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Enantioselective Reduction of 3-Substituted Quinolines with a Cyclopentadiene-Based Chiral Brønsted Acid

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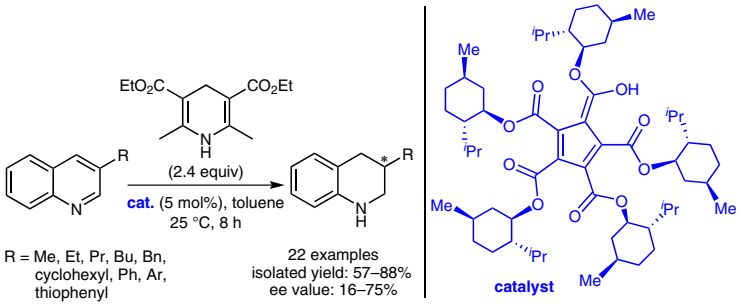

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Abstract Enantioselective reduction of 3-substituted quinolines has been achieved using a cyclopentadiene-based chiral Brønsted acid as catalyst and Hantzsch ester as hydrogen donor, affording the corresponding tetrahydroquinolines in good enantioselectivities.

Key words tetrahydroquinolines, transfer hydrogenation, 3-substituted quinolones, enantioselectivity, chiral Brønsted acid

Chiral 3-substituted tetrahydroquinolines are important structural units in a number of natural products and a wide variety of biologically active compounds and pharmaceuticals.[1] For example, (21*S*)-argatroban is a synthetic peptidomimetic small molecule, serving as an antithrombotic drug;[2] API 1 is a peptide-like drug for treating diabetes;[3] (–)-sumanirole is a potential drug for the treatment of Parkinson's disease and restless leg syndrome;[4] JNJ-26076713 is a $\alpha v\beta_3/\alpha v\beta_5$ integrin antagonist for the treatment of eye disease (Figure 1).[5] The chirality of these compounds plays very important role in the relevant bioactivities. Therefore, it is highly desirable to develop efficient methods to prepare these chiral heterocycles.

Since the pioneering work reported by Zhou in 2003,[6] some exciting advances have been achieved in transition-metal-catalyzed asymmetric hydrogenation and transfer hydrogenation of quinoline derivatives.[7–12] Using the reported methods, excellent enantioselectivities have been achieved for 2-substituted and 2,3-disubstituted quinoline derivatives. However, in sharp contrast, asymmetric hydrogenation of 3-substituted quinolines is not yet successful, with one example giving a racemic mixture.[9i] This is not unexpected, since the mechanism shows a reduction pathway involving 1,4-dihydride addition, isomerization, and then 1,2-dihydride addition.[9i] Therefore, the asymmetric reduction of 3-substituted quinolines has become a challenging task. The first example of asymmetric transfer hydrogenation of 3-substituted quinolines was reported by Rueping in 2008, using a chiral phosphoric acid with a Hantzsch ester as the hydrogen donor;[11b] moderate enantioselectivities and yields were achieved. The chirality is likely to be induced via a good chiral environment created by the chiral phosphoric acid in the proton transfer process. Very recently, an example of highly enantioselective transfer hydrogenation of 3-tosylamide quinoline was reported.[11l] Hydrogen bonding between the substrate and chiral phosphoric acid may be responsible for the results. Considering the importance of chiral 3-substituted tetrahydroquinolines, pursuing the synthesis of such compounds is still an interesting topic. Herein, we report our results on the asymmetric reduction of 3-substituted quinolines via transfer hydrogenation using chiral Brønsted acids.

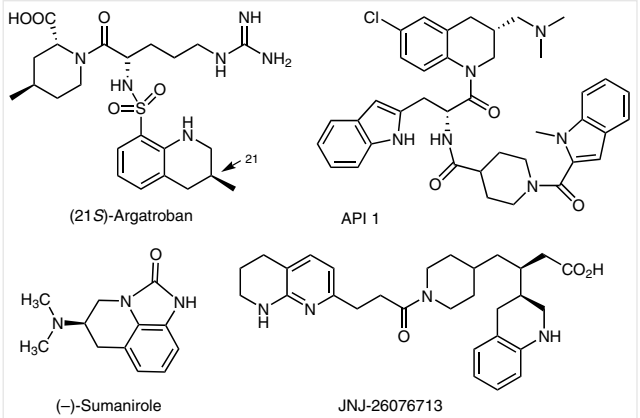


Figure 1 Some examples of chiral 3-substituted tetrahydroquinolines

Very recently, a novel chiral Brønsted acid (Figure 2, A) based on 1,2,3,4,5-pentacarboxycyclopentadiene was synthesized by Lambert and co-workers.[13] Compared to chiral phosphoric acids, this kind of acid can be obtained easily from some simple starting materials in three steps, and furthermore, their acidity can be adjusted by combing different chiral alcohols or amines. Given the excellent performance of such Brønsted acids in the Mukaiyama–Mannich reaction, their well-defined chiral environment and good catalytic activity might afford an opportunity for the efficient asymmetric reduction of 3-substituted quinolines. With this hypothesis in mind, we synthesized the chiral Brønsted acids **A** and **B** derived from (–)-menthol and (+)-isopinocampheol, respectively.

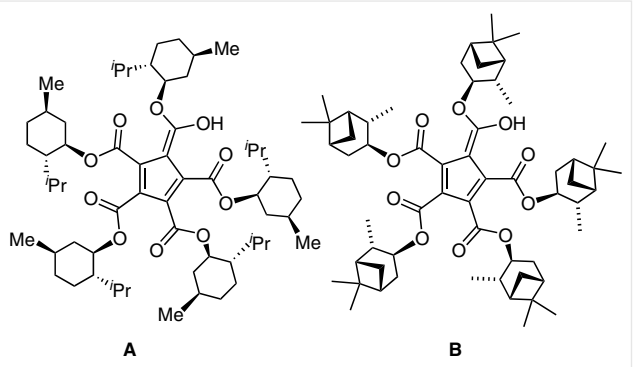


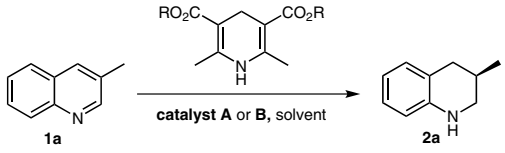
Figure 2 Chiral Brønsted acids **A** and **B** based on cyclopentadiene

With catalysts **A** and **B** in hand, we initially investigated the transfer hydrogenation of 3-methylquinoline (**1a**) with different Hantzsch esters (Table 1, entries 1–5) using diethyl ether as the solvent. The results demonstrated that the reaction proceeded with better enantioselectivity and yield using **A** as the catalyst. To our surprise, catalyst **B** almost gave a racemic product (cf. **A** and **B** in Table 1, entries 1–5). Evaluation of the temperature revealed that a lower or higher temperature gave a lower enantioselectivity (Table 1, entries 6 and 7). Considering the well-known effect of solvent on hydrogen bonding, a series of solvents were next investigated (Table 1, entries 8–13). Whilst most solvents gave good product yields, the best enantioselectivity was obtained in the nonpolar toluene. In addition, decreasing the catalyst loading resulted in lower conversions and enantioselectivities (Table 1, entries 14 and 15). Increasing the catalyst loading (10 mol%) resulted in an improved conversion, but only a slightly higher enantioselectivity (Table 1, entry 16).

Having established the best conditions for the transfer hydrogenation of 3-methylquinoline (**1a**), we turned our attention to exploring the scope of 3-substituted quinolines **1a–v**. The results are listed in Table 2. As can be seen, all the substrates were smoothly reduced under the optimized reaction conditions, affording moderate to good isolated yield. For alkyl substituents on the 3-position (Table 2, entries 1–6), it was found that the reaction system was somewhat sensitive to steric effects. In particular, the presence of the sterically much hindered cyclohexyl group led to a better enantioselectivity, but a lower yield (Table 2, entry 5, cf. entries 1–4 and 6). Interestingly, changing 3-substituted quinolines to the analogous 2-substituted quinolines **1a′–d′,k′,p′** gave some higher yields, but lower enantioselectivities under the conditions employed (Table 2, entries 1–4). For quinolines containing aryl groups on the 3-position, the substituents on the phenyl ring showed more significant effects on the enantioselectivities (Table 2, entries 7–21).

Thus, substrates containing electron-denoting groups on the phenyl ring, at either the *para*- or *meta*- position, afforded similar enantioselectivities at ca. 50% ee (Table 2, entries 8–12, except **2j**), close to the non-substituted sub-

Table 1 Optimization of Reaction Conditions for Transfer Hydrogenation of 3-Methylquinoline (**1a**)[a]



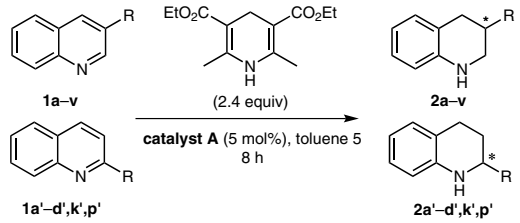
Entry	R	Solvent	Cat. (mol%)	T (°C)	Conv. (%)[b]	ee (%)[c,d]
1	Me	Et_2O	**A** (5) **B** (5)	25	30 30	32 5
2	Et	Et_2O	**A** (5) **B** (5)	25	95 95	36 4
3	allyl	Et_2O	**A** (5) **B** (5)	25	75 49	32 4
4	*t*-Bu	Et_2O	**A** (5) **B** (5)	25	58 63	17 2
5	Bn	Et_2O	**A** (5) **B** (5)	25	90 95	21 4
6	Et	Et_2O	**A** (5)	50	99	27
7	Et	Et_2O	**A** (5)	10	30	26
8	Et	toluene	**A** (5) **B** (5)	25	95 70	46 3
9	Et	benzene	**A** (5)	25	95	41
10	Et	THF	**A** (5)	25	84	36
11	Et	MeCN	**A** (5)	25	71	31
12	Et	CH_2Cl_2	**A** (5)	25	95	26
13	Et	dioxane	**A** (5)	25	87	41
14	Et	toluene	**A** (1)	25	37	32
15	Et	toluene	**A** (3)	25	70	45
16	Et	toluene	**A** (10)	25	99	48

[a] Reaction conditions: **1a** (0.1 mmol), catalyst **A** or **B**, Hantzsch ester (2.4 equiv), solvent (2 mL), 8 h.
[b] The conversion was determined by ^{1}H NMR spectroscopy.
[c] The ee values were determined by HPLC analysis using a chiral stationary column.
[d] The absolute configuration was assigned as *R* by for **A** or *S* for **B** based on the optical rotation and HPLC analysis.[14]

strate (Table 2, entry 7). However, enantioselectivities of more than 60% ee were obtained when electron-withdrawing groups were installed at these positions (Table 2, entries 15–19). On the other hand, depending on the substitution position, the enantioselectivity varied considerably, ranging from the lowest to the highest ees observed for the substrates in Table 2. Thus, when the fluoro substituent was placed at the *ortho* position, a dramatic decrease in the ee was noted (Table 2, entries 14 and 20). The effect of the substitution on the reaction rates appears less clear under the conditions employed, however. For a comparison, we also carried out the transfer hydrogenation of 2-aryl-substituted quinolones. The results demonstrated that the yields and enantioselectivities decreased for both electron-denoting and electron-withdrawing groups (Table 2, entries 11 and 16).

In summary, we have demonstrated a new method for the asymmetric transfer hydrogenation of challenging 3-substituted quinolines, using a cyclopentadiene-based chiral Brønsted acid as catalyst. A series of chiral 3-substituted tetrahydroquinolines were obtained with good isolated yields and enantioselectivities.

Table 2 Asymmetric Transfer Hydrogenation of 3-Substituted or 2-Substituted Quinolines[a]



Entry	Product	R	Yield (%)[b]	ee (%)[c]	Config.[d]
1	**2a**	Me	87	46	*R*
	2a′		90	35	*S*
2	**2b**	Et	74	55	*R*
	2b′		93	5	*R*
3	**2c**	Pr	83	52	*R*
	2c′		95	10	*R*
4	**2d**	Bu	75	51	*R*
	2d′		95	9	*R*
5	**2e**	Cy	65[f]	60	*S*
6	**2f**	Bn	81[f]	41	*S*
7	**2g**	Ph	72	53	*S*
8	**2h**	3-MeC_6H_4	84	47	*S*
9	**2i**	4-MeC_6H_4	87	49	*S*
10	**2j**	3-MeOC_6H_4	60	39	*S*
11	**2k**	4-MeOC_6H_4	87	53	*S*
	2k′		84	23	*S*
12	**2l**	3,5-$Me_2C_6H_3$	72	53	*S*
13	**2m**	2-naphthyl	64	53	*R*
14	**2n**	2-FC_6H_4	57	16	*S*
15	**2o**	3-FC_6H_4	70	60	*S*
16	**2p**	4-FC_6H_4	88	75	*S*
	2p′		67	30	*S*
17	**2q**	4-ClC_6H_4	87	70	*S*
18	**2r**	4-BrC_6H_4	71	66	*S*
19	**2s**	4-F_3C-C_6H_4	82	60	*S*
20	**2t**	2,4-$F_2C_6H_4$	82	49	*S*
21	**2u**	3,5-$F_2C_6H_4$	71	49	*S*
22	**2v**	3-thienyl	77[e]	48	*S*

[a] Reaction conditions: **1a–v** or **1a′–d′**,**k′**,**p′** (0.25 mmol), catalyst **A** (5 mol%), Hantzsch ethyl ester (2.4 equiv), toluene (5 mL), 8 h.
[b] Isolated yield.
[c] The ee values were determined by HPLC analysis using a chiral stationary column.
[d] The absolute configuration was assigned based on the optical rotation (**2a**,[14] **2f**,[16b] **2g**,[11b] **2j**,[11b] **2l–n**[11b]) or HPLC in comparison with the literature results.
[e] The reaction time was 12 h.

^{1}H and ^{13}C NMR spectra were recorded on Bruker 400 spectrometers relative to TMS (δ = 0.00) using $CDCl_3$ as solvent (^{1}H) or to solvent carbon (δ = 77.0 for $CDCl_3$) (^{13}C). IR spectra were recorded on a Bruker Tensor 27 FT-IR spectrophotometer. HRMS were recorded on Bruker LC-MS spectrometer with ESI resource. Melting points were measured on RDY-1B micro melting point apparatus and are uncorrected. Optical rotations were measured on an Autopol IV-T spectrometer at the wavelength of the Na D-line (589 nm). TLC was performed on 10–40 μm silica gel plates. Column chromatography was carried out with silica gel (200–300 mesh) using mixtures of EtOAc and petroleum ether (PE) as eluent. HPLC analysis was performed on Shimadzu equipment using Daicel Chiralpak OJ-H or OD-H columns. GC analysis was performed on Shimadzu G2014T equipment using a Supelco Beta-DEX 225 chromatographic column.

Unless otherwise specified, all reagents were commercially purchased and used without further purification. Et_2O and toluene were distilled from Na/benzophenone. 3-Methylquinoline (**1a**) was commercially available of analytical grade and used without purification. All other substrates **1b–v** were prepared according to the literature[19]

Data for 2-substituted products **2a′–d′**,**k′**,**p′** are given in the Supporting Information.

3-Aryl- or 3-Alkyltetrahydroquinolines 2a–v; General Procedure

Quinoline **1** (0.25 mmol), catalyst **A** (5 mol%), and Hantzsch dihydropyridine (2.40 equiv) were suspended in toluene (5 mL) in a screw-capped vial. The resulting yellow solution was stirred at 25 °C for 8 h. The solvent was evaporated under vacuum and the residue was purified by column chromatography (silica gel, hexane/EtOAc, 15:1) to afford the tetrahydroquinoline.

(*R*)-3-Methyl-1,2,3,4-tetrahydroquinoline (2a)[14]

Yellow oil; yield: 32 mg (87%); 46% ee; R_f = 0.67 (PE/EtOAc, 5:1); $[\alpha]_D^{20}$ –38 (*c* 0.1, CH_2Cl_2). HPLC [Daicel Chiralpak OJ-H, λ = 210 nm, eluent: *i*-PrOH/hexane (10:90), flow rate: 0.5 mL/min]: t_R = 27.00 (major), 33.55 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.00–6.95 (m, 2 H), 6.62 (t, *J* = 7.2 Hz, 1 H), 6.50 (d, *J* = 8.0 Hz, 1 H), 3.83 (br s, 1 H), 3.29–3.27 (m, 1 H), 2.91 (t, *J* = 10.4 Hz, 1 H), 2.79 (dd, *J* = 15.6, 4.0 Hz, 1 H), 2.46–2.42 (m, 1 H), 2.09–2.06 (m, 1 H), 1.06 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.3, 129.5, 126.6, 121.1, 116.9, 113.8, 48.8, 35.4, 27.2, 19.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{14}N$: 148.1121; found: 148.1121.

(*R*)-3-Ethyl-1,2,3,4-tetrahydroquinoline (2b)[15]

Yellow oil; yield: 30 mg (74%); 55% ee; R_f = 0.67 (PE/EtOAc, 5:1); $[\alpha]_D^{20}$ –50 (*c* 0.1, CH_2Cl_2). GC (Beta-DEX 225, chromatographic column T = 80 °C, t = 100 min, heating rate 4 °C/min, T = 120 °C, t = 50 min]: t_R = 136.68 (major), 138.16 min (minor).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.97 (t, *J* = 7.2 Hz, 2 H), 6.61 (t, *J* = 7.2 Hz, 1 H), 6.49 (d, *J* = 7.6 Hz, 1 H), 3.84 (br s, 1 H), 3.35–3.32 (m, 1 H), 2.92 (t, *J* = 10.4 Hz, 1 H), 2.83 (dd, *J* = 16.0, 4.8 Hz, 1 H), 2.47–2.41 (m, 1 H), 1.86–1.81 (m, 1 H), 1.43–1.36 (m, 2 H), 1.00 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.6, 129.6, 126.7, 121.2, 117.0, 113.9, 47.1, 34.1, 33.5, 26.6, 11.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{16}N$: 162.1283; found: 162.1278.

(*R*)-3-Propyl-1,2,3,4-tetrahydroquinoline (2c)[15]

Yellow oil; yield: 36.3 mg (83%); 52% ee; R_f = 0.67 (PE/EtOAc, 5:1); $[\alpha]_D^{20}$ –42 (*c* 0.1, CH_2Cl_2). HPLC [Daicel Chiralpak OJ-H, λ = 210 nm, eluent: *i*-PrOH/hexane (10:90), flow rate: 0.5 mL/min]: t_R = 22.04 (minor), 24.51 min (major).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.97 (t, *J* = 7.6 Hz, 2 H), 6.61 (t, *J* = 7.2 Hz, 1 H), 6.48 (d, *J* = 8.0 Hz, 1 H), 3.82 (br s, 1 H), 3.32 (dd, *J* = 10.8, 1.6 Hz, 1 H), 2.92 (t, *J* = 10.4 Hz, 1 H), 2.81 (d, *J* =14.8 Hz, 1 H), 2.47–2.41 (m, 1 H), 1.94 (d, *J* = 0.8 Hz, 1 H), 1.47–1.40 (m, 2 H).1.36–1.31 (m, 2 H), 0.95 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.6, 129.5, 126.6, 121.1, 116.9, 113.8, 47.3, 36.0, 33.7, 31.9, 20.0, 14.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{18}N$: 176.1439; found: 176.1432.

(*R*)-3-Butyl-1,2,3,4-tetrahydroquinoline (2d)[15]

Yellow oil; yield: 35.4 mg; (75%); 51% ee; R_f = 0.67 (PE/EtOAc, 5:1); $[\alpha]_D^{20}$ –42 (*c* 0.1, CH_2Cl_2). HPLC [Daicel Chiralpak OJ-H, λ = 210 nm, eluent: *i*-PrOH/hexane (10:90), flow rate: 0.5 mL/min]: t_R = 22.04 (minor), 24.55 min (major).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.98 (t, *J* = 8.0 Hz, 2 H), 6.62 (td, *J* =7.2, 1.2 Hz, 1 H), 6.49 (d, *J* = 8.0 Hz, 1 H), 3.84 (br s, 1 H), 3.34–3.30 (m, 1 H), 2.92 (t, *J* = 10.2 Hz, 1 H), 2.85–2.80 (m, 1 H), 2.45 (dd, *J* = 16, 10.0 Hz, 1 H), 1.94–1.89 (m, 1 H), 1.41–1.33 (m, 6 H), 0.94 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.5, 129.5, 126.6, 121.1, 116.8, 113.8, 47.3, 33.7, 33.4, 32.1, 29.1, 22.8, 14.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{20}N$: 190.1596; found: 190.1591.

(*S*)-3-Cyclohexyl-1,2,3,4-tetrahydroquinoline (2e)

White solid; yield: 35.1 mg (65%); 60% ee; mp 81–82 °C; R_f = 0.67 (PE/EtOAc, 5:1); $[\alpha]_D^{20}$ –54 (*c* 0.1, CH_2Cl_2). HPLC [Daicel Chiralpak OJ-H, λ = 210 nm, eluent: *i*-PrOH/hexane (10:90), flow rate: 0.5 mL/min]: t_R = 25.45 (minor), 29.18 min (major).

IR (KBr, film): 3469.75, 3408.03, 2920.07, 2852.56, 1506.32, 1373.24, 1269.09 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.96 (t, *J* = 6.8 Hz, 2 H), 6.60 (t, *J* = 7.2 Hz, 1 H), 6.48 (d, *J* = 8.0 Hz, 1 H), 3.83 (br s, 1 H), 3.37–3.35 (m, 1 H), 2.97 (t, *J* = 10.4 Hz, 1 H), 2.80 (dd, *J* = 16.0, 4.0 Hz, 1 H), 2.55 (dd, *J* = 15.6, 10.8 Hz, 1 H), 1.86–1.66 (m, 6 H), 1.30–1.16 (m, 4 H), 1.10–1.01 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.7, 129.6, 126.6, 121.5, 116.9, 113.7, 45.2, 40.3, 37.8, 31.1, 30.4, 30.2, 26.6, 26.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{22}N$: 216.1747; found: 216.1747.

(*S*)-3-Benzyl-1,2,3,4-tetrahydroquinoline (2f)[16]

Yellow solid; yield: 45 mg (81%); 41% ee; mp 70–73 °C; R_f = 0.5 (PE/EtOAc, 5:1); $[\alpha]_D^{20}$ –42 (*c* 0.1, CH_2Cl_2). HPLC [Daicel Chiralpak OJ-H, λ = 220 nm, eluent: *i*-PrOH/hexane (10:90), flow rate: 0.5 mL/min]: t_R = 48.25 (minor), 57.30 min (major).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (t, *J* = 7.2 Hz, 2 H), 7.24–7.20 (m, 3 H), 6.97 (t, *J* = 7.6 Hz, 1 H), 6.93 (d, *J* = 7.6 Hz, 1 H), 6.61 (t, *J* = 7.2 Hz, 1 H), 6.48 (d, *J* = 8.0 Hz, 1 H), 3.81 (br s, 1 H), 3.30–3.27 (m, 1 H), 3.01–2.96 (m, 1 H), 2.80 (dd, *J* = 16.0, 4.8 Hz, 1 H), 2.67 (dd, *J* = 7.2, 2.8 Hz, 2 H), 2.56–2.50 (m, 1 H), 2.31–2.22 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.3, 140.1, 129.6, 129.0, 128.3, 126.7, 126.0, 120.4, 116.9, 113.8, 46.5, 39.8, 34.0, 33.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{18}N$: 224.1434; found: 224.1434.

(*S*)-3-Phenyl-1,2,3,4-tetrahydroquinoline (2g)[11b]

White solid; yield: 37.6 mg (72%); 53% ee; mp 55–61 °C; R_f = 0.50 (PE/EtOAc, 5:1); $[\alpha]_D^{20}$ –24 (*c* 0.1, CH_2Cl_2). HPLC [Daicel Chiralpak OD-H, λ = 220 nm, eluent: *i*-PrOH/hexane (10:90), flow rate: 0.6 mL/min]: t_R = 19.68 (minor), 23.89 min (major).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (t, *J* = 7.2 Hz, 2 H), 7.25–7.23 (d, *J* = 8.0 Hz, 3 H), 7.01 (t, *J* = 7.2 Hz, 2 H), 6.64 (t, *J* = 7.2 Hz, 1 H), 6.54 (d, *J* = 8.0 Hz, 1 H), 4.01 (br s, 1 H), 3.47–3.43 (m, 1 H), 3.33 (t, *J* = 10.4 Hz, 1 H), 3.18–3.10 (m, 1 H), 3.05–2.97 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.0, 143.8, 129.5, 128.6, 127.2, 126.9, 126.6, 121.3, 117.1, 114.0, 48.3, 38.7, 34.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{16}N$: 210.1277; found: 210.1273.

(*S*)-3-(*m*-Tolyl)-1,2,3,4-tetrahydroquinoline (2h)

White solid; yield: 47 mg (84%); 47% ee; mp 43–44 °C; R_f = 0.75 (PE/EtOAc, 5:1); $[\alpha]_D^{20}$ –20 (*c* 0.1, CH_2Cl_2). HPLC [Daicel Chiralpak OD-H, λ = 220 nm, eluent: *i*-PrOH/hexane (10:90), flow rate: 0.6 mL/min]: t_R = 20.86 (minor), 24.26 min (major).

IR (KBr, film): 3465.89, 3400.32, 1631.69, 1504.39, 1377.10 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (t, *J* = 8.4 Hz, 1 H), 7.06 (t, *J* = 8.0 Hz, 3 H), 7.01 (d, *J* = 7.2 Hz, 2 H), 6.64 (t, *J* = 7.2 Hz, 1 H), 6.54 (d, *J* = 8.0 Hz, 1 H), 4.01 (br s, 1 H), 3.44 (dd, *J* = 10.8, 1.2 Hz, 1 H), 3.32 (t, *J* = 10.4 Hz, 1 H), 3.14–2.92 (m, 3 H), 2.36 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.0, 143.8, 138.1, 129.5, 128.5, 128.0, 127.4, 126.9, 124.1, 121.4, 117.0, 114.0, 48.3, 38.6, 34.7, 21.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{18}N$: 224.1439; found: 224.1437.

(*S*)-3-(*p*-Tolyl)-1,2,3,4-tetrahydroquinoline (2i)

White solid; yield: 48.3 mg (87%); 49% ee; mp 75–78 °C; R_f = 0.50 (PE/EtOAc, 5:1); $[\alpha]_D^{20}$ –18 (*c* 0.1, CH_2Cl_2). HPLC [Daicel Chiralpak OD-H, λ = 220 nm, eluent: *i*-PrOH/hexane (10:90), flow rate: 0.6 mL/min]: t_R = 14.70 (minor), 18.42 min (major).

IR (KBr, film): 3512.18, 3388.74, 1647.12, 1506.32, 1365.52 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.18–7.14 (m, 4 H), 7.03 (t, *J* = 7.2 Hz, 2 H), 6.66 (t, *J* = 7.2 Hz, 1 H), 6.56 (d, *J* = 8.0 Hz, 1 H), 4.03 (br s, 1 H), 3.46–3.43 (m, 1 H), 3.33 (t, *J* = 10.4 Hz, 1 H), 3.17–3.09 (m, 1 H), 3.06–2.94 (m, 2 H), 2.36 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.0, 140.8, 136.1, 129.5, 129.2, 127.0, 126.7, 121.3, 117.0, 114.0, 48.4, 38.2, 34.6, 21.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{18}N$: 224.1434; found: 224.1433.

(*S*)-3-(3-Methoxyphenyl)-1,2,3,4-tetrahydroquinoline (2j)[11b]

White solid; yield: 35.9 mg (60%); 39% ee; mp 57–59 °C; R_f = 0.50 (PE/EtOAc, 5:1); $[\alpha]_D^{20}$ –12 (*c* 0.1, CH_2Cl_2). HPLC [Daicel Chiralpak OD-H, λ = 220 nm, eluent: *i*-PrOH/hexane (10:90), flow rate: 0.6 mL/min]: t_R = 27.80 (minor), 36.00 min (major).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.22 (m, 1 H), 6.99 (t, *J* = 7.2 Hz, 2 H), 6.82 (d, *J* = 7.6 Hz, 1 H), 6.78–6.77 (m, 2 H), 6.62 (t, *J* = 7.2 Hz, 1 H), 6.52 (d, *J* = 8.4 Hz, 1 H), 4.00 (br s, 1 H), 3.78 (s, 3 H), 3.45–3.42 (m, 1 H), 3.31 (t, *J* = 10.4 Hz, 1 H), 3.14–2.92 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.8, 145.5, 144.0, 129.5, 129.4, 126.9, 121.2, 119.6, 117.1, 114.0, 113.3, 111.5, 55.1, 48.2, 38.7, 34.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{18}NO$: 240.1383; found: 240.1372.

(*S*)-3-(4-Methoxyphenyl)-1,2,3,4-tetrahydroquinoline (2k)

White solid; yield: 52 mg (87%); 53% ee; mp 77–79 °C; R_f = 0.50 (PE/EtOAc, 5:1); $[\alpha]_D^{20}$ –50 (*c* 0.1, CH_2Cl_2). HPLC [Daicel Chiralpak OD-H, λ = 220 nm, eluent: *i*-PrOH/hexane (10:90), flow rate: 0.6 mL/min]: t_R = 21.12 (minor), 26.11 min (major).

IR (KBr, film): 3487.11, 3408.03, 2964.43, 2862.20, 1612.40, 1257.52, 1103.22 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.17 (d, *J* = 8.4 Hz, 2 H), 7.02 (t, *J* = 7.2 Hz, 2 H), 6.89 (d, *J* = 8.4 Hz, 2 H), 6.65 (t, *J* = 7.6 Hz, 1 H), 6.55 (d, *J* = 8.0 Hz, 1 H), 4.03 (br s, 1 H), 3.81 (s, 3 H), 3.45–3.42 (m, 1 H), 3.30 (t, *J* = 10.8 Hz, 1 H), 3.15–3.03 (m, 1 H), 2.99–2.92 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.3, 144.0, 135.9, 129.5, 128.1, 126.9, 121.4, 117.1, 114.0, 55.3, 48.6, 37.8, 34.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{18}NO$: 240.1383; found: 240.1385.

(*S*)-3-(3,5-Dimethylphenyl)-1,2,3,4-tetrahydroquinoline (2l)[11b]

White solid; yield: 42.8 mg (72%); 53% ee; mp 72–74 °C; R_f = 0.67 (PE/EtOAc, 5:1); $[\alpha]_D^{20}$ –26 (*c* 0.1, CH_2Cl_2). HPLC [Daicel Chiralpak OD-H, λ = 220 nm, eluent: *i*-PrOH/hexane (10:90), flow rate: 0.6 mL/min]: t_R = 11.60 (minor), 12.99 min (major).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.04 (t, *J* = 7.6 Hz, 2 H), 6.93 (s, 1 H), 6.89 (s, 2 H), 6.67 (t, *J* = 7.2 Hz, 1 H), 6.57 (d, *J* = 7.6 Hz, 1 H), 4.04 (br s, 1 H), 3.45 (d, *J* = 10.4 Hz, 1 H), 3.34 (t, *J* = 10.4 Hz, 1 H), 3.13–2.94 (m, 3 H), 2.35 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.0, 143.8, 138.0, 129.5, 128.3, 126.9, 125.0, 121.4, 116.9, 113.9, 48.4, 38.6, 34.7, 21.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{20}N$: 238.1590; found: 238.1589.

(*R*)-3-(Naphthalen-2-yl)-1,2,3,4-tetrahydroquinoline (2m)[11b]

White solid; yield: 41.5 mg (64%); 51% ee; mp 130–133 °C; R_f = 0.50 (PE/EtOAc, 5:1); $[\alpha]_D^{20}$ –12 (*c* 0.1, CH_2Cl_2). HPLC [Daicel Chiralpak OD-H, λ = 220 nm, eluent: *i*-PrOH/hexane (10:90), flow rate: 0.6 mL/min]: t_R = 25.65 (minor), 31.01 min (major).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.85–7.81 (m, 3 H), 7.69 (s, 1 H), 7.50–7.44 (m, 2 H), 7.41 (d, *J* = 8.4 Hz, 1 H), 7.05 (t, *J* = 6.4 Hz, 2 H), 6.68 (t, *J* = 7.6 Hz, 1 H), 6.59 (d, *J* = 8.4 Hz, 1 H), 4.08 (br s, 1 H), 3.55 (dd, *J* = 10.8, 1.2 Hz, 1 H), 3.45 (t, *J* = 10.4 Hz, 1 H), 3.36–3.29 (m, 1 H), 3.19–3.04 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.0, 141.2, 133.5, 132.4, 129.5, 128.2, 127.6, 127.5, 127.0, 126.0, 125.9, 125.5, 125.3, 121.3, 117.1, 114.0, 48.3, 38.7, 34.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{18}N$: 260.1434; found: 260.1432.

(*S*)-3-(2-Fluorophenyl)-1,2,3,4-tetrahydroquinoline (2n)[11b]

White solid; yield: 32.4 mg (57%); 16% ee; mp 70–72 °C; R_f = 0.50 (PE/EtOAc, 5:1); $[\alpha]_D^{20}$ –8 (*c* 0.1, CH_2Cl_2). HPLC [Daicel Chiralpak OD-H, λ = 220 nm, eluent: *i*-PrOH/hexane (10:90), flow rate: 0.6 mL/min]: t_R = 18.84 (minor), 24.90 min (major).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.19 (m, 2 H), 7.14–7.01 (m, 4 H), 6.67 (t, *J* = 7.6 Hz, 1 H), 6.56 (d, *J* = 8.4 Hz, 1 H), 4.01 (br s, 1 H), 3.57–3.47 (m, 2 H), 3.38 (t, *J* = 10.4 Hz, 1 H), 3.09–2.97 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.0, 159.5, 144.0, 130.5 (d, $J_{C\text{-}F}$ = 14.3 Hz), 129.5, 127.5 (d, $J_{C\text{-}F}$ = 7.7 Hz), 127.0, 124.3 (d, $J_{C\text{-}F}$ = 3.4 Hz), 120.9, 117.2, 115.4 (d, $J_{C\text{-}F}$ = 22.5 Hz), 114.1, 46.9, 33.1, 31.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{15}FN$: 228.1183; found: 228.1184.

(*S*)-3-(3-Fluorophenyl)-1,2,3,4-tetrahydroquinoline (2o)

Colorless oil; yield: 39.7 mg (70%); 60% ee; R_f = 0.50 (PE/EtOAc, 5:1); $[\alpha]_D^{20}$ –20 (*c* 0.1, CH_2Cl_2). HPLC [Daicel Chiralpak OD-H, λ = 220 nm, eluent: *i*-PrOH/hexane (10:90), flow rate: 0.6 mL/min]: t_R = 28.47 (minor), 36.63 min (major).

IR (KBr, film): 3487.11, 3419.60, 1612.40, 1504.39, 1367.45 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.28 (m, 1 H), 7.04 (t, *J* = 8.0 Hz, 3 H), 6.98–6.94 (m, 2 H), 6.68 (t, *J* = 7.2 Hz, 1 H), 6.57 (d, *J* = 7.6 Hz, 1 H), 4.03 (br s, 1 H), 3.48 (dd, *J* = 11.2, 3.2 Hz, 1 H), 3.33 (t, *J* = 10.8 Hz, 1 H), 3.21–3.13 (m, 1 H), 3.00 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.2, 161.8, 146.4 (d, $J_{C\text{-}F}$ = 7.0 Hz), 143.9, 130.0 (d, $J_{C\text{-}F}$ = 8.3 Hz), 129.5, 127.1, 122.9 (d, $J_{C\text{-}F}$ = 2.8 Hz), 120.8, 117.2, 114.1 (t, $J_{C\text{-}F}$ = 9.7 Hz), 113.4 (d, $J_{C\text{-}F}$ = 20.9 Hz), 48.0, 38.4, 34.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{15}FN$: 228.1183; found: 228.1186.

(*S*)-3-(4-Fluorophenyl)-1,2,3,4-tetrahydroquinoline (2p)[17]

White crystal; 50 mg (88%); 75% ee; mp 82–84 °C; R_f = 0.67 (PE/EtOAc, 5:1); $[\alpha]_D^{20}$ –24 (*c* 0.1, CH_2Cl_2). HPLC [Daicel Chiralpak OD-H, λ = 220 nm, eluent: *i*-PrOH/hexane (10:90), flow rate: 0.6 mL/min]: t_R = 20.13 (minor), 27.95 min (major).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23–7.20 (m, 2 H), 7.04 (t, *J* = 8.8 Hz, 4 H), 6.67 (t, *J* = 7.2 Hz, 1 H), 6.56 (d, *J* = 7.6 Hz, 1 H), 4.03 (br s, 1 H), 3.45 (dd, *J* = 11.2, 3.6 Hz, 1 H), 3.31 (t, *J* = 10.4 Hz, 1 H), 3.19–3.12 (m, 1 H), 2.99 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.6 (d, J_{C-F} = 243 Hz), 143.9, 139.5 (d, J_{C-F} = 3.1 Hz), 129.5, 128.5 (d, J_{C-F} = 7.8 Hz), 127.0, 121.0, 117.2, 115.3 (d, J_{C-F} = 21 Hz), 114.0, 48.4, 37.9, 34.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{15}FN$: 228.1183; found: 228.1182.

(*S*)-3-(4-Chlorophenyl)-1,2,3,4-tetrahydroquinoline (2q)

White solid; yield: 52.8 mg (87%); 70% ee; mp 99–103 °C; R_f = 0.50 (PE/EtOAc, 5:1); $[\alpha]_D^{20}$ –16 (*c* 0.1, CH_2Cl_2). HPLC [Daicel Chiralpak OD-H, λ = 220 nm, eluent: *i*-PrOH/hexane (10:90), flow rate: 0.6 mL/min]: t_R = 23.11 (minor), 32.81 min (major).

IR (KBr, film): 3504.47, 3438.89, 3388.74, 1606.61, 1496.68, 1363.59, 750.26 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (d, *J* = 8.4 Hz, 2 H), 7.18 (d, *J* = 8.4 Hz, 2 H), 7.06–7.01 (m, 2 H), 6.67 (t, *J* = 7.2 Hz, 1 H), 6.56 (d, *J* = 8.0 Hz, 1 H), 4.03 (br s, 1 H), 3.45 (dd, *J* = 10.8, 3.2 Hz, 1 H), 3.31 (t, *J* = 10.4 Hz, 1 H), 3.18–3.11 (m, 1 H), 2.98 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.9, 142.3, 132.3, 129.5, 128.7, 128.5, 127.0, 120.9, 117.2, 114.1, 48.1, 38.1, 34.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{15}ClN$: 244.0888; found: 244.0886.

(*S*)-3-(4-Bromophenyl)-1,2,3,4-tetrahydroquinoline (2r)

White solid; yield: 51.3 mg (71%); 66% ee; mp 107–109 °C; R_f = 0.50 (PE/EtOAc, 5:1); $[\alpha]_D^{20}$ = +6 (*c* 0.1, CH_2Cl_2). HPLC [Daicel Chiralpak OD-H, λ = 220 nm, eluent: *i*-PrOH/hexane (10:90), flow rate: 0.6 mL/min]: t_R = 25.51 (minor), 36.48 min (major).

IR (KBr, film): 3487.11, 3417.67, 1620.11, 1485.10, 1257.52 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, *J* = 8.0 Hz, 2 H), 7.13 (d, *J* = 8.0 Hz, 2 H), 7.06–7.02 (m, 2 H), 6.68 (t, *J* = 7.6 Hz, 1 H), 6.57 (d, *J* = 8.0 Hz, 1 H), 4.02 (br s, 1 H), 3.45 (dd, *J* = 10.8, 3.2 Hz, 1 H), 3.31 (t, *J* = 10.4 Hz, 1 H), 3.17–3.10 (m, 1 H), 2.98 (d, *J* = 7.6 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.9, 142.8, 131.6, 129.5, 128.9, 127.0, 120.8, 120.4, 117.2, 114.1, 48.1, 38.1, 34.4.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{15}BrN$: 288.0382; found: 288.0383.

(*S*)-3-[4-(Trifluoromethyl)phenyl]-1,2,3,4-tetrahydroquinoline (2s)[18]

White solid; yield: 56.5 mg (82%); 60% ee; mp 93–95 °C; R_f = 0.50 (PE/EtOAc, 5:1); $[\alpha]_D^{20}$ –12 (*c* 0.1, CH_2Cl_2). HPLC [Daicel Chiralpak OD-H, λ = 220 nm, eluent: *i*-PrOH/hexane (10:90), flow rate: 0.6 mL/min]: t_R = 25.12 (minor), 39.53 min (major).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 8.0 Hz, 2 H), 7.36 (d, *J* = 8.0 Hz, 2 H), 7.04 (t, *J* = 8.8 Hz, 2 H), 6.67 (t, *J* = 7.2 Hz, 1 H), 6.57 (d, *J* = 8.0 Hz, 1 H), 4.04 (br s, 1 H), 3.48 (dd, *J* = 11.2, 3.6 Hz, 1 H), 3.36 (t, *J* = 11.2 Hz, 1 H), 3.27–3.20 (m, 1 H), 3.02 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.9, 143.8, 129.5, 128.9 (d, J_{C-F} = 32 Hz), 127.6, 127.1, 125.5 (q, J_{C-F} = 3.7 Hz), 122.9, 120.7, 117.3, 114.1, 47.9, 38.6, 34.3.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{15}F_3N$: 278.1151; found: 278.1155.

(*S*)-3-(2,4-Difluorophenyl)-1,2,3,4-tetrahydroquinoline (2t)

White solid; yield: 50.3 mg (82%); 49% ee; mp 89–93 °C; R_f = 0.50 (PE/EtOAc, 5:1); $[\alpha]_D^{20}$ –4 (*c* 0.1, CH_2Cl_2). HPLC [Daicel Chiralpak OD-H, λ = 220 nm, eluent: *i*-PrOH/hexane (10:90), flow rate: 0.6 mL/min]: t_R = 22.12 (minor), 28.32 min (major).

IR (KBr, film): 3487.11, 3406.10, 1610.47, 1498.60, 1265.23 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18–7.12 (m, 1 H), 7.06–7.00 (m, 2 H), 6.86–6.79 (m, 2 H), 6.66 (t, *J* = 7.2 Hz, 1 H), 6.55 (d, *J* = 8.0 Hz, 1 H), 4.00 (br s, 1 H), 3.51–3.45 (m, 2 H), 3.34 (t, *J* = 10.4 Hz, 1 H), 3.00 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.9, 129.5, 128.6 (dd, J_{C-F} = 9.4, 6.3 Hz), 127.1, 126.5, 126.3 (d, J_{C-F} = 3.7 Hz), 120.6, 117.3, 114.2, 111.2 (dd, J_{C-F} = 20.7, 3.7 Hz), 103.9 (t, J_{C-F} =25.7 Hz), 46.8, 33.1, 31.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{14}F_2N$: 246.1089; found: 246.1088.

(*S*)-3-(3,5-Difluorophenyl)-1,2,3,4-tetrahydroquinoline (3u)

White solid; yield: 43.5 mg (71%); 49% ee; mp 61–63 °C; R_f = 0.50 (PE/EtOAc, 5:1); $[\alpha]_D^{20}$ –16 (*c* 0.1, CH_2Cl_2). HPLC [Daicel Chiralpak OD-H, λ = 220 nm, eluent: *i*-PrOH/hexane (10:90), flow rate: 0.6 mL/min]: t_R = 29.51 (minor), 37.83 min (major).

IR (KBr, film): 3525.68, 3386.81, 1600.83, 1504.39, 1361.67 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.06–7.01 (m, 2 H), 6.78 (d, *J* = 6.8 Hz, 2 H), 6.73–6.66 (m, 2 H), 6.57 (d, *J* = 8.0 Hz, 1 H), 4.02 (br s, 1 H), 3.47 (dd, *J* = 11.2, 2.0 Hz, 1 H), 3.31 (t, *J* = 10.4 Hz, 1 H), 3.19–3.12 (m, 1 H), 3.04–2.92 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.1 (dd, J_{C-F} = 246.5, 12.9 Hz), 147.8, 143.7, 129.5, 127.2, 120.4, 117.4, 114.1, 110.0 (dd, J_{C-F} = 18.2, 6.5 Hz), 102.0 (t, J_{C-F} = 25.1 Hz), 47.7, 38.4, 34.2.

HRMS(ESI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{14}F_2N$: 246.1089; found: 246.1091.

(*S*)-3-(Thiophen-3-yl)-1,2,3,4-tetrahydroquinoline (2v)

White solid; yield: 41.1 mg (77%); 48% ee; mp 70–71 °C; R_f = 0.50 (PE/EtOAc, 5:1); $[\alpha]_D^{20}$ –12 (*c* 0.1, CH_2Cl_2). HPLC [Daicel Chiralpak OD-H, λ = 220 nm, eluent: *i*-PrOH/hexane (10:90), flow rate: 0.6 mL/min]: t_R = 23.31 (minor), 29.67 min (major).

IR (KBr, film): 3647.19, 3313.52, 1508.25, 1350.09, 1317.31, 742.55 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (t, *J* = 3.6 Hz, 1 H), 7.06–7.01 (m, 4 H), 6.67 (t, *J* = 7.2 Hz, 1 H), 6.55 (d, *J* = 8.0 Hz, 1 H), 3.99 (br s, 1 H), 3.58–3.51 (m, 1 H), 3.36–3.28 (m, 2 H), 3.10–2.96 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.5, 144.0, 129.5, 127.0, 126.9, 125.5, 120.7, 119.8, 117.2, 114.0, 48.0, 34.4, 34.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{14}NS$: 216.0847; found: 216.0842.

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Supporting Information

Supporting information for this article is available online at https://doi.org /10.1055/s-0036-1589012.

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