.09 (t, J = 7.6 Hz, 1H), 11.50 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 13.7, 13.9, 25.2, 29.3, 83.8, 115.5, 120.8, 124.0, 127.5, 127.9, 137.9, 153.6, 169.5; HRMS Calcd for $C_{15}H_{21}N_2O$ $[M+H]^+$ 245.1654, found: 245.1647.

4.2.1.13. (*Z*)-2-(3,4-Dihydroquinolin-2(1*H*)-ylidene)-1-(3,4-dimethoxyphenyl)ethanone 1m. Yield 28%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.72 (t, J = 6.8 Hz, 2H), 2.86 (t, J = 7.6 Hz,2H), 3.93 (s, 3H), 3.96 (s, 3H), 5.85 (s, 1H), 6.87–6.93 (m, 3H), 6.95 (d, J = 7.2 Hz, 1H), 7.10 (t, J = 7.6 Hz, 1H), 7.51–7.56 (m, 2H), 12.78 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 24.5, 28.8, 56.1, 56.2, 92.1, 110.0, 110.3, 116.7, 120.8, 123.0, 125.1, 127.9, 128.3, 132.8, 136.8, 149.0, 151.9, 158.4, 188.6; HRMS Calcd for $C_{19}H_{20}NO_3$ $[M+H]^+$ 310. 1443, found: 310.1448.

4.2.2. Typical procedure for the Ir-catalyzed asymmetric hydrogenation of exocyclic enamines 1

A mixture of $[Ir(COD)Cl]_2$ (0.9 mg, 0.00125 mmol) and (*S*)-MeO-Biphep (1.6 mg, 0.00275 mmol) in benzene (2 mL) was stirred at room temperature for 10 min in a glovebox, then the mixture was transferred by a syringe to stainless steel autoclave, in which I_2 (3.2 mg, 0.0125 mmol) and substrate (0.125 mmol) were placed beforehand. The hydrogenation was performed at room temperature under H_2 (600 psi) for 16 h. After carefully releasing the hydrogen, the reaction mixture was purified by a silica gel column eluted with petroleum/EtOAc to give pure product. The enantiomeric excesses were determined by chiral HPLC with chiral columns (OD-H, OJ-H and AD-H).

4.2.2.1. (*R*)-2-(1,2,3,4-Tetrahydroquinolin-2-yl)-1-phenylethanone 2a. Pale yellow oil, 96% ee, $[\alpha]_D^{25} = -96.6$ (c 0.54, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.80–1.84 (m, 1H), 2.00–2.04 (m, 1H), 2.74–2.80 (m, 1H), 2.84–2.88 (m, 1H), 3.16–3.18 (m, 2H), 3.92–3.96 (m, 1H), 4.58 (br s, 1H), 6.48 (d, J = 8.2 Hz, 1H), 6.61 (t, J = 7.4 Hz, 1H), 6.96 (t, J = 7.2 Hz, 2H), 7.46 (t, J = 7.5 Hz, 2H), 7.57 (t, J = 7.0 Hz, 1H), 7.95 (d, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 25.8, 28.4, 45.2, 47.3, 114.9, 117.4, 121.0, 127.0, 128.2, 128.8, 129.4, 133.6, 137.0, 144.4, 199.6; HRMS Calcd for $C_{17}H_{17}NONa$ $[M+Na]^+$ 274.1208, found: 274.1204; HPLC (OD-H column, n-hexane/2-propanol = 80/20, flow rate = 0.8 mL min^{-1}): t_1 = 8.8 min; t_2 = 10.6 min.

4.2.2.2. (*R*)-1-(1,2,3,4-Tetrahydroquinolin-2-yl)propan-2-one 2b. Pale yellow oil, 94% ee, $[\alpha]_D^{25} = -87.3$ (c 1.06, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.63–1.72 (m, 1H), 1.88–1.91 (m, 1H), 2.17 (s, 3H), 2.64–2.72 (m, 3H), 2.79–2.84 (m, 1H), 3.72–3.75 (m, 1H), 4.44 (br s, 1H), 6.46 (d, J = 7.9 Hz, 1H), 6.60 (t, J = 7.1 Hz, 1H), 6.92–6.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 25.7, 28.0, 30.7, 47.0, 50.0, 114.8, 117.5, 121.0, 127.0, 129.3, 144.3, 208.6; HRMS Calcd for $C_{12}H_{15}NONa$ $[M+Na]^+$ 212.1051, found: 212.1056; HPLC (OD-H column, n-hexane/2-propanol = 80/20, flow rate = 0.8 mL min^{-1}): t_1 = 8.6 min; t_2 = 9.5 min.

4.2.2.3. (*R*)-1-(1,2,3,4-Tetrahydroquinolin-2-yl)pentan-2-one 2c. Colorless oil, 85% ee, $[\alpha]_D^{25} = -93.1$ (c 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (t, J =7.4 Hz, 3H), 1.59–1.68 (m, 3H), 1.88–1.89 (m, 1H), 2.39(t, J = 7.4 Hz, 2H), 2.59–2.61 (m, 2H), 2.68–2.79 (m, 1H), 2.80–2.87 (m, 1H), 3.72–3.76 (m, 1H), 4.48 (br s, 1H), 6.46 (d, J = 7.9 Hz, 1H), 6.60 (t, J = 7.4 Hz, 1H), 6.92–6.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 13.9, 17.3, 25.8, 28.1, 45.5, 47.0, 49.1, 114.8, 117.4, 121.0, 127.0, 129.3, 144.4, 210.9; HRMS Calcd for $C_{14}H_{20}NO$ $[M+H]^+$ 218.1545, found: 218.1541; HPLC (OD-H column, n-hexane/2-propanol = 80/20, flow rate = 0.8 mL min^{-1}): t_1 = 6.7 min; t_2 = 7.5 min.

4.2.2.4. (*R*)-1-(4-(Trifluoromethyl)phenyl)-2-(1,2,3,4-tetrahydroquinolin-2-yl)ethanone 2d. Colorless oil, 94% ee, $[\alpha]_D^{25} = -80.0$ (c 1.12, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.78–1.87 (m, 1H), 2.02–2.06 (m, 1H), 2.76–2.80 (m, 1H), 2.86–2.91 (m, 1H), 3.20 (d, J = 6.0 Hz, 2H), 3.96–3.98 (m, 1H), 4.55 (br s, 1H), 6.49 (d, J = 8.2 Hz, 1H), 6.63 (t, J = 7.0 Hz, 1H), 6.96–6.99 (m, 2H), 7.73 (d, J = 7.7 Hz, 2H), 8.06 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 25.7, 28.3, 45.6, 47.2, 114.9, 117.7, 121.0, 125.9, 126.2, 127.1, 128.6, 129.4, 134.7, 139.5, 144.2, 198.7; HRMS Calcd for $C_{18}H_{17}NOF_3$ $[M+H]^+$ 320.1262, found: 320.1248; HPLC (OD-H column, n-hexane/2-propanol = 80/20, flow rate = 0.8 mL min^{-1}): t_1 = 10.1 min; t_2 = 17.0 min.

4.2.2.5. (*R*)-2-(1,2,3,4-Tetrahydroquinolin-2-yl)-1-(4-isopropyl phenyl)ethanone 2e. Pale yellow oil, 95% ee, $[\alpha]_D^{25} = -70.3$ (c 1.32, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24–1.28 (m, 6H), 1.79–1.82 (m, 1H), 1.99–2.03 (m, 1H), 2.74–2.79 (m, 1H), 2.84–2.98 (m, 2H), 3.13–3.15 (m, 2H), 3.90–3.93 (m, 1H), 4.58 (br s, 1H), 6.47 (d, J = 8.0 Hz, 1H), 6.61 (t, J = 7.4 Hz, 1H), 6.94 (m, 2H), 7.30 (d, J = 7.9 Hz, 2H), 7.89 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 23.8, 25.9, 28.4, 34.4, 45.1, 47.4, 114.9, 117.4, 121.0, 126.9, 127.0, 128.5, 128.7, 129.3, 134.9, 144.5, 155.1, 199.3; HRMS Calcd for $C_{20}H_{24}NO$ $[M+H]^+$ 294.1858, found: 294.1855; HPLC (OD-H column, n-hexane/2-propanol = 80/20, flow rate = 0.8 mL min^{-1}): t_1 = 7.5 min; t_2 = 9.7 min.

4.2.2.6. (*R*)-2-(1,2,3,4-Tetrahydroquinolin-2-yl)-1-o-tolyl-ethanone (2f). Pale yellow oil, 96% ee, $[\alpha]_D^{25} = -94.9$ (c 1.06, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.77–1.80 (m, 1H), 1.97–2.01 (m, 1H), 2.52 (s, 3H), 2.73–2.78 (m, 1H), 2.83–2.87 (m, 1H), 3.10 (d, J = 6.3 Hz, 2H), 3.89–3.92 (m, 1H), 4.57 (br s, 1H), 6.49 (d, J = 7.8 Hz, 1H), 6.61 (t, J = 7.3 Hz, 1H), 6.94–6.98 (m, 2H), 7.24–7.27 (m, 2H), 7.38 (t, J = 7.4 Hz, 1H), 7.64 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 21.6, 25.8, 28.3, 47.6, 47.9, 114.9, 117.4, 121.1, 125.9, 127.0, 128.8, 129.4, 131.8, 132.3, 137.7, 138.4, 144.4, 203.7; HRMS Calcd for $C_{18}H_{20}NO$ $[M+H]^+$ 266.1545, found: 266.1537; HPLC (OD-H column, n-hexane/2-propanol = 80/20, flow rate = 0.8 mL min^{-1}): t_1 = 8.1 min; t_2 = 9.0 min.

4.2.2.7. (*R*)-2-(1,2,3,4-Tetrahydroquinolin-2-yl)-1-(naphthalen-1-yl)ethanone 2g. Colorless oil, 96% ee, $[\alpha]_D^{25} = -145.7$ (c 1.12, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.79–1.85 (m, 1H), 2.00–2.04 (m, 1H), 2.74–2.80 (m, 1H), 2.84–2.90 (m, 1H), 3.25–3.27 (m, 2H), 3.98–4.02 (m, 1H), 4.65 (br s, 1H), 6.51 (d, J = 7.8 Hz, 1H), 6.63 (t, J = 7.3 Hz, 1H), 6.95–6.99 (m, 2H), 7.46–7.53(m, 2H), 7.55–7.62 (m, 1H), 7.87 (d, J = 7.0 Hz, 2H), 7.98 (d, J = 8.2 Hz, 1H), 8.64 (d, J = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 25.8, 28.3, 47.9, 48.5, 114.9, 117.5, 121.1, 124.5, 125.8, 126.7, 127.0, 128.1, 128.3, 128.7, 129.4, 130.2, 133.2, 134.1, 135.7, 144.4, 203.9; HRMS Calcd for $C_{21}H_{20}NO$ $[M+H]^+$ 302.1545, found: 302.1556; HPLC (OD-H column, n-hexane/2-propanol = 80/20, flow rate = 0.8 mL min^{-1}): t_1 = 14.7 min; t_2 = 18.9 min.

4.2.2.8. (*R*)-1-(1,2,3,4-Tetrahydroquinolin-2-yl)-4-phenylbutan-2-one 2h. Colorless oil, 90% ee, $[\alpha]_D^{25} = -57.8$ (c 1.12, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.64–1.66 (m, 1H), 1.86–1.89 (m, 1H),

2.59–2.60 (m, 2H), 2.66–2.81 (m, 4H), 2.89–2.93 (m, 2H), 3.73–3.75 (m, 1H), 4.41 (br s, 1H), 6.45 (d, J = 7.6 Hz, 1H), 6.61 (t, J = 7.6 Hz, 1H), 6.94 (m, 2H), 7.17–7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): 25.7, 28.1, 29.8, 45.0, 47.0, 49.4, 114.9, 117.5, 121.0, 126.4, 127.0, 128.5, 128.7, 129.4, 140.9, 144.3, 209.8; HRMS Calcd for $C_{19}H_{22}NO$ $[M+H]^+$ 280.1701, found: 280.1689; HPLC (OD-H column, n-hexane/2-propanol = 80/20, flow rate = 0.8 mL min^{-1}): t_1 = 13.7 min; t_2 = 18.0 min.

4.2.2.9. (*R*)-2-(6-Fluoro-1,2,3,4-tetrahydroquinolin-2-yl)-1-phenylethanone 2i. Pale yellow oil, 96% ee, $[\alpha]_D^{25} = -48.9$ (c 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.78–1.81 (m, 1H), 1.99–2.02 (m, 1H), 2.72–2.77 (m, 1H), 2.84–2.88 (m, 1H), 3.11–3.22 (m, 2H), 3.87–3.91 (m, 1H), 4.51 (br s, 1H), 6.40 (m, 1H), 6.66–6.70 (m, 2H), 7.47 (t, J = 7.6 Hz, 2H), 7.58 (t, J = 7.3 Hz, 1H), 7.96 (d, J = 6.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 26.1, 28.2, 45.0, 47.6, 113.4, 113,7, 115.3, 115.6, 115.7, 128.2, 128.9, 133.6, 136.9, 140.6, 157.0, 199.6; HRMS Calcd for $C_{17}H_{17}NOF$ $[M+H]^+$ 270.1294, found: 270.1286; HPLC (OD-H column, n-hexane/2-propanol = 80/20, flow rate = 0.8 mL min^{-1}): t_1 = 8.8 min; t_2 = 9.3 min.

4.2.2.10. (*R*)-2-(1,2,3,4-Tetrahydro-6-methylquinolin-2-yl)-1-phenylethanone 2j. Colorless oil, 90% ee, $[\alpha]_D^{25} = -48.7$ (c 0.34, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.79–1.83 (m, 1H), 1.99–2.03 (m, 1H), 2.20 (s, 3H), 2.72–2.77 (m, 1H), 2.82–2.86 (m, 1H), 3.16–3.18 (m, 2H), 3.90–3.92 (m, 1H), 4.45 (br s, 1H), 6.42 (d, J = 3.6 Hz, 1H), 6.77 (d, J = 6.3 Hz, 2H), 7.47 (t, J = 7.6 Hz, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.95 (d, J = 7.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 20.6, 25.8, 28.6, 45.1, 47.5, 115.1, 121.1, 126.7, 127.6, 128.2, 128.8, 129.9, 133.5, 137.0, 142.0, 199.7; HRMS Calcd for $C_{18}H_{20}NO$ $[M+H]^+$ 266.1545, found: 266.1547; HPLC (OD-H column, n-hexane/2-propanol = 80/20, flow rate = 0.8 mL min^{-1}): t_1 = 8.2 min; t_2 = 8.8 min.

4.2.2.11. (*R*)-Methyl 2-(1,2,3,4-tetrahydroquinolin-2-yl)acetate 2k, known compound, see: Ref 3. Colorless oil, 89% ee, $[\alpha]_D^{25} = -77.2$ (c 0.74, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.68–1.74 (m, 1H), 1.93–1.97 (m, 1H), 2.51–2.52 (m, 2H), 2.69–2.75 (m, 1H), 2.79–2.83 (m, 1H), 3.68–3.74 (m, 4H), 4.46 (br s, 1H), 6.49 (d, J = 7.9 Hz, 1H), 6.61 (t, J = 7.4 Hz, 1H), 6.93–6.98 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 25.7, 28.1, 40.8, 47.9, 51.9, 114.7, 117.5, 121.0, 127.0, 129.4, 144.1, 172.9; HPLC (OD-H column, n-hexane/2-propanol = 90/10, flow rate = 0.8 mL min^{-1}): t_1 = 9.8 min; t_2 = 11.0 min.

4.2.2.12. (*R*)-*N*,*N*-Diethyl-2-(1,2,3,4-tetrahydroquinolin-2-yl)-acetamide 2l. Colorless oil, 78% ee, $[\alpha]_D^{25} = -69.8$ (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10–1.17 (m, 6H), 1.70 (m, 1H), 1.92 (m, 1H), 2.48 (m, 2H), 2.72 (m, 1H), 2.85 (m, 1H), 3.24–3.31 (m, 2H), 3.35–3.41 (m, 2H), 3.75–3.76 (m, 1H), 4.97 (br s, 1H), 6.48 (d, J = 7.8 Hz, 1H), 6.58 (t, J = 7.4 Hz, 1H), 6.91–6.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 13.2, 14.2, 26.0, 28.5, 39.6, 40.1, 41.9, 48.1, 114.8, 117.0, 121.0, 126.8, 129.1, 144.7, 170.6; HRMS Calcd for $C_{15}H_{22}N_2ONa$ $[M+Na]^+$ 269.1630, found: 269.1624; HPLC (OJ-H column, n-hexane/2-propanol = 90/10, flow rate = 0.8 mL min^{-1}): t_1 = 11.9 min; t_2 = 15.3 min.

4.2.2.13. (*R*)-2-(1,2,3,4-Tetrahydroquinolin-2-yl)-1-(3,4-dimethoxyphenyl)ethanone 2m. Yellow oil, 94% ee, $[\alpha]_D^{25} = -53.9$ (c 1.21, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.79–1.83 (m, 1H), 1.99–2.04 (m, 1H), 2.75–2.80 (m, 1H), 2.84–2.88 (m, 1H), 3.12–3.14 (m, 2H), 3.91–3.96 (m, 7H), 4.57 (br s, 1H), 6.47 (d, J = 8.4 Hz, 1H), 6.61(t, J = 7.2 Hz, 1H), 6.86 (dd, J = 2.0, 8.4 Hz, 1H), 6.94–6.98 (m, 2H), 7.53–7.55 (m, 1H), 7.55–7.60 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 25.8, 28.4, 44.6, 47.6, 56.1, 56.2, 110.1, 11.0.2, 114.8, 117.4, 121.0, 123.0, 127.0, 129.3, 130.3, 144.4, 149.2, 153.7, 198.2; HRMS Calcd for $C_{19}H_{22}NO_3$ $[M+H]^+$ 312.1600, found: 312.1605; HPLC (OD-H column, n-hexane/2-propanol = 80/20, flow rate = 0.8 mL min^{-1}): t_1 = 18.2 min; t_2 = 23.6 min.

4.2.3. (*S*)-2-(3,4-Dimethoxyphenethyl)-1,2,3,4-tetrahydroquinoline 3. Compound **3** was prepared according to the literature.[14b] To a stirred solution of **2m** (74 mg, 0.25 mmol) in 1.0 mL trifluoroacetic acid, triethylsilane (1.78 mmol) was added dropwise. After the addition, the solution was stirred for 24 h at room temperature. The reaction mixture was evaporated to give the crude product. The crude product was dissolved in CH_2Cl_2 and then washed with three 10 mL portions of 1 N KOH. The solution was dried over potassium carbonate and was evaporated in vacuo. Purification was performed by a silica gel column eluted with ethyl acetate/petroleum to give the product **3** with 47% yield and recovered starting material **2m** (45%). 94% ee, $[\alpha]_D^{25} = -59.9$ (c 1.00, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 1.65 (m, 1H), 1.81 (m, 2H), 1.98 (m, 1H), 2.67 (m, 4H), 2.77 (m, 1H), 3.28 (m, 1H), 3.85 (s, 3H), 3.86 (s, 3H), 6.44 (d, J = 8.0 Hz, 1H), 6.59 (m, 1H), 6.74 (m, 3H), 6.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 26.6, 28.5, 32.3, 38.8, 51.7, 56.3, 56.4, 111.8, 112.1, 114.6, 117.5, 120.6, 121.7, 127.2, 129.7, 134.9, 144.9, 147.8, 149.4; HPLC (OD-H, n-hexane/2-propanol = 80/20, 0.8 mL min^{-1}), t_1 = 14.6 min, t_2 = 16.9 min.

4.2.4. (*S*)-Cuspareine 4. To a stirred solution of (*S*)-2-(3,4-dimethoxyphenethyl)-1,2,3,4-tetrahydroquinoline (74 mg, 0.25 mmol) and 0.2 mL (2.5 mmol) of 37% aqueous formaldehyde in 2.5 mL of acetonitrile was added 48 mg of sodium cyanoborohydride. Glacial acetic acid (250 μL) was added, and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was poured into 30 mL of ether and then washed with three 10 mL portions of 1 N KOH and one portion of brine. The ether solution was dried over potassium carbonate and evaporated in vacuo to give crude product as a yellow oil, purification was performed by a silica gel column eluted with ethyl acetate/petroleum to give pure (*S*)-cuspareine (76 mg, 98% yield).[13c] $[\alpha]_D^{25} = -27.2$ (c 0.87, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 1.78 (m, 1H), 1.98 (m, 3H), 2.57 (m, 1H), 2.69 (m, 2H), 2.83 (m, 1H), 2.94 (s, 3H), 3.31 (m, 1H), 3.88 (s, 3H), 3.90 (s, 3H), 6.58 (d, J = 8.2 Hz, 1H), 6.65 (t, J = 7.3 Hz, 1H), 6.78 (m, 2H), 6.84 (d, J = 7.2 Hz, 2H), 7.01 (d, J = 7.2 Hz, 1H), 7.11 (t, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 23.8, 24.6, 32.1, 33.3, 38.3, 56.1, 56.2, 58.6, 110.8, 11.5, 111.8, 115.6, 120.3, 121.9, 127.3, 128.9, 134.9, 145.5, 147.4, 149.1.

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