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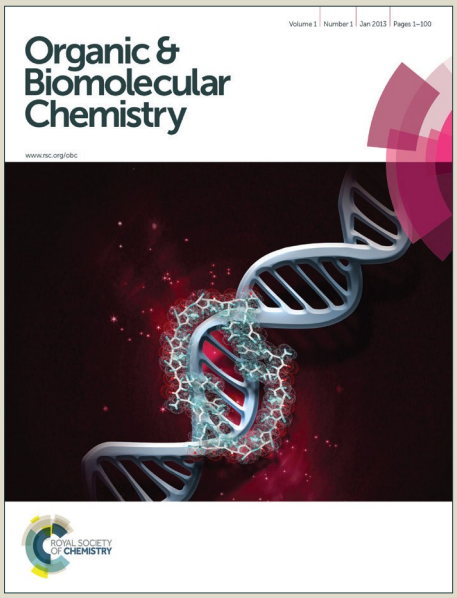

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ARTICLE TYPE

Organocatalytic asymmetric intramolecular aza-Henry reaction: Facile synthesis of *trans*-2,3-disubstituted tetrahydroquinolines

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An enantio- and diastereoselective organocatalytic intramolecular aza-Henry (nitro-Mannich) reaction has been developed. The *trans*-2-aryl-3-nitro-tetrahydroquinoline products are obtained in high yields and in good enantioselectivities with a bifunctional tertiary amine-thiourea catalyst. Excellent enantioselectivities were obtained after single recrystallization for some products.

The interest for the synthesis of nitrogen heterocycles is persistent due to their importance in medicinal chemistry and presence in a plethora of natural products. The tetrahydroquinoline system is one of the privileged scaffolds present in drugs and natural products.[1] Thus the development of new strategies and protocols for the synthesis of tetrahydroquinoline derivatives, particularly in enantiomerically pure form, is an important task for synthetic chemists.[2] Asymmetric Povarov reaction,[3] reduction of quinolines,[4] aza-Michael additions[5] and internal redox processes[6] are the common four strategies for the synthesis of enantiopure tetrahydroquinolines.

Here in we wish to report an enantio and diastereoselective synthesis of *trans*-2-aryl/alkyl-3-nitro-tetrahydroquinolines using an alternate strategy namely intramolecular direct aza-Henry reaction.[7] Xu and co-workers earlier reported an asymmetric tandem Michael/aza-Henry reaction for the synthesis of trisubstituted terahydroquinolines having 2-aryl and 3-nitro functionalities (Figure 1, eq. 1).[8a] Recently, similar types of compounds with *N*-protections were synthesized by aza-Michael-Michael strategies using nitroolefins (eq. 2).[5] But a simple direct aza-Henry reaction for the synthesis of disubstituted chiral tetrahydroquinolines is still not known and importantly such skeleton is present in Benzastatin D,[9] a potent cholesteryl ester transfer protein inhibitor and in P antagonist substance. Chiral 2-aryl-3-nitro-1,2,3,4-tetrahydroquinolines have been previously synthesized by chiral phosphoric acid catalyzed transfer hydrogenation of 2-aryl-3-nitroquinolines but only *cis* diastereoselectivity was observed (eq. 3).[4j] Here we demonstrate an approach that provides *trans*-isomer as the predominant product (eq. 4) and follows an intramolecular nitro-Mannich reaction whose achiral version was previously reported by Anderson and co-workers.[10]

We started our experiments by treating a mixture of nitroalkane **1a** and benzaldehyde (**2a**) with Takemoto catalyst (**I**) in toluene at room temperature. After stirring for three days the

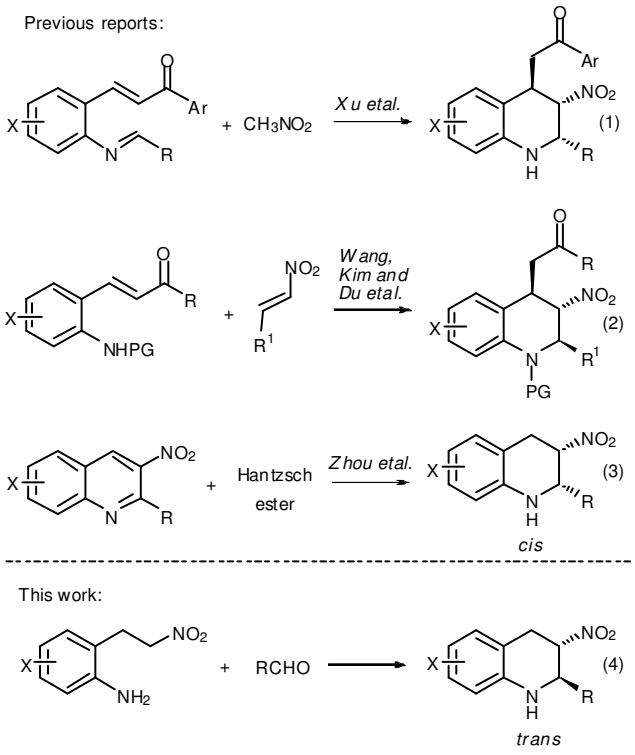

Figure 1 Synthetic approaches to 2,(4)-(di)functionalized-3-nitro-tetrahydroquinolines

desired intramolecular nitro-Mannich product **3a** was isolated in 65% yield with 40% ee in perfect diastereoselectivity (Table 1, entry 1). However, a racemic product was obtained with catalyst **II** having pyrrolidine moiety (entry 2). Then bifunctional tertiary amine-squaramide catalyst (**III**) was prepared. Surprisingly, with this catalyst, no product was obtained. Then catalyst **IV** with an extra chiral centre has been screened. Though desired product **3a** was obtained with catalyst **IV**, the enantioselectivity was poor (entry 4). Gratifyingly, both yield and enantioselectivity was improved with quinine derived bifunctional thiourea catalyst **V** (entry 5).[11] An enhancement in enantioselectivity (66% ee) was observed by changing the solvent to chloroform (entry 6). Finally the best solvent was found to be a mixture of pentane and dichloromethane (5:1) that provided the product in 85% yield and 74%ee (entry 7, see supporting information for solvent

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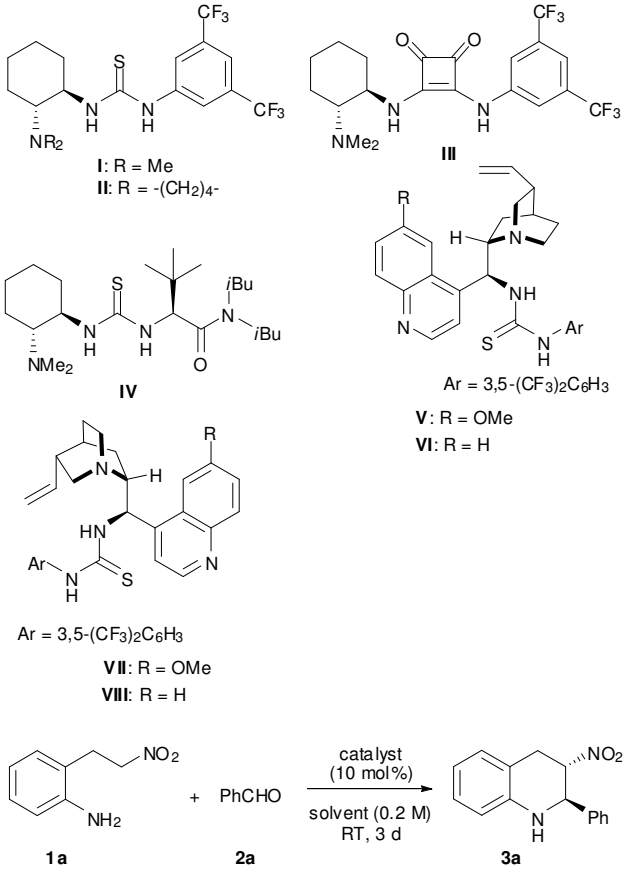
Table 1 Catalyst screening and optimization of reaction condition

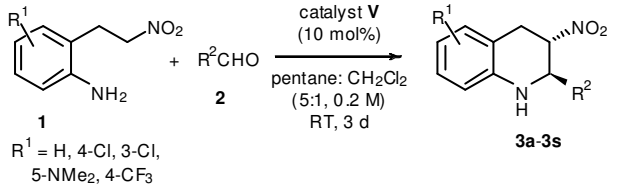


entry[a]	catalyst	solvent	yield[b]	ee[c]
1	**I**	toluene	65	-40
2	**II**	toluene	50	0
3	**III**	toluene	0	-
4	**IV**	toluene	50	5
5	**V**	toluene	70	48
6	**V**	$CHCl_3$	75	66
7	**V**	pentane/CH_2Cl_2 (5:1)	85	74
8	**VI**	pentane/CH_2Cl_2 (5:1)	85	-60
9	**VII**	pentane/CH_2Cl_2 (5:1)	80	-60
10	**VIII**	pentane/CH_2Cl_2 (5:1)	81	55

[a]Reaction condition: 0.12 mmol of **1a** with 0.16 mmol of **2a** in 0.6 mL solvent using 10 mol% catalyst. [b]Isolated yield after silica gel column chromatography. [c]Determined by HPLC using stationary phase chiral column.

screening). Under this condition other *Cinchona* alkaloid derived thiourea catalysts **VI**-**VIII** were screened (entries 8-10). Unfortunately, the enantioselectivity did not improve with these catalysts. Lowering the temperature to 0 °C improves the enantioselectivity to 80% ee but the diastereoselectivity was poor (1:1). To our delight, a single recrystallization from ethanol at room temperature improved the enantioselectivity of product **3a** from 74% to 98% enantiomeric excess.

Table 2 Substrate scope for the intramolecular aza-Henry reaction



R^1 = H, 4-Cl, 3-Cl, 5-NMe_2, 4-CF_3

entry[a]	R^1	R^2	**3**	yield[b]	ee[c]
1	H	Ph	**3a**	85	74 (98)
2	H	4-MeC_6H_4	**3b**	90	67 (94)
3	H	4-$tBuC_6H_4$	**3c**	78	61
4	H	4-$iPrC_6H_4$	**3d**	75	52
5	H	4-ClC_6H_4	**3e**	83	70 (96)
6	H	4-BrC_6H_4	**3f**	80	58 (94)
7	H	4-FC_6H_4	**3g**	80	68 (99)
8	H	4-$OMeC_6H_4$	**3h**	60	60
9	H	4-PhC_6H_4	**3i**	95	61 (78)
10	H	2-ClC_6H_4	**3j**	75	40 (99)
11	H	3-BrC_6H_4	**3k**	85	47
12	H	2,4-$(Me)_2C_6H_3$	**3l**	91	70 (95)
13	H	Cinnamyl	**3m**	75	28
14	H	*n*Bu	**3n**	82	68
15	H	*n*Pr	**3o**	81	63
16	4-Cl	Ph	**3p**	70	75 (88)
17	3-Cl	Ph	**3q**	72	62 (74)
18	5-NMe_2	Ph	**3r**	80	64 (76)
19	4-CF_3	Ph	**3s**	69	76 (82)

[a]Reaction condition: 0.12 mmol of **1** with 0.16 mmol of **2** in 0.6 mL solvent using 10 mol% catalyst. [b]Isolated yield after silica gel column chromatography. [c]Determined by HPLC using stationary phase chiral column, ees in parenthesis are after recrystallization.

After the detection of optimized condition, we ventured in the scope of the reaction. Initially, different aldehydes were reacted with nitroalkane **1a** and our reaction condition was found to be suitable for a variety of aryl and aliphatic aldehydes affording only *trans*-isomer (Table 2). In particular different *para*-substituted benzaldeydes were found to provide the products in high yields with good enantioselectivities (entries 1-9). 4-Methylbenzaldehyde (**2b**) afforded the product **3b** in 67% ee and pleasingly it was improved to 94% ee after recrystallization (entry 2). However other 4-alkyl substituted benzaldehyde derived products are sticky liquids and did not crystallize under various conditions (entries 3-4). Interestingly, solid crystalline products (**3e**-**3g**) were obtained from 4-halo substituted benzaldehydes in high yields with good optical purities (entries 5-7). Excellent enantioselectivities could be attained after single recrystallization for these products. Anisaldehyde delivered a sticky liquid product in moderate yield with modest enantioselectivity (entry 8). On the other hand a solid product **3i** was attained from biphenyl-4-carbaldehyde in excellent yield (95%) with similar enantioselectivity which could be enhanced to

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78% ee after recrystallization (entry 9). Decreased enantioselectivities were obtained for the products derived from *ortho*- and *meta*-substituted benzaldehydes (entries 10-11). However, the enantioslectivity of product **3j** could be improved to excellent 99% ee after single crystallization (entry 10). 2,4-Dimethylbenzaldehyde provided product **3l** in 91% yield with 70% ee and here also the enantioselecitivity could be improved to 95% ee after recrystallization (entry 12). Cinnamaldehyde could also be used in our reaction but poor enantioselectivity was attained for the product **3m** (entry 13). Aliphatic aldehydes are challenging substrates for this kind of reaction due to imine-enamine tautomerization. Gratifyingly, aliphatic aldehydes were successfully enagaged in our reaction and moderate enantioselectivities were obtained for the products **3m** and **3o** (entries 14-15). Then different nitroalkanes having substitutions on the aryl group were prepared and reacted with benzaldehyde under the reaction condition (entries 16-19). 4-Chloro-substituted nitroalkane **1b** provided product **3p** in 70% yield with 75% ee which can be boosted upto 88% ee after crystallization (entry 16). Similarly 3-chloro-substituted nitroalkane **1c** resulted in the formation of product **3q** in 72% yield and with slightly lower enantioselectivity (62% ee). The enantioselectivity can be augmented to 74% ee after crystallization (entry 17). The chloro functionalities in products **3p** and **3q** could be exploited in Pd catalyzed cross-coupling reactions. Then nitroalkane **1d** having dimethylamino functionality was prepared and it was found to be tolerant under the reaction condition providing product **3r** in 80% yield and 64% ee (entry 18). Here also crystallization helps to improve the enantioselectivity (upto 76% ee). Finally CF_3 substituted product **3s** was obtained from nitroalkane **1e** in moderate yield (69%) and enantioselectivity (76% ee) that can be increased to 82% ee after crystallization.

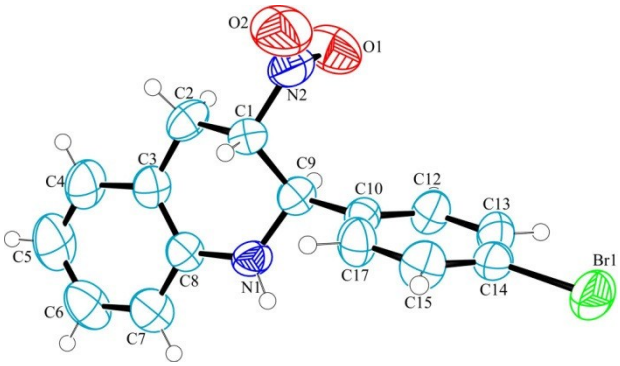

Figure 2 X-ray crystallographic structure of **3f**

The absolute configuration of the product was determined to be (2*R*, 3*S*) by X-ray crystallography[12] (Figure 2) as well as by comparison of the optical rotation with literature value[4j] (see supporting information for details). On the basis of the absolute configuration, a plausible transition state (**A**) has been drawn in Figure 3. It dictates that the quinine derived thiourea catalyst binds in bifunctional mode with the substrate.[13] The thiourea moiety presumably activates the nitronate moiety[14] that is generated from the niroalkane by deprotonation. Then the attack of the nitronate group takes place from the *Si* face of the imine.

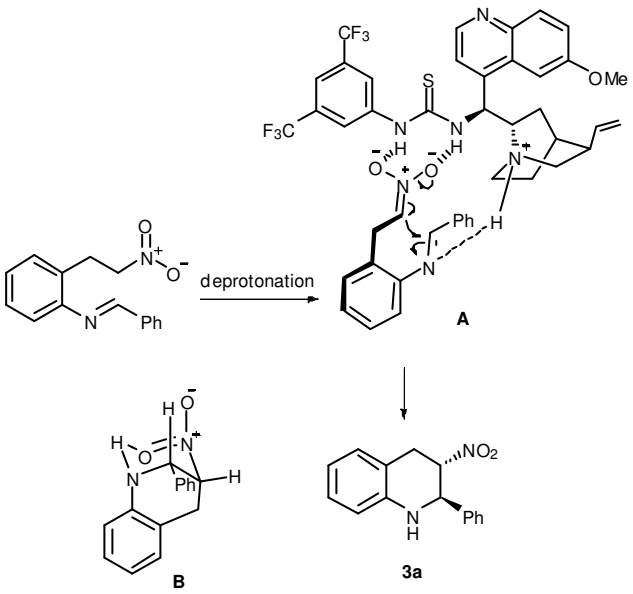

Figure 3 Plausible TS and explanation for diastereoselectivity

Simultaneous activation of the imine by the protonated tertiary amino group takes place from the *Re* face and the desired product **3a** is formed. The extra stability of the *trans*-product could be explained by the model (**B**) where the nitro group and amino group are connected through intramolecular H-bond and the phenyl group takes the equatorial position.[10]

Conclusions

In summary, we have developed asymmetric synthesis of *trans*-2-aryl/alkyl-3-nitro-tetrahydroquinolines using a direct intramolecular aza-Henry reaction. Easily available quinine alkaloid derived bifunctional thiourea catalyst and straightforwardly synthesized amino nitroalkanes were utilized for this purpose. Further applications of these catalysts in other reactions are in progress in our laboratory.

Experimental

General

Chemicals and solvents were purchased from commercial suppliers and used as received. ^{1}H NMR spectra were recorded on 400 MHz and 600 MHz spectrometer.^{13}C NMR spectra were recorded on 100MHz and 150MHz. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.26), carbon (chloroform δ 77.23). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), bs (broad singlet). Coupling constants were reported in Hertz (Hz) HRMS spectra were recorded using ESI mode. Melting points were measured using BüCHI melting point B-540 apparatus. All melting points were measured in open glass capillary and values are uncorrected. Enantiomeric ratios were determined by HPLC analysis using Dionex (Ultimate 3000) instrument with chiral columns in comparison with authentic racemic materials. FT-IR spectra were recorded using Perkin Elmer IR spectrometer. For single crystal

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X-ray analysis the intensity data we recollected using Bruker Smart Apex-II.

All solvent were purified using standard procedure and store under MS 4 A^o .Silica gel (60-120 mesh) was used for column chromatography. Reactions were monitored by TLC on silica gel 60 F_{254} (0.25mm).

Procedure for the intramolecular nitro-Mannich reaction

A solution of nitro-amine **1** (0.12 mmol, 1 equiv) and aldehyde **2** (0.156 mmol, 1.3 equiv) in pentane:*n*-hexane (5:1) was stirred at RT for 2-3h. Then 10 mol% organocatalyst was added to the mixture and stirred for 3 days. After 3 days the crude reaction mixture subjected to column chromatography on silica gel using mixtures of hexanes and ethyl acetate as eluent to afford the corresponding product. Recrystallization was done in ethanol at room temperature.

Characterization of the products

(2*R*, 3*S*)-1,2,3,4-tetrahydro-3-nitro-2-phenylquinoline (3a): Prepared according to the general procedure**:** Yellow solid (26 mg, 85% yield), mp 100-101 ^{o}C (lit. [1] mp 98-99^o C). **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 3.25 (dd, *J* = 4.4, 15.2 Hz, 1H), 3.57 (dd, *J* = 8.6, 15.8 Hz, 1H), 4.14 (bs, 1H), 4.87 (d, *J* = 7.6 Hz, 1H), 4.90-4.96 (m, 1H), 6.60 (d, *J* = 7.6 Hz, 1H), 6.75 (t, *J* = 7.4 Hz, 1H), 7.05-7.11 (m, 2H), 7.34-7.40 (m, 5H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) 31.4, 59.0, 85.3, 114.2, 116.7, 118.6, 127.3, 128.1, 129.2, 129.5, 138.7, 142.7; **ESI-MS** m/z calcd. for $C_{15}H_{14}N_2O_2$ $[M+H]^+$ 255.1128, found 255.1123; FT-IR (KBr) : 3407, 3030, 1604, 1547, 1493, 1371 cm^{-1}. The ee value 74% (τ_{minor} = 10.62 min, τ_{major} = 16.82 min), after recrystallization ee value 98% (τ_{minor} = 10.05 min, τ_{majorr} = 15.66 min) were measured by HPLC analysis using a Chiralpak AS-H column, 254 nm, 25 ^{o}C, n-Hexane/i-propanol = 80:20, flow rate = 1mL/min. The optical rotation of **3a** was $[\alpha]_D^{23}$ = +42.0 (c 0.17, $CHCl_3$).

(2*R*, 3*S*)-1,2,3,4-tetrahydro-3-nitro-2-p-tolylquinoline (3b): Prepared according to the general procedure: White solid (29 mg, 90% yield), mp 105-106 ^{o}C (lit.[1] mp 107-109^o C). **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 3.25 (dd, *J* = 4.8, 16 Hz, 1H), 3.57 (dd, *J* = 8.8, 16.2 Hz, 1H), 4.11 (bs, 1H), 4.81 (d, *J* = 8.8 Hz, 1H), 4.88-4.93 (m, 1H), 6.59 (d, *J* = 7.6 Hz, 1H), 6.74 (t, *J* = 8.4 Hz, 1H), 7.05-7.10 (m, 2H), 7.16-7.18 (m, 2H), 7.26-7.28 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) 21.3, 31.6, 58.9, 85.5, 114.2, 116.7, 118.5, 127.2, 128.1, 129.5, 129.9, 135.5, 139.1, 142.8; **ESI-MS** m/z calcd for $C_{16}H_{16}N_2O_2$ $[M+H]^+$ 269.1285, found 269.1283; **FT-IR (KBr)** 3390, 2920, 2850, 1603, 1546, 1454, 1366, 1204 cm^{-1}. The ee value 67% (τ_{minor} = 9.76 min, τ_{major} = 13.14 min) and after recrystallization ee value 94% (τ_{minor} = 10.05 min, τ_{major} = 13.37 min) were determined by HPLC analysis using Chiralpak AS-H column, 254 nm, 25 ^{o}C, n-Hexane/i-Propanol = 80:20, flow rate = 1 mL/min. The optical rotation of **3b** was $[\alpha]_D^{23}$ = +41.0 (c 0.15, $CHCl_3$).

(2*R*,3*S*)-2-(4-tert-butylphenyl)-1,2,3,4-tetrahydro-3-nitro-quinoline (3c): Prepared according to the general procedure: Yellow oil (23.8 mg, 78% yield); **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 1.30 (s, 9H), 3.26 (dd, *J* = 4.8, 16 Hz, 1H), 3.56 (dd, *J* = 9.2, 16 Hz, 1H), 4.12 (bs, 1H), 4.84 (d, *J* = 9.2 Hz, 1H), 4.90-4.96 (m, 1H), 6.58 (d, *J* = 8, 1H), 6.74 (t, *J* = 7.6 Hz, 1H), 7.06-7.11 (m, 2H), 7.31-7.32 (m, 2H), 7.37-7.39 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) 31.4, 31.6, 58.7, 85.2, 114.2, 116.7, 118.5, 126.1, 127.1, 128.1, 129.5, 135.5, 142.8, 152.2; **ESI-MS** m/z calcd for $C_{19}H_{22}N_2O_2$ $[M+H]^+$ 311.1754, found 311.1753**; FT-IR (KBr)** 3374, 2964, 2924, 1607, 1546, 1370 cm^{-1}. The ee value 61% (τ_{minor} = 12.24 min, τ_{major} = 14.36 min) was determined by HPLC analysis using Chiralpak IA column, 254 nm, 25 ^{o}C, n-Hexane/i-Propanol = 99.5:0.5, flow rate = 1 mL/min. The optical rotation of **3c** was $[\alpha]_D^{23}$ = +20.0 (c 0.75, $CHCl_3$).

(2*R*, 3*S*)-1,2,3,4-tetrahydro-2-(4-isopropylphenyl)-3-nitro-quinoline (3d): Prepared according to the general procedure: Yellow oil (26.7 mg, 75% yield); **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 1.23 (d, *J* = 6.4 Hz, 6H), 2.86-2.93 (m, 1H), 3.26 (dd, *J* = 5.2, 16.28 Hz, 1H), 3.56 (dd, *J* = 9.2, 16.2 Hz, 1H), 4.12 (bs, 1H), 4.83 (d, *J* = 8 Hz, 1H), 4.91-4.95 (m, 1H), 6.58 (d, *J* = 8 Hz, 1H), 6.74 (t, *J* = 7.2 Hz, 1H), 7.05-7.10 (m, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 7.2 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) 24.0, 24.1, 31.6, 34.0, 58.8, 85.3, 114.2, 116.7, 118.5, 127.3, 127.3, 128.1, 129.5, 135.9, 142.8, 150.0; **ESI-MS** m/z calcd for $C_{18}H_{20}N_2O_2$ $[M+H]^+$ 297.1598, found 297.1595; **FT-IR (KBr)** 3427, 2965, 2928, 1726, 1607, 1550, 1493, 1370 cm^{-1}. The ee value 52% (τ_{minor} = 12.53 min, τ_{major} = 17.15 min) was determined by HPLC analysis using Chiralpak IA column, 254 nm, 25 ^{o}C, n-Hexane/i-Propanol = 99.5:0.5, flow rate = 1 mL/min. The optical rotation of **3a** was $[\alpha]_D^{24}$ = +25.0 (c 0.27, $CHCl_3$).

(2*R*,3*S*)-2-(4-chlorophenyl)-1,2,3,4-tetrahydro-3-nitro-quinoline (3e): Prepared according to the general procedure: Pale yellow solid (28.7 mg, 83% yield), mp 119-120 ^{o}C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 3.24 (dd, *J* = 4.8, 17 Hz, 1H), 3.57 (dd, *J* = 8.4, 16.4 Hz, 1H), 4.11 (bs, 1H), 4.85(d, *J* = 7.6 Hz, 1H), 4.88-4.91 (m, 1H), 6.61 (d, *J* = 8.8 Hz, 1H), 6.76 (t, *J* = 6.8 Hz, 1H), 7.06-7.12 (m, 2H), 7.32-7.35 (m, 4H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) 31.3, 58.4, 85.2, 114.4, 116.6, 119.0, 128.2, 128.8, 129.5, 129.5, 135.1, 137.2, 142.5; **ESI-MS** m/z calcd for $C_{15}H_{13}N_2O_2Cl$ $[M+H]^+$ 289.0738, found 289.0736; **FT-IR (KBr)** 3398, 2924, 2850, 1607, 1548, 1484, 1370, 1337 cm^{-1}. The ee value 70% (τ_{minor} = 9.07 min, τ_{major} = 11.52 min) and after recrystallization ee value 96% (τ_{minor} = 9.06 min, τ_{major} = 11.54 min) were determined by HPLC analysis using a chiralpak AS-H column, 254 nm, 25 ^{o}C, n-Hexane/i-propanol = 70:30, flow rate = 1 mL/min. The optical rotation of **3e** was $[\alpha]_D^{25}$ = +44.0 (c 0.25, $CHCl_3$).

(2*R*, 3*S*)-2-(4-bromophenyl)-1,2,3,4-tetrahydro-3-nitro-quinoline (3f): Prepared according to the general procedure: Yellow solid (31.9 mg, 80% yield), mp 128-129 ^{o}C (lit.[1] mp 125-127^o C). **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 3.24 (dd, *J* = 4.8, 16.4 Hz, 1H), 3.56 (dd, *J* = 8.4, 16 Hz, 1H), 4.12 (bs, 1H), 4.84-4.91 (m, 2H), 6.61 (d, *J* = 8 Hz, 1H), 6.76(t, *J* = 7.6 Hz, 1H), 7.06-7.12 (m, 2H), 7.26-7.29(m, 2H), 7.50 (d, *J* = 8.4 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) 31.2, 58.4, 85.1, 114.4, 116.6, 118.9, 123.2, 128.2, 129.0, 129.5, 132.4, 137.7, 142.4; **ESI-MS** m/z calcd for $C_{15}H_{13}N_2O_2Br$ $[M+H]^+$ 333.0233, found 333.0231; FT-IR (KBr) 3398, 2924, 2854, 1607, 1550, 1488, 1374 cm^{-1}. The ee value 58% (τ_{minor} = 20.09 min, τ_{major} = 25.19 min) and after recrystallization ee value 96% (τ_{minor} = 20.12 min, τ_{major} = 25.25 min) were determined by HPLC analysis using a Chiralpak AS-H column, 254 nm, 25 ^{o}C, n-Hexane/i-Propanol = 80:20, flow rate = 1 mL/min. The optical rotation of **3f** was $[\alpha]_D^{25}$ = +14.0 (c 0.25, $CHCl_3$).

(2*R*, 3*S*)-2-(4-fluorophenyl)-1,2,3,4-tetrahydro-3-nitro-

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quinoline (3g): Prepared according to the general procedure: Pale yellow solid (26 mg, 80% yield), mp 130-131 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 3.26 (dd, *J* = 4.8, 16 Hz, 1H), 3.58 (dd, *J* = 9.2, 16.2 Hz, 1H), 4.11 (bs, 1H), 4.82-4.91 (m, 2H), 6.61 (d, *J* = 7.6 Hz, 1H), 6.76 (t, *J* = 7.2 Hz, 1H), 7.04-7.11 (m, 4H), 7.37-7.40 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) 31.6, 58.5, 85.5, 114.4, 116.2 (d, *J* = 22 Hz), 116.7, 118.9, 128.2, 129.2 (d, *J* = 9 Hz), 129.5, 134.5, 134.3, 142.6, 162.0, 164.4; **ESI-MS** m/z calcd for $C_{15}H_{13}N_2O_2F$ $[M+H]^+$ 273.1034, found 273.1030; **FT-IR (KBr)** 3407, 2920, 2850, 1730, 1546, 1370, 1337 cm^{-1}. The ee value 68% (τ_{minor} = 14.7 min, τ_{major} = 22.73 min) and after recrystallization ee value 99% (τ_{minor} = 14.88 min, τ_{major} = 22.43 min) were determined by HPLC analysis using chiralpak IA column, 254 nm, 25 °C, n-Hexane/i-Propanol = 95:5, flow rate = 1 mL/min. The optical rotation of **3g** was $[\alpha]_D^{26}$ = +57.0 (c 0.27, $CHCl_3$).

(2*R*, 3*S*)-1,2,3,4-tetrahydro-2-(4-methoxyphenyl)-3-nitro-quinoline (3h): Prepared according to the general procedure: brown oil (20.5 mg 60% yield), **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 3.27 (dd, *J* = 4.8, 16 Hz, 1H), 3.57 (dd, *J* = 9.6, 16 Hz, 1H), 3.80 (s, 3H), 4.09 (bs, 1H), 4.77 (d, *J* = 8.4 Hz, 1H), 4.87-4.92 (m, 1H), 6.59 (d, *J* = 8 Hz,1H), 6.74 (t, *J* = 7.6 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 2H), 7.06-7.10 (m, 2H),7.31 (d, *J* = 8.8 Hz, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) 31.9, 55.5, 58.8, 85.7, 114.2, 114.6, 116.8, 118.6, 128.1, 128.6, 129.5, 130.3, 142.9, 160.3; **ESI-MS** m/z calcd for $C_{16}H_{16}N_2O_2$ $[M+H]^+$ 285.1234, found 285.1237; **FT-IR (KBr)** 3382, 3345, 2924, 2854, 1730, 1603, 1546, 1509, 1374, 1337 cm^{-1}. The ee value 60% (τ_{minor} = 26.31 min, τ_{major} = 31.05 min) was determined by HPLC analysis using AS-H Chiralpak column, 254 nm, 25 °C, n-Hexane/i-Propanol = 80:20, flow rate = 1 mL/min. The optical rotation of **3h** was $[\alpha]_D^{27}$ = +33.0 (c 0.15, $CHCl_3$).

(2*R*, 3*S*)-2-(Biphenyl)-1,2,3,4-tetrahydro-3-nitroquinoline (3i): Prepared according to the general procedure: Yellow solid (37.6 mg, 95% yield), mp 187-189 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 3.29 (dd, *J* = 4.8, 16 Hz, 1H), 3.59 (dd, *J* = 9.2, 16.2 Hz, 1H), 4.18 (bs,1H), 4.92-5.00 (m, 2H), 6.63 (d, *J* = 8 Hz,1H), 6.76 (t, *J* = 7.2 Hz, 1H), 7.07-7.12 (m, 2H), 7.34-7.38 (m, 1H), 7.42-7.48 (m, 4H), 7.56-7.60 (m, 4H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ 31.4, 58.7, 85.2, 114.3, 116.7, 118.7, 127.3, 127.8, 127.9, 128.1, 129.0, 129.5, 137.6, 140.5, 142.1, 142.7; **ESI-MS** m/z calcd for $C_{21}H_{18}N_2O_2$ $[M+H]^+$ 331.1441, found 331.1441; **FT-IR (KBr)** 3411, 2924, 2854, 1734, 1611, 1546, 1480, 1370, 1333 cm^{-1}. The ee value 61% (τ_{minor} = 20.57 min, τ_{major} = 23.57 min) and recrystallization ee 78% (τ_{minor} = 20.46 min, τ_{major} = 23.58 min) were determined by HPLC analysis using Chiralpak IA column, 254 nm, 25 °C, n-Hexane/i-Propanol = 98:2, flow rate = 1 mL/min. The optical rotation of **3i** was $[\alpha]_D^{27}$ = +51.0 (c 0.30, $CHCl_3$).

(2*R*, 3*S*)-2-(2-chlorophenyl)-1,2,3,4-tetrahydro-3-nitro-quinoline (3j): Prepared according to the general procedure: Pale yellow solid (25.9 mg, 75% yield), mp 129-130 °C (lit.[1] mp 126-128° C). **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 2.99 (dd, *J* = 4.8, 17 Hz, 1H), 3.51 (dd, *J* = 4.6, 17.2 Hz, 1H), 4.27 (bs, 1H), 5.03-5.06 (m, 1H), 5.64-5.66 (m, 1H), 6.68 (d, J = 8 Hz, 1H), 6.74 (t, *J* = 7.8 Hz, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 7.22-7.29 (m, 2H), 7.38- 7.45 (m, 2H); **^{13}C NMR (100 MHz, $CDCl_3$)** δ (ppm) 28.1, 54.3, 80.5, 114.1, 115.6, 118.6, 127.8, 128.3, 128.7, 129.6, 129.9, 130.2, 132.3, 137.7, 142.0; **ESI-MS** m/z calcd for $C_{15}H_{13}N_2O_2Cl$ $[M+H]^+$ 289.0738, found 289.0737; **FT-IR (KBr)** 3398, 2924, 2854, 1726, 1607, 1546, 1464, 1484, 1362, 1259 cm^{-1}. The ee value 40% (τ_{minor} = 7.55 min, τ_{major} = 10.05 min) and recrystallization ee value 99% (τ_{minor} = 7.55 min, τ_{major} = 10.09 min) were determined by HPLC analysis using Chiralpak AS-H column, 254 nm, 25 °C, n-Hexane/i-Propanol = 80:20, flow rate = 1 mL/min. The optical rotation of **3j** was $[\alpha]_D^{30}$ = +04.0 (c 0.15, $CHCl_3$).

(2*R*, 3*S*)-2-(3-bromophenyl)-1,2,3,4-tetrahydro-3-nitro-quinoline (3k): Prepared according to the general procedure: Yellow solid (33.8 mg, 85% yield), mp 108-110 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 3.24 (d, *J* = 16 Hz, 1H), 3.56 (dd, *J* = 8.4, 17.2 Hz, 1H), 4.14 (bs, 1H), 4.88 (bs, 2H), 6.62 (d, *J* = 8 Hz, 1H), 6.77 (t, *J* = 7.6 Hz, 1H), 7.08(t, *J* = 8.4 Hz, 2H), 7.22-7.25 (m.1H), 7.32 (d, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.57 (bs, 1H); **^{13}C NMR (100 MHz,$CDCl_3$)** δ (ppm) 31.2, 58.3, 85.0, 114.4, 116.5, 119.0, 123.3, 126.2, 128.2, 129.5, 130.4, 130.8, 132.4, 141.1, 142.3; **ESI-MS** m/z calcd for $C_{15}H_{13}N_2O_2Br$ $[M+H]^+$ 333.0233, found 333.0233; **FT-IR (KBr)** 3407, 2924, 2854, 1607, 1546, 1468, 1362 cm^{-1}. The ee value 47% (τ_{minor} = 29.71 min, τ_{major} = 37.24 min) was determined by HPLC analysis using a Chiralpak AS-H column, 254 nm, 25 °C, n-Hexane/i-Propanol = 95:5, flow rate = 1 mL/min. The optical rotation of **3k** was $[\alpha]_D^{28}$ = +06.0 (c 0.28, $CHCl_3$).

(2*R*, 3*S*)-1,2,3,4-tetrahydro-2-(2,4-dimethylphenyl)-3-nitro-quinoline (3l): Prepared according to the general procedure: White solid (31 mg, 91% yield), mp 126-128 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 2.29 (s, 3H), 2.39 (s, 3H), 3.25 (dd, *J* = 4.8, 16.4 Hz,1H), 3.56 (dd, *J* = 4.8, 16.4 Hz, 1H), 3.99 (bs, 1H), 4.92-4.97 (m, 1H), 5.14 (d, *J* = 7.6 Hz, 1H), 6.57 (d, *J* = 8 Hz, 1H), 6.74 (t, *J* = 7.2 Hz, 1H), 6.99-7.03 (m, 2H), 7.06-7.10 (m, 2H), 7.27-7.29 (m, 1H); **^{13}C NMR (100 MHz,$CDCl_3$)** δ (ppm) 19.2, 21.2, 31.3, 54.8, 83.6, 114.1, 116.5, 118.4, 126.9, 127.7, 128.1, 129.5, 132.0, 133.8, 136.1, 138.6, 142.9; **ESI-MS** m/z cacld for $C_{17}H_{18}N_2O_2$ $[M+H]^+$ 283.1441, found 283.1443; **FT-IR (KBr)** 3374, 3345, 2924, 1607, 1546, 1337 cm^{-1}. The ee value 70% (τ_{minor} = 7.59 min, τ_{major} = 8.58 min) and recrystallization ee value 95% (τ_{minor} = 7.82 min, τ_{major} = 8.52 min) were determined by HPLC analysis using Chiralpak IA column, 254 nm, 25 °C, n-Hexane/ i-Propanol = 98.5:1.5, flow rate = 1 mL/min. The optical rotation of **3l** was $[\alpha]_D^{30}$ = +18.0 (c 0.05, $CHCl_3$).

(2*R*, 3*S*)-1,2,3,4-tetrahydro-3-nitro-2-styrylquinoline (3m): Prepared according to the general procedure: Yellow oil (25.2 mg 75% yield), **^{1}H NMR (400 MHz, $CDCl_3$)** δ (ppm) 3.28 (dd, *J* = 5.2, 16.2 Hz, 1H), 3.54 (dd, *J* = 8.4, 16.2 Hz, 1H), 4.02 (bs, 1H), 4.46-4.50 (m ,1H), 4.76-4.81 (m, 1H), 6.16 (dd, *J* = 7.6, 15.6 Hz, 1H), 6.59 (d, *J* = 9.2 Hz, 1H), 6.70-6.76 (m ,2H), 7.04-7.10 (m, 2H), 7.35-7.38 (m, 5H); **^{13}C NMR (100 MHz,$CDCl_3$)** δ (ppm) 30.7, 57.4, 83.8, 114.5, 116.7, 118.7, 125.5, 126.9, 128.1, 128.6, 128.8, 129.5, 135.4, 135.7, 142.0; **ESI-MS** m/z calcd for $C_{17}H_{16}N_2O_2$ $[M+H]^+$ 281.1285, found 281.1276**; FT-IR (KBr)** 3411, 2928, 2850, 1544, 1484, 1452, 1372 cm^{-1}. The ee value 28% (τ_{major} = 18.04 min, τ_{minor} = 37.99 min) was determined by HPLC analisis using Daicel Chiralpak OD-H column, 254 nm, 25 °C, n-Hexane/i-Propanol = 70:30, flow rate = 1 mL/min. The optical rotation of **3m** was $[\alpha]_D^{28}$ = +16.0 (c 0.23, $CHCl_3$).

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(2*R*, 3*S*)-2-butyl-1,2,3,4-tetrahydro-3-nitroquinoline (3n): Prepared according to the general procedure: Yellow oil (23 mg, 82% yield), **^{1}H NMR (400 MHz, CDCl$_3$)** δ (ppm) 0.92 (t, *J* = 7.2 Hz, 3H), 1.32-141 (m, 3H), 1.47-1.56 (m, 3H), 3.20 (dd, *J* = 5.2, 16.4 Hz, 1H), 3.49 (dd, *J* = 7.6, 16.4 Hz, 1H), 3.76-3.81 (m, 1H), 3.89 (bs, 1H), 4.63-4.68 (m, 1H), 6.55 (d, *J* = 8 Hz, 1H), 6.70 (t, *J* = 7.2 Hz, 1H), 7.02-7.06 (m, 2H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ (ppm) 14.1, 22.7, 27.4, 30.4, 32.7, 54.1, 83.6, 114.7, 116.9, 118.4, 127.9, 129.4, 142.2; **ESI-MS** m/z calcd for $C_{13}H_{18}N_2O_2$ $[M+H]^+$ 235.1441, found 235.1443; **FT-IR (KBr**) 3415, 2957, 2928, 1726, 1603, 1546, 1488, 1378, 1268 cm^{-1}. The ee value 68% (τ_{minor} = 14.43 min, τ_{major} = 16.48 min) was determined by HPLC analysis using Chiralpak IA column, 254 nm, 25 °C, n-Hexane/i-Propanol = 99:1, flow rate = 1 mL/min. The optical rotation of **3n** was $[\alpha]_D^{28}$ = +27.0 (c 0.78, $CHCl_3$).

(2*R*, 3*S*)-1,2,3,4-tetrahydro-3-nitro-2-propylquinoline (3o): Prepared according to the general procedure: Yellow oil (21.4 mg, 81% yield), **^{1}H NMR (400 MHz, CDCl$_3$)** δ (ppm) 0.87-0.98 (m, 5H), 1.56 (m, 2H), 3.22 (dd, *J* = 6.4, 17 Hz, 1H), 3.38 (dd, *J* = 6.4, 17.4 Hz, 1H), 3.71 (bs, 1H), 3.92 (bs, 1H), 4.93-4.97 (m, 1H), 6.58 (d, *J* = 8.4 Hz, 1H), 6.74 (t, *J* = 7.2 Hz, 1H), 7.02-7.07 (m , 2H); **^{13}C NMR (150 MHz, CDCl$_3$)** δ (ppm) 14.0, 19.2, 29.1, 32.8, 53.3, 81.2, 115.1, 117.3, 118.9, 127.6, 129.5, 142.4; **ESI-MS** m/z calcd for $C_{12}H_{16}N_2O_2$ $[M+H]^+$ 221.1285, found 221.1283; **FT-IR (KBr)** 3415, 2957, 2928, 1726, 1603, 1546, 1488, 1378, 1268 cm^{-1}. The ee value 63% (τ_{major} = 33.06 min, τ_{minor} = 55.86 min) was determined by HPLC analysis using Daicel Chiralpak OD-H column, 254 nm, 25 °C, n-Hexane/i-Propanol = 93:7, flow rate 1 mL/min. The optical rotation of **3o** was $[\alpha]_D^{28}$ = +28.0 (c 1.05, $CHCl_3$).

(2*R*, 3*S*)-6-chloro-1,2,3,4-tetrahydro-3-nitro-2-phenylquinoline (3p): Prepared according to the general procedure: Yellow oil (24 mg, 70% yield), **^{1}H NMR (600 MHz, CDCl$_3$)** δ (ppm) 3.16 (dd, *J* = 4.8, 16.8 Hz, 1H), 3.51(dd, *J* = 7.8, 16.5 Hz, 1H), 4.18-4.22 (m, 1H), 4.88-4.94 (m, 2H), 6.53-6.55 (m, 1H), 7.03-7.39 (m, 5H); **^{13}C NMR (150 MHz, CDCl$_3$)** δ (ppm) 32.1, 58.7, 94.5, 115.2, 118.1, 123.2, 127.5, 128.1, 129.1, 129.3, 129.3, 138.6, 141.2; **ESI-MS** m/z calcd for $C_{15}H_{13}ClN_2O_2$ $[M+H]^+$ 289.0733, found 289.0737; **FT-IR (KBr)** 3398, 2924, 2850, 1607, 1548, 1484, 1370, 1337 cm^{-1}. The ee value 75% (τ_{major} = 13.43 min, τ_{minor} = 18.90 min) and recrystalliszation ee 88% (τ_{major} = 13.42 min, τ_{minor} = 18.63 min) were determined by HPLC analysis using Daicel Chiralpak OD-H column, 254 nm, 25 °C, n-Hexane/i-Propanol = 70:30, flow rate = 1 mL/min. The optical rotation of **3p** was $[\alpha]_D^{28}$ = +46.0 (c 0.10, $CHCl_3$).

(2*R*, 3*S*)-5-chloro-1,2,3,4-tetrahydro-3-nitro-2-phenylquinoline (3q): Prepared according to the general procedure: Yellow solid (25mg, 72% yield), mp 165-166 °C. **^{1}H NMR (600 MHz, CDCl$_3$)** δ (ppm) 3.31 (dd, *J* = 5.8, 16.8 Hz, 1H), 3.52 (dd, *J* = 7.8, 17.1 Hz, 1H), 4.27 (bs, 1H), 4.87 (d, *J* = 7.8 Hz, 1H), 4.93-4.96 (m, 1H), 6.52 (d, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 7.02 (t, *J* = 7.8 Hz, 1H), 7.36-7.39 (m, 5H); **^{13}C NMR (100 MHz, CDCl$_3$)** δ (ppm) 28.8, 58.3, 85.0, 112.6, 115.1, 119.2, 127.2, 128.5, 129.3, 134.8, 138.2, 144.2; **ESI-MS** m/z calcd for $C_{15}H_{13}ClN_2O_2$ $[M+H]^+$ 289.0733, found 289.0735; **FT-IR (KBr)** 3393, 2923, 1599, 1545, 1493, 1475, 1334, 1316 cm^{-1}. The ee value 62% (τ_{major} = 15.77 min, τ_{minor} = 22.52 min) and after recrystallization 74% (τ_{major} = 14.75 min, τ_{minor} = 20.21 min) were determined by HPLC analysis using Daicel Chiralpak OD-H column , 254 nm, 25 °C, n-Hexane/i-propanol = 80:20, flow rate = 1 mL/min. The optical rotation of **3q** was $[\alpha]_D^{29}$ = +31.0 (c 0.25, $CHCl_3$).

(2*R*, 3*S*)-1,2,3,4-tetrahydro-N,N-dimethyl-3-nitro-2-phenylquinolin-7-amine (3r): Prepared according to the general procedure: Red solid (29 mg, 80% yield), mp 109-111 °C. **^{1}H NMR (400 MHz, CDCl$_3$) δ (ppm)** 3.19 (dd, *J* = 4.8, 15.6 Hz, 1H), 3.48 (dd, *J* = 9.6, 15.6 Hz, 1H), 4.07 (bs, 1H), 4.82 (d, *J* = 7.2 Hz, 1H), 4.88-4.93 (m, 1H), 5.95 (d, *J* = 2.4 Hz, 1H), 6.23 (dd, *J* = 2.8, 8.4 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 1H), 7.33-7.41 (m, 5H)**; ^{13}C NMR (100 MHz, CDCl$_3$)** δ (ppm) 31.0, 40.8, 59.2, 86.0, 97.8, 104.4, 105.3, 127.4, 129.1, 129.1, 129.9, 138.8, 143.3, 150.9; **ESI-MS** m/z calcd for $C_{17}H_{19}N_3O_2$ $[M+H]^+$ 298.1550, found 298.1551; **FT-IR (KBr)** 3316, 2871, 1579, 1619, 1553,1520, 1479, 1451, 1336, 1372 cm^{-1}. The ee value 64% (τ_{minor} = 33.56 min, τ_{major} = 40.16 min) and recrystallization 76% (τ_{minor} = 33.28 min, τ_{major} = 39.41 min.) were determined by HPLC analysis using Chiralpak IA column, 254 nm, 25 °C, n-Hexane/i-propanol = 80:2, flow rate = 0.8 mL/min. The optical rotation of **3r** was $[\alpha]_D^{29}$ = +04.0 (c 0.75, $CHCl_3$).

(2*R*, 3*S*)-6-(trifluoromethyl)-1,2,3,4-tetrahydro-3-nitro-2-phenylquinoline (3s): Prepared according to the general procedure: White solid (27 mg, 69% yield), mp 125-127 °C. **^{1}H NMR (600 MHz, CDCl$_3$)** δ (ppm) 3.22 (dd, *J* = 4.8, 16.8 Hz, 1H), 3.57 (dd, *J* = 8.4, 16.8 Hz, 1H), 4.38 (bs, 1H), 4.90-4.93 (m, 2H), 6.84 (bs, 1H), 6.97 (d, *J* = 7.2 Hz, 1H), 7.16 (d, *J* = 7.8 Hz, 1H), 7.35-7.40 (m, 5H); **^{13}C NMR (150 MHz, CDCl$_3$)** δ (ppm) 30.3, 56.5, 84.2, 110.7, 114.9, 115.0, 120.0, 123.3, 125.1, 127.0, 127.0, 129.4 (d, *J* = 36 Hz), 130.1, 138.5, 142.7; **ESI-MS** m/z calcd for $C_{16}H_{13}F_3N_2O_2$ $[M+H]^+$ 323.1002, found 323.1005; **FT-IR (KBr)** 3401, 2923, 2853, 1622, 1595, 1563, 1549, 1487, 1369, 1337 cm^{-1}.The ee value 76% (τ_{major} = 8.45 min, τ_{minor} = 9.91 min) and recrystallization ee 82% (τ_{major} = 9.26 min, τ_{minor} = 10.78 min) were determined by HPLC analysis using Daicel Chiralpak OD-H column, 254 nm, 25 °C, n-Hexane/i-propanol = 70:30, flow rate = 1 ml/min. The optical rotation of **3s** was $[\alpha]_D^{29}$ = +25.0 (c 0.40, $CHCl_3$).

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Notes and references

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