An Asymmetric Organocatalytic Povarov Reaction with 2-Hydroxystyrenes

Feng Shi,[†] Gui-Juan Xing,[†] Zhong-Lin Tao,[‡] Shi-Wei Luo,^{*,‡} Shu-Jiang Tu,[†] and Liu-Zhu Gong^{*,‡}

[†]School of Chemistry & Chemical Engineering, Jiangsu Normal University, Xuzhou, 221116, China

[‡]Hefei National Laboratory for Physical Sciences at the Microscale and Department of Chemistry, University of Science and Technology of China, Hefei, 230026, China

Supporting Information

ABSTRACT: An organocatalytic asymmetric three-component Povarov reaction involving 2-hydroxystyrenes has been established to provide an efficient method to access structurally diverse *cis*-disubstituted tetrahydroquinolines in high stereoselectivities of up to >99:1 *dr* and 97% *ee*. This protocol also provides an easy access to tetrahydroquinolines with chiral quaternary stereocenters upon using α -alkyl 2-



hydroxystyrenes as substrates. The theoretical studies revealed that the Povarov reaction proceeded through a sequential vinylogous Mannich reaction and an intramolecular Friedel–Crafts reaction, wherein the phosphoric acid acted as bifunctional catalyst to activate 2-hydroxystyrene and aldimine simultaneously.

INTRODUCTION

The prevalent appearance of tetrahydroquinoline skeleton in natural products and unnatural bioactive molecules¹ has led to a great demand for efficient synthetic methods. The Povarov reaction,² an inverse electron-demand aza-Diels–Alder reaction between 2-azadienes and electronically rich olefins catalyzed by either a Lewis or Brønsted acid, represents the most facile and synthetically practical approach to access 1,2,3,4-tetrahydroquinolines in high structural diversity.

Although the development of efficient Povarov reaction has drawn the attention from the chemists for a long time,^{2,3} the reports describing successful asymmetric variants are still rather limited.⁴ In particular, highly reactive olefins such as enamides,^{4f,g,i,j} enol ethers^{4a,e,i} and cyclopentadiene^{4a,c} are mostly selected as substrates (eq 1). So far, there is only one example of



highly enantioselective protocol catalyzed by a chiral scandium complex describing the use of styrene derivatives as the olefin component, very recently established by Feng and co-workers (eq 2),^{4d} while nearly no organocatalytic asymmetric alternatives have been reported, yet.

Herein, we will report the chiral Brønsted acid-catalyzed Povarov reaction involving 2-hydroxystyrene derivatives as the dienophile component,⁵ giving a structurally diverse spectrum of *cis*-tetrahydroquinolines in high stereoselectivities (up to >99:1 *dr*, 97% *ee*) (eq 3).



RESULTS AND DISCUSSION

The chiral phosphoric acids have proven to be privileged organocatalysts that have enabled a large number of highly enantioselective transformations.⁶ However, the nucleophiles activated by the Lewis basic phosphoryl oxygen are commonly enamides (enamines, enols) or their analogues and precursor-s.^{6,4e-k} Our continuous interest in the Brønsted acid-catalyzed multicomponent reactions⁷ prompted us to envisage that the 2-hydroxystyrene, structurally similar to an dienol species, is principally able to participate in a vinylogous Mannich reaction with an aldimine generated from an aldehyde and aniline under the catalysis of a chiral phosphoric acid,⁸ forming a transient intermediate **I**, which principally undergoes an intramolecular Friedel–Crafts reaction (the 1,4-addition of aniline to the enone functionality), again under the catalysis of the same phosphoric acid⁹ to afford enantioenriched multiply substituted tetrahydroquinolines (Scheme 1).

Received: June 6, 2012

Scheme 1. Proposed Reaction Pathway







^{*a*}Unless indicated otherwise, the reaction was carried out in 0.1 mmol scale in a solvent (1 mL) with MS (100 mg) for 60 h, and the ratio of 1/2a/3a was 1.2/1/1.2. ^{*b*}Isolated yield. ^{*c*}The *dr* was determined by ¹H NMR. ^{*d*}The *ee* was determined by HPLC. ^{*c*}Performed in anhydrous and under argon condition with 150 mg of 5 Å MS. ^{*f*}In the presence of 5 mol % **5e**. ^{*g*}In the absence of MS in anhydrous and under argon condition. ^{*h*}The reaction time was 84 h. ^{*i*}The ratio of 1b/2a/3a was 1.2/1/2.

The initial attempt to validate our hypothesis examined a three-component reaction of 4-nitrobenzaldehyde 1a, 4methoxyaniline 2a and 2-hydroxystyrene 3a, which was performed in the presence of 10 mol % of chiral phosphoric acids 5 in dichloromethane at room temperature (Table 1). The preliminary results revealed that the 3,3'-triphenylsilyl binolbased phosphoric acid 5e turned out to be much more promising than other analogues in terms of stereochemical control, capable of delivering the highest level of enantioselectivity of up to 94% ee (entries 1-4 vs 5), whereas the yield was relatively much lower (19%). Thus, further efforts were devoted to optimize the reaction conditions to improve the yield and enantioselectivity. The evaluation of molecular sieves (MS) found that the addition of 5 Å MS rendered a much cleaner reaction that provided 73% yield, but accompanying with a slight erosion of both enantioselectivity and diastereoselectivity (entry 7). The presence of more amounts of 5 Å MS and conducting the

reaction under argon resulted in a high yield of 74% and an excellent enantioselectivity of 95% ee (entry 8). Lowering the catalyst loading had no obvious effect on the yield, but led to a decreased enantioselectivity, albeit with increased diastereoselectivity (entry 9). In the absence of 5 Å MS, the enantioselectivity was sacrificed to some extent, while the yields were nearly the same as that with 5 Å MS, which indicated that 5 Å MS played some important role in controlling the enantioselectivity of the reaction (entry 10). However, the application of the optimized reaction conditions as listed in entry 8 to an electronically neutral benzaldehyde 1b led to unsatisfactory results (82% ee) (entry 11). Thus, the reaction conditions for electronically neutral and rich aldehyde substrates were subsequently reoptimized. The survey of the solvents found that toluene was a more suitable reaction media, in which a high enantioselectivity of 92% ee was offered, albeit in a low yield (entry 13). To our delight, tuning the stoichiometry of 2-

hydroxystyrene **3a** rendered the reaction to proceed in a much higher yield with an improved diastereoselectivity and nearly maintained enantioselectivity (entry 14 vs 13).

With the optimal conditions in hand, the generality for aldehydes 1 was then explored by the reaction with 4-methoxyaniline 2a and 2-hydroxystyrene 3a. As shown in Table 2, this protocol is amenable to a wide scope of aldehydes

 Table 2. Scope of the Aldehydes^a



^{*a*}Unless indicated otherwise, the reaction was carried out in 0.1 mmol scale in toluene (1 mL) with 5 Å MS (150 mg) for 84 h under argon, and the ratio of **1/2a/3a** was 1.2/1/2. ^{*b*}Isolated yield. ^{*c*}The *dr* was determined by ¹H NMR. ^{*d*}The *ee* was determined by HPLC. ^{*e*}Performed in dichloromethane (1 mL) for 60 h, and the ratio of **1a/2a/3a** was 1.2/1/1.2. ^{*f*}The ratio of **1m/2a/3a** was 1.2/1/4. ^{*g*}The ratio of **1n/2a/3a** was 1.2/1/7. ^{*h*}In the presence of 20 mol % **5e**.

including benzaldehydes bearing either of an electronically poor, neutral, or rich substituent, heteroaromatic and aliphatic aldehydes in high enantioselectivities (up to 95% ee) and diastereoselectivities (up to >99:1 dr). Basically, the benzaldehydes substituted with an electron-withdrawing group participated in the reaction to give relatively higher stereoselectivities (entries 1-7, 90-95% ees, 6:1-25:1 drs) and good yields. Moreover, disubstituted benzaldehydes appeared to be suitable substrates, offering high yields and good stereoselectivities (entries 8-9). More importantly, even if electronically rich benzaldehydes and a heteroaromatic aldehyde were applied, high stereoselectivities could also be delivered (entries 11-14, 83-94% ees, $20:1 \rightarrow 99:1 drs$). However, in some cases the relatively lower yields were observed because of the low reactivity associated with the aldehydes (entries 13-14). The presence of excess amounts of 2-hydroxylstyrene 3a was found to efficiently enhance the yields but leading to a slight erosion of the enantioselectivity (entries 13-14, in parentheses). More interestingly, aliphatic aldehydes can also be applied to this reaction in moderate to high enantioselectivity and diastereoselectivity but with a low yield, as exemplified by 3phenylpropanal (entry 15). Increasing the loading of catalyst **5e** resulted in a greatly improved enantioselectivity of 85% *ee* and diastereoselectivity of 25:1 *dr*, but still with a low yield (entry 15, in parentheses).

The substrate scope with respect to anilines was then explored by the reaction with 4-nitrobenzaldehyde 1a and 2-hydroxystyrene 3a (Table 3, entries 1-5). A variety of anilines substituted with either electron-donating or -withdrawing groups served as appropriate substrates, providing the corresponding products in high yields (70-77%) and good enantioselectivities (82-95% ees). The generality for 2-hydroxystyrenes was also examined by the reaction with 4-nitrobenzaldehyde 1a and 4-methoxyaniline **2a** (Table 3, entries 6–11). Both 2-hydroxystyrenes and α -alkyl 2-hydroxystyrenes bearing different substituents on their aromatic rings were accommodated and led to the generation of desired products in good to excellent stereoselectivities (6:1 to >99:1 drs, 83–97% ees). Significantly, the use of the α -alkyl 2hydroxystyrenes afforded tetrahydroquinolines with an allcarbon quaternary stereogenic center in high enantioselectivity. More interestingly, the α -alkyl 2-hydroxystyrenes provided a cleaner reaction than 2-hydroxystyrenes, giving much higher yields but with slightly lower enantioselectivities (entries 8-11 vs 1, 6-7). Notably, in the case of 4-ethoxyaniline **2b** as a reaction component, α -methyl 2-hydroxystyrenes 3d exhibited higher reactivity, delivering a higher yield of 87% and a higher enantioselectivity of 94% ee than 2-hydroxystyrene 3a (entry 12 vs 2). In addition, 3,4-dichlorobenzaldehvde 1i was employed instead of 4-nitrobenzaldehyde 1a as aldehyde component to react with aniline 2a and α -alkyl 2-hydroxystyrene 3f, affording tetrahydroquinoline 4iaf in excellent yield and good stereoselectivity, which could form a single crystal with >99% ee (entry 13).

The absolute configuration of compounds **4faa**, **4aag** and **4iaf** (>99% *ee* after recrystallization) were unambiguously determined to be (2*S*,4*S*) by single-crystal X-ray diffraction analysis.¹⁰ Moreover, the relative configurations of compounds **4faa**, **4eaa**, **4haa**, **4aad**, **4aag** and **4iaf** were all confirmed to be *cis* by their X-ray structures.¹⁰ The relative and absolute configurations of other tetrahydroquinolines were assigned by analogy. It is interesting to mention that the relative configurations of tetrahydroquino-lines **4** generated from our protocol (eq 3) are different from those obtained by Feng's procedure (eq 2),^{4d} which always afforded *trans*-tetrahydroquinolines with high enantioselectivity.

In order to examine the utility of our protocol, the reaction to prepare tetrahydroquinoline **4aad** bearing a quaternary stereocenter was performed at 1 mmol scale under the optimized conditions, which is 10 times larger than the scale of the original reaction shown in Table 3, entry 8. The result revealed that the protocol could be successfully scaled up with an increased yield and enantioselectivity, albeit with a slightly decreased diastereoselectivity (Scheme 2).

As proposed in Scheme 1, the phosphoric acid **5e** acted as a bifunctional catalyst to activate both 2-hydroxystyrenes and imines by hydrogen-bonding interaction. To illustrate the crucial role of O-H group in 2-hydroxystyrenes and to test our hypothesis on the activation mode shown in Scheme 1, a control experiment was carried out with 2-methoxystyrene **3h** (Scheme 3). However, no reaction occurred, indicating that the O-H group in 2-hydroxystyrenes **3** was essentially important for both the enantioselectivity and reactivity.

To understand the stereochemistry experimentally observed, theoretical calculations were performed on key intermediates and transition states (TS) of the 2-hydroxystyrene-involved Table 3. Scope of Anilines and Styrenes^a



^{*a*}Unless indicated otherwise, the reaction was carried out in 0.1 mmol scale in solvent (1 mL) with 5 Å MS (150 mg) under argon for 60 h. ^{*b*}Isolated yield. ^{*c*}The *dr* was determined by ¹H NMR. ^{*d*}The *ee* was determined by HPLC. ^{*c*}Performed in dichloromethane at 25 °C, and the ratio of 1a/2/3 was 1.2/1/1.2. ^{*f*}Performed in toluene at 25 °C, and the ratio of 1a/2e/3a was 1.2/1/4. ^{*s*}Performed in toluene at 25 °C, and the ratio of 1a/2e/3a was 1.2/1/4. ^{*b*}Performed in toluene at 0 °C for 84 h, and the ratio of 1/2/3 was 1.2/1/4.8. ^{*i*}3,4-Dichlorobenzaldehyde (1i) was employed as aldehyde component. ^{*j*}After recrystallization.

Scheme 2. Large Scale Synthesis of Tetrahydroquinoline 4aad



Scheme 3. Control Experiment Involving 2-Methoxystyrene



Povarov reaction. On the basis of our previous studies,^{7f,g} the hybrid density functional theory (DFT) B3LYP method¹¹ combined with the 6-31G(d) basis set,¹² as implemented in the Gaussian03 program,¹³ was used for geometry optimization of all intermediates and TS structures, although the B3LYP functional was reported in certain instances not to account for attractive dispersion forces properly.¹⁴ To save computing resource, unsubstituted benzaldehyde and aniline was used to model the intermediate imine and unsubstituted 2-hydroxystyrene for TS structures.

The optimized structures of key intermediate Z- and E-imines and 2-hydroxystyrene with different orientations were shown in Figure 1. The E-imine was predicted to be more stable than Z- isomer by about >6 kcal/mol, indicating that the observed products resulted mainly from the *E*-imine. However, the 2hydroxystyrene could assume various conformations as indicated by the located structures with different stabilization by predicted relative energetic difference less than 1 kcal/mol. This implied that 2-hydroxystyrene may take *S*-*cis* or *S*-*trans* orientations in the transition state when reacting with *E*-imine in the chiral Brønsted acid-catalyzed Povarov reaction pathway.

The located TS structures confirmed our proposed reaction pathway in Scheme 1. The 3,3'-bi(triphenylsilyl)phosphoric acid **5e** acted as a bifunctional catalyst to activate both 2hydroxystyrene and *E*-imine by hydrogen-bonding interaction, and 2-hydroxystyrene may take *S-cis* or *S-trans* orientations to



Figure 1. Full optimized intermediate structures and relative energies in enthalpy (blue) and Gibbs free energy (red) in kcal/mol.



Figure 2. Located transition state structures with distance parameters in Angstroms and relative energies in enthalpy (blue) and Gibbs free energy (red) in kcal/mol.

approach the *E*-imine from its *R*-face or *S*-face (Figure 2). Four transition states were identified, as shown in Figure 2, in which both *o*-OH of the styrenes and key intermediate *E*-imine were activated simultaneously by the phosphoric acid **5e** by means of hydrogen-bonding interaction and thereby accelerating the vinylogous Mannich reaction and the subsequent intramolecular Friedel–Crafts reaction.¹⁵ The located TS structure TS-SproS, corresponding to the major product experimentally observed, was predicted to be more preferable than the other three ones by about ~4 kcal/mol because of the steric repulsion between the

phenol ring of the 2-hydroxystyrene and triphenylsilyl group of the catalyst **5e**. As a result, the experimentally observed *SS*configured product was predominantly formed.

In summary, we have established an efficient organocatalytic asymmetric Povarov reaction with 2-hydroxystyrenes. This protocol combines the merits of both organocatalysis and multicomponent reactions, tolerating a wide range of aldehydes, anilines and styrenes to furnish structurally diverse *cis*-

Article

tetrahydroquinolines in high stereoselectivities of up to >99:1 dr and 97% ee. Moreover, the current protocol not only provides a facile access to tetrahydroquinolines with chiral quaternary stereocenters upon using α -alkyl 2-hydroxystyrenes as substrates, but also furnishes an efficient method to synthesize *cis*disubstituted tetrahydroquinolines with high enantioselectivity. The theoretical studies revealed that the Povarov reaction proceeded through a sequential vinylogous Mannich reaction and an intramolecular Friedel–Crafts reaction, wherein the phosphoric acid acted as a bifunctional catalyst to activate the reaction components and intermediates involved by hydrogenbonding interaction.

EXPERIMENTAL SECTION

General Information. NMR spectra were measured at 400 and 100 MHz, respectively. The solvent used for NMR spectroscopy was CDCl₃, using tetramethylsilane as the internal reference. HRMS spectra were measured with electrospray ionization (ESI) and Orbitrap mass analyzer. Enantiomeric excesses (*ee*) were determined by chiral high-performance liquid chromatography (chiral HPLC). The chiral columns used for the determination of enantiomeric excesses by chiral HPLC were Chiralpak OD, IC, IA and AD columns. Optical rotation values were measured with instruments operating at $\lambda = 589$ nm, corresponding to the sodium D line at the temperatures indicated. Analytical grade solvents for the column chromatography and commercially available reagents were used as received. Toluene and dichloromethane were dried and distilled prior to use.

Typical Procedure for the Asymmetric Povarov Reaction with α -Unsubstituted Styrenes. After a solution of aldehydes 1 (0.12 mmol), anilines 2 (0.1 mmol), the catalyst 5e (0.01 mmol), and 5 Å molecular sieves (150 mg) in toluene (0.5 mL) was stirred at room temperature for 20 min (1 h for aldehyde 1o) under argon, the solution of styrenes 3a-3c (0.2 mmol) in toluene (0.5 mL) was added. In most reactions involving 4-nitrobenzaldehyde 1a, dichloromethane was used as solvent instead of toluene, and the ratio of 1a/2/3 was 1.2/1/1.2. After being stirred at 25 °C for 60–84 h under argon, the reaction mixture was filtered to remove molecular sieves, and the solid powder was washed with ethyl acetate. The resultant solution was concentrated under the reduced pressure to give the residue, which was purified through flash column chromatography on silica gel to afford pure products.

Typical Procedure for the Asymmetric Povarov Reaction with α -Alkyl Styrenes. After a solution of aldehydes 1 (0.12 mmol), anilines 2 (0.1 mmol), the catalyst Se (0.01 mmol), and 5 Å molecular sieves (150 mg) in toluene (0.5 mL) was stirred at room temperature for 20 min under argon, the solution of α -alkyl styrenes 3d-3g (0.48 mmol) in toluene (0.5 mL) was added. After being stirred at 0 °C for 84 h under argon, the reaction mixture was filtered to remove molecular sieves, and the solid powder was washed with ethyl acetate. The resultant solution was concentrated under the reduced pressure to give the residue, which was purified through flash column chromatography on silica gel to afford pure products.

2-((2*S*,4*S*)-1,2,3,4-Tetrahydro-6-methoxy-2-(4-nitrophenyl)quinolin-4-yl)phenol (4aaa). Data: Flash column chromatography eluent, petroleum ether/ethyl acetate = 6/1; reaction time = 60 h; yield 74% (27.9 mg); 6/1 dr; yellow sticky oil; $[\alpha]_D^{20} = -72.1$ (*c* 0.18, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 8.20 (d, *J* = 8.8 Hz, 2H), 7.64 (d, *J* = 8.7 Hz, 2H), 7.19–7.09 (m, 2H), 6.89 (td, *J* = 7.5, 1.1 Hz, 1H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.73–6.67 (m, 1H), 6.63 (d, *J* = 8.7 Hz, 1H), 6.44 (d, *J* = 2.0 Hz, 1H), 4.95 (s, 1H), 4.62 (dd, *J* = 10.6, 3.3 Hz, 1H), 4.57 (dd, *J* = 11.0, 6.9 Hz, 1H), 3.93 (s, 1H), 3.63 (s, 3H), 2.38– 2.15 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ (ppm) 153.6, 153.1, 151.2, 147.5, 138.8, 130.3, 128.2, 127.6, 123.9, 121.2, 116.8, 116.3, 114.4, 114.0, 57.2, 55.7, 40.2, 39.4; IR (KBr) γ 3504, 3364, 2934, 2843, 1598, 1517, 1501, 1456, 1346, 1226, 1111, 1036, 854, 755 cm⁻¹; ESI FTMS exact mass calcd for (C₂₂H₂₀N₂O₄ + H)⁺ requires *m/z* 377.1501, found *m/z* 377.1498; Enantiomeric excess 95%, determined by HPLC (Daicel Chirapak AD-H, hexane/isopropanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm); $t_{\rm R}$ = 11.573 min (minor), $t_{\rm R}$ = 13.674 min (major).

2-((2S,4S)-1,2,3,4-Tetrahydro-6-methoxy-2-phenylquinolin-4-yl)phenol (4baa). Data: Flash column chromatography eluent, petroleum ether/ethyl acetate = 8/1; reaction time = 84 h; yield 69%(22.9 mg); 30/1 dr; pale yellow sticky oil; $[\alpha]_D^{20} = -82.5$ (c 0.46, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 7.40–7.33 (m, 2H), 7.30–7.24 (m, 2H), 7.23–7.18 (m, 1H), 7.08 (dd, J = 7.5, 1.6 Hz, 1H), 7.04 (td, J = 7.6, 1.6 Hz, 1H), 6.79 (td, J = 7.5, 1.2 Hz, 1H), 6.72 (dd, J = 8.0, 1.0 Hz, 1H), 6.62–6.57 (m, 1H), 6.51 (d, J = 8.6 Hz, 1H), 6.38 (d, J = 2.1 Hz, 1H), 5.07 (s, 1H), 4.49-4.34 (m, 2H), 3.98 (s, 1H), 3.54 (s, 3H), 2.25–2.15 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ (ppm) 152.7, 151.8, 142.5, 138.6, 129.8, 129.3, 127.6, 127.0, 126.7, 125.7, 119.9, 115.9, 115.1, 113.4, 112.9, 57.0, 54.7, 39.8, 38.4; IR (KBr) γ 3372, 3017, 2922, 2853, 2833, 1708, 1593, 1502, 1453, 1267, 1231, 1035, 807, 756, 702, 666 cm⁻¹; ESI FTMS exact mass calcd for $(C_{22}H_{21}NO_2 + H)^+$ requires m/z 332.1651, found m/z 332.1645; Enantiomeric excess 90%, determined by HPLC (Daicel Chirapak OD-H, hexane/isopropanol = 90/10, flow rate 1.0 mL/min, T = 30 °C, 254 nm); $t_{\rm R} = 13.064$ min (major), $t_{\rm R} = 16.459$ min (minor).

2-((25,45)-1,2,3,4-Tetrahydro-6-methoxy-2-(3-nitrophenyl)quinolin-4-yl)phenol (4caa). Data: Flash column chromatography eluent, petroleum ether/ethyl acetate = 6/1 then 5/1; reaction time = 84 h; yield 82% (30.8 mg); 20/1 dr; yellow sticky oil; $[\alpha]_D^{20} = -61.5$ (c 0.62, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 8.25 (d, J = 1.7 Hz, 1H), 8.05 (dd, J = 8.1, 2.1 Hz, 1H), 7.73 (d, J = 7.7 Hz, 1H), 7.43 (t, J = 7.9 Hz, 1H), 7.10-7.00 (m, 2H), 6.80 (t, J = 7.3 Hz, 1H), 6.71 (d, J = 8.0Hz, 1H), 6.61 (dd, J = 8.7, 2.8 Hz, 1H), 6.55 (d, J = 8.7 Hz, 1H), 6.35 (d, *J* = 2.5 Hz, 1H), 4.95 (s, 1H), 4.54 (dd, *J* = 10.5, 3.5 Hz, 1H), 4.52–4.43 (m, 1H), 3.86 (s, 1H), 3.55 (s, 3H), 2.27–2.12 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ (ppm) 152.6, 152.0, 147.5, 145.0, 137.9, 131.9, 129.3, 128.6, 127.1, 123.1, 121.7, 120.7, 120.1, 115.7, 115.3, 113.4, 112.9, 56.0, 54.7, 40.5, 38.5; IR (KBr) γ 3364, 2934, 2835, 1734, 1708, 1594, 1530, 1500, 1349, 1233, 1043, 808, 756, 737, 689 cm⁻¹; ESI FTMS exact mass calcd for $(C_{22}H_{20}N_2O_4 + H)^+$ requires m/z 377.1501, found m/z377.1496; Enantiomeric excess 93%, determined by HPLC (Daicel Chirapak OD-H, hexane/isopropanol = 80/20, flow rate 1.0 mL/min, T = 30 °C, 254 nm); $t_{\rm R}$ = 15.508 min (major), $t_{\rm R}$ = 19.569 min (minor).

2-((2S,4S)-1,2,3,4-Tetrahydro-6-methoxy-2-(2-nitrophenyl)quinolin-4-yl)phenol (4daa). Data: Flash column chromatography eluent, petroleum ether/ethyl acetate = 6/1; reaction time = 84 h; yield 77% (29.0 mg); 25/1 dr; yellow sticky oil; $[\alpha]_D^{20} = -60.9$ (c 0.58, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 7.88 (dd, J = 7.9, 1.2 Hz, 1H), 7.74 (dd, J = 8.1, 1.2 Hz, 1H), 7.53 (td, J = 7.9, 1.1 Hz, 1H), 7.38-7.29 (m, 1H), 7.10 (dd, J = 7.6, 1.6 Hz, 1H), 7.08-7.01 (m, 1H), 6.81 (td, *J* = 7.5, 1.1 Hz, 1H), 6.71 (dd, *J* = 8.0, 1.1 Hz, 1H), 6.60 (ddd, *J* = 8.7, 2.8, 0.6 Hz, 1H), 6.54 (d, J = 8.7 Hz, 1H), 6.37 (d, J = 2.7 Hz, 1H), 5.10 (s, 1H), 4.85 (dd, J = 11.0, 2.4 Hz, 1H), 4.46 (dd, J = 11.5, 6.3 Hz, 1H), 3.84 (s, 1H), 3.54 (s, 3H), 2.42 (ddd, J = 13.1, 6.3, 2.5 Hz, 1H), 2.25-2.12 (m, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ (ppm) 152.7, 152.1, 148.2, 138.1, 137.1, 132.3, 129.4, 129.3, 127.7, 127.3, 127.1, 123.1, 120.0, 115.9, 115.6, 113.2, 113.1, 54.7, 51.3, 39.8, 37.2; IR (KBr) γ 3488, 3356, 2926, 1711, 1595, 1525, 1500, 1454, 1349, 1228, 1037, 855, 754 cm⁻¹; ESI FTMS exact mass calcd for $(C_{22}H_{20}N_2O_4 + H)^+$ requires m/z377.1501, found m/z 377.1496; Enantiomeric excess 91%, determined by HPLC (Daicel Chirapak IA, hexane/isopropanol = 85/15, flow rate 1.0 mL/min, $T = 30 \,^{\circ}$ C, 254 nm); $t_{\rm R} = 16.338 \, {\rm min} \, ({\rm major}), t_{\rm R} = 19.019$ min (minor).

4-((2*S***,4***S***)-1,2,3,4-Tetrahydro-4-(2-hydroxyphenyl)-6-methoxyquinolin-2-yl)benzonitrile (4eaa).** Data: Flash column chromatography eluent, petroleum ether/ethyl acetate = 4/1; reaction time = 84 h; yield 71% (25.3 mg); 7/1 dr; white solid; mp 215–217 °C; $[\alpha]_D^{20} = -63.3 (c 0.37, CHCl_3)$; ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 7.56 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 8.3 Hz, 2H), 7.06 (dd, *J* = 11.9, 4.5 Hz, 2H), 6.81 (td, *J* = 7.5, 1.1 Hz, 1H), 6.72 (d, *J* = 7.5 Hz, 1H), 6.62 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.54 (d, *J* = 8.7 Hz, 1H), 6.36 (d, *J* = 2.0 Hz, 1H), 4.87 (s, 1H), 4.50–4.44 (m, 2H), 3.82 (s, 1H), 3.55 (s, 3H), 2.26–2.09 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ (ppm) 153.7, 153.1, 149.2, 139.0, 132.6, 130.4, 128.2, 127.6, 121.2, 118.8, 116.9, 116.4, 114.4, 114.1, 111.6, 57.6, 55.8, 40.5, 39.5; IR (KBr) γ 3365, 2931, 2854, 1720, 123.2,

1653, 1618, 1590, 1493, 1455, 1229, 819, 754 cm⁻¹; ESI FTMS exact mass calcd for $(C_{23}H_{20}N_2O_2 + H)^+$ requires m/z 357.1603, found m/z 357.1600; Enantiomeric excess 92%, determined by HPLC (Daicel Chirapak AD-H, hexane/isopropanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm); t_R = 8.968 min (minor), t_R = 13.107 min (major).

2-((2S,4S)-2-(4-Chlorophenyl)-1,2,3,4-tetrahydro-6-methoxyquinolin-4-yl)phenol (4faa). Data: Flash column chromatography eluent, petroleum ether/ethyl acetate = 9/1; reaction time = 84 h; yield 43% (15.8 mg); 9/1 dr; colorless solid; mp 171–173 °C; $[\alpha]_D^{20} = -70.8$ $(c 0.22, CHCl_3)$; ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 7.39 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.5 Hz, 2H), 7.18–7.09 (m, 2H), 6.88 (td, J = 7.5, 1.2 Hz, 1H), 6.80 (dd, J = 8.0, 1.1 Hz, 1H), 6.70-6.64 (m, 1H), 6.59 (d, J = 8.7 Hz, 1H), 6.47–6.41 (m, 1H), 5.10 (s, 1H), 4.56–4.47 (m, 1H), 4.45 (dd, J = 10.0, 4.1 Hz, 1H), 3.88 (s, 1H), 3.62 (s, 3H), 2.31-2.18 (m, 2H); ^{13}C NMR (CDCl₃, 100 MHz) δ (ppm) 153.7, 153.0, 142.1, 139.3, 133.4, 130.6, 130.4, 128.8, 128.1, 124.0, 121.0, 117.0, 116.2, 114.4, 114.0, 57.3, 55.7, 40.9, 39.4; IR (KBr) γ 3327, 2931, 2856, 1596, 1497, 1464, 1348, 1257, 1089, 1014, 829, 814, 754, 738, 686 cm⁻¹; ESI FTMS exact mass calcd for $(C_{22}H_{20}CINO_2 + H)^+$ requires m/z 366.1261, found m/z366.1256; Enantiomeric excess 94%, determined by HPLC (Daicel Chirapak AD-H, hexane/isopropanol = 80/20, flow rate 1.0 mL/min, T = 30 $^{\circ}$ C, 254 nm); $t_{\rm R}$ = 10.752 min (minor), $t_{\rm R}$ = 14.044 min (major).

2-((2S,4S)-2-(4-Bromophenyl)-6-methoxy-1,2,3,4-tetrahydroquinolin-4-yl)phenol (4qaa). Data: Flash column chromatography eluent, petroleum ether/ethyl acetate = 9/1; reaction time = 84 h; yield 54% (22.3 mg); 8/1 dr; pale yellow sticky oil; $[\alpha]_{D}^{20} = -71.2$ (c 0.26, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 7.39 (d, J = 8.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 7.11–7.03 (m, 2H), 6.81 (td, J = 7.5, 1.1 Hz, 1H), 6.72 (dd, J = 8.0, 1.0 Hz, 1H), 6.60 (ddd, J = 8.0, 2.8, 0.8 Hz, 1H), 6.52 (d, J = 8.7 Hz, 1H), 6.36 (d, J = 2.0 Hz, 1H), 5.04 (s, 1H), 4.49-4.40 (m, 1H), 4.36 (dd, J = 10.1, 4.0 Hz, 1H), 3.80 (s, 1H), 3.54 (s, 3H), 2.23–2.08 (m, 2H); 13 C NMR (CDCl₃, 100 MHz) δ (ppm) 152.7, 151.9, 141.6, 138.3, 130.7, 129.6, 129.3, 127.4, 127.1, 123.0, 120.4, 120.0, 115.8, 115.2, 113.3, 112.9, 56.3, 54.7, 39.7, 38.4; IR (KBr) γ 3364, 2940, 1727, 1654, 1625, 1597, 1496, 1452, 1235, 1040, 1012, 816, 759 cm⁻¹ ESI FTMS exact mass calcd for $(C_{22}H_{20}BrNO_2 + H)^+$ requires m/z410.0756, found m/z 410.0754; Enantiomeric excess 90%, determined by HPLC (Daicel Chirapak OD-H, hexane/isopropanol = 70/30, flow rate 1.0 mL/min, $T = 30 \,^{\circ}$ C, 254 nm); $t_{\rm R} = 5.813 \, \text{min} \, (\text{major}), t_{\rm R} = 8.019$ min (minor).

2-((2S,4S)-2-(4-(Trifluoromethyl)phenyl)-1,2,3,4-tetrahydro-6-methoxyquinolin-4-yl)phenol (4haa). Data: Flash column chromatography eluent, petroleum ether/ethyl acetate = 9/1; reaction time = 84 h; yield 76% (30.2 mg); 8/1 dr; white solid; mp 158–160 °C; $[\alpha]_{\rm D}^{20} = -71.8 (c \, 0.38, \text{CHCl}_3); {}^{1}\text{H} \text{NMR} (\text{CDCl}_3, 400 \text{ MHz}) \,\delta (\text{ppm})$ 7.56-7.47 (m, 4H), 7.06 (ddd, J = 15.4, 7.6, 1.5 Hz, 2H), 6.81 (td, J = 7.5, 1.0 Hz, 1H), 6.72 (d, J = 8.0 Hz, 1H), 6.61 (dd, J = 8.7, 2.7 Hz, 1H), 6.53 (d, J = 8.7 Hz, 1H), 6.37 (d, J = 2.3 Hz, 1H), 5.01 (s, 1H), 4.49-4.44 (m, 2H), 3.83 (s, 1H), 3.55 (s, 3H), 2.25–2.11 (m, 2H); ¹³C NMR $(\text{CDCl}_3, 100 \text{ MHz}) \delta$ (ppm) 152.6, 151.9, 146.7, 138.1, 129.3 (J = 15.6) Hz), 128.8, 127.1, 126.0, 125.0, 123.0, 121.7, 120.1, 115.9, 115.2, 113.4, 112.9, 56.5, 54.7, 39.5, 38.4. IR (KBr) γ 3331, 2926, 2851, 1618, 1591, 1499, 1454, 1325, 1164, 1124, 1067, 1017, 840, 754; ESI FTMS exact mass calcd for $(C_{23}H_{20}F_3NO_2 + H)^+$ requires m/z 400.1524, found m/z400.1518; Enantiomeric excess 91%, determined by HPLC (Daicel Chirapak OD-H, hexane/isopropanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm); $t_{\rm R}$ = 5.01 min (major), $t_{\rm R}$ = 7.117 min (minor).

2-((25,45)-2-(3,4-Dichlorophenyl)-1,2,3,4-tetrahydro-6-methoxyquinolin-4-yl)phenol (4iaa). Data: Flash column chromatography eluent, petroleum ether/ethyl acetate = 9/1; reaction time = 84 h; yield 63% (25.3 mg); 14/1 dr; pale yellow sticky oil; $[\alpha]_D^{20} = -51.7$ (*c* 0.24, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 7.57 (d, *J* = 2.0 Hz, 1H), 7.40 (d, *J* = 8.3 Hz, 1H), 7.28 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.15–7.10 (m, 2H), 6.88 (td, *J* = 7.5, 1.2 Hz, 1H), 6.79 (d, *J* = 7.7 Hz, 1H), 6.68 (ddd, *J* = 8.7, 2.8, 0.7 Hz, 1H,), 6.60 (d, *J* = 8.7 Hz, 1H), 6.43 (dd, *J* = 2.7, 0.7 Hz, 1H), 4.95 (s, 1H), 4.51 (dd, *J* = 10.9, 7.0 Hz, 1H), 4.45 (dd, *J* = 10.6, 3.3 Hz, 1H), 3.86 (s, 1H), 3.62 (s, 3H), 2.29–2.14 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ (ppm) 153.6, 153.0, 144.0, 139.0, 132.7, 131.5, 130.6, 130.4, 130.3, 128.7, 128.1, 126.1, 124.0, 121.1, 116.8, 116.3, 114.4, 114.0, 56.8, 55.7, 40.5, 39.4; IR (KBr) γ 3504, 3364, 2926, 1612, 1594, 1500, 1467, 1452, 1331, 1225, 1031, 824, 754 cm⁻¹; ESI FTMS exact mass calcd for $(C_{22}H_{19}Cl_2NO_2 + H)^+$ requires m/z 400.0871, found m/z 400.0866; Enantiomeric excess 92%, determined by HPLC (Daicel Chirapak AD-H, hexane/isopropanol = 80/20, flow rate 1.0 mL/min, T = 30 °C, 254 nm); t_R = 8.845 min (minor), t_R = 10.892 min (major).

2-((25,45)-2-(3,4-Difluorophenyl)-1,2,3,4-tetrahydro-6-methoxyquinolin-4-yl)phenol (4jaa). Data: Flash column chromatography eluent, petroleum ether/ethyl acetate = 9/1; reaction time = 84 h; yield 77% (28.1 mg); 15/1 dr; white solid; mp 124–126 °C; $[\alpha]_{\rm D}^{20}$ = -77.8 (c 0.43, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ (ppm)7.22 (ddd, J = 11.3, 7.7, 1.9 Hz, 1H), 7.12-7.00 (m, 4H), 6.81 (td, J = 7.5, 1.1 Hz, 1H), 6.71 (dd, J = 7.9, 0.9 Hz, 1H), 6.60 (ddd, J = 8.7, 2.8, 0.6 Hz, 1H), 6.52 (d, J = 8.7 Hz, 1H), 6.35 (d, J = 2.0 Hz, 1H), 4.94 (s, 1H), 4.44 (dd, J = 10.9, 6.9 Hz, 1H), 4.37 (dd, J = 10.8, 3.1 Hz, 1H), 3.77 (s, 1H), 3.54 (s, 3H), 2.22–2.06 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ (ppm) 152.6, 151.9, 150.7 (J = 12.7 Hz), 149.9 (J = 12.7 Hz), 148.2 (J = 12.7 Hz)12.7 Hz), 147.5 (J = 12.8 Hz), 139.8, 138.1, 129.4 (J = 17.8 Hz), 127.1, 123.0, 121.5, 120.1, 116.3 (J = 17.1 Hz), 115.8, 115.2, 114.6 (J = 17.7 Hz), 113.1 (*J* = 43.0 Hz), 55.9, 54.7, 39.5, 38.6; IR (KBr) γ 3372, 2926, 2855, 1609, 1501, 1455, 1436, 1355, 1275, 1216, 1112, 1034, 816, 757 cm⁻¹; ESI FTMS exact mass calcd for $(C_{22}H_{19}F_2NO_2 + H)^+$ requires m/z 368.1462, found m/z 368.1456; Enantiomeric excess 91%, determined by HPLC (Daicel Chirapak OD-H, hexane/isopropanol = 85/15, flow rate 1.0 mL/min, T = 30 °C, 254 nm); $t_{\rm R} = 9.610$ min (major), $t_{\rm R} =$ 13.934 min (minor).

2-((25,45)-1,2,3,4-Tetrahydro-6-methoxy-2-m-tolylquinolin-4-yl)phenol (4kaa). Data: Flash column chromatography eluent, petroleum ether/ethyl acetate = 10/1; reaction time = 84 h; yield 43% (14.9 mg); 31/1 dr; pale yellow sticky oil; $[\alpha]_D^{20} = -5.4$ (c 0.29, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 7.20 (s, 1H), 7.16 (d, J = 5.1 Hz, 2H), 7.09 (dd, J = 7.5, 1.6 Hz, 1H), 7.07-7.01 (m, 2H), 6.80 (td, *J* = 7.5, 1.1 Hz, 1H), 6.73 (dd, *J* = 8.0, 1.0 Hz, 1H), 6.60 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.51 (d, J = 8.6 Hz, 1H), 6.38 (d, J = 2.2 Hz, 1H), 5.22 (s, 1H), 4.42 (t, J = 9.0 Hz, 1H), 4.38–4.31 (m, 1H), 4.04 (s, 1H), 3.55 (s, 3H), 2.28 (s, 3H), 2.25–2.19 (m, 2H); 13 C NMR (CDCl₃, 100 MHz) δ (ppm) 152.7, 151.8, 142.4, 138.6, 137.3, 129.8, 129.3, 127.5, 127.0, 126.3, 122.8, 120.0, 115.9, 115.2, 113.4, 112.9, 56.9, 54.7, 40.0, 38.3, 20.4; IR (KBr) γ 3298, 2926, 2851, 1608, 1592, 1492, 1454, 1263, 1226, 1092, 1034, 801, 755 cm⁻¹; ESI FTMS exact mass calcd for (C₂₃H₂₃NO₂) + H)⁺ requires m/z 346.1807, found m/z 346.1800; Enantiomeric excess 83%, determined by HPLC (Daicel Chirapak OD-H, hexane/ isopropanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm); $t_{\rm R} =$ 5.032 min (major), $t_{\rm R} = 6.374$ min (minor).

2-((25,45)-1,2,3,4-Tetrahydro-6-methoxy-2-(3methoxyphenyl)quinolin-4-yl)phenol (4laa). Data: Flash column chromatography eluent, petroleum ether/ethyl acetate = 8/1; reaction time = 84 h; yield 57% (20.7 mg); 20/1 dr; pale yellow sticky oil; $[\alpha]_D^2$ $= -61.1 (c \ 0.28, \text{CHCl}_3);^{1}\text{H NMR} (\text{CDCl}_3, 400 \text{ MHz}) \delta (\text{ppm}) 7.21 -$ 7.15 (m, 1H), 7.08 (dd, J = 7.9, 1.6 Hz, 1H), 7.04 (td, J = 7.9, 1.7 Hz, 1H), 6.98–6.92 (m, 2H), 6.80 (td, J = 7.4, 1.2 Hz, 1H), 6.77–6.71 (m, 2H), 6.60 (dd, J = 8.7, 2.8 Hz, 1H), 6.53 (t, J = 8.6 Hz, 1H), 6.37 (d, J = 2.2 Hz, 1H), 5.05 (s, 1H), 4.47-4.40 (m, 1H), 4.38 (dd, J = 10.0, 4.1 Hz, 1H), 4.01 (s, 1H), 3.73 (s, 3H), 3.55 (s, 3H), 2.30–2.13 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ (ppm) 158.9, 152.7, 151.8, 144.2, 138.5, 129.7, 129.3, 128.6, 127.0, 119.9, 118.0, 115.8, 115.2, 113.4, 112.9, 112.3, 111.0, 56.9, 54.7, 54.3, 39.9, 38.3; IR (KBr) γ 3372, 3009, 2934, 2844, 1597, 1500, 1452, 1337, 1260, 1226, 1153, 1039, 851, 788, 755, 697, 665 cm⁻¹; ESI FTMS exact mass calcd for $(C_{23}H_{23}NO_3 + H)^+$ requires m/z362.1756, found m/z 362.1750; Enantiomeric excess 86%, determined by HPLC (Daicel Chirapak AD-H, hexane/isopropanol = 90/10, flow rate 1.0 mL/min, T = 30 °C, 254 nm); $t_{\rm R} = 25.643$ min (major), $t_{\rm R} =$ 29.178 min (minor).

2-((25,45)-1,2,3,4-Tetrahydro-6-methoxy-2-*p***-tolylquinolin-4-yl)phenol (4maa).** Data: Flash column chromatography eluent, petroleum ether/ethyl acetate = 10/1; reaction time = 84 h; yield 21% (7.4 mg); 26/1 dr; yellow sticky oil; $[\alpha]_D^{20} = -76.4 (c \ 0.11, CHCl_3)$; ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 7.26 (d, *J* = 8.0 Hz, 2H), 7.11–7.07 (m, 3H), 7.04 (dd, *J* = 7.7, 1.6 Hz, 1H), 6.80 (td, *J* = 7.5, 1.0 Hz, 1H), 6.74 (d, *J* = 8.7 Hz, 1H), 6.59 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.51 (d, *J* = 8.6

Hz, 1H), 6.38 (d, *J* = 2.4 Hz, 1H), 5.13 (s, 1H), 4.41 (t, *J* = 9.0 Hz, 1H), 4.35 (t, *J* = 7.3 Hz, 1H), 3.88 (s, 1H), 3.55 (s, 3H), 2.27 (s, 3H), 2.24– 2.18 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ (ppm) 152.7, 151.9, 139.4, 138.6, 136.4, 129.8, 129.3, 128.3, 127.0, 125.6, 119.8, 115.9, 115.2, 113.4, 112.9, 56.8, 54.7, 40.1, 38.3, 20.1; IR (KBr) γ 3397, 2926, 1594, 1500, 1456, 1265, 1230, 1038, 817, 754 cm⁻¹; ESI FTMS exact mass calcd for ($C_{23}H_{23}NO_2 + H$)⁺ requires *m*/*z* 346.1807, found *m*/*z* 346.1801; Enantiomeric excess 88%, determined by HPLC (Daicel Chirapak OD-H, hexane/isopropanol = 70/30, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm); *t*_R = 5.018 min (major), *t*_R = 6.342 min (minor).

2-((25,45)-1,2,3,4-Tetrahydro-6-methoxy-2-(thiophen-2-yl)quinolin-4-yl)phenol (4naa). Data: Flash column chromatography eluent, petroleum ether/ethyl acetate = 8/1; reaction time = 84 h; yield 20% (6.8 mg); >99:1 dr; pale yellow sticky oil; $[\alpha]_D^{20} = -23.0$ (c 0.11, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 7.16 (dd, J = 5.1, 1.0 Hz, 1H), 7.11–7.04 (m, 2H), 6.99 (d, J = 3.0 Hz, 1H), 6.90 (dd, J = 5.0, 3.5 Hz, 1H), 6.82 (td, J = 7.5, 1.1 Hz, 1H), 6.74 (d, J = 8.0 Hz, 1H), 6.60 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.53 (d, *J* = 8.7 Hz, 1H), 6.36 (d, *J* = 2.1 Hz, 1H), 5.03 (s, 1H), 4.74 (dd, J = 10.8, 3.1 Hz, 1H), 4.45 (dd, J = 11.0, 7.1 Hz, 1H), 3.99 (s, 1H), 3.55 (s, 3H), 2.39–2.22 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ (ppm) 152.7, 152.0, 146.3, 137.9, 129.4, 127.1, 125.6, 123.3, 122.8, 120.0, 115.3, 113.3, 112.9, 54.7, 52.4, 39.3; IR (KBr) γ 3364, 3009, 2926, 2851, 1591, 1502, 1454, 1240, 1103, 1035, 850, 809, 757, 705 cm⁻¹; ESI FTMS exact mass calcd for $(C_{20}H_{19}NO_2S + H)^+$ requires m/z 338.1215, found m/z 338.1210; Enantiomeric excess 94%, determined by HPLC (Daicel Chirapak IC, hexane/isopropanol = 90/ 10, flow rate 1.0 mL/min, $T = 30 \degree C$, 254 nm); $t_R = 6.851 \text{ min (minor)}$, $t_{\rm R} = 8.380 \, {\rm min} \, ({\rm major}).$

2-((2R,4S)-1,2,3,4-Tetrahydro-6-methoxy-2-phenethylquinolin-4-yl)phenol (40aa). Data: Flash column chromatography eluent, petroleum ether/ethyl acetate = 8/1; reaction time = 84 h; yield 20% (7.3 mg); 25/1 dr; yellow sticky oil; $[\alpha]_D^{20} = -17.0 (c \ 0.11, \text{CHCl}_3); {}^1\text{H}$ NMR (CDCl₃, 400 MHz) δ (ppm) 7.32–7.27 (m, 2H), 7.23–7.18 (m, 3H), 7.16–7.10 (m, 2H), 6.88 (td, J = 7.4, 1.0 Hz, 1H), 6.81 (d, J = 7.8 Hz, 1H), 6.63 (dd, J = 8.6, 2.6 Hz, 1H), 6.51 (d, J = 8.6 Hz, 1H), 6.40 (d, *J* = 2.2 Hz, 1H), 4.89 (s, 1H), 4.30 (dd, *J* = 10.7, 7.1 Hz, 1H), 3.94 (s, 1H), 3.59 (s, 3H), 3.41-3.30 (m, 1H), 2.77-2.69 (m, 2H), 2.24 (ddd, J = 13.2, 6.9, 2.7 Hz, 1H), 2.00-1.91 (m, 1H), 1.86 (dd, J = 14.4, 7.7 Hz, 2H); ^{13}C NMR (CDCl₃, 100 MHz) δ (ppm) 153.8, 152.9, 141.6, 139.2, 131.2, 130.4, 128.6, 128.4, 128.0, 126.1, 120.8, 117.1, 116.2, 114.3, 113.8, 55.7, 52.7, 40.7, 38.1, 36.5, 32.1; IR (KBr) γ 3364, 2967, 2926, 2851, 1721, 1560, 1500, 1455, 1261, 1089, 1035, 804, 754, 700 cm⁻¹; ESI FTMS exact mass calcd for $(C_{24}H_{25}NO_2 + H)^+$ requires m/z 360.1964, found m/z 360.1957; Enantiomeric excess 85%, determined by HPLC (Daicel Chirapak AD-H, hexane/isopropanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm); $t_{\rm R} = 6.465$ min (major), $t_{\rm R} = 8.535$ min (minor).

2-((2S,4S)-6-Ethoxy-1,2,3,4-tetrahydro-2-(4-nitrophenyl)quinolin-4-yl)phenol (4aba). Data: Flash column chromatography eluent, petroleum ether/ethyl acetate = 8/1; reaction time = 60 h; yield 70% (27.2 mg); >99:1 dr; yellow sticky oil; $[\alpha]_D^{20} = -43.3$ (c 0.26, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 8.20 (d, J = 8.8 Hz, 2H), 7.64 (d, J = 8.7 Hz, 2H), 7.16-7.09 (m, 2H), 6.88 (td, J = 7.5, 1.1 Hz, 1H), 6.79 (d, J = 7.9 Hz, 1H), 6.69 (dd, J = 8.6, 2.3 Hz, 1H), 6.62 (d, J = 8.6 Hz, 1H), 6.44 (d, J = 2.0 Hz, 1H), 4.98 (s, 1H), 4.62 (dd, J = 10.5, 3.3 Hz, 1H), 4.55 (dd, J = 10.6, 7.0 Hz, 1H), 4.01 (s, 1H), 3.87-3.79 (m, 2H), 2.31–2.25 (m, 2H), 1.29 (t, J = 7.0 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ (ppm) 153.6, 152.4, 151.2, 147.5, 138.8, 130.3, 128.2, 127.5, 123.9, 121.2, 116.8, 116.3, 115.2, 114.7, 64.0, 57.2, 40.4, 39.5, 14.8; IR (KBr) *γ* 3496, 3372, 2975, 2925, 2860, 1598, 1519, 1501, 1457, 1346, 1265, 1225, 1171, 1114, 1043, 1016, 958, 856, 753, 700 cm⁻¹; ESI FTMS exact mass calcd for $(C_{23}H_{22}N_2O_4 + H)^+$ requires m/z 391.1658, found m/z 391.1652; Enantiomeric excess 90%, determined by HPLC (Daicel Chirapak OD-H, hexane/isopropanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm); $t_{\rm R} = 8.712$ min (major), $t_{\rm R} = 10.662$ min (minor)

2-((25,45)-1,2,3,4-Tetrahydro-2-(4-nitrophenyl)-6-phenoxyquinolin-4-yl)phenol (4aca). Data: Flash column chromatography eluent, petroleum ether/ethyl acetate = 8:1; reaction time = 60 h; yield 70% (30.7 mg); 6/1 dr; yellow sticky oil; $[\alpha]_D^{20} = -14.8$ (c 0.25, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 8.21 (d, *J* = 8.8 Hz, 2H), 7.65 (d, *J* = 8.7 Hz, 2H), 7.26–7.20 (m, 2H), 7.14–7.07 (m, 2H), 6.97 (t, *J* = 7.4 Hz, 1H), 6.89–6.83 (m, 3H), 6.81–6.73 (m, 2H), 6.65 (d, *J* = 8.6 Hz, 1H), 6.60 (d, *J* = 2.5 Hz, 1H), 4.81 (s, 1H), 4.70 (dd, *J* = 10.3, 3.5 Hz, 1H), 4.67–4.56 (m, 1H), 4.07 (s, 1H), 2.31–2.24 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ (ppm) 158.7, 153.5, 151.0, 148.4, 147.5, 141.3, 130.1, 129.9, 129.4, 128.1, 127.5, 124.5, 123.9, 121.9, 121.3, 121.0, 119.9, 116.9, 116.5, 116.1, 57.0, 39.2, 30.9; IR (KBr) γ 3504, 3381, 3066, 3025, 2926, 2851, 1602, 1520, 1488, 1457, 1348, 1262, 1219, 1164, 1105, 1015, 953, 855, 754, 695 cm⁻¹; ESI FTMS exact mass calcd for (C₂₇H₂₂N₂O₄ + H)⁺ requires *m*/*z* 439.1658, found *m*/*z* 439.1654; Enantiomeric excess 89%, determined by HPLC (Daicel Chirapak AD-H, hexane/isopropanol = 70/30, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm); *t*_R = 8.672 min (minor), *t*_R = 10.185 min (major).

2-((2S,4S)-1,2,3,4-Tetrahydro-6-methyl-2-(4-nitrophenyl)quinolin-4-yl)phenol (4ada). Data: Flash column chromatography eluent, petroleum ether/ethyl acetate = 10/1; reaction time = 60 h; yield 74% (26.5 mg); 4/1 dr; yellow sticky oil; $[\alpha]_D^{20} = -48.4$ (c 0.39, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 8.21 (d, J = 8.7 Hz, 2H), 7.64 (d, J = 8.7 Hz, 2H), 7.18–7.13 (m, 2H), 6.93–6.88 (m, 2H), 6.82 (d, J = 7.9 Hz, 1H), 6.67 (s, 1H), 6.59 (d, J = 8.1 Hz, 1H), 4.82 (s, 1H), 4.65 (dd, J = 9.2, 4.7 Hz, 1H), 4.57-4.47 (m, 1H), 4.00 (s, 1H), 2.29-2.23 (m, 2H), 2.14 (s, 3H); 13 C NMR (CDCl₃, 100 MHz) δ (ppm) 153.8, 151.9, 148.3, 142.6, 130.6, 130.5, 129.3, 128.9, 128.7, 128.3, 127.7, 124.1, 121.3, 117.1, 115.6, 57.5, 41.4, 40.6, 20.7; IR (KBr) γ 3438, 2926, 1604, 1520, 1506, 1456, 1344, 1102, 855, 752 cm⁻¹; ESI FTMS exact mass calcd for $(C_{22}H_{20}N_2O_3 + H)^+$ requires m/z 361.1552, found m/z361.1547; Enantiomeric excess 95%, determined by HPLC (Daicel Chirapak OD-H, hexane/isopropanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm); $t_{\rm R}$ = 8.133 min (major), $t_{\rm R}$ = 14.449 min (minor).

2-((2S,4S)-6-Fluoro-1,2,3,4-tetrahydro-2-(4-nitrophenyl)quinolin-4-yl)phenol (4aea). Data: Flash column chromatography eluent, petroleum ether/ethyl acetate = 8/1; reaction time = 60 h; yield 77% (28.0 mg); 8/1 dr; yellow sticky oil; $[\alpha]_D^{20} = -67.8$ (c 0.28, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 8.21 (d, *J* = 8.7 Hz, 2H), 7.64 (d, J = 8.8 Hz, 2H), 7.17–7.09 (m, 2H), 6.91 (td, J = 7.5, 1.2 Hz, 1H), 6.83–6.74 (m, 2H), 6.59 (dd, J = 8.7, 4.8 Hz, 1H), 6.53 (dd, J = 9.6, 2.3 Hz, 1H), 4.84 (s, 1H), 4.67 (dd, J = 10.3, 3.6 Hz, 1H), 4.64-4.54 (m, 1H), 4.03 (s, 1H), 2.33–2.18 (m, 2H); 13 C NMR (CDCl₃, 100 MHz) δ (ppm) 157.6, 155.2, 153.5, 150.9, 147.5, 140.9, 129.9 (J = 30.4 Hz), 129.6, 128.2, 127.5, 123.9, 121.3, 116.1, 115.8, 115.4, 115.1, 114.5, 114.3, 67.9, 57.0, 39.0; IR (KBr) γ 3504, 3381, 3075, 3034, 2926, 2860, 1604, 1519, 1499, 1453, 1344, 1259, 1216, 1174, 1147, 1111, 1042, 1016, 950, 854, 812, 752, 700, 674 cm⁻¹; ESI FTMS exact mass calcd for $(C_{21}H_{17}FN_2O_3 + H)^+$ requires m/z 365.1301, found m/z 365.1296; Enantiomeric excess 82%, determined by HPLC (Daicel Chirapak OD-H, hexane/isopropanol = 70/30, flow rate 1.0 mL/min, $T = 30^{\circ}$ C, 254 nm); $t_{\rm R} = 6.671 \text{ min (major)}, t_{\rm R} = 8.590 \text{ min (minor)}.$

2-((2S,4S)-1,2,3,4-Tetrahydro-6-methoxy-2-(4-nitrophenyl)quinolin-4-yl)-4-methylphenol (4aab). Data: Flash column chromatography eluent, petroleum ether/ethyl acetate = 7/1; reaction time = 60 h; yield 45% (17.6 mg); 42/1 dr; yellow sticky oil; $[\alpha]_D^{20} = -68.8$ (c 0.17, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 8.20 (d, J = 8.8 Hz, 2H), 7.64 (d, J = 8.7 Hz, 2H), 6.97–6.89 (m, 2H), 6.69 (d, J = 7.8 Hz, 2H), 6.63 (d, J = 8.6 Hz, 1H), 6.44 (d, J = 2.0 Hz, 1H), 4.82 (s, 1H), 4.62 (dd, J = 9.6, 4.3 Hz, 1H), 4.55–4.47 (m, 1H), 3.99 (s, 1H), 3.63 (s, 3H), 2.30–2.25 (m, 2H), 2.24 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ (ppm) 153.1, 151.3, 151.2, 147.5, 138.7, 130.7, 130.4, 129.9, 128.6, 127.5, 123.9, 116.6, 116.3, 114.4, 113.9, 57.3, 55.7, 40.3, 39.4, 20.5; IR (KBr) *γ* 3372, 3281, 2934, 1604, 1510, 1498, 1352, 1257, 1108, 1016, 859, 817 cm⁻¹; ESI FTMS exact mass calcd for $(C_{23}H_{22}N_2O_4 + H)^+$ requires m/z 391.1658, found m/z 391.1652; Enantiomeric excess 97%, determined by HPLC (Daicel Chirapak AD-H, hexane/isopropanol = 85/15, flow rate 1.0 mL/min, T = 30 °C, 254 nm); $t_{\rm R} = 23.637$ min (minor), $t_{\rm R} = 27.618$ min (major).

2-((25,45)-1,2,3,4-Tetrahydro-6-methoxy-2-(4-nitrophenyl)quinolin-4-yl)-4-methoxyphenol (4aac). Data: Flash column chromatography eluent, petroleum ether/ethyl acetate = 6/1 then 5/1; reaction time = 60 h; yield 44% (18.0 mg); 6/1 dr; yellow sticky oil; $[\alpha]_{\rm D}^{20} = -54.7$ (c 0.16, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 8.20 (d, *J* = 8.7 Hz, 2H), 7.64 (d, *J* = 8.7 Hz, 2H), 6.74 (d, *J* = 8.5 Hz, 1H), 6.72–6.66 (m, 3H), 6.62 (d, *J* = 8.7 Hz, 1H), 6.44 (d, *J* = 2.2 Hz, 1H), 5.06 (s, 1H), 4.62 (dd, *J* = 9.7, 4.1 Hz, 1H), 4.54–4.47 (m, 1H), 3.92 (s, 1H), 3.73 (s, 3H), 3.63 (s, 3H), 2.29–2.22 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ (ppm) 154.0, 153.1, 147.5, 131.3, 127.6, 123.9, 117.5, 116.4, 115.8, 114.3, 114.0, 113.0, 57.2, 55.7, 39.2, 30.9; IR (KBr) γ 33752, 3017, 2934, 2835, 1604, 1503, 1345, 1110, 1039, 853, 807, 754, 700, 672 cm⁻¹; ESI FTMS exact mass calcd for (C₂₃H₂₂N₂O₅ + H)⁺ requires *m*/*z* 407.1607, found *m*/*z* 407.1601; Enantiomeric excess 91%, determined by HPLC (Daicel Chirapak AD-H, hexane/isopropanol = 80/20, flow rate 1.0 mL/min, *T* = 30 °C, 254 nm); *t*_R = 24.357 min (minor), *t*_R = 27.423 min (major).

2-((2S,4S)-1,2,3,4-Tetrahydro-6-methoxy-4-methyl-2-(4nitrophenyl)quinolin-4-yl)phenol (4aad). Data: Flash column chromatography eluent, petroleum ether/ethyl acetate = 10/1; reaction time = 84 h; yield 75% (29.2 mg); 54/1 dr; yellow solid; 199-202 °C; $[\alpha]_{D}^{20} = -138.9$ (c 0.47, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 8.18 (d, J = 8.8 Hz, 2H), 7.63 (d, J = 8.7 Hz, 2H), 7.47 (dd, J = 7.9, 1.5 Hz, 1H), 7.16 (td, J = 7.9, 1.6 Hz, 1H), 6.95 (td, J = 7.7, 1.3 Hz, 1H), 6.79 (dd, J = 8.0, 1.3 Hz, 1H), 6.72 (dd, J = 8.7, 2.8 Hz, 1H), 6.66 (d, J = 8.7 Hz, 1H), 6.42 (d, J = 2.8 Hz, 1H), 4.84 (s, 1H), 4.68 (dd, J = 11.8, 2.7 Hz, 1H), 4.07 (s, 1H), 3.61 (s, 3H), 2.47 (dd, J = 13.3, 12.2 Hz, 1H), 1.86 (s, 3H), 1.80 (dd, J = 13.7, 2.8 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ (ppm) 153.5, 153.3, 151.0, 147.5, 137.4, 134.1, 128.4, 127.6, 127.2, 126.8, 123.9, 120.6, 118.2, 116.6, 114.7, 113.2, 55.6, 53.8, 45.0, 40.2, 31.1; IR (KBr) γ 3471, 3363, 2967, 2934, 2851, 1603, 1520, 1499, 1345, 1274, 1231, 1209, 1170, 1109, 1037, 1012, 851, 815, 754, 704, 672 cm⁻¹; ESI FTMS exact mass calcd for $(C_{23}H_{22}N_2O_4 + H)^+$ requires m/z391.1658, found m/z 391.1653; Enantiomeric excess 93%, determined by HPLC (Daicel Chirapak OD-H, hexane/isopropanol = 85/15, flow rate 1.0 mL/min, T = 30 °C, 254 nm); $t_{\rm R} = 12.691$ min (minor), $t_{\rm R} =$ 14.253 min (major).

2-((2S,4S)-1,2,3,4-Tetrahydro-6-methoxy-4-methyl-2-(4nitrophenyl)quinolin-4-yl)-4-methylphenol (4aae). Data: Flash column chromatography eluent, petroleum ether/ethyl acetate = 8/1; reaction time = 84 h; yield 86% (34.8 mg); 8/1 dr; yellow sticky oil; $[\alpha]_{D}^{20} = -105.7$ (c 0.48, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 8.18 (d, J = 8.8 Hz, 2H), 7.62 (d, J = 8.7 Hz, 2H), 7.25 (s, 1H), 6.95 (dd, J = 8.1, 1.6 Hz, 1H), 6.73-6.67 (m, 2H), 6.64 (d, J = 8.7 Hz, 1H), 6.43 (d, J = 2.8 Hz, 1H), 4.67 (dd, J = 11.8, 2.6 Hz, 1H), 4.61 (s, 1H), 4.06 (s, 1H), 3.61 (s, 3H), 2.51-2.42 (m, 1H), 2.32 (s, 3H), 1.84 (s, 3H), 1.79 (dd, J = 13.6, 2.7 Hz, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ (ppm) 153.3, 151.3, 151.1, 147.5, 133.9, 129.6, 128.8, 127.6, 127.5, 123.9, 118.1, 116.6, 114.7, 113.3, 55.7, 53.9, 45.1, 40.2, 31.2, 20.9; IR (KBr) y 3472, 3364, 2926, 1604, 1522, 1501, 1345, 1270, 1109, 1039, 851, 813, 754, 704, 662 cm⁻¹; ESI FTMS exact mass calcd for $(C_{24}H_{24}N_2O_4 + H)^+$ requires m/z 405.1814, found m/z 405.1810; Enantiomeric excess 83%, determined by HPLC (Daicel Chirapak OD-H, hexane/isopropanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm); $t_{\rm R} = 6.337$ min (minor), $t_{\rm R} = 8.087$ min (major).

2-((2S,4S)-1,2,3,4-Tetrahydro-6-methoxy-4-methyl-2-(4nitrophenyl)quinolin-4-yl)-4-methoxyphenol (4aaf). Data: Flash column chromatography eluent, petroleum ether/ethyl acetate = 8:1; reaction time = 84 h; yield 89% (37.4 mg); 25/1 dr; yellow solid; mp 93–96 °C; $[\alpha]_D^{20} = -100.8$ (c 0.62, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 8.17 (d, J = 8.7 Hz, 2H), 7.62 (d, J = 8.7 Hz, 2H), 7.06 (d, *J* = 2.4 Hz, 1H), 6.76–6.67 (m, 3H), 6.64 (d, *J* = 8.7 Hz, 1H), 6.42 (d, *J* = 2.7 Hz, 1H), 4.67 (dd, J = 11.8, 2.5 Hz, 1H), 4.45 (s, 1H), 4.07 (s, 1H), 3.79 (s, 3H), 3.61 (s, 3H), 2.50 (t, J = 12.7 Hz, 1H), 1.82 (s, 3H), 1.78 $(dd, J = 13.6, 2.7 Hz, 1H); {}^{13}C NMR (CDCl_3, 100 MHz) \delta (ppm) 153.6,$ 153.3, 151.1, 147.5, 137.5, 135.6, 127.6, 127.1, 123.9, 118.7, 116.7, 114.8, 114.1, 113.1, 112.0, 55.7, 53.8, 44.7, 40.5, 31.0; IR (KBr) y 3472, 3364, 2926, 2851, 2835, 1604, 1517, 1502, 1421, 1344, 1276, 1222, 1207, 1168, 1112, 1061, 1040, 849, 810, 753, 700, 679 cm⁻¹; ESI FTMS exact mass calcd for $(C_{24}H_{24}N_2O_5 + H)^+$ requires m/z 421.1763, found m/z421.1758; Enantiomeric excess 84%, determined by HPLC (Daicel Chirapak OD-H, hexane/isopropanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm); $t_{\rm R}$ = 8.156 min (minor), $t_{\rm R}$ = 11.553 min (major).

2-((2S,4S)-4-Ethyl-1,2,3,4-tetrahydro-6-methoxy-2-(4nitrophenyl)quinolin-4-yl)phenol (4aag). Data: Flash column chromatography eluent, petroleum ether/ethyl acetate = 15/1; reaction time = 84 h; yield 95% (38.3 mg); >99:1 dr; yellow solid; mp 192–195 °C; $[\alpha]_{D}^{20} = -113.7$ (c 0.41, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 8.17 (d, J = 8.8 Hz, 2H), 7.62 (d, J = 8.7 Hz, 2H), 7.39 (dd, J = 7.9, 1.5 Hz, 1H), 7.13 (ddd, J = 8.9, 7.7, 1.6 Hz, 1H), 6.92 (td, J = 7.8, 1.4 Hz, 1H), 6.79 (dd, J = 8.0, 1.3 Hz, 1H), 6.73 (dd, J = 8.7, 2.8 Hz, 1H), 6.67 (d, J = 8.7 Hz, 1H), 6.43 (d, J = 2.7 Hz, 1H), 5.33 (s, 1H), 4.68 (dd, J =11.9, 3.2 Hz, 1H), 4.09 (s, 1H), 3.63 (s, 3H), 2.43-2.31 (m, 2H), 2.25-2.18 (m, 1H), 1.95 (dd, *J* = 14.1, 3.3 Hz, 1H), 1.08 (t, *J* = 7.3 Hz, 3H); $^{13}{\rm C}\,{\rm NMR}\,({\rm CDCl}_{3},100\,{\rm MHz})\,\delta\,({\rm ppm})$ 154.1,152.9,151.2,147.5,137.7, 132.9, 128.2, 127.5, 127.3, 124.9, 123.9, 120.4, 118.6, 116.6, 114.7, 114.3, 55.7, 54.2, 43.5, 43.3, 33.9, 9.8; IR (KBr) γ 3447, 3381, 2934, 2885, 1604, 1523, 1499, 1459, 1348, 1267, 1249, 1232, 1211, 1159, 1109, 1037, 862, 850, 818, 757, 702, 679 cm^{-1} ; ESI FTMS exact mass calcd for $(C_{24}H_{24}N_2O_4 + H)^+$ requires m/z 405.1814, found m/z 405.1810; Enantiomeric excess 88%, determined by HPLC (Daicel Chirapak AD-H, hexane/isopropanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm); $t_{\rm R} = 7.622 \text{ min (minor)}, t_{\rm R} = 9.913 \text{ min (major)}.$

2-((25,45)-6-Ethoxy-1,2,3,4-tetrahydro-4-methyl-2-(4nitrophenyl)quinolin-4-yl)phenol (4abd). Data: Flash column chromatography eluent, petroleum ether/ethyl acetate = 8/1; reaction time = 84 h; yield 87% (35.0 mg); 17/1 dr; yellow sticky oil; $[\alpha]_{\rm D}^{20}$ = -135.5 (c 0.45, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 8.18 (d, J = 8.8 Hz, 2H), 7.63 (d, J = 8.7 Hz, 2H), 7.46 (dd, J = 7.9, 1.5 Hz, 1H), 7.16 (td, J = 7.5, 1.6 Hz, 1H), 6.95 (td, J = 7.7, 1.3 Hz, 1H), 6.79 (dd, J = 8.0, 1.3 Hz, 1H), 6.71 (dd, *J* = 8.7, 2.8 Hz, 1H), 6.64 (d, *J* = 8.7 Hz, 1H), 6.43 (d, J = 2.7 Hz, 1H), 4.85 (s, 1H), 4.68 (dd, J = 11.8, 2.6 Hz, 1H), 4.06 (s, 1H), 3.87-3.76 (m, 2H), 2.53-2.39 (m, 1H), 1.85 (s, 3H), 1.80 (dd, J = 13.7, 2.8 Hz, 1H), 1.28 (t, J = 7.0 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ (ppm) 153.6, 152.6, 151.0, 147.5, 134.2, 128.4, 127.6, 126.9, 123.9, 120.6, 118.2, 116.7, 115.4, 114.1, 63.9, 53.9, 45.1, 40.3, 31.2, 14.8; IR (KBr) y 3472, 3372, 2976, 2926, 2867, 1604, 1519, 1502, 1346, 1272, 1229, 1204, 1176, 1112, 1045, 853, 814, 754 cm⁻¹; ESI FTMS exact mass calcd for $(C_{24}H_{24}N_2O_4 + H)^+$ requires m/z 405.1814, found m/z 405.1810; Enantiomeric excess 94%, determined by HPLC (Daicel Chirapak AD-H, hexane/isopropanol = 70/30, flow rate 1.0 mL/min, T = 30 °C, 254 nm); $t_{\rm R} = 7.413$ min (minor), $t_{\rm R} = 8.985$ min (major).

2-((25,45)-2-(3,4-Dichlorophenyl)-6-methoxy-4-methyl-1,2,3,4-tetrahydroquinolin-4-yl)-4-methoxyphenol (4iaf). Data: Flash column chromatography eluent, petroleum ether/ethyl acetate = 18/1; reaction time = 84 h; yield 92% (40.7 mg); >99/1 dr; yellow solid; mp 152–154 °C; ¹H NMR (CDCl₃, 400 MHz) δ (ppm) 7.48 (d, J = 2.0 Hz, 1H), 7.31 (d, J = 8.3 Hz, 1H), 7.20 (dd, J = 8.3, 2.0 Hz, 1H), 6.98 (d, J = 2.6 Hz, 1H), 6.69–6.60 (m, 3H), 6.54 (d, J = 8.7 Hz, 1H), 6.33 (d, J =2.8 Hz, 1H), 4.42 (dd, J = 11.8, 2.6 Hz, 1H), 4.17 (s, 1H), 3.72 (s, 3H), 3.53 (s, 3H), 2.43–2.33 (m, 1H), 1.72 (s, 3H), 1.68 (dd, J = 13.6, 2.7 Hz, 1H); 13 C NMR (CDCl₃, 100 MHz) δ (ppm) 152.4, 152.1, 146.4, 142.8, 136.7, 134.7, 131.6, 130.5, 129.5, 127.7, 126.0, 125.1, 117.6, 115.5, 113.7, 113.0, 112.0, 110.9, 54.7, 54.6, 52.2, 43.7, 39.4, 28.6; IR (KBr) γ 3471, 3370, 2961, 2926, 2852, 2832, 1500, 1483, 1464, 1423, 1392, 1260, 1169, 1103, 1031, 866, 796, 739, 678 cm⁻¹; ESI FTMS exact mass calcd for $(C_{24}H_{23}Cl_2NO_3 + H)^+$ requires m/z 444.1133, found m/z 444.1118; Enantiomeric excess 85%, determined by HPLC (Daicel Chirapak AD-H, hexane/isopropanol = 70/30, flow rate 1.0 mL/min, $T = 30^{\circ}$ C, 254 nm); $t_{\rm R}$ = 7.977 min (minor), $t_{\rm R}$ = 9.194 min (major).

Typical Procedure for the Large Scale Synthesis of Tetrahydroquinoline 4aad. After a solution of aldehydes 1a (1.2 mmol), anilines 2a (1 mmol), the catalyst 5e (0.1 mmol), and 5 Å molecular sieves (1.5 g) in toluene (8 mL) was stirred at room temperature for 40 min under argon and then was cooled to 0 °C, the cooled solution (0 °C) of α -alkyl styrene 3d (4.8 mmol) in toluene (2 mL) was added. After being stirred at 0 °C for 72 h under argon, the reaction mixture was filtered to remove molecular sieves, and the solid powder was washed with ethyl acetate. The resultant solution was concentrated under the reduced pressure to give the residue, which was purified through flash column chromatography on silica gel to afford pure product 4aad.

S Supporting Information

Characterization data (including ¹H, ¹³C NMR and HPLC spectra) for all products, crystal data (CIF) of compounds **4faa**, **4aag**, **4iaf**, **4eaa**, **4haa**, and **4aad**, and computational data for transition state. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*E-mail: gonglz@ustc.edu.cn; luosw@ustc.edu.cn.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are grateful for financial support from MOST (973 Project 2009CB82530), Ministry of Education and NSFC (21072181 and 21002083).

REFERENCES

(1) For reviews, see: (a) Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031. (b) Sridharan, V.; Suryavanshi, P.; Menéndez, J. C. *Chem. Rev.* **2011**, *111*, 7157. For selected examples: (c) Paris, D.; Cottin, M.; Demonchaux, P.; Augert, G.; Dupassieux, P.; Lenoir, P.; Peck, M. J.; Jasserand, D. *J. Med. Chem.* **1995**, *38*, 669. (d) Xia, Y.; Yang, Z.-Y.; Xia, P.; Bastow, K. F.; Tachibana, Y.; Kuo, S.-C.; Hamel, E.; Hackl, T.; Lee, K.-H. *J. Med. Chem.* **1998**, *41*, 1155. (e) Wallace, O. B.; Lauwers, K. S.; Jones, S. A.; Dodge, J. A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1907. (f) Rano, T. A.; McMaster, E. S.; Pelton, P. D.; Yang, M.; Demarest, K. T.; Kuo, G. H. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2456.

(2) For reviews, see: (a) Waldmann, H. Synthesis 1994, 535.
(b) Jørgensen, K. A. Angew. Chem., Int. Ed. 2000, 39, 3558. (c) Johnson, J. S.; Evans, D. A. Acc. Chem. Res. 2000, 33, 325. (d) Buonora, P.; Olsen, J.-C.; Oh, T. Tetrahedron 2001, 57, 6099. (e) Kobayashi, S.; Jørgensen, K. A. Cycloaddition Reactions in Organic Synthesis; Wiley-VCH: Weinheim, Germany, 2002.

(3) For selected examples: (a) Grieco, P. A.; Bahsas, A. Tetrahedron Lett. 1988, 29, 5855. (b) Kobayashi, S.; Nagayama, S. J. Am. Chem. Soc. 1996, 118, 8977. (c) Ma, Y.; Qian, C.; Xie, M.; Sun, J. J. Org. Chem. 1999, 64, 6462. (d) Batey, R. A.; Powell, D. A. Chem. Commun. 2001, 2362.
(e) Lavilla, R.; Bernadeu, M. C.; Carranco, I.; Díaz, J. L. Org. Lett. 2003, 5, 717.

(4) For metal-catalyzed transformations: (a) Ishitani, H.; Kobayashi, S. *Tetrahedron Lett.* **1996**, *37*, 7357. (b) Sundararajan, G.; Prabagaran, N.; Varghese, B. Org. Lett. **2001**, *3*, 1973. (c) Xie, M.-S.; Chen, X.-H.; Zhu, Y.; Gao, B.; Lin, L.-L.; Liu, X.-H.; Feng, X.-M. Angew. Chem., Int. Ed. **2010**, *49*, 3799. (d) Xie, M.; Liu, X.; Zhu, Y.; Zhao, X.; Xia, Y.; Lin, L.; Feng, X. Chem.—Eur. J. **2011**, *17*, 13800. For organocatalyzed transformations: (e) Akiyama, T.; Morita, H.; Fuchibe, K. J. Am. Chem. Soc. **2006**, *128*, 13070. (f) Liu, H.; Dagousset, G.; Masson, G.; Retailleau, P.; Zhu, J. J. Am. Chem. Soc. **2009**, *131*, 4598. (g) Wang, C.; Han, Z.-Y.; Luo, H.-W.; Gong, L.-Z. Org. Lett. **2010**, *12*, 2266. (h) Bergonzini, G.; Gramigna, L.; Mazzanti, A.; Fochi, M.; Bernardi, L.; Ricci, A. Chem. Commun. **2010**, *46*, 327. (i) Xu, H.; Zuend, S. J.; Woll, M. G.; Tao, Y.; Jacobsen, E. N. Science **2010**, *327*, 986. (j) Dagousset, G.; Zhu, J.; Masson, G. J. Am. Chem. Soc. **2011**, *133*, 14804. (k) Dagousset, G.; Retailleau, P.; Masson, G.; Zhu, J. Chem.—Eur. J. **2012**, *18*, 5869.

(5) Jørgensen and co-workers recently reported an organocatalytic cascade reaction comprising an intramolecular Povarov reaction of styrene-type substrates while the stereoselectivity is induced by the first asymmetric Michael addition. See: Dickmeiss, G.; Jensen, K. L.; Worgull, D.; Franke, P. T.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 1580.

(6) For early examples: (a) Akiyama, T.; Itoh, J.; Yokota, K.; Fuchibe, K. Angew. Chem., Int. Ed. 2004, 43, 1566. (b) Uraguchi, D.; Terada, M. J. Am. Chem. Soc. 2004, 126, 5356. For reviews, see: (c) Akiyama, T.

Chem. Rev. 2007, 107, 5744. (d) Doyle, A. G.; Jacobsen, E. N. Chem. Rev. 2007, 107, 5713. (e) Terada, M. Chem. Commun. 2008, 4097. (f) Terada, M. Synthesis 2010, 1929.

(7) For a review, see: (a) Yu, J.; Shi, F.; Gong, L.-Z. Acc. Chem. Res. **2011**, 44, 1156. For selected examples: (b) Guo, Q.-X.; Liu, H.; Guo, C.; Luo, S.-W.; Gu, Y.; Gong, L.-Z. J. Am. Chem. Soc. **2007**, 129, 3790. (c) Jiang, J.; Yu, J.; Sun, X.-X.; Rao, Q.-Q.; Gong, L.-Z. Angew. Chem., Int. Ed. **2008**, 47, 2458. (d) Chen, X.-H.; Zhang, W.-Q.; Gong, L.-Z. J. Am. Chem. Soc. **2008**, 130, 5652. (e) Yu, J.; He, L.; Chen, X.-H.; Song, J.; Chen, W.-J.; Gong, L.-Z. Org. Lett. **2009**, 11, 4946. (f) Shi, F.; Luo, S.-W.; Tao, Z.-L.; He, L.; Yu, J.; Tu, S.-J.; Gong, L.-Z. Org. Lett. **2011**, 13, 4680. (g) He, L.; Chen, X.-H.; Wang, D.-N.; Luo, S.-W.; Zhang, W.-Q.; Yu, J.; Ren, L.; Gong, L.-Z. J. Am. Chem. Soc. **2011**, 133, 13504.

(8) (a) Sickert, M.; Schneider, C. Angew. Chem., Int. Ed. 2008, 47, 3631.
(b) Akiyama, T.; Honma, Y.; Itoh, J.; Fuchibe, K. Adv. Synth. Catal. 2008, 350, 399. (c) Giera, D. S.; Sickert, M.; Schneider, C. Org. Lett. 2008, 10, 4259.

(9) For the phosphoric acid-catalyzed F–C reaction to unsaturated carbonyl compounds, see: (a) Rueping, M.; Nachtsheim, B. J.; Moreth, S. A.; Bolte, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 593. (b) Zeng, M.; Kang, Q.; He, Q.-L.; You, S.-L. *Adv. Synth. Catal.* **2008**, *349*, 2169. (c) Gu, Q.; Rong, Z.-Q.; Zheng, C.; You, S.-L. *J. Am. Chem. Soc.* **2010**, *132*, 4056.

(10) CCDC 879362 for 4faa, CCDC 891219 for 4aag, CCDC 891220 for 4iaf, CCDC 879360 for 4eaa, CCDC 879361 for 4haa, CCDC 879359 for 4aad. See the Supporting Information for details.

(11) Becke, A. D. J. Chem. Phys. 1993, 98, 5648.

(12) Gill, P. M. W.; Johnson, B. G.; Pople, J. A.; Frisch, M. J. Chem. Phys. Lett. **1992**, 197, 499.

(13) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. Gaussian 03, Revision D.03; Gaussian, Inc.: Wallingford, CT, 2004.

(14) (a) Schwabe, T.; Huenerbein, R.; Grimme, S. Synlett 2010, 1431.
(b) Grimme, S. Org. Lett. 2010, 12, 4670. (c) Schwabe, T.; Grimme, S. Phys. Chem. Chem. Phys. 2007, 9, 3397. (d) Grimme, S.; Steinmetz, M.; Korth, M. J. Org. Chem. 2007, 72, 2118. (e) Grimme, S.; Diedrich, C.; Korth, M. Angew. Chem., Int. Ed. 2006, 45, 625. (f) Grimme, S. J. Comput. Chem. 2006, 27, 1787.

(15) For an excellent review on theoretical studies on asymmetric organocatalysis, see: Cheong, P. H.-Y.; Legault, C. Y.; Um, J. M.; Çelebi-Ölçüm, N.; Houk, K. N. *Chem. Rev.* **2011**, *111*, 5042.