Asymmetric Transfer Hydrogenation of 3-(Trifluoromethyl)quinolines

Ran-Ning Guo,[a,b] Zhang-Pei Chen,[b] Xian-Feng Cai,[b] Yong-Gui Zhou*[b]

[a] Department of Chemistry, Dalian University of Technology, Dalian 116012, P. R. of China

[b] State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, P. R. of China
Fax +86(411)84379220; E-mail: ygzhou@dicp.ac.cn

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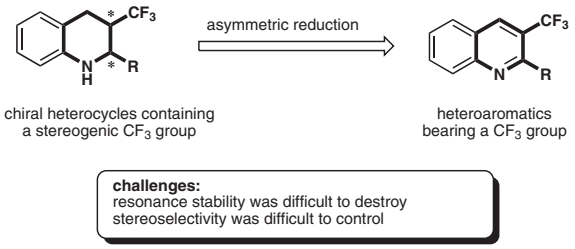
Abstract: A chiral phosphoric acid-catalyzed asymmetric transfer hydrogenation of 3-(trifluoromethyl)quinolines was successfully developed with up to 98% ee. The new method provides a direct and facile access to chiral 2,3-disubstituted 1,2,3,4-tetrahydroquinoline derivatives containing a stereogenic trifluoromethyl group.

Key words: chiral phosphoric acid, transfer hydrogenation, quinolines, trifluoromethyl group

Enantiopure trifluoromethylated (CF_3) molecules have received increasing attention in the field of medicinal, agricultural, and material chemistry,[1] mainly due to the enhanced metabolic stability, lipophilicity, bioavailability, and binding selectivity upon introduction of the CF_3 group into parent molecules.[2] Especially, heterocycles containing a stereogenic CF_3 group represent a major structural class of biologically active compounds.[3] In view of the ready availability and easy preparation of the heteroaromatic compounds bearing a CF_3 group,[4] the asymmetric reduction of such compounds would provide an efficient and straightforward access to the corresponding chiral heterocycles containing a stereogenic CF_3 group. However, because of their resonance stability and the difficulty to control the stereoselectivity, there is little information available in literature on the asymmetric reduction of CF_3-substituted aromatics.

Chiral phosphoric acids (CPAs) and derivatives, originally developed by Akiyama et al.[5] and Terada et al.[6] in 2004, have emerged as an attractive and powerful tool in asymmetric catalysis.[7] The interest towards CPA-catalyzed asymmetric transfer hydrogenation (ATH) was developed in 2005, when Rueping et al.[8] and List et al.[9] independently reported the ATH of ketimines. Over the last few years, much progress has been made in the CPA-catalyzed ATH of C=C, C=N, and C=O double bonds[10] as well as heteroaromatics[11] with Hantzsch esters (HEH)[12] as the hydrogen source. As part of our ongoing research program toward the asymmetric reduction of aromatic compounds,[13] herein, we report the first CPA-catalyzed transfer hydrogenation of heteroaromatics bearing a CF_3 group – 3-(trifluoromethyl)quinolines[14] – with up to 98% ee (Scheme 1).



Scheme 1 Retrosynthetic analysis of the asymmetric reduction of 3-(trifluoromethyl)quinolines

Our studies began by using 2-phenyl-3-(trifluoromethyl)quinoline (**1a**) as a model substrate. First, the reaction was carried out in toluene using CPA (*S*)-**3a** as the catalyst and HEH **2a** as the hydrogen source at 25 °C. The reaction proceeded smoothly to give the desired product **4a** in 94% yield with 25% ee (Table 1, entry 1).

Encouraged by the promising result, the effect of the solvent was tested subsequently (Table 1, entries 2–5). The survey showed that the yield of **4a** was uniformly good in most solvents, whereas the enantioselectivity exhibited a significant dependence upon the solvent identity and the best ee value was obtained when CH_2Cl_2 was employed (35% ee; entry 3). Further investigation on various commercially available CPAs showed that catalyst (*S*)-**3d** was the best choice (entries 6–8), which gave the target product **4a** with the highest enantioselectivity (97% ee; entry 8). It is noteworthy that the steric bulk of the aryl moieties at the 3,3′-positions of CPA displayed a dramatic influence on the stereoselectivities, the sterically demanding catalyst (*S*)-**3b**, (*S*)-**3c**, and (*S*)-**3d** gave the product (2*R*,3*S*)-**4a** (entries 6–8) while the catalyst (*S*)-**3a** with the smaller phenyl group yielded the opposite enantiomer (2*S*,3*R*)-**4a** (entry 3). The reasons for the different stereoselectivities are elusive for the moment. Lastly, several dihydropyridines **2** were evaluated (entries 9–11). The ee value of **4a** was improved to 98% by using **2d** bearing acetyl group at 3,3′-position as the hydrogen source (entry 11). Thus, the optimized reaction conditions are: CPA (*S*)-**3d** (5 mol%), dihydropyridine **2d** (2.4 equiv), CH_2Cl_2.

Having established the optimized reaction conditions, a series of 3-(trifluoromethyl)quinolines were investigated, and the results are summarized in Table 2. For 2-aryl-substituted substrates, the reactions proceeded smoothly to deliver the corresponding products with high to excellent ee values and in high yields (93–98% ee, 89–96% yields;

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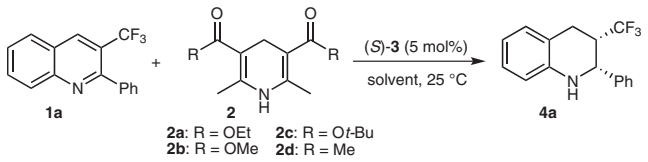
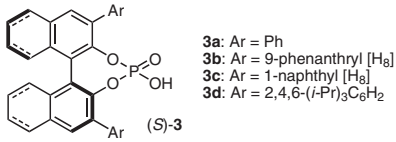
Table 1 Evaluation of Reaction Parameters[a]



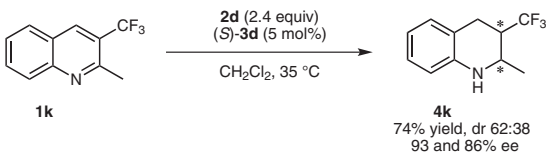


Entry	Solvent	2	(*S*)-3	Yield (%)[b]	ee (%)[c]
1	toluene	**2a**	**3a**	94	25
2	benzene	**2a**	**3a**	94	20
3	CH_2Cl_2	**2a**	**3a**	87	35[d]
4	$CHCl_3$	**2a**	**3a**	97	3[d]
5	$ClCH_2CH_2Cl$	**2a**	**3a**	97	34[d]
6	CH_2Cl_2	**2a**	**3b**	87	50
7	CH_2Cl_2	**2a**	**3c**	94	72
8	CH_2Cl_2	**2a**	**3d**	94	97
9	CH_2Cl_2	**2b**	**3d**	90	97
10	CH_2Cl_2	**2c**	**3d**	<5	–
11	**CH_2Cl_2**	**2d**	**3d**	**94**	**98**

[a] Conditions: 2-Phenyl-3-(trifluoromethyl)quinoline (**1a**; 0.10 mmol), dihydropyridine **2** (2.4 equiv), chiral phosphoric acid (*S*)-**3** (5 mol%), solvent (3 mL), 25 °C, 19 h.
[b] Isolated yield of **4a** based on **1a**.[15]
[c] Determined by HPLC analysis.
[d] The opposite enantiomer was obtained.

Table 2, entries 1–9). Both electron-donating and electron-withdrawing groups were tolerated under the standard reaction conditions. The hydrogenation of 6-methoxy-substituted substrate **1j** gave the product **4j** in 81% yield with good 84% ee (entry 10).

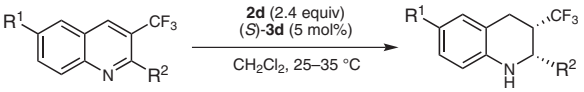
This method was successfully applied to the 2-methyl-substituted substrate **1k**, the desired product **4k** was obtained with low diastereoselectivity (62:38) albeit with high ee values (Scheme 2).



Scheme 2 Asymmetric transfer hydrogenation of 2-methyl-3-(trifluoromethyl)quinoline (**1k**)

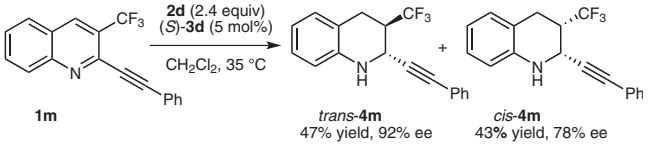
The 2-alkynyl-substituted 2-(phenylethynyl)-3-(trifluoromethyl)quinoline (**1m**) could also be completely transformed while the conjugated C≡C triple bond was preserved. The corresponding products were obtained in high yield, poor diastereoselectivity, and high enantioselectivities (Scheme 3).

Table 2 Asymmetric Transfer Hydrogenation of 3-(Trifluoromethyl)quinolines **1**[a]



Entry	R^1, R^2	Temp (°C)	Yield (%)[b]	ee (%)[c]
1	H, Ph	25	94 (**4a**)	98 (–)
2	H, 3-MeC_6H_4	25	96 (**4b**)	97 (–)
3	H, 4-MeC_6H_4	25	89 (**4c**)	97 (–)
4	H, 4-*t*-BuC_6H_4	35	93 (**4d**)	94 (–)
5	H, 3-$MeOC_6H_4$	35	95 (**4e**)	97 (–)
6	H, 4-$MeOC_6H_4$	35	91 (**4f**)	95 (2*R*,3*S*)
7	H, 4-ClC_6H_4	35	96 (**4g**)	97 (–)
8	H, 4-$CF_3C_6H_4$	35	96 (**4h**)	97 (–)
9	H, 2-naphthyl	35	92 (**4i**)	93 (–)
10	MeO, Ph	35	81 (**4j**)	84 (–)

[a] Conditions: 3-(Trifluoromethyl)quinoline **1** (0.10 mmol), dihydropyridine **2d** (2.4 equiv), chiral phosphoric acid (*S*)-**3d** (5 mol%), CH_2Cl_2 (3 mL), 18–48 h.
[b] Isolated yields based on **1**.[15]
[c] Determined by HPLC analysis.



Scheme 3 Asymmetric transfer hydrogenation of 3-(trifluoromethyl)quinoline **1m**[16]

After recrystallization from CH_2Cl_2–hexane, enantiomerically pure product **4f** (>99% ee) was obtained as colorless crystals. Its absolute configuration was determined to be *cis*-(2*R*,3*S*) based on single crystal X-ray diffraction analysis[17] (Figure 1).

In conclusion, we have developed a chiral phosphoric acid-catalyzed asymmetric transfer hydrogenation of 3-(trifluoromethyl)quinolines, with up to 98% ee. The different diastereoselectivities for the different substrates maybe attributed to the different electronic effect of aryl, alkyl, and alkynyl substituents. This method provides a direct and facile access to optically pure 2,3-disubstituted 1,2,3,4-tetrahydroquinoline derivatives containing a stereogenic CF_3 group. Notably, this is the first report on highly asymmetric reduction of CF_3-substituted aromat-

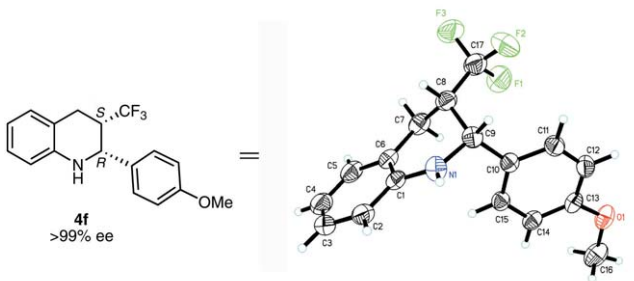


Figure 1 Absolute configuration of the asymmetric transfer hydrogenation product **4f**

ics. Further work will be devoted to the application of the developed strategy.

Commercially available reagents were used without further purification. Solvents were purified prior to use according to the standard methods. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded at r.t. in $CDCl_3$ on a 400 MHz instrument with TMS as internal standard. Enantiomeric excess was determined by HPLC analysis, using chiral columns described below in detail. Optical rotations were measured by polarimeter. Flash column chromatography was performed on silica gel (200–300 mesh).

Asymmetric Transfer Hydrogenation of 3-(Trifluoromethyl)quinolines; General Procedure

A mixture of the appropriate 3-(trifluoromethyl)quinoline **1** (0.10 mmol), dihydropyridine **2d** (46 mg, 0.24 mmol, 2.4 equiv), and chiral phosphoric acid (*S*)-**3d** (3.8 mg, 0.005 mmol, 5 mol%) in CH_2Cl_2 (3 mL) was stirred under N_2 for 18–48 h. After completion of reaction (TLC monitoring, eluent: hexane–EtOAc, 20:1), the solvent was removed under reduced pressure. Purification was performed by silica gel column chromatography eluting with hexane–EtOAc (80:1 to 20:1) to give the desired product (Table 2). The enantiomeric excesses were determined by chiral HPLC.

(–)-2-Phenyl-3-(trifluoromethyl)-1,2,3,4-tetrahydroquinoline (4a)

Yield: 26 mg (94%); 98% ee; colorless oil; R_f = 0.70 (hexane–EtOAc, 20:1); $[\alpha]_D^{20}$ –153.1 (*c* 0.52, CH_2Cl_2).

HPLC: Chiracel OD-H column, 254 nm, 30 °C, *n*-hexane–*i*-PrOH (70:30), flow = 0.7 mL/min, t_R = 11.9 min (major) and 16.0 min.

IR (film): 3060, 2928, 2859, 1613, 1495, 1442, 1388, 1330, 1275, 1134, 1030 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.19 (m, 5 H), 7.11–7.01 (m, 2 H), 6.71 (td, *J* = 7.4, 1.0 Hz, 1 H), 6.55 (d, *J* = 8.0 Hz, 1 H), 4.81 (d, *J* = 3.9 Hz, 1 H), 4.40 (s, 1 H), 3.11–2.97 (m, 1 H), 2.93 (d, *J* = 9.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.1, 141.5, 129.5, 128.3, 127.9, 127.9, 127.5, 126.6 (q, $^1J_{F,C}$ = 277.3 Hz), 117.5, 117.3, 113.7, 53.4 (q, $^3J_{F,C}$ = 2.4 Hz), 42.2 (q, $^2J_{F,C}$ = 26.3 Hz), 22.6 (q, $^3J_{F,C}$ = 2.6 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –67.6.

MS (ESI): *m*/*z* = 278.1 ([M + H]$^+$), 257.9, 238.0, 200.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{14}F_3N$: 278.1151; found: 278.1163.

(–)-2-(*m*-Tolyl)-3-(trifluoromethyl)-1,2,3,4-tetrahydroquinoline (4b)

Yield: 28 mg (96%); 97% ee; colorless oil; R_f = 0.45 (hexane–EtOAc, 20:1); $[\alpha]_D^{20}$ –166.6 (*c* 0.56, CH_2Cl_2).

HPLC: Chiracel OD-H column, 254 nm, 30 °C, *n*-hexane–*i*-PrOH (70:30), flow = 0.7 mL/min, t_R = 9.2 min (major) and 13.3 min.

IR (film): 3022, 2927, 2863, 1603, 1494, 1453, 1386, 1329, 1274, 1165, 1134 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.07 (t, *J* = 7.9 Hz, 1 H), 7.03–6.92 (m, 5 H), 6.66–6.60 (m, 1 H), 6.47 (d, *J* = 8.0 Hz, 1 H), 4.69 (d, *J* = 3.7 Hz, 1 H), 4.29 (s, 1 H), 3.01–2.83 (m, 3 H), 2.21 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.1, 141.5, 137.9, 130.8, 129.5, 128.7, 128.2, 127.9, 126.6 (q, $^1J_{FC}$ = 277.4 Hz), 124.5, 117.4, 117.4, 113.7, 53.5 (q, $^3J_{F,C}$ = 2.2 Hz), 42.2 (q, $^2J_{F,C}$ = 26.3 Hz), 22.7 (q, $^3J_{F,C}$ = 2.5 Hz), 21.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –67.5.

MS (ESI): *m*/*z* = 292.0 ([M + H]$^+$), 272.0, 252.0, 199.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{17}F_3N$: 292.1308; found: 292.1325.

(–)-2-(*p*-Tolyl)-3-(trifluoromethyl)-1,2,3,4-tetrahydroquinoline (4c)

Yield: 26 mg (89%); 98% ee; colorless oil; R_f = 0.45 (hexane–EtOAc, 20:1); $[\alpha]_D^{20}$ –128.1 (*c* 0.54, CH_2Cl_2).

HPLC: Chiracel OD-H column, 254 nm, 30 °C, *n*-hexane–*i*-PrOH (70:30), flow = 0.7 mL/min, t_R = 8.9 min (major) and 13.2 min.

IR (film): 3025, 2926, 2860, 1608, 1497, 1441, 1387, 1328, 1217, 1116, 1027 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14–7.01 (m, 6 H), 6.70 (t, *J* = 7.4 Hz, 1 H), 6.55 (d, *J* = 8.0 Hz, 1 H), 4.79 (d, *J* = 3.8 Hz, 1 H), 4.40 (s, 1 H), 3.10–2.97 (m, 1 H), 2.93 (dd, *J* = 12.8, 5.9 Hz, 2 H), 2.31 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.1, 137.5, 136.6, 128.5, 128.0, 126.8, 126.4, 125.6 (q, $^1J_{F,C}$ = 277.5 Hz), 116.4, 116.3, 112.6, 52.1 (q, $^3J_{F,C}$ = 2.4 Hz), 41.1 (q, $^2J_{F,C}$ = 26.3 Hz), 21.6 (q, $^3J_{F,C}$ = 2.4 Hz), 20.0.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –67.6.

MS (ESI): *m*/*z* = 292.0 ([M + H]$^+$), 272.0, 252.0, 199.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{17}F_3N$: 292.1308; found: 292.1315.

(–)-2-(4-*tert*-Butylphenyl)-3-(trifluoromethyl)-1,2,3,4-tetrahydroquinoline (4d)

Yield: 31 mg (93%); 94% ee; white solid; mp 100–102 °C; R_f = 0.35 (hexane–EtOAc, 20:1); $[\alpha]_D^{20}$ –156.8 (*c* 0.62, CH_2Cl_2).

HPLC: Chiracel OD-H column, 254 nm, 30 °C, *n*-hexane–*i*-PrOH (70:30), flow = 0.7 mL/min, t_R = 7.6 min (major) and 11.3 min.

IR (KBr): 3056, 2959, 2866, 1615, 1494, 1427, 1384, 1327, 1271, 1123, 1064 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.25 (m, 2 H), 7.14 (d, *J* = 8.4 Hz, 2 H), 7.06 (dd, *J* = 13.2, 7.1 Hz, 2 H), 6.70 (td, *J* = 7.4, 1.0 Hz, 1 H), 6.54 (d, *J* = 8.0 Hz, 1 H), 4.78 (d, *J* = 3.7 Hz, 1 H), 4.38 (s, 1 H), 3.11–2.87 (m, 3 H), 1.28 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.9, 143.2, 138.4, 129.5, 127.8, 127.2, 126.6 (q, $^1J_{F,C}$ = 277.3 Hz), 125.2, 117.4, 117.4, 113.7, 53.1 (q, $^3J_{F,C}$ = 2.4 Hz), 42.2 (q, $^2J_{F,C}$ = 26.2 Hz), 34.5, 31.3, 22.7 (q, $^3J_{F,C}$ = 2.5 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –67.6.

MS (ESI): *m*/*z* = 334.0 ([M + H]$^+$), 294.0, 278.0, 199.9.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{20}H_{23}F_3N$: 334.1777; found: 334.1775.

(–)-2-(3-Methoxyphenyl)-3-(trifluoromethyl)-1,2,3,4-tetrahydroquinoline (4e)

Yield: 29 mg (95%); 97% ee; white solid; mp 63–65 °C; R_f = 0.35 (hexane–EtOAc, 20:1); $[\alpha]_D^{20}$ –154.5 (*c* 0.58, CH_2Cl_2).

HPLC: Chiracel OD-H column, 254 nm, 30 °C, *n*-hexane–*i*-PrOH (70:30), flow = 0.7 mL/min, t_R = 10.8 min (major) and 17.5 min.

IR (KBr): 3030, 2930, 2849, 1606, 1494, 1451, 1385, 1327, 1276, 1163, 1130, 1094, 1048 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.18 (t, *J* = 7.9 Hz, 1 H), 7.05 (dd, *J* = 13.7, 7.2 Hz, 2 H), 6.84–6.75 (m, 3 H), 6.70 (td, *J* = 7.4, 1.0 Hz, 1 H), 6.55 (d, *J* = 7.6 Hz, 1 H), 4.77 (d, *J* = 3.7 Hz, 1 H), 3.71 (s, 3 H), 3.09–2.98 (m, 1 H), 2.95 (dd, *J* = 10.1, 4.6 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.5, 143.1, 143.0, 129.5, 129.3, 127.9, 126.6 (q, $^1J_{FC}$ = 277.2 Hz), 119.9, 117.6, 117.3, 113.7, 113.6, 113.0, 55.1, 53.4 (q, $^3J_{F,C}$ = 2.4 Hz), 42.2 (q, $^2J_{F,C}$ = 26.3 Hz), 22.7 (q, $^3J_{F,C}$ = 2.5 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –67.6.

MS (ESI): *m*/*z* = 307.9 ($[M + H]^+$), 288.0, 267.9, 200.1.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{17}F_3NO$: 308.1257; found: 308.1257.

(2*R*,3*S*)-2-(4-Methoxyphenyl)-3-(trifluoromethyl)-1,2,3,4-tetrahydroquinoline (4f)

Yield: 28 mg (91%); 95% ee; white solid; mp 98–100 °C; R_f = 0.30 (hexane–EtOAc, 20:1); $[\alpha]_D^{20}$ –141.4 (*c* 0.42, CH_2Cl_2, for >99% ee).

HPLC: Chiracel OD-H column, 254 nm, 30 °C, *n*-hexane–*i*-PrOH (70:30), flow = 0.7 mL/min, t_R = 11.0 min (major) and 16.7 min.

IR (KBr): 2926, 2850, 1617, 1503, 1386, 1329, 1261, 1166, 1120, 1098, 1026 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.13 (d, *J* = 8.6 Hz, 2 H), 7.06 (dd, *J* = 14.2, 7.3 Hz, 2 H), 6.79 (d, *J* = 8.7 Hz, 2 H), 6.70 (t, *J* = 7.4 Hz, 1 H), 6.55 (d, *J* = 8.0 Hz, 1 H), 4.77 (s, 1 H), 4.3 8 (s, 1 H), 3.77 (s, 3 H), 3.09–2.96 (m, 1 H), 2.92 (d, *J* = 8.3 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3, 143.1, 133.6, 129.5, 128.6, 127.9, 126.6 (q, $^1J_{F,C}$ = 277.2 Hz), 117.4, 117.3, 113.7, 113.6, 55.2, 52.8 (q, $^3J_{F,C}$ = 2.4 Hz), 42.2 (q, $^2J_{F,C}$ = 42.2 Hz), 22.5 (q, $^3J_{F,C}$ = 2.5 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –67.7.

MS (ESI): *m*/*z* = 308.0 ($[M + H]^+$), 288.0, 200.0.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{17}F_3NO$: 308.1257; found: 308.1259.

(–)-2-(4-Chlorophenyl)-3-(trifluoromethyl)-1,2,3,4-tetrahydroquinoline (4g)

Yield: 30 mg (96%); 97% ee; colorless oil; R_f = 0.45 (hexane–EtOAc, 20:1); $[\alpha]_D^{20}$ –152.7 (*c* 0.60, CH_2Cl_2).

HPLC: Chiracel OD-H column, 254 nm, 30 °C, *n*-hexane–*i*-PrOH (70:30), flow = 0.7 mL/min, t_R = 9.4 min (major) and 17.2 min.

IR (film): 3058, 2928, 2861, 1602, 1493, 1399, 1330, 1274, 1100, 1013 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.20 (m, 2 H), 7.14 (d, *J* = 8.5 Hz, 2 H), 7.07 (dd, *J* = 16.3, 7.8 Hz, 2 H), 6.72 (td, *J* = 7.4, 0.9 Hz, 1 H), 6.56 (d, *J* = 8.0 Hz, 1 H), 4.80 (d, *J* = 3.9 Hz, 1 H), 4.39 (s, 1 H), 3.12–2.98 (m, 1 H), 2.98–2.81 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.7, 140.0, 133.8, 129.6, 128.9, 128.5, 128.0, 126.5 (q, $^1J_{F,C}$ = 277.3 Hz), 117.7, 117.0, 113.7, 52.8 (q, $^3J_{F,C}$ = 2.5 Hz), 42.1 (q, $^2J_{F,C}$ = 26.4 Hz), 22.4.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –67.5.

MS (ESI): *m*/*z* = 313.0 ($[M + H]^+$), 293.0, 273.0, 199.9.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{14}ClF_3N$: 312.0761; found: 312.0761.

(–)-3-(Trifluoromethyl)-2-[4-(trifluoromethyl)phenyl]-1,2,3,4-tetrahydroquinoline (4h)

Yield: 33 mg (96%); 97% ee; colorless oil; R_f = 0.70 (hexane–CH_2Cl_2, 2:1); $[\alpha]_D^{20}$ –146.7 (*c* 0.66, CH_2Cl_2).

HPLC: Chiracel OD-H column, 254 nm, 30 °C, *n*-hexane–*i*-PrOH (70:30), flow = 0.7 mL/min, t_R = 8.6 min (major) and 18.7 min.

IR (film): 2925, 2859, 1623, 1498, 1425, 1390, 1329, 1275, 1164, 1121, 1066, 1023 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.52 (d, *J* = 8.2 Hz, 2 H), 7.34 (d, *J* = 8.1 Hz, 2 H), 7.09 (dd, *J* = 16.4, 7.9 Hz, 2 H), 6.74 (t, *J* = 7.4 Hz, 1 H), 6.58 (d, *J* = 8.0 Hz, 1 H), 4.88 (d, *J* = 4.0 Hz, 1 H), 4.01 (s, 1 H), 3.15–3.01 (m, 1 H), 3.00–2.83 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.4, 142.5, 130.2 (q, $^2J_{F,C}$ = 32.4 Hz), 129.6, 128.1, 127.9, 126.4 (q, $^1J_{F,C}$ = 277.2 Hz), 125.3 (q, $^3J_{F,C}$ = 3.7 Hz), 124.0 (q, $^1J_{F,C}$ = 270.4 Hz), 117.9, 117.0, 113.8, 53.1 (q, $^3J_{F,C}$ = 2.3 Hz), 42.1 (q, $^2J_{F,C}$ = 26.7 Hz), 22.4 (q, $^3J_{F,C}$ = 2.5 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –62.6, –67.5.

MS (ESI): *m*/*z* = 346.0 ($[M + H]^+$), 326.0, 306.0, 199.9.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{14}F_6N$: 346.1025; found: 346.1027.

(–)-2-(Naphthalen-2-yl)-3-(trifluoromethyl)-1,2,3,4-tetrahydroquinoline (4i)

Yield: 30 mg (92%); 93% ee; white solid; mp 110–112 °C; R_f = 0.35 (hexane–EtOAc, 20:1); $[\alpha]_D^{20}$ –238.3 (*c* 0.60, CH_2Cl_2).

HPLC: Chiracel OD-H column, 254 nm, 30 °C, *n*-hexane–*i*-PrOH (70:30), flow = 0.7 mL/min, t_R = 15.1 min (major) and 19.3 min.

IR (KBr): 3050, 2924, 2855, 1614, 1494, 1387, 1332, 1270, 1160, 1117 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.81–7.75 (m, 1 H), 7.75–7.69 (m, 2 H), 7.66 (s, 1 H), 7.47–7.40 (m, 2 H), 7.32 (dd, *J* = 8.6, 1.4 Hz, 1 H), 7.09 (dd, *J* = 15.9, 7.7 Hz, 2 H), 6.74 (td, *J* = 7.4, 1.0 Hz, 1 H), 6.61–6.55 (m, 1 H), 4.95 (d, *J* = 3.8 Hz, 1 H), 4.36 (s, 1 H), 3.15–3.04 (m, 1 H), 3.04–2.89 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.1, 139.0, 133.1, 133.0, 129.6, 128.1, 128.0, 128.0, 127.6, 126.6 (q, $^1J_{FC}$ = 277.3 Hz), 126.5, 126.2, 126.1, 125.5, 117.6, 117.4, 113.7, 53.6 (q, $^3J_{F,C}$ = 2.3 Hz), 42.3 (q, $^2J_{F,C}$ = 26.3 Hz), 22.8 (q, $^3J_{F,C}$ = 2.5 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –67.4.

MS (ESI): *m*/*z* = 328.0 ($[M + H]^+$), 308.0, 288.0, 200.0.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{17}F_3N$: 328.1308; found: 328.1310.

(–)-6-Methoxy-2-phenyl-3-(trifluoromethyl)-1,2,3,4-tetrahydroquinoline (4j)

Yield: 25 mg (81%); 85% ee; colorless oil; R_f = 0.15 (hexane–CH_2Cl_2 2:1); $[\alpha]_D^{20}$ –133.4 (*c* 0.50, CH_2Cl_2).

HPLC: Chiracel OD-H column, 254 nm, 30 °C, *n*-hexane–*i*-PrOH (70:30), flow = 0.7 mL/min, t_R = 9.3 min and 18.0 min (major).

IR (film): 2926, 2851, 1616, 1501, 1435, 1386, 1261, 1166, 1119, 1098, 1025 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.26 (m, 3 H), 7.26–7.21 (m, 2 H), 6.73 (dd, *J* = 8.6, 2.8 Hz, 1 H), 6.67 (d, *J* = 2.8 Hz, 1 H), 6.54 (d, *J* = 8.6 Hz, 1 H), 4.79 (d, *J* = 3.9 Hz, 1 H), 4.21 (s, 1 H), 3.78 (s, 3 H), 3.16–3.01 (m, 1 H), 2.99–2.90 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.2, 141.8, 137.4, 128.5, 128.0, 127.6, 126.8 (q, $^1J_{F,C}$ = 277.3 Hz) 118.6, 115.0, 114.8, 114.4, 56.0, 53.8 (q, $^3J_{F,C}$ = 2.3 Hz), 42.4 (q, $^2J_{F,C}$ = 26.1 Hz), 23.2 (q, $^3J_{F,C}$ = 2.7 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –62.7.

MS (ESI): *m*/*z* = 308.0 ($[M + H]^+$), 293.0, 288.0, 230.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{17}F_3NO$: 308.1257; found: 308.1257.

2-Methyl-3-(trifluoromethyl)-1,2,3,4-tetrahydroquinoline (4k)
Yield: 16 mg (74%, inseparable mixture of two diastereoisomers); 62:38 dr; 93% and 86% ee; colorless oil; R_f = 0.55 (hexane–EtOAc, 20:1).

HPLC (for 93% ee): Chiracel OD-H column, 254 nm, 30 °C, *n*-hexane–*i*-PrOH (70:30), flow = 0.7 mL/min, t_R = 6.6 min and 7.8 min (major).

HPLC (for 86% ee): Chiracel OD-H column, 254 nm, 30 °C, *n*-hexane–*i*-PrOH (70:30), flow = 0.7 mL/min, t_R = 6.9 min (major) and 8.9 min.

IR (film): 2963, 2925, 2859, 1628, 1455, 1395, 1262, 1095, 1026 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.93 (t, *J* = 6.9 Hz, 2 H), 6.59 (t, *J* = 7.2 Hz, 1 H), 6.43 (d, *J* = 8.3 Hz, 1 H), 3.76–3.68 (m, 0.38 H), 3.58 (s, 1 H), 3.46–3.36 (m, 1 H), 2.96–2.78 (m, 2 H), 2.76–2.46 (m, 0.38 H), 2.34–2.19 (m, 0.62 H), 1.26 (d, *J* = 6.2 Hz, 1.89 H), 1.13 (d, *J* = 6.5 Hz, 1.14 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.5, 142.3, 129.5, 129.2, 127.5, 127.4, 127.2 (q, $^1J_{F,C}$ = 278.1 Hz), 127.0 (q, $^1J_{F,C}$ = 277.4 Hz), 118.6, 117.9, 117.7, 117.3, 114.8, 114.0, 47.2 (q, $^3J_{F,C}$ = 2.1 Hz), 44.8 (q, $^3J_{F,C}$ = 2.7 Hz), 43.6 (q, $^2J_{F,C}$ = 25.2 Hz), 41.1 (q, $^2J_{F,C}$ = 26.6 Hz), 26.6 (q, $^3J_{F,C}$ = 3.4 Hz), 22.4 (q, $^3J_{F,C}$ = 2.9 Hz), 20.9 (q, $^4J_{F,C}$ = 1.6 Hz), 17.4 (q, $^4J_{F,C}$ = 1.4 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –68.6, –68.7.

MS (ESI): *m*/*z* = 216.0 ([M + H]$^+$), 196.0, 176.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{11}H_{13}F_3N$: 216.0995; found: 216.0998.

***trans*-2-(Phenylethynyl)-3-(trifluoromethyl)-1,2,3,4-tetrahydroquinoline (*trans*-4m)**
Yield: 14 mg (47%); 92% ee; colorless oil; R_f = 0.70 (hexane–EtOAc, 20:1); $[\alpha]_D^{20}$ –128.9 (*c* 0.28, CH_2Cl_2).

HPLC: Chiracel OD-H column, 254 nm, 30 °C, *n*-hexane–*i*-PrOH (70:30), flow = 0.7 mL/min, t_R = 7.1 min (major) and 8.0 min.

IR (film): 3063, 2927, 2858, 2227, 1602, 1490, 1435, 1384, 1300, 1255, 1161, 1121 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.29 (m, 2 H), 7.27–7.19 (m, 3 H), 7.02–6.92 (m, 2 H), 6.67 (t, *J* = 7.1 Hz, 1 H), 6.53 (d, *J* = 7.8 Hz, 1 H), 4.48 (d, *J* = 6.6 Hz, 1 H), 4.00 (s, 1 H), 3.16 (dd, *J* = 16.5, 5.8 Hz, 1 H), 2.95–2.71 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.1, 131.7, 129.1, 128.6, 128.3, 127.4, 126.4 (q, $^1J_{F,C}$ = 278.4 Hz), 122.3, 118.9, 118.4, 114.8, 87.2, 84.3, 43.4 (q, $^3J_{F,C}$ = 3.0 Hz), 42.5 (q, $^2J_{F,C}$ = 25.9 Hz), 25.0 (q, $^3J_{F,C}$ = 2.6 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –69.7.

MS (ESI): *m*/*z* = 302.0 ([M + H]$^+$), 282.0, 262.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{15}F_3N$: 302.1151; found: 302.1148.

***cis*-2-(Phenylethynyl)-3-(trifluoromethyl)-1,2,3,4-tetrahydroquinoline (*cis*-4m)**
Yield: 13 mg (43%); 78% ee; white solid; mp 55–57 °C; R_f = 0.55 (hexane–EtOAc, 20:1); $[\alpha]_D^{20}$ –185.8 (*c* 0.26, CH_2Cl_2).

HPLC: Chiracel OD-H column, 254 nm, 30 °C, *n*-hexane–*i*-PrOH (70:30), flow = 0.7 mL/min, t_R = 8.3 min (major) and 10.8 min.

IR (KBr): 3063, 2925, 2858, 2224, 1602, 1488, 1439, 1388, 1330, 1264, 1162, 1100 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (dd, *J* = 7.5, 1.9 Hz, 2 H), 7.26–7.21 (m, 3 H), 7.05 (dd, *J* = 7.1, 4.3 Hz, 2 H), 6.76 (t, *J* = 7.2 Hz, 1 H), 6.65–6.57 (m, 1 H), 4.69 (s, 1 H), 3.35 (dd, *J* = 16.6, 14.1 Hz, 1 H), 3.01–2.85 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.6, 131.7, 129.5, 128.4, 128.2, 127.4, 126.1 (q, $^1J_{F,C}$ = 277.0 Hz), 122.5, 119.1, 118.6, 115.6, 86.0, 84.9, 42.3 (q, $^3J_{F,C}$ = 3.6 Hz), 41.8 (q, $^2J_{F,C}$ = 27.1 Hz), 23.4 (q, $^3J_{F,C}$ = 2.1 Hz).

^{19}F NMR (376 MHz, $CDCl_3$): δ = –70.0.

MS (ESI): *m*/*z* = 302.0 ([M + H]$^+$), 282.0, 262.0.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{15}F_3N$: 302.1151; found: 302.1151.

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(15) The *cis*-isomers of products are formed in high selectivity and, unless otherwise stated, they are the only visible products.

(16) The relative configuration are proposed by comparison of their coupling constants in ^{1}H NMR spectra and also by analogy with the compound **4f**.

(17) CCDC 998021 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk.

