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Chiral phosphoric acid catalyzed asymmetric transfer hydrogenation of quinolines in a sustainable solvent

Ganesh V. More, Bhalchandra M. Bhanage *

Department of Chemistry, Institute of Chemical Technology, Matunga, Mumbai 400019, India

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ABSTRACT

The use of diethyl carbonate as a sustainable solvent for organocatalytic asymmetric transfer hydrogenations of 2-substituted quinolines using highly efficient chiral phosphoric acid catalysts with Hantzsch esters as a hydrogen source is reported for the first time. The asymmetric transfer hydrogenation reaction in diethyl carbonate provides enantiomerically pure 1,2,3,4-tetrahydroquinolines with high yields and excellent enantioselectivities (up to 99% ee). These results clearly confirm that this green and sustainable solvent is an excellent replacement for organic solvents, which are harmful to the environment, and transition metal based catalysts are not required. The effects of different chiral phosphoric acids, solvents, catalyst loading, temperature effect, and reaction time on the conversion and enantioselectivity of desired product are discussed.

1. Introduction

Enantiomerically pure 1,2,3,4-tetrahydroquinoline derivatives are vital synthetic intermediates and structural moieties in biologically active compounds and alkaloids required for pharmaceutical and agrochemical synthesis.[1,2] Some examples (Fig. 1) of bioactive alkaloids containing enantiomerically pure tetrahydroquinoline motifs include antibacterial drug cholesteryl ester transfer protein,[3a] (*R*)-oxamniquine,[3b,c] torcetrapib,[3d] angustureine,[3e] cuspareine,[3f] and galipinine.[3g]

Therefore the development of greener, efficient, and environmentally benign methodologies is of the great interest for the synthesis of enantiomerically pure saturated cyclic heterocycles in industry as well as academia.

Enantioselective hydrogenation of aromatic and heteroaromatic molecules is one of the most important, efficient, and atom-economic methods for the synthesis of chiral heterocycles and their derivatives, as a conventional direct cyclization approach is difficult to synthesize these enantiopure cyclic compounds.[4–7] Efforts have been made with chiral Rh, Ru, and Ir complexes for the asymmetric hydrogenation of prochiral olefins, ketones, and imines,[8] however most of these chiral metal complexes failed to give outstanding results in the asymmetric hydrogenation of heteroaromatic moieties due to their high aromatic stability and coordinating ability.[9] In 2003, Zhou et al. reported the first asymmetric protocol for the hydrogenation of 2,6-disubstituted quinolines with (*R*)-MeO-BIPHEP as the chiral ligand using iodine as an additive for the synthesis of chiral 1,2,3,4-tetrahydroquinolines (up to 96% ee).[10] Subsequently, a variety of phosphine ligands with iridium metal precursors have been developed for asymmetric hydrogenations of 2-substituted quinolines with iodine as an additive under H_2 pressure.[11] All of these methodologies provide good to excellent enantioselectivities of the desired product, but there is still an opportunity to develop greener and easier protocols by avoiding phosphine based ligands, high pressure autoclave, additives, organic solvent and by improving the enantioselectivity of 1,2,3,4-tetrahydroquinolines.

Over the past decade, chiral phosphoric acid catalysts have become a green alternative to metal catalysts; the use of chiral phosphoric acids as catalysts for asymmetric transfer hydrogenations of C=C, C=N, and C=O double bonds with Hantzsch esters as hydrogen source are well studied.[12] In addition, the chiral phosphoric acid catalyzed asymmetric transfer hydrogenation of 2-substituted quinolines is reported with Hantzsch esters as the hydrogen source.[13] The transition metal catalyzed asymmetric transfer hydrogenation of 2-substituted quinoline using HCOONa as the hydrogen source in water has also been reported.[14] In chiral phosphoric acid catalyzed asymmetric transfer hydrogenation protocols, benzene has been used as a reaction medium, but the use of benzene is not a green protocol, so there is a chance to develop a greener protocol by replacing the reaction medium with a sustainable solvent. On the other hand, the combination of the Au complex

* Corresponding author. Fax: +91 22 3361 1020.
E-mail addresses: bm.bhanage@gmail.com, bm.bhanage@ictmumbai.edu.in (B.M. Bhanage).

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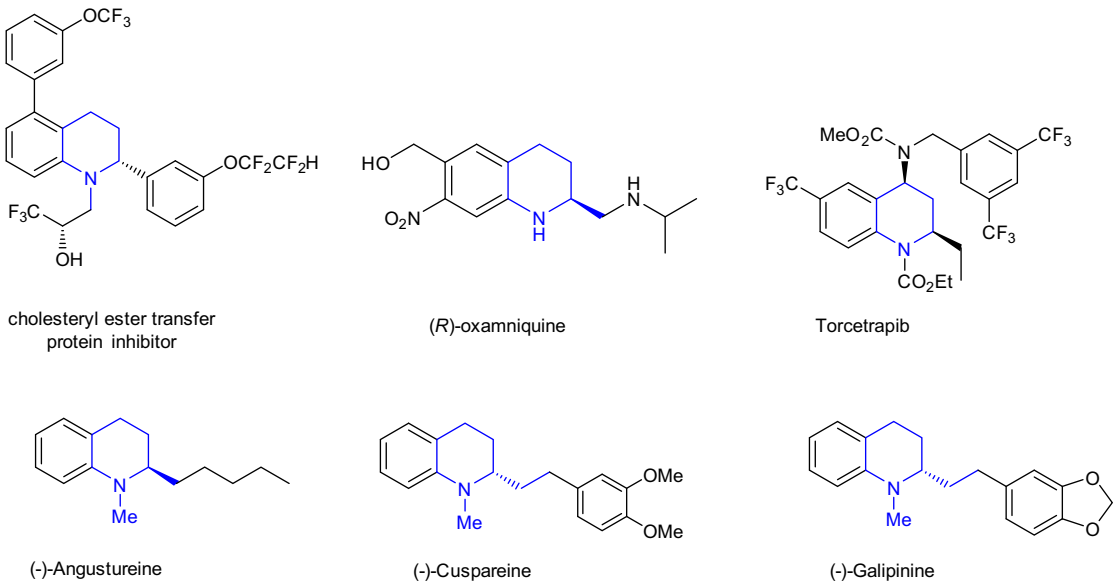


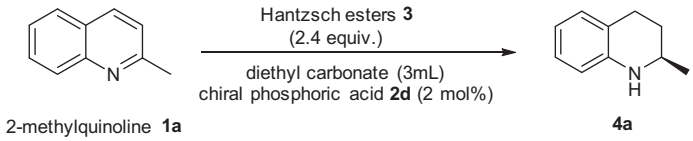
Figure 1. Bioactive alkaloids containing chiral tetrahydroquinoline derivatives.

with a chiral Brønsted acid binary system and asymmetric transfer hydrogenation by chiral gold phosphate catalyzed protocols have also been developed to access enantiopure tetrahydroquinolines.[15]

In general, while the use of carcinogenic organic solvents such as benzene, tetrahydrofuran, toluene, dichloromethane, DMSO or alcohols as reaction media, shows the catalytic benefits these solvents are environmentally harmful and have several disadvantages such as toxicity, low boiling points, and flammability. Therefore, replacing these environmentally hazardous solvents with a sustainable solvent with high catalytic activity is a most interesting and challenging task.[16] In recent years, various methodologies have been investigated, which use sustainable solvent instead of organic solvents for various enantioselective transformations.[17] To the best of our knowledge, there is no example on chiral Brønsted acid catalyzed asymmetric transfer hydrogenations of quinolines in sustainable solvents. In continuation of our ongoing research on the development of green protocols for various reactions,[18] we herein report the chiral Brønsted acid catalyzed asymmetric hydrogenation of 2-substituted quinolines with Hantzsch esters as the hydrogen source in diethyl carbonate as the solvent (Scheme 1).

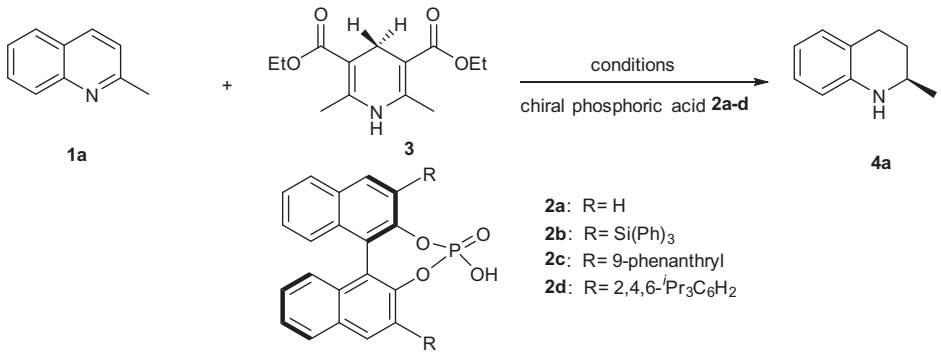
2. Results and discussion

In order to check the efficiency of chiral Brønsted acid catalysts in sustainable solvents, the asymmetric transfer hydrogenation reaction of quinolines was selected as a test reaction. We chose chiral phosphoric acid **2a** as the catalyst, Hantzsch ester **3** as the hydrogen source, and 2-methylquinoline **1a** as the model substrate for the asymmetric transfer hydrogenation reaction. The asymmetric transfer hydrogenation reaction provides full conversion of **4a** with enantioselectivity. The influence of various reaction parameters such as solvent, catalyst, catalyst loading, temperature, and time on the yield and enantioselectivity of desired product was examined. Initially the effect of sustainable solvents on asymmetric transfer hydrogenation reaction was investigated (Table 1, entries 1–3). Various cyclic and non-cyclic organic carbonates such as propylene carbonate, dimethyl carbonate, and diethyl carbonate were screened. The polar solvent propylene carbonate led to high conversion, but gave the desired product in racemic form. To overcome this issue, we used non-polar solvents, such as dimethyl carbonate and diethyl carbonate; the conversion along with the enantioselectivity of the desired product with significantly higher in dimethyl carbonate (Table 1, entry 2), while diethyl carbonate provided the same conversion with higher enantioselectivity (Table 1, entry 3). This indicated that the non-polar solvent diethyl carbonate gave the best results and therefore it was used for further studies. A literature survey also showed that a nonpolar solvent was essential for high enantioselectivity.[13a] BINOL backbone chiral phosphoric acids **2a**–**2e** were screened for the asymmetric transfer hydrogenation of quinoline to improve the enantioselectivity of the desired product. Unsubstituted chiral phosphoric acid **2a** provided >99% conversion but gave poor enantioselectivity 10% ee. From these results, we thought that the bulky substituents at the 3,3′-position of the BINOL backbone might play a key role on enantioselectivity of desired product. We screened various chiral phosphoric acid catalysts with bulky groups (Table 1, entries 4–6). Chiral phosphoric acid **2b** with a bulky substituent {-3,3′-bis (triphenylsilyl)} gave low enantioselectivity (44% ee); when the reaction was carried out with chiral phosphoric acid **2c**, which had more steric hindrance, it provided >99% conversion and 63% ee for the desired product. Again increasing the steric bulk {bis(2,4,6-triisopropylphenyl)} on the BINOL backbone at the same positions exhibited a slightly higher catalytic activity compared to the chiral phosphoric acid **2c**; the enantioselectivity of desired product was increased to 66% ee with full conversion (Table 1, entry 6). This



Scheme 1. Asymmetric transfer hydrogenation of quinolines.

Table 1
Effect of the reaction parameters on the asymmetric transfer hydrogenation of **1a**[a]



Sr. no.	Solvent	(*R*)-**2**	Temp (°C)	Time (h)	Conv.[b] (%)	ee[c] (%)
Effect of solvent						
1	Propylene carbonate	**2a**	rt	24	>99	Racemic
2	Dimethyl carbonate	**2a**	rt	24	>99	9
3	Diethyl carbonate	**2a**	rt	24	>99	10
Effect of catalyst						
4	Diethyl carbonate	**2b**	rt	24	>99	44
5	Diethyl carbonate	**2c**	rt	24	>99	63
6	Diethyl carbonate	**2d**	rt	24	>99	66
Effect of catalyst loading						
7[d]	Diethyl carbonate	**2d**	rt	24	>99	56
8[e]	Diethyl carbonate	**2d**	rt	24	>99	66
9[f]	Diethyl carbonate	**2d**	rt	24	>99	66
Effect of temperature						
10	Diethyl carbonate	**2d**	45	24	>99	56
11	Diethyl carbonate	**2d**	−10	24	>99	87
Effect of time						
12	Diethyl carbonate	**2d**	−10	2	89	87
13	Diethyl carbonate	**2d**	−10	6	>99	87
14	Diethyl carbonate	**2d**	−10	12	>99	87
15	Diethyl carbonate	**2d**	−10	24	>99	87

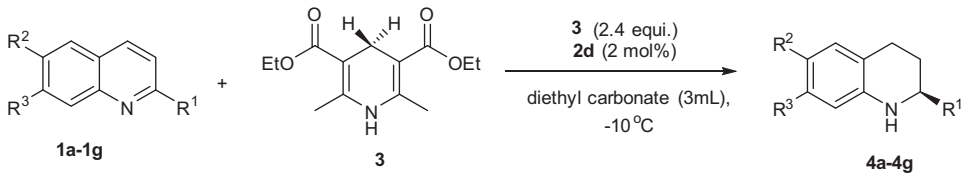
[a] Reaction conditions: **1** (0.2 mmol), chiral phosphoric acid **2** (2 mol %), **3** (2.4 equiv), diethyl carbonate (3 mL), rt, 24 h.
[b,c] Determined by chiral HPLC analysis on a Chiralcel OD-H column.
[d] Chiral phosphoric acid 1 mol %.
[e] Chiral phosphoric acid 3 mol %.
[f] Chiral phosphoric acid 5 mol %.

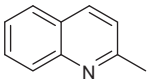
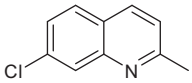
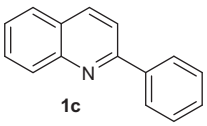
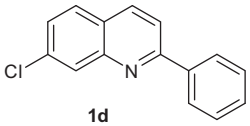
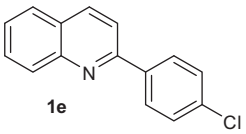
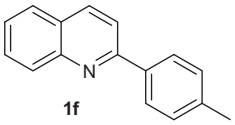
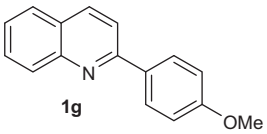
clearly confirms that higher enantioselectivity depends on sterically more demanding 3,3′-substituents in the BINOL backbone of the chiral phosphoric acid catalyst. Considering the higher activity of chiral phosphoric acid **2d**, this catalyst was selected for further optimization studies.

Subsequently, we studied the effect of the catalyst loading on the yield and the enantioselectivity of 1,2,3,4-tetrahydroquinolines. The catalyst loading was screened in range of 1–5 mol % (Table 1, entries 7–9). The best result was obtained when the reaction was carried out by using 2 mol % of the catalyst, which provided >99% conversion and 67% ee (Table 1, entry 6). Increasing the catalyst loading to 5 mol % had no profound effect on the conversion or the enantioselectivity of the desired product. When the catalyst loading was decreased to 1 mol %, the enantioselectivity decreased to 56% ee but the yield remained unaffected (Table 1, entry 7). Therefore, further optimization studies were carried out using 2 mol % of catalyst. At this stage, it seemed that the enantioselectivity of the desired product did not increase when increasing the catalyst loading. The enantioselectivity can be effectively improved by changing the reaction temperature; hence we attempted to increase the enantioselectivity of the desired products by varying the reaction temperature. In this context we performed the reactions at various temperatures ranging from 45 °C to −10 °C (Table 1, entries 10 and 11). It was observed that at room temperature, the enantioselectivity of the desired product was 66% ee with >99% conversion; increasing the temperature to 45 °C decreased the enantioselectivity of product to 56% ee. When we carried out the reaction at −10 °C, the enantioselectivity of the desired product increased to 87% ee. Thus the temperature was fixed at −10 °C. We next examined the effect of reaction time ranging from 2 to 24 h and it was observed that after 6 h, the highest conversion and enantioselectivity of the desired product was observed. Hence, the optimized reaction parameters for the asymmetric transfer hydrogenation reaction were established as **1a** (0.2 mmol), Hantzsch ester (2.4 equiv), **2d** (2 mol %), diethyl carbonate (3 mL) at −10 °C for 5 h.

Previous reports on the hydrogenation of substituted quinolines demonstrated that 2-alkyl-substituted quinoline derivatives give high conversions and good enantioselectivities. A lower enantioselectivity was obtained when the alkyl group was replaced by a phenyl group. Therefore the enantioselective hydrogenation of 2-phenyl-substituted quinolines still remains as a challenging task.[11a,c,d,f,k] Thus with these optimized reaction conditions in hand, we performed the chiral phosphoric acid **2d** catalyzed asymmetric transfer hydrogenation reaction of various substituted quinoline derivatives in sustainable solvents and we observed that the enantioselectivity depended on the substitution pattern at the 2-position of the substrate (Table 2). A slightly decreased

Table 2
Catalytic asymmetric transfer hydrogenation of quinoline derivatives[a]



Sr. no.	Reactant	Product	Yield[b] (%)	ee[c] (%)
1	 1a	**4a**	99	87
2	 1b	**4b**	99	98
3	 1c	**4c**	94	99
4	 1d	**4d**	97	97
5	 1e	**4e**	91	98
6	 1f	**4f**	95	96
7	 1g	**4g**	96	98

[a] Reaction conditions: quinoline **1**, **2d** chiral phosphoric acid (2 mol %), **3** (2.4 equiv), diethyl carbonate (3 mL).
[b] Isolated yield.
[c] Determined by chiral HPLC analysis on a Chiralcel OD-H column.

enantioselectivity of 87% ee was observed in the hydrogenation of 2-alkyl substituted substrate **1a**, while 2,7-disubstituted quinoline **1b** gave full conversion with high enantioselectivity 98% ee (Table 2, entries 1 and 2). Changing the alkyl group to a phenyl ring at the 2-position gave high conversion as well as excellent enantioselectivity. The asymmetric hydrogenation of 2-phenylquinoline **1c** and 2,7-disubstituted quinoline **1d** gave high conversion with 99% ee (Table 2, entries 3 and 4). A *para*-substituent on the phenyl ring also provided high conversion and excellent enantioselectivity as —Cl (98% ee), —Me (96% ee) and —OMe (98% ee). This clearly demonstrates that the developed methodology is widely applicable for 2-substituted alkyl and phenyl group with excellent results.

3. Conclusions

In conclusion, we have developed a chiral Brønsted acid catalyzed protocol that is highly efficient, greener and environmentally benign protocol for asymmetric transfer hydrogenations of 2-alkyl substituted and 2-phenyl substituted quinoline derivatives in diethyl carbonate as a sustainable solvent. The developed protocol provides enantiomerically pure 1,2,3,4 tetrahydroquinoline derivatives with high yield (up to >99%) and excellent enantioselectivity (up to 99% ee). This new asymmetric transfer hydrogenation protocol has competitive advantages such low catalyst loading, is metal and additive free, requires a shorter reaction time and uses a sustainable solvent with high catalytic activity.

4. Experimental

4.1. General

Chiral phosphoric acids and 2-methylquinoline were commercially purchased from Sigma–Aldrich and were used as such. All other chemicals and solvents were purchased from M/S Sigma–Aldrich, S.D. Fine Chemicals, spectrochem, Avra Pvt. Ltd and used without further purification. GC–MS-QP 2010 instrument (Rtx-17, 30 m × 25 mm ID, film thickness (df) = 0.25 μm) (column flow 2 mL min^{-1}, 100–240 °C at 10 °C min^{-1} rise) was used for the mass

analysis of the desired products. Products were purified by column chromatography on silica gel (60–120 mesh). The ^{1}H and ^{13}C NMR spectroscopic data were analyzed with a 400 MHz spectrometer in either $CDCl_3$. The enantiomeric excesses (ee) of the desired products were determined by HPLC analysis with an Agilent 1260 Infinity-HPLC model on Daicel Chiralcel OD-H chiral columns using *i*-propan-2-ol/*n*-hexane as the eluent. The products were confirmed by Chiral HPLC, GC–MS, ^{1}H and ^{13}C NMR spectroscopic analysis.

4.2. General procedure for the asymmetric transfer hydrogenation of 2-substituted quinoline

A dry 10 mL glass stoppered tube was charged with 2-substituted quinoline (1 equiv), chiral phosphoric acid **2d** (2 mol %) and 3 mL of diethyl carbonate. The reaction mass was cooled to −10 °C, and Hantzsch dihydropyridine **3** (2.4 equiv) was added. The resulting mixture was stirred at −10 °C for the appropriate time. The solvent was removed under reduced pressure and purification of the crude product by column chromatography on silica gel (ethyl acetate/hexane) afforded enantiomerically pure 1,2,3,4-tetrahydroquinoline. The enantiomeric excesses (ee) of the product were determined by HPLC analysis with an Agilent-HPLC on Chiralcel OD-H chiral columns using propan-2-ol/*n*-hexane as the eluent. The structure of the product was confirmed by GC–MS, ^{1}H NMR, ^{13}C NMR spectroscopic techniques.

4.2.1. (*S*)-2-Methyl-1,2,3,4-tetrahydroquinoline 4a[13b]; (Table 2, entry 1)

The enantiomeric excess was determined by HPLC using a Daicel Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 98/02, flow rate = 0.5 mL/min, 254 nm; t_1 = 12.4 min (major), t_2 = 14.4 min (minor); 87% ee; $[\alpha]_D^{22}$ = −75.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.95–6.92 (m, 2H), 6.58 (t, *J* = 7.6 Hz, 1H), 6.45 (d, *J* = 8.0 Hz, 1H), 3.40–3.36 (m, 1H), 2.82–2.71 (m, 2H), 1.92–1.89 (m, 1H), 1.59–1.56 (m, 1H), 1.19 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.3, 129.2, 126.6, 121.0, 116.9, 113.9, 47.1,30.0, 26.6, 22.5; GC–MS: (EI, 70 eV): *m*/*z*: 147, 132, 117, 103, 91, 77, 65.

4.2.2. (*S*)-7-Chloro-2-methyl-1,2,3,4-tetrahydroquinoline 4b[11k]; (Table 2, entry 2)

The enantiomeric excess was determined by HPLC using a Daicel Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 98/02, flow rate = 0.5 mL/min, 254 nm; t_1 = 12.5 min (major), t_2 = 13.9 min (minor); 98% ee; $[\alpha]_D^{20}$ = −76.4 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.83 (d, *J* = 8.0 Hz, 1H), 6.53–6.51 (m, 1H), 6,41 (s, 1H), 3.71 (br s, 1H), 3.37–3.35 (m, 1H), 2.74–2.67 (m, 2H), 1.92–1.88 (m, 1H), 1.55–1.52 (m, 1H), 1.18 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.6, 131.8, 130.1, 119.2, 116.5, 113.2, 46.9, 29.7, 26.0, 22.4; GC–MS: (EI, 70 eV): *m*/*z*: 183, 181, 166, 149, 131, 117, 103, 89, 77, 65.

4.2.3. (*S*)-2-Phenyl-1,2,3,4-tetrahydroquinoline 4c[13b]; (Table 2, entry 3)

The enantiomeric excess was determined by HPLC using a Daicel Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 95/05, flow rate = 0.6 mL/min, 254 nm; t_1 = 18.3 min (major), t_2 = 24.5 min (minor); 99% ee; $[\alpha]_D^{25}$ = −39.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.26 (m, 5H), 7.02–6.98 (m, 2H), 6.64 (t, *J* = 7.2 Hz, 1H), 6.54 (d, *J* = 8.4 Hz, 1H), 4.43 (dd, *J* = 9.2, 2.8 Hz, 1H), 4.03 (br s, 1H), 2.99–2.76 (m, 1H), 2.72 (dt. *J* = 16.4, 4.8 Hz, 1H), 2.13–2.10 (m, 1H), 2.09–1.93 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.7, 144.6, 129.2, 128.5, 127.40, 126.8, 126.5, 120.8, 117.1, 113.9, 56.2, 30.9, 26.3; GC–MS: (EI, 70 eV): *m*/*z*: 209, 194, 180, 167, 152, 132, 118, 104, 91, 71, 57.

4.2.4. (*S*)-7-Chloro-2-phenyl-1,2,3,4-tetrahydroquinoline 4d[15a] (Table 2, entry 4)

The enantiomeric excess was determined by HPLC using a Daicel Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 95/05, flow rate = 0.6 mL/min, 254 nm; t_1 = 19.3 min (major), t_2 = 24.8 min (minor); 97% ee; $[\alpha]_D^{20}$ = −54.1 (*c* 0.9, EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36–7.24 (m, 5H), 6.88 (d, *J* = 8.0 Hz, 1H), 6.59 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.50 (d, *J* = 2.0 Hz, 1H), 4.42 (dd, *J* = 9.2, 3.6 Hz, 1H), 4.09 (br s, 1H), 2.87–2.79 (m, 1H), 2.66 (dt, *J* = 16.4, 4.8 Hz, 1H), 2.14–2.07 (m, 1H), 1.99–1.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.6, 144.2, 132.0, 130.1, 128.6, 127.5, 126.4, 119.1, 116.7, 113.2, 55.8, 30.5, 25.6; GC–MS: (EI, 70 eV): *m*/*z*: 243, 228, 214, 206, 193, 168, 166, 152, 131, 117, 103, 91, 77, 63.

4.2.5. (*S*)-2-(4-Chlorophenyl)-1,2,3,4-tetrahydroquinoline 4e[13b] (Table 2, entry 5)

The enantiomeric excess was determined by HPLC using a Daicel Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 90/10, flow rate = 0.6 mL/min, 254 nm; t_1 = 15.8 min (major), t_2 = 30.8 min (minor); 98% ee; $[\alpha]_D^{20}$ = −40.2 (*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.30 (m, 4H), 7.02–6.95 (m, 2H), 6.65 (t, *J* = 7.2 Hz, 1H), 6.53 (d, *J* = 8.0 Hz, 1H), 4.41 (dd, *J* = 9.2, 3.2 Hz, 1H), 4.0 (br s, 1H), 2.92–2.73 (m, 1H), 2.71 (dt, *J* = 16.4, 4.8 Hz, 1H), 2.10–2.07 (m, 1H), 1.98 (m, 1H); GC–MS: (EI, 70 eV): *m*/*z*: 243, 228, 214, 208, 193, 180, 165, 140, 132, 118, 97, 77, 57.

4.2.6. (*S*)-2-(*p*-Tolyl)-1,2,3,4-tetrahydroquinoline 4f[13b]; (Table 2, entry 6)

The enantiomeric excess was determined by HPLC using a Daicel Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 90/10, flow rate = 0.6 mL/min, 254 nm; t_1 = 11.4 min (major), t_2 = 19.5 min (minor); 96% ee; $[\alpha]_D^{20}$ = −23.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 7.6 Hz, 2H), 7.00–6.97 (m, 2H), 6.62 (t, *J* = 7.2 Hz, 1H), 6.51 (d, *J* = 8.0 Hz, 1H), 4.38 (dd, *J* = 9.2, 2.8 Hz, 1H), 3.99 (br s, 1H), 2.93–2.86 (m, 1H), 2.72 (dt, *J* = 16.0, 4.0 Hz, 1H), 2.33 (s, 3H), 2.10–2.07 (m, 1H), 2.06–1.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.7, 141.7, 137.0, 129.2, 129.1, 126.8, 120.8, 117.0, 113.8, 55.9, 30.9, 26.4, 21.0; GC–MS: (EI, 70 eV): *m*/*z*: 223, 208, 193, 180, 165, 152, 132, 118, 105, 91, 77,65.

4.2.7. (*S*)-2-(4-Methoxyphenyl)-1,2,3,4-tetrahydroquinoline 4g[13b] (Table 2, entry 7)

The enantiomeric excess was determined by HPLC using a Daicel Chiralcel OD-H column, *n*-hexane/*i*-PrOH = 90/10, flow rate = 0.6 mL/min, 254 nm; t_1 = 14.9 min (major), t_2 = 24.0 min (minor); 98% ee; $[\alpha]_D^{25}$ = −27.1 (*c* 1.0, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.28 (m, 2H), 7.0–6.97 (m, 2H), 6.88–6.86 (m, 2H), 6.51 (dd, *J* = 7.2, 0.8 Hz, 1H), 6.51, (dd, *J* = 8.0, 1.2 Hz, 1H), 4.36 (dd, *J* = 9.6, 2.8 Hz, 1H), 3.97 (br s, 1H), 3.8 (s, 3H), 2.92–2.87 (m, 1H), 2.74 (dt, *J* = 16.0, 4.0 Hz, 1H), 2.09–2.06 (m, 1H), 2.05–1.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.9, 144.7, 136.8, 129.2, 127.5, 126.8, 120.8, 117.0, 113.9, 113.8, 55.6, 55.2, 31.0, 26.5; GC–MS: (EI, 70 eV): *m*/*z*: 239, 224, 223, 208, 194, 180, 167, 145, 132, 118, 103, 91, 77, 65.

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