Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 6844

www.rsc.org/obc

PAPER

Direct enantioselective access to 4-substituted tetrahydroquinolines by catalytic asymmetric transfer hydrogenation of quinolines†

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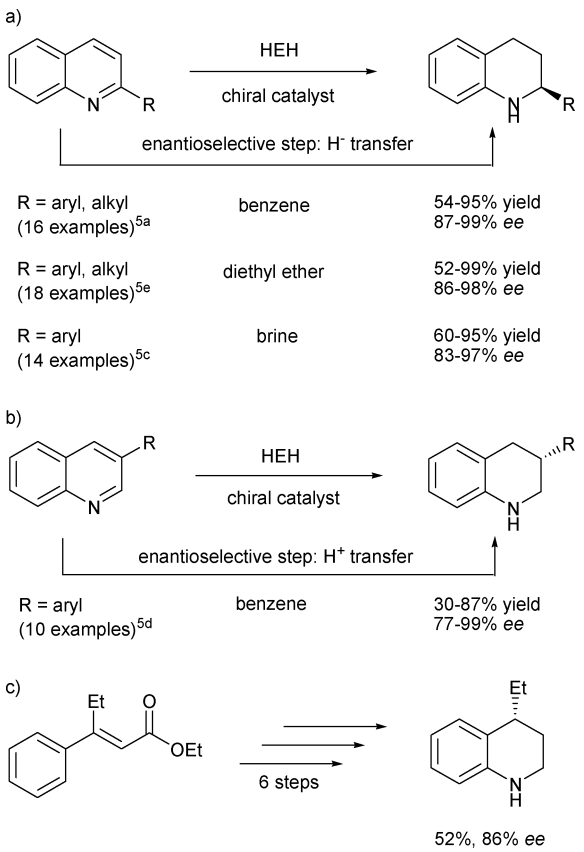
Received 1st June 2011, Accepted 11th July 2011
DOI: 10.1039/c1ob05870c

A convenient protocol for the enantioselective synthesis of 4-substituted tetrahydroquinolines has been developed. Chiral BINOL phosphoric acids promote the reduction of a wide range of 4-substituted quinolines with Hantzsch esters with good to high levels of enantioselectivity.

Introduction

In recent years, chiral Brønsted acid catalyzed transfer hydrogenation emerged as a generally applicable strategy for the enantioselective reduction of various acyclic as well as cyclic systems containing carbon nitrogen double bonds.[1,2] In this context, several successful approaches have been disclosed for the efficient reduction of acyclic imines, leading to chiral amines under mild reaction conditions.[3,4] Furthermore, notable achievements have also been registered in the organocatalyzed reduction of cyclic imines and various nitrogen-containing heteroaromatic systems which offer access to diverse enantioenriched nitrogen heterocycles.[5–9] Among them, quinoline reduction[5,6] constitutes a challenging field since it allows formation of the corresponding tetrahydroquinolines, which are common structural motifs in alkaloids and biologically active compounds. Given the importance of this class of molecules, considerable efforts have been made in order to develop improved methods for their synthesis.

Although several methods have been developed for the asymmetric reduction of 2-substituted quinolines (Scheme 1a), the 3- and 4-substituted analogs have received considerably less attention (Scheme 1b). To date, no direct approach for the generation of optically active 4-substituted tetrahydroquinolines has been described.[10] Typically, synthetic routes consist of several steps as, for instance, shown in the enantioselective synthesis of 4-ethyl substituted tetrahydroquinoline (Scheme 1c).[11] Given the high industrial interest in enantioenriched 4-substituted tetrahydroquinolines we decided to develop a first general catalytic asymmetric route.



Scheme 1 a, b) Asymmetric reduction of 2- and 3-substituted quinolines. c) Asymmetric synthesis of 4-ethyltetrahydroquinoline.

Results and discussion

Our investigation started with the evaluation of various chiral BINOL phosphoric acids[12–14] in the reduction of 4-methylquinoline (lepidine, **1a**) using dihydropyridines as a hydride source. The most successful catalyst previously employed for organocatalytic

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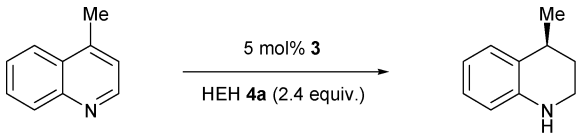
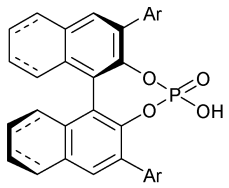
† Electronic supplementary information (ESI) available: ^{1}H- and ^{13}C-NMR spectra and HPLC chromatograms are provided for all synthesized compounds. See DOI: 10.1039/c1ob05870c

Table 1 Evaluation of different Brønsted acids





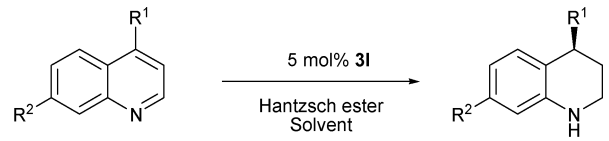
3

3a: Ar = Phenyl
3b: Ar = 3,5-$(CF_3)C_6H_3$
3c: Ar = 3,5-$(t\text{-Bu})_2$PMP
3d: Ar = 4-Biphenyl
3e: Ar = 1-Naphthyl
3f: Ar = 2-Naphthyl
3g: Ar = 9-Phenanthryl
3h: Ar = 1-Pyrene
3i: Ar = 1-Ethynyl-4-methylbenzene
3j: Ar = 9-Ethynylphenanthrene
3k: Ar = Ethynyltriphenylsilane
3l: Ar = $[H]_8Ph_3Si$

Entry[a]	Catalyst	ee[b] (%)
1	**3a**	35
2	**3b**	36
3	**3c**	14
4	**3d**	48
5	**3e**	54
6	**3f**	41
7	**3g**	66
8	**3h**	58
9	**3i**	33
10	**3j**	11
11	**3k**	33
12	**3l**	67

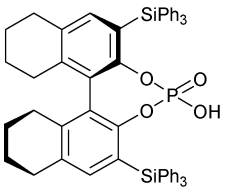
[a] Reactions were performed with lepidine, HEH (Hantzsch 1,4-dihydropyridine) **4a** (2.4 equiv.) and **3** (5 mol%) at 60 °C. [b] Enantiomeric excess was determined by HPLC using a Chiralcel OD-H column.

Table 2 Solvent and Hantzsch ester evaluation

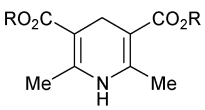


1a: R^1 = Me, R^2 = H
5a: R^1 = Ph, R^2 = Cl

2a
6a



3l



Hantzsch ester

4

4a: R = Et
4b: R = allyl
4c: R = *i*-Pr
4d: R = *t*-Bu
4e: R = Bn

Entry[a]	Substrate	HEH	Solvent	ee[b] (%)
1	**1a**	**4a**	$CHCl_3$	57
2	**1a**	**4a**	Bu_2O	69
3	**1a**	**4a**	$C_6H_5CF_3$	65
4	**1a**	**4a**	$C_6H_5CH_3$	66
5	**1a**	**4a**	C_6H_6	67
6	**1a**	**4b**	C_6H_6	64
7	**1a**	**4c**	C_6H_6	64
8	**1a**	**4d**	C_6H_6	62
9	**1a**	**4e**	C_6H_6	61
10	**5a**	**4a**	C_6H_6	88
11	**5a**	**4b**	C_6H_6	90
12	**5a**	**4c**	C_6H_6	91
13	**5a**	**4d**	C_6H_6	91
14	**5a**	**4e**	C_6H_6	89

[a] Reactions were performed with quinolines **1a**/**5a**, HEH **4a–e** (2.4 equiv.) and **3l** (5 mol%) at 60 °C in 2 mL solvent. [b] Enantiomeric excess was determined by HPLC using a Chiralcel OD-H column.

reductions proved less selective, yielding the desired product **2a** with just 66% ee (Table 1, entry 7). Hence, further work was devoted to the synthesis of BINOL-phosphates bearing bulkier residues in the 3,3′-positions. To follow the known aryl-substitution pattern (phenyl, naphthyl, phenanthryl), we synthesized the pyrenyl derivative, but the result was disappointing (Table 1, entry 8).

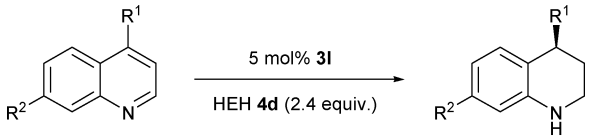
Subsequently, in order to improve the enantioselectivity, chiral phosphates **3i–k** with elongated residues into the space, were synthesized. However, all the acetylene-bridge extended derivatives **3i–k** exhibited only a low level of selectivity (Table 1, entries 9–11). Compared to the phenanthryl derivative which afforded the product with 66% ee, the acetylene elongated one yielded the product with only 11% ee (Table 1, entry 7 *vs.* 10). A slight increase in the selectivity (67% ee) has been observed with the octahydro-BINOL-phosphate bearing triphenylsilyl residues (Table 1, entry 12).

With the best catalyst **3l** in hand, the subsequent investigation concentrated on the influence of the solvent employed (Table 2). Comparable results in terms of selectivity were obtained in both aromatic solvents and dibutyl ether (Table 2, entries 2–5). In addition, the influence of the reducing agent was also examined (Table 2, entries 5–9). Various Hantzsch ester derivatives were evaluated and the best result in the reduction of lepidine was obtained with the ethyl derivative **4a** (Table 2, entry 5). Bulkier ester-derivatives **4b–e** led to a decrease of the ee values (Table 2, entries 6–9). In contrast to the alkyl-substituted quinolines, the corresponding aryl-derivatives prefer sterically more hindered Hantzsch esters **4c–d** as the hydrogen source (Table 2, entries 12–13). It seems that the steric demand of the NADH-synthon is diametrically opposed between alkyl- and aryl-4-substituted quinolines.

The effect of catalyst loading and temperature on the reaction yield and selectivity was also analyzed. First the catalyst loading was varied in the range of 10 to 0.1 mol%. Whereas the enantiomeric excess is nearly constant over the whole range, a better yield was obtained with 5 mol% catalyst. Regarding the influence of the temperature, with lowering the temperature (60→50→40 °C), the enantiomeric excess increased, but the conversion of the reaction considerably decreased. Therefore, the overall best conditions with regard to reaction time and asymmetric induction are 5 mol% of catalyst at 50 °C in benzene or toluene.

Under these optimized conditions we explored the scope of the first asymmetric transfer hydrogenation of various 4-substituted quinolines (Table 3). In general, high enantioselectivities and good yields are observed for various 4-substituted alkyl- and aryl-tetrahydroquinolines (Table 3, entries 1–7 and 8–17 respectively). Especially the chloro-containing substrates could be reduced with high enantioselectivities and excellent yields. In this case, in addition to the activation by the catalyst, the electron

Table 3 Scope of the catalytic enantioselective reduction



1a-g
5a-j

2a-g
6a-j

Entry[a]	Product	R^1	R^2	Yield[b] (%)	ee[c] (%)
1[d]	**2a**	Me	H	67	73
2[d]	**2b**	Me	Cl	85	85
3[d]	**2c**	Et	Cl	88	85
4[d]	**2d**	*i*-Pr	Cl	81	90
5[d]	**2e**	Bu	Cl	82	84
6[d]	**2f**	Bn	Cl	96	84
7	**2g**	CO_2Me	H	67	75
8	**6a**	C_6H_5	Cl	96	92
9	**6b**	C_6H_5	H	84	81
10	**6c**	4-Me-C_6H_5	Cl	92	91
11	**6d**	4-Me-C_6H_5	H	77	83
12	**6e**	4-MeO-C_6H_5	Cl	95	90
13	**6f**	4-MeO-C_6H_5	H	90	72
14	**6g**	3-MeO-C_6H_5	Cl	92	92
15	**6h**	3-MeO-C_6H_5	H	80	82
16	**6i**	2-Naphthyl	Cl	98	90
17	**6j**	4-Biphenyl	Cl	96	75

[a] Reactions were performed with quinolines **1**/**5**, HEH **4d** (2.4 equiv.) and **3l** (5 mol%) at 50 °C. [b] Yield after chromatography. [c] Enantiomeric excess was determined by HPLC using Chiralcel OD-H or Chiralpak AD-H. [d] HEH **4a** was used.

withdrawing effect of the chlorine atom most probably enhances the electrophilicity of the substrate by decreasing the electron density of the heteroaromatic ring, thus enabling the attack of the H^- nucleophile.

This rationale is best illustrated by the difference in yield in the case of **2a** and **2b** which were obtained with 67 and 85% yield, respectively (Table 3, entries 1–2). In the case of quinoline derivatives bearing aryl groups in the 4-position, the electronic nature of this moiety plays a less relevant role since electron donating groups are well tolerated in this reaction. Furthermore, quinoline **1g** with an ester group, that might be further functionalized, is also applicable in this procedure (Table 3, entry 7).

The absolute configuration of the product **6j** has been determined as *R* by X-ray crystal structure analysis (Fig. 1).

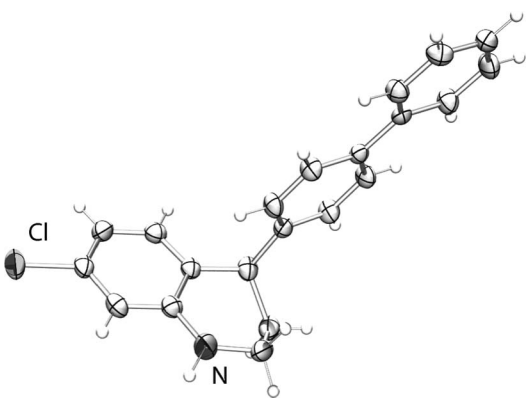
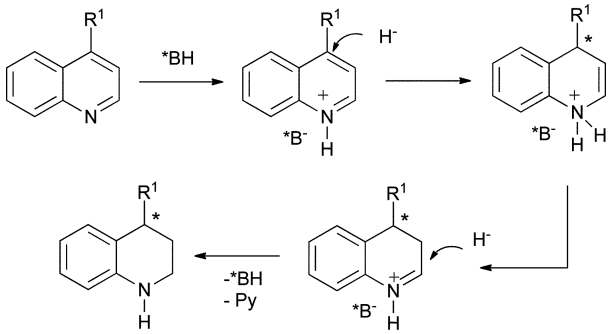


Fig. 1 X-ray crystal structure of tetrahydroquinoline **6j**.

Regarding the mechanism of the reaction (Scheme 2), a first step protonation of the substrate yields the corresponding iminium ion. Hydride transfer from the HEH to the substrate takes place selectively, from the less hindered face and gives a chiral enamine intermediate along with a pyridinium salt which undergoes proton transfer to liberate the catalyst. Isomerization of the enamine yields the corresponding chiral iminium ion which is subjected to second hydride transfer. Finally, protonation will regenerate the catalyst.



*BH - chiral BINOL phosphoric acid, Py - pyridine derivative

Scheme 2 Proposed mechanism for the asymmetric reduction.

Our initial catalyst evaluation revealed a strong correlation between the steric bulk of the catalyst substituents in the 3,3-position and the selectivity of the reaction, whereby larger residues lead to superior enantioselectivities. Furthermore, when comparing the catalysts bearing large groups directly attached to the BINOL framework with the ones bearing an acetylene-bridge or less bulky groups, better results were obtained with the former. This result is explained by the position of the developing stereocenter which is far away from the protonated nitrogen and the catalytic center of the phosphoric acid catalyst. In the case of BINOL derivatives **3l** and **3g**, the triphenylsilyl and phenanthryl substituents are able to provide the necessary environment for a selective reaction. In contrast, in the case of **3j** and **3k**, the acetylene-bridge provides too much space around the substrate and, therefore, none of the faces can be effectively shielded.

Conclusions

In summary, we have succeeded in developing the first asymmetric hydrogenation of biologically relevant 4-substituted quinolines. The protocol provides direct access to a large variety of 4-aryl- and 4-alkyl-substituted tetrahydroquinolines in good yields and good to high enantiomeric excesses. Further work will be devoted to the application of this methodology in the synthesis of more complex molecular architectures.

Experimental

General methods

All reactions were performed under an argon atmosphere. Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification. Solvents for extraction and chromatography were technical grade and distilled

prior to use. Solvents used in reactions were reagent grade and distilled from the indicated drying agents: benzene (Na). For thin-layer chromatography (TLC), silica gel coated aluminum plates (Merck, silica gel 60 F_{254}) were used and chromatograms were visualized by irradiation with UV light at 254 nm. Column chromatography was performed using Merck silica gel 60 (particle size 0.040–0.063 mm). Solvents mixtures are understood as volume/volume.

^{1}H-NMR and ^{13}C-NMR were recorded on a Bruker AM 250 spectrometer in $CDCl_3$. Data are reported in the following order: chemical shift (δ) in ppm; multiplicities are indicated as (bs (broadened singlet), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet)); coupling constants (J) are in hertz (Hz). Field Desorption (FD) mass spectra were obtained with Finnigan MAT 95 instrument. Infrared (IR) spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer and are reported in terms of frequency of absorption (cm^{-1}). The enantiomeric excesses were determined by HPLC analysis using a chiral stationary phase column (column, Daicel Co. CHIRALCEL OD-H and CHIRALPAK AD-H; eluent: hexane/2-propanol). The chiral HPLC method was calibrated with the corresponding racemic mixtures. Optical rotations were measured on a Perkin Elmer 241 polarimeter.

General procedure for the transfer hydrogenation of quinolines

In a typical experiment quinoline **1/5**, catalyst **3l** (5 mol%), Hantzsch dihydropyridine **4a/4d** (2.4 equiv.) and benzene (2.0 mL) were added to a screw-capped vial and the mixture was exposed to an argon atmosphere. The resulting yellow solution was allowed to stir at 50 °C for 35–50h. The solvent was evaporated under vacuum, and the residue was purified by column chromatography on silica gel to afford the corresponding amine. The yields and enantiomeric excesses are given in Table 3.

(4*S*)-4-Methyl-1,2,3,4-tetrahydro-quinoline (2a, Table 3, entry 1). Eluted from silica gel using toluene as eluent.

^{1}H-NMR ($CDCl_3$): δ = 7.08 (d, J = 7.6 Hz, 1H), 6.97 (t, J = 7.6 Hz, 1H), 6.63 (dt, J = 1.2, 7.4 Hz, 1H), 6.48 (dd, J = 1.2, 8.0 Hz, 1H), 3.85 (bs, 1H), 3.40–3.22 (m, 2H), 3.02–2.84 (m, 1H), 2.07–1.92 (m, 1H), 1.76–1.61 (m, 1H), 1.30 (d, J = 7.0 Hz, 3H); ^{13}C-NMR ($CDCl_3$): δ = 144.2, 128.4, 126.7, 126.6, 116.9, 114.1, 39.0, 30.2, 29.9, 22.6; MS (FD): m/z (%) = 147.8 (100) [M$^+$]; IR (KBr): 3407, 3051, 3016, 2955, 2925, 2864, 1606, 1498, 1315, 745 cm^{-1}. HPLC conditions: OD-H column, n-hexane/2-propanol = 98/2, flow rate = 0.6 mL min^{-1}, major enantiomer: t_R = 17.15 min; minor enantiomer: t_R = 18.63 min; $[\alpha]_D^{25}$ −23.6 (c 1.0, $CHCl_3$).

(4*S*)-7-Chloro-4-methyl-1,2,3,4-tetrahydro-quinoline (2b, Table 3, entry 2). Eluted from silica gel using toluene as eluent. ^{1}H-NMR ($CDCl_3$): δ = 6.94 (dd, J = 0.8, 8.1 Hz, 1H), 6.57 (dd, J = 2.1, 8.1 Hz, 1H), 6.44 (d, J = 2.1 Hz, 1H), 3.92 (bs, 1H), 3.39–3.21 (m, 2H), 2.93–2.79 (m, 1H), 2.01–1.88 (m, 1H), 1.72–1.58 (m, 1H), 1.26 (d, J = 7.0 Hz, 3H); ^{13}C-NMR ($CDCl_3$): δ = 145.2, 132.0, 129.4, 124.8, 116.6, 113.3, 38.8, 29.9, 29.4, 22.4; MS (FD): m/z (%) = 181.8 (100) [M$^+$], 183.7 (Cl_2 pattern); IR (KBr): 3417, 2957, 2925, 2867, 1604, 1575, 1496, 1469, 1308, 1088, 1067, 872, 841, 792 cm^{-1}. HPLC conditions: AD-H column, n-hexane/2-propanol = 99/1, flow rate = 0.45 mL min^{-1}, major enantiomer: t_R = 28.92 min; minor enantiomer: t_R = 31.56 min; $[\alpha]_D^{25}$ −18.0 (c 0.5, $CHCl_3$).

(4*S*)-7-Chloro-4-ethyl-1,2,3,4-tetrahydro-quinoline (2c, Table 3, entry 3). Eluted from silica gel using toluene as eluent.

^{1}H-NMR ($CDCl_3$): δ = 6.91 (d, J = 8.1 Hz, 1H), 6.55 (dd, J = 2.1, 8.1 Hz, 1H), 6.44 (d, J = 2.1 Hz, 1H), 3.91 (bs, 1H), 3.37–3.18 (m, 2H), 2.66–2.55 (m, 1H), 1.96–1.42 (m, 4H), 0.97 (t, J = 7.4 Hz, 3H); ^{13}C-NMR ($CDCl_3$): δ = 145.2, 132.0, 130.1, 123.6, 116.2, 113.3, 38.2, 36.8, 28.9, 25.4, 11.5; MS (FD): m/z (%) = 195.0 (100) [M$^+$], 197.0 (Cl_2 pattern); IR (KBr): 3393, 2958, 2921, 2844, 1602, 1497, 1093, 844, 798 cm^{-1}. HPLC conditions: AD-H column, n-hexane/2-propanol = 99/1, flow rate = 0.45 mL min^{-1}, major enantiomer: t_R = 27.88 min; minor enantiomer: t_R = 31.48 min; $[\alpha]_D^{25}$ −23.8 (c 0.5, $CHCl_3$).

(4*S*)-7-Chloro-4-isopropyl-1,2,3,4-tetrahydro-quinoline (2d, Table 3, entry 4). Eluted from silica gel using toluene as eluent.

^{1}H-NMR ($CDCl_3$): δ = 6.89 (dd, J = 0.6, 8.1 Hz, 1H), 6.54 (dd, J = 2.1, 8.1 Hz, 1H), 6.44 (d, J = 2.1 Hz, 1H), 3.89 (bs, 1H), 3.38–3.22 (m, 2H), 2.53–2.42 (m, 1H), 2.05–1.85 (m, 2H), 1.82–1.68 (m, 1H), 0.97 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 6.8 Hz, 3H); ^{13}C-NMR ($CDCl_3$): δ = 145.4, 132.0, 130.4, 122.6, 115.8, 113.2, 41.9, 39.1, 30.2, 22.6, 21.4, 18.6; MS (FD): m/z (%) = 209.0 (100) [M$^+$]; IR (KBr): 3390, 2955, 2928, 2851, 1603, 1496, 1090, 842, 799 cm^{-1}. HPLC conditions: AD-H column, n-hexane/2-propanol = 99/1, flow rate = 0.45 mL min^{-1}, major enantiomer: t_R = 25.94 min; minor enantiomer: t_R = 37.14 min; $[\alpha]_D^{25}$ −9.1 (c 0.5, $CHCl_3$).

(4*S*)-7-Chloro-4-butyl-1,2,3,4-tetrahydro-quinoline (2e, Table 3, entry 5). Eluted from silica gel using toluene as eluent.

^{1}H-NMR ($CDCl_3$): δ = 6.90 (d, J = 8.1 Hz, 1H), 6.55 (dd, J = 2.1, 8.1 Hz, 1H), 6.44 (d, J = 2.1 Hz, 1H), 3.91 (bs, 1H), 3.38–3.19 (m, 2H), 2.74–2.64 (m, 1H), 1.96–1.72 (m, 2H), 1.70–1.22 (m, 6H), 0.92 (t, J = 7.0 Hz, 3H); ^{13}C-NMR ($CDCl_3$): δ = 145.1, 131.9, 130.1, 123.9, 116.2, 113.3, 38.1, 36.1, 35.1, 29.1, 25.8, 22.8, 14.1; MS (FD): m/z (%) = 223.8 (100) [M$^+$], 225.8 (Cl_2 pattern); IR (KBr): 3419, 2954, 2927, 2857, 1604, 1576, 1496, 1468, 1355, 1309, 1089, 839 cm^{-1}. HPLC conditions: OD-H column, n-hexane/2-propanol = 97/3, flow rate = 0.6 mL min^{-1}, major enantiomer: t_R = 12.35 min; minor enantiomer: t_R = 11.38 min; $[\alpha]_D^{25}$ −8.6 (c 0.5, $CHCl_3$).

(4*S*)-7-Chloro-4-benzyl-1,2,3,4-tetrahydro-quinoline (2f, Table 3, entry 6). Eluted from silica gel using toluene as eluent.

^{1}H-NMR ($CDCl_3$): δ = 7.27–7.06 (m, 5H), 6.76 (d, J = 8.1 Hz, 1H), 6.46 (dd, J = 2.1, 8.1 Hz, 1H), 6.40 (d, J = 2.1 Hz, 1H), 3.88 (bs, 1H), 3.35–3.23 (m, 1H), 3.19–3.09 (m, 1H), 3.02–2.86 (m, 2H), 2.69–2.54 (m, 1H), 1.78–1.56 (m, 2H); ^{13}C-NMR ($CDCl_3$): δ = 145.2, 140.0, 132.3, 130.2, 129.3, 128.3, 126.1, 122.7, 116.4, 113.4, 42.9, 37.9, 37.1, 25.0; MS (FD): m/z (%) = 257.8 (100) [M$^+$], 259.9 (Cl_2 pattern); IR (KBr): 3404, 3042, 3024, 3000, 2953, 2932, 1605, 1504, 1310, 1084, 1028, 844, 796, 704 cm^{-1}. HPLC conditions: OD-H column, n-hexane/2-propanol = 90/10, flow rate = 0.6 mL min^{-1}, major enantiomer: t_R = 15.62 min; minor enantiomer: t_R = 13.73 min; $[\alpha]_D^{25}$ −115.9 (c 1.0, $CHCl_3$).

(4*S*)-1,2,3,4-Tetrahydro-quinoline-4-carboxylic acid methyl ester (2g, Table 3, entry 7)

Eluted from silica gel using hexane/ethylacetat in a ratio of 20 : 1 as eluent.

^{1}H-NMR ($CDCl_3$): δ = 7.03 (d, J = 7.6 Hz, , 1H), 6.96 (t, J = 8.4 Hz, 1H), 6.56 (dt, J = 1.1, 7.6 Hz, 1H), 6.44 (dd, J = 1.1, 8.0 Hz,

1H), 3.87 (bs, 1H), 3.72 (t, J = 5.0 Hz, 1H), 3.64 (s, 3H), 3.42–3.30 (m, 1H), 3.27–3.16 (m, 1H), 2.27–2.14 (m, 1H), 2.01–1.85 (m, 1H); ^{13}C-NMR ($CDCl_3$): δ = 174.7, 144.4, 130.3, 128.1, 117.0, 114.7, 52.1, 41.7, 38.8, 24.6; MS (FD): m/z (%) = 191.0 (100) [M^+]; IR (KBr): 3407, 2951, 2926, 2855, 1731, 1601, 1503, 1194, 1164, 748 cm^{-1}. HPLC conditions: AD-H column, n-hexane/2-propanol = 80/20, flow rate = 0.6 mL min^{-1}, major enantiomer: t_R = 10.82 min; minor enantiomer: t_R = 13.01 min; $[\alpha]_D^{25}$ −61.2 (c 0.5, $CHCl_3$).

(4*R*)-7-Chloro-4-phenyl-1,2,3,4-tetrahydro-quinoline (6a, Table 3, entry 8). Eluted from silica gel using toluene as eluent.

^{1}H-NMR ($CDCl_3$): δ = 7.26–7.10 (m, 3H), 7.05–7.00 (m, 2H), 6.57 (d, J = 7.7 Hz, 1H), 6.45–6.40 (m, 2H), 4.01 (t, J = 6.0 Hz, 1H), 3.93 (bs, 1H), 3.26–3.06 (m, 2H), 2.16–2.03 (m, 1H), 2.01–1.88 (m, 1H); ^{13}C-NMR ($CDCl_3$): δ = 146.0, 145.8, 132.6, 131.4, 128.5, 128.3, 126.3, 121.6, 116.7, 113.4, 42.3, 38.9, 30.6; MS (FD): m/z (%) = 243.8 (100) [M^+], 245.9 (Cl_2 pattern); IR (KBr): 3418, 3058, 3024, 2948, 2924, 2854, 1602, 1494, 1311, 1087, 701 cm^{-1}. HPLC conditions: OD-H column, n-hexane/2-propanol = 90/10, flow rate = 0.6 mL min^{-1}, major enantiomer: t_R = 21.58 min, minor enantiomer: t_R = 12.28 min; $[\alpha]_D^{25}$ −70.8 (c 1.0, $CHCl_3$).

(4*R*)-4-Phenyl-1,2,3,4-tetrahydro-quinoline (6b, Table 3, entry 9). Eluted from silica gel using toluene as eluent.

^{1}H-NMR ($CDCl_3$): δ = 7.25–7.03 (m, 5H), 6.93 (t, J = 7.0 Hz, 1H), 6.67 (d, J = 7.3 Hz, 1H), 6.51–6.44 (m, 2H), 4.07 (t, J = 6.1 Hz, 1H), 3.85 (bs, 1H), 3.27–3.10 (m, 2H), 2.20–2.06 (m, 1H), 2.03–1.90 (m, 1H); ^{13}C-NMR ($CDCl_3$): δ = 146.7, 145.0, 130.4, 128.7, 128.3, 127.3, 126.1, 123.4, 117.0, 114.2, 42.8, 39.2, 31.1; MS (FD): m/z (%) = 209.9 (100) [M^+]; IR (KBr): 3414, 3057, 3021, 2951, 2919, 2896, 2850, 2831, 1607, 1505, 1491, 1315, 741, 703 cm^{-1}. HPLC conditions: OD-H column, n-hexane/2-propanol = 90/10, flow rate = 0.6 mL min^{-1}, major enantiomer: t_R = 22.32 min; minor enantiomer: t_R = 14.61 min; $[\alpha]_D^{25}$ −60.8 (c 1.0, $CHCl_3$).

(4*R*)-7-Chloro-4-*p*-tolyl-1,2,3,4-tetrahydro-quinoline (6c, Table 3, entry 10). Eluted from silica gel using toluene as eluent.

^{1}H-NMR ($CDCl_3$): δ = 7.11 (d, J = 7.9 Hz, 2H), 7.00 (d, J = 8.1 Hz, 2H), 6.66 (d, J = 7.7 Hz, 1H), 6.53–6.47 (m, 2H), 4.05 (t, J = 6.0 Hz, 1H), 4.00 (bs, 1H), 3.33–3.18 (m, 2H), 2.33 (s, 3H), 2.22–2.10 (m, 1H), 2.07–1.94 (m, 1H); ^{13}C-NMR ($CDCl_3$): δ = 145.9, 143.0, 135.8, 132.5, 131.4, 129.1, 128.4, 121.9, 116.7, 113.4, 41.9, 38.9, 30.7, 21.0; MS (FD): m/z (%) = 257.0 (100) [M^+], 259.0 (Cl_2 pattern); IR (KBr): 3391, 2956, 2919, 2855, 1604, 1493, 1302, 1088, 816, 796, 536 cm^{-1}. HPLC conditions: OD-H column, n-hexane/2-propanol = 98/2, flow rate = 0.6 mL min^{-1}, major enantiomer: t_R = 24.83 min; minor enantiomer: t_R = 16.75 min; $[\alpha]_D^{25}$ −70.9 (c 1.0, $CHCl_3$).

(4*R*)-4-*p*-Tolyl-1,2,3,4-tetrahydro-quinoline (6d, Table 3, entry 11). Eluted from silica gel using toluene as eluent.

^{1}H-NMR ($CDCl_3$): δ = 7.13–6.97 (m, 5H), 6.77 (d, J = 8.1 Hz, 1H), 6.60–6.53 (m, 2H), 4.12 (t, J = 6.1 Hz, 1H), 3.93 (bs, 1H), 3.36–3.19 (m, 2H), 2.34 (s, 3H), 2.28–2.12 (m, 1H), 2.10–1.97 (m, 1H); ^{13}C-NMR ($CDCl_3$): δ = 145.0, 143.7, 135.6, 130.4, 129.0, 128.6, 127.2, 123.6, 117.0, 114.2, 42.4, 39.2, 31.2, 21.0; MS (FD): m/z (%) = 223.0 (100) [M^+]; IR (KBr): 3403, 3050, 3020, 2947, 2922, 2852, 1605, 1502, 1313, 741 cm^{-1}. HPLC conditions: OD-H column, n-hexane/2-propanol = 90/10, flow rate = 0.6 mL min^{-1}, major enantiomer: t_R = 15.41 min; minor enantiomer: t_R = 13.38 min; $[\alpha]_D^{25}$ −57.8 (c 1.0, $CHCl_3$).

(4*R*)-7-Chloro-4-(4-methoxy-phenyl)-1,2,3,4-tetrahydro-quinoline (6e, Table 3, entry 12). Eluted from silica gel using toluene as eluent.

^{1}H-NMR ($CDCl_3$): δ = 7.03 (d, J = 8.6 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 6.66 (d, J = 7.8 Hz, 1H), 6.54–6.58 (m, 2H), 4.04 (t, J = 6.0 Hz, 1H), 4.00 (bs, 1H), 3.79 (s, 3H), 3.34–3.15 (m, 2H), 2.21–2.07 (m, 1H), 2.05–1.92 (m, 1H); ^{13}C-NMR ($CDCl_3$): δ = 158.1, 145.8, 138.1, 132.5, 131.4, 129.4, 122.0, 116.7, 113.8, 113.4, 55.3, 41.5, 38.9, 30.7; MS (FD): m/z (%) = 273.0 (100) [M^+], 275.0 (Cl_2 pattern); IR (KBr): 3417, 2952, 2928, 2832, 1607, 1506, 1247, 1086, 1032, 844 cm^{-1}. HPLC conditions: OD-H column, n-hexane/2-propanol = 90/10, flow rate = 0.6 mL min^{-1}, major enantiomer: t_R = 19.33 min; minor enantiomer: t_R = 14.58 min; $[\alpha]_D^{25}$ −77.3 (c 1.0, $CHCl_3$).

(4*R*)-4-(4-Methoxy-phenyl)-1,2,3,4-tetrahydro-quinoline (6f, Table 3, entry 13). Eluted from silica gel using toluene as eluent.

^{1}H-NMR ($CDCl_3$): δ = 7.06 (d, J = 8.6 Hz, 2H), 6.99 (d, J = 7.6 Hz, 1H), 6.84 (d, J = 8.7 Hz, 2H), 6.76 (d, J = 7.3 Hz, 1H), 6.60–6.50 (m, 2H), 4.10 (t, J = 6.0 Hz, 1H), 3.93 (bs, 1H), 3.80 (s, 3H), 3.35–3.18 (m, 2H), 2.25–2.12 (s, 1H), 2.08–1.95 (m, 1H); ^{13}C-NMR ($CDCl_3$): δ = 157.9, 144.9, 138.8, 130.4, 129.6, 127.2, 123.8, 117.0, 114.2, 113.7, 55.3, 42.0, 39.2, 31.2; MS (FD): m/z (%) = 239.1 (100) [M^+]; IR (KBr): 3338, 3028, 2948, 2926, 2832, 1607, 1497, 1247, 1033, 746 cm^{-1}. HPLC conditions: OD-H column, n-hexane/2-propanol = 90/10, flow rate = 0.6 mL min^{-1}, major enantiomer: t_R = 22.54 min; minor enantiomer: t_R = 25.68 min; $[\alpha]_D^{25}$ −55.4 (c 1.0, $CHCl_3$).

(4*R*)-7-Chloro-4-(3-methoxy-phenyl)-1,2,3,4-tetrahydro-quinoline (6g, Table 3, entry 14). Eluted from silica gel using toluene as eluent.

^{1}H-NMR ($CDCl_3$): δ = 7.22 (t, J = 7.9 Hz, 1H), 6.79–6.64 (m, 4H), 6.54–6.48 (m, 2H), 4.06 (t, J = 6.0 Hz, 1H), 4.00 (bs, 1H), 3.77 (s, 3H), 3.34–3.16 (m, 2H), 2.24–1.96 (m, 2H); ^{13}C-NMR ($CDCl_3$): δ = 159.6, 147.7, 145.8, 132.6, 131.5, 129.3, 121.5, 121.0, 116.8, 114.6, 113.4, 111.3, 55.2, 42.4, 38.9, 30.5; MS (FD): m/z (%) = 273.0 (100) [M^+], 275.0 Cl_2 pattern; IR (KBr): 3415, 2951, 2925, 2834, 1603, 1494, 1312, 1256, 1087, 1046 cm^{-1}. HPLC conditions: OD-H column, n-hexane/2-propanol = 90/10, flow rate = 0.6 mL min^{-1}, major enantiomer: t_R = 27.35 min; minor enantiomer: t_R = 15.72 min; $[\alpha]_D^{25}$ −70.7 (c 1.0, $CHCl_3$).

(4*R*)-4-(3-Methoxy-phenyl)-1,2,3,4-tetrahydro-quinoline (6h, Table 3, entry 15). Eluted from silica gel using toluene as eluent.

^{1}H-NMR ($CDCl_3$): δ = 7.22 (t, J = 7.9 Hz, 1H), 7.01 (t, J = 7.6 Hz, 1H), 6.79–6.69 (m, 4H), 6.61–6.51 (m, 2H), 4.12 (t, J = 6.1 Hz, 1H), 3.93 (s, 1H), 3.77 (s, 3H), 3.36–3.19 (m, 2H), 2.28–2.15 (m, 1H), 2.13–2.00 (m 1H); ^{13}C-NMR ($CDCl_3$): δ = 159.6, 148.3, 144.9, 130.4, 129.2, 127.3, 123.2, 121.2, 117.0, 114.7, 114.2, 111.2, 55.2, 42.9, 39.3, 31.0; MS (FD): m/z (%) = 239.1 (100) [M^+]; IR (KBr): 3408, 3059, 2999, 2951, 2922, 2892, 2830, 1277, 1253, 746 cm^{-1}. HPLC conditions: OD-H column, n-hexane/2-propanol = 90/10, flow rate = 0.6 mL min^{-1}, major enantiomer: t_R = 30.19 min; minor enantiomer: t_R = 23.32 min; $[\alpha]_D^{25}$ −51.0 (c 1.0, $CHCl_3$).

(4*R*)-7-Chloro-4-naphthalen-2-yl-1,2,3,4-tetrahydro-quinoline (6i, Table 3, entry 16). Eluted from silica gel using toluene as eluent.

^{1}H-NMR ($CDCl_3$): δ = 7.86–7.72 (m, 3H), 7.53–7.40 (m, 3H), 7.30 (dd, J = 1.8, 8.5 Hz, 1H), 6.68 (dd, J = 0.6, 8.1 Hz, 1H),

6.58–6.48 (m, 2H), 4.25 (t, J = 6.1 Hz, 1H), 4.05 (bs, 1H), 3.37–3.19 (m, 2H), 2.30–2.07 (m, 2H); ^{13}C-NMR ($CDCl_3$): δ = 145.7, 143.3, 133.4, 132.7, 132.2, 131.6, 128.1, 127.7, 127.6, 127.4, 126.6, 126.0, 125.5, 121.7, 117.1, 113.7, 42.5, 39.0, 30.5; MS (FD): m/z (%) = 293.9 (100) [M$^+$], 296.1 (Cl_2 pattern); IR (KBr): 3418, 3051, 2923, 2853, 1602, 1495, 1310, 1087, 820, 755, 743, 477 cm^{-1}. HPLC conditions: OD-H column, n-hexane/2-propanol = 90/10, flow rate = 0.6 mL min^{-1}, major enantiomer: t_R = 21.03 min; minor enantiomer: t_R = 16.54 min; $[\alpha]_D^{25}$ –89.0 (c 1.0, $CHCl_3$).

(4*R*)-4-Biphenyl-4-yl-7-chloro-1,2,3,4-tetrahydro-quinoline (6j, Table 3, entry 17). Eluted from silica gel using toluene as eluent. ^{1}H-NMR ($CDCl_3$): δ = 7.62–7.50 (m, 4H), 7.44 (t, J = 7.3 Hz, 2H), 7.34 (t, J = 7.2 Hz, 1H), 7.19 (d, J = 8.2 Hz, 2H), 6.71 (d, J = 8.4 Hz, 1H), 6.55–6.50 (m, 2H), 4.14 (t, J = 5.9 Hz, 1H), 4.03 (bs, 1H), 3.38–3.18 (m, 2H), 2.29–2.14 (m, 1H), 2.13–2.00 (m, 1H); ^{13}C-NMR ($CDCl_3$): δ = 145.9, 145.1, 140.9, 139.3, 132.7, 131.5, 128.9, 128.7, 127.1, 127.1, 127.0, 121.5, 116.8, 113.5, 42.0, 38.9, 30.6; MS (FD): m/z (%) = 320.0 (100) [M$^+$], 322.0 (Cl_2 pattern); IR (KBr): 3419, 2954, 2925, 2867, 1604, 1496, 1308, 1088 cm^{-1}. HPLC conditions: OD-H column, n-hexane/2-propanol = 90/10, flow rate = 0.6 mL min^{-1}, major enantiomer: t_R = 24.90 min; minor enantiomer: t_R = 17.84 min; $[\alpha]_D^{25}$ –64.0 (c 0.8, $CHCl_3$).

Acknowledgements

Financial support by the DFG (SPP 1179) is gratefully acknowledged.

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