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Diastereoselective and Enantioselective Synthesis of Unsymmetric β,β-Diaryl-α-Amino Acid Esters via Organocatalytic 1,6-Conjugate Addition of *para*-Quinone Methides

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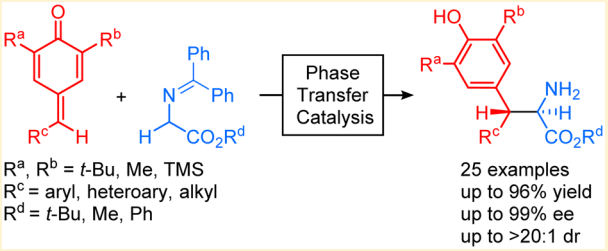
Supporting Information

ABSTRACT: A novel strategy based on phase transfer catalysis for the diastereoselective and enantioselective direct assembly of unsymmetric β,β-diaryl-α-amino acid esters via 1,6-conjugate addition of *para*-quinone methides and glycine derivatives is described. This protocol also provides an alternative route to the synthetically interesting functionalized chiral tetrahydroisoquinoline and its analogues.



The β,β-diarylalanine units as important building blocks exist in many natural products and drugs such as Hyalachelin A,[1] Doxanthrine,[2] and HIV inhibitors[3e] (Figure 1). These molecules bearing such unique structural motifs have

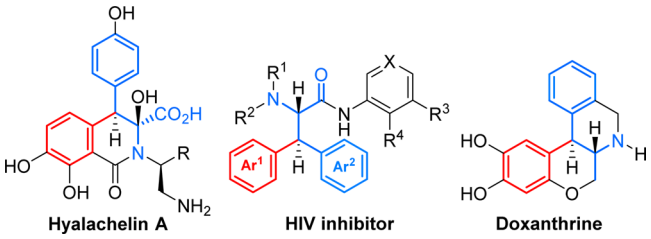


Figure 1. Selected bioactive unsymmetric β,β-diarylalanine derivatives.

displayed several biological properties including antithrombosis,[3a] anticancer,[3b] antidiabetic[3d] and anti-HIV activity.[3e] Additionally, β,β-diarylalanines have also been demonstrated to have the potential of improving the bioactivity and selectivity of certain peptides.[4] Because of these promising biological activities, the development of methodologies for access to these structural units has received considerable attention in the synthetic community.[5] Compared with the fact that numerous methods have been extensively disclosed for the synthesis of symmetrical β,β-diaryl-substituted alanines, however, less attention has been devoted to the catalytic enantioselective construction of the unsymmetrical β,β-diarylalanine units containing two vicinal stereogenic centers.[6,7] Recently, the Chen[8a] and Hou[8b] groups have synthesized the α-amino acid esters through catalytic asymmetric Friedel−Crafts-type conjugate addition and alkylation, respectively. Notably, only tryptophan derivatives could be gained in their cases, wherein the method developed by Chen showed poor diastereoselectivities (Scheme 1). Very recently, Molinaro et al. demonstrated the synthesis of unsymmetrically substituted β,β-diaryl-α-amino acid esters via asymmetric catalytic hydrogenation of stereodefined tetrasubstituted olefins.[9] Despite this successful method, the requirement at least of two steps (Suzuki−Miyura coupling and asymmetric hydrogenation) and expensive metal (rhodium) may represent limitations for this protocol. Therefore, the development of straightforward catalytic enantioselective approaches to unsymmetric β,β-diaryl-α-amino acid esters remains highly desirable.

p-Quinone methides (*p*-QMs)[10,11] containing a cyclohexadiene core and featuring an exocyclic alkylidene and a carbonyl residue disposed at the para position have been known as important structure motifs found in many natural products,[12] and the transient *p*-QM entities formed in situ are also involved in many chemical, medicinal, and biological processes.[13] Recently, methodologies of *p*-QMs as excellent Michael acceptors and diarylmethine precursors are mainly focused on 1,6-conjugate addition reactions.[14,15] We envisaged that a series of synthetically interesting alanine derivatives having different β,β-diaryl substituents would be accessed through 1,6-addition of *p*-QMs with glycine derivatives.[16,17] With our interest in the

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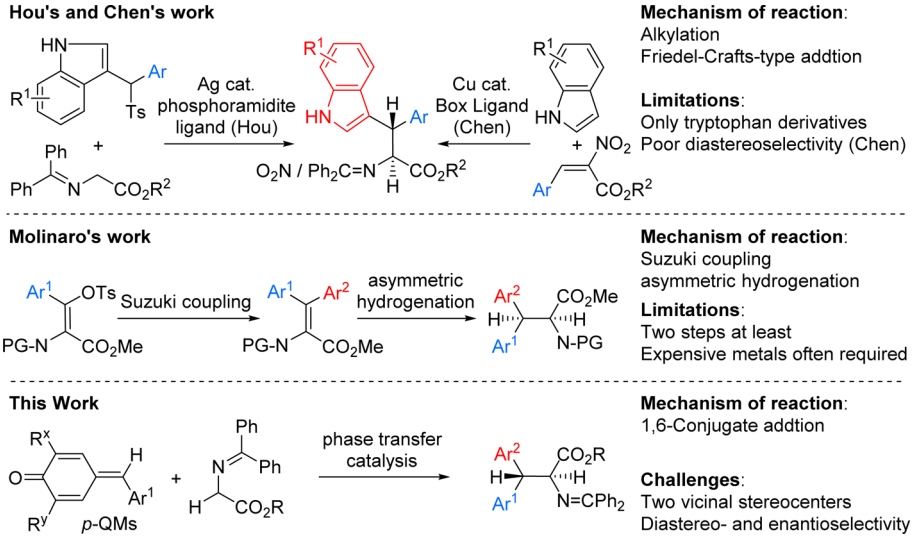
Scheme 1. Catalytic Enantioselective Approaches to Unsymmetric *β,β*-Diaryl-*α*-Amino Acid Esters

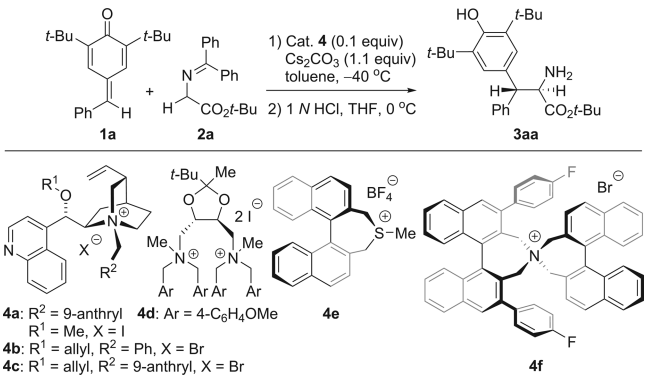


development of methodologies of *p*-QMs in asymmetric catalysis,[15a] we herein report a novel catalytic enantioselective synthesis of chiral unsymmetric *β,β*-diaryl-*α*-amino acid esters via 1,6-conjugate addition of *p*-QMs under phase transfer catalysis (Scheme 1).[18,19]

Initially, to probe our designed protocol, we selected *p*-QM **1a** and glycine derivative **2a** as our model substrates with Cs_2CO_3 as the base and a series of ammonium and sulfonium salts as catalysts (Table 1). First, *N*-bridged *Cinchona*-related ammonium salts **4a**[20a] and **4b**[20b] (entries 1 and 2) were subjected to the model reaction, and desired product **3aa** could be gained with good diastereoselectivity but in only moderate yields and enantioselectivity. Pleasingly, catalyst **4c**[20c] (entry 3), having the combined modification of the side chain by the introduction of the allyl on oxygen and the 9-anthracenylmethyl on nitrogen, not only increased the catalytic activity (92% yield) but also obviously improved the diastereoselectivity and enantioselectivity (>20:1 dr, 87% ee). When employing tartrate-derived bis-ammonium iodide **4d**[20d] (entry 4) and C_2-symmetrical biaryl-derived sulfonium salt **4e**[20e] (entry 5), poor stereocontrol was observed in this model reaction. Compared with the positive result using *Cinchona* quaternary ammonium salt **4c** (entry 3), it should be noted that the axially chiral *N*-spiro ammonium salt **4f**[20f] (entry 6), which as a catalyst showed the excellent efficiency in our previous report,[15a] gave moderate reactivity (66% yield) and decreased stereoselectivity (12.6:1 dr, 70% ee). To further improve the stereocontrol of the model reaction, we subsequently examnined the influence of temperature (entries 7–9).[21] To our delight, lowering the temperature to −40 °C (entry 9) eventually delivered the optimal result in both reactivity and stereoselectivity (96% yield, >20:1 dr, and 96% ee).

With the optimized conditions in hand, as listed in Table 2, the substrate scope was then explored. A series of *p*-QMs **1a**–**1p** having different electron-donating or -withdrawing aromatic substituents (R^2 = Ar) at *δ* position were reacted with glycine derivative **2a** (R^3 = *t*-Bu), and the corresponding *β,β*-diaryl-*α*-amino acid esters **3aa**–**3pa** were generally afforded in good to excellent yields (up to 96% yield) and high diastereo- and enantioselectivities (>20:1 dr, 90–98% ee). The absolute configuration of **3da** was determined by crystallographic X-ray analysis.[22] Notably, *p*-QM **1q** bearing a 2-pyridinyl group (R^2 = 2-pyridinyl) at the *δ* position was also employed, and desired product **3qa** was achieved in high yield and excellent enantioselectivitity (96% yield, >20:1 dr, 98% ee). When employing *p*-QM **1r** containing a 2-thienyl group (R^2 = 2-thienyl), only moderate yield (43% yield) was observed despite good stereoselectivity (9.7:1 dr, 90% ee). Moreover, *p*-QM **1s** with an alkyl substituent (R^2 = Me) at the *δ* position was also considered, but poor diastereoselectivity (1.5:1 dr) for addition product **3sa** was obtained. Notably, two additional *p*-QMs with the different *α,α′*-substituted R^1 groups instead of *tert*-butyl, **1t**

Table 1. Optimization of Reaction Conditions[a]



entry	cat.	*T* (°C)	*t* (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	**4a**	25	24	60	9.9:1	69 (21)
2	**4b**	25	3	85	8.9:1	70 (58)
3	**4c**	25	5	92	>20:1	87
4	**4d**	25	24	56	2.5:1	30 (0)
5	**4e**	25	17	85	1.3:1	0 (0)
6	**4f**	25	24	66	12.6:1	70 (28)
7	**4c**	0	7	94	>20:1	92
8	**4c**	−20	18	96	>20:1	94
9	**4c**	−40	36	96	>20:1	96

[a]Reactions for the first step were performed with **1a** (0.1 mmol) and **2a** (0.11 mmol) in the presence of catalyst **4** (0.01 mmol) and Cs_2CO_3 (0.11 mmol) in toluene (2.0 mL) at the indicated temperature. [b]Yield of isolated products. [c]Determined by HPLC. [d]Determined by HPLC analysis using a chiral stationary phase. Values in parentheses referred to the ee of the minor diastereoisomer.

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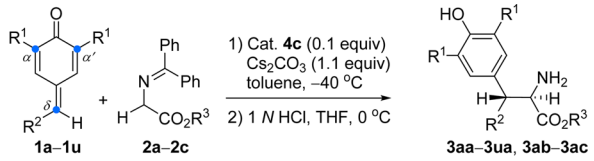
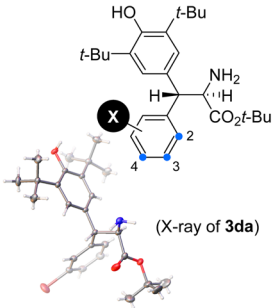
Table 2. Substrate Scope for Asymmetric Catalytic 1,6-Conjugate Addition[a,b]

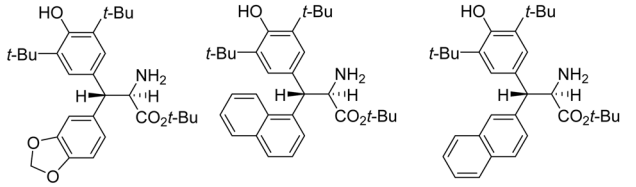


1a–1u 2a–2c 3aa–3ua, 3ab–3ac

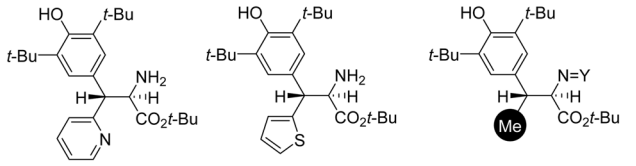


3aa–3ma (> 20:1 *dr*)

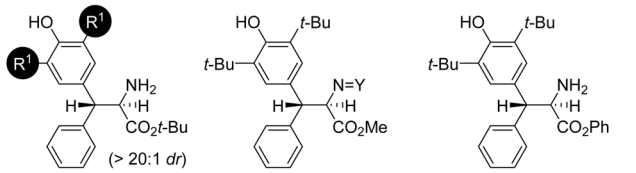
3aa: X = H (36 h, 96% yield, 96% *ee*)
3ba: X = 2-Cl (14 h, 96% yield, 98% *ee*)
3ca: X = 2-Br (23 h, 92% yield, 97% *ee*)
3da: X = 3-Br (23 h, 96% yield, 97% *ee*)
3ea: X = 4-Br (23 h, 96% yield, 93% *ee*)
3fa: X = 4-Cl (23 h, 96% yield, 93% *ee*)
3ga: X = 4-F (24 h, 91% yield, 95% *ee*)
3ha: X = 4-NO_2 (14 h, 95% yield, 92% *ee*)
3ia: X = 4-CO_2Me (24 h, 94% yield, 95% *ee*)
3ja: X = 4-Me (46 h, 96% yield, 96% *ee*)
3ka: X = 4-MeO (48 h, 88% yield, 94% *ee*)
3la: X = 3,4-$(MeO)_2$ (48 h,73% yield, 90% *ee*)
3ma: X = 3,4-$(Cl)_2$ (23 h, 94% yield, 93% *ee*)



3na (> 20:1 *dr*) (48 h, 94% yield, 94% *ee*) **3oa** (> 20:1 *dr*) (49 h, 94% yield, 98% *ee*) **3pa** (> 20:1 *dr*) (14 h, 96% yield, 93% *ee*)



3qa (> 20:1 *dr*) (20 h, 96% yield) (98% *ee*) **3ra** (9.7:1 *dr*) (59 h, 43% yield) (90% *ee*) **3sa**: Y = CPh_2 (25 h, 88% yield, 1.5:1 *dr*) 92% *ee* (major), 96% *ee* (minor)



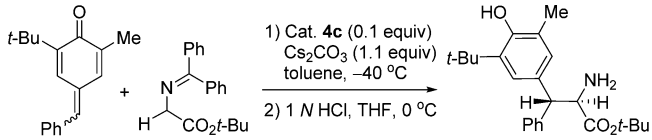
3ta: R^1 = Me (25 °C)[c] (8 h, 79% yield, 93% *ee*) **3ua**: R^1 = $SiMe_3$ (30 h, 88% yiel, 98% *ee*) **3ab**: Y = CPh_2 (29 h, 96% yield, 1.9:1 *dr*) 90% *ee* (major) 64% *ee* (minor) **3ac** (6.3:1 *dr*) (10 h, 96% yield, 69% *ee*)

[a]Unless otherwise noted, all reactions for the first step were performed with **1a–1u** (0.1 mmol) and **2a–2c** (0.11 mmol) in the presence of catalyst **4c** (0.01 mmol) and Cs_2CO_3 (0.11 mmol) in toluene (2.0 mL) at −40 °C. The yields were referred to the isolated products, and the dr values were determined by HPLC. The ee values referred to the major diastereoisomer and were determined by HPLC. [b]The unhydrolyzed addition products **3sa** (Y = CPh_2) and **3ab** (Y = CPh_2) were directly used for the ee value determination due to our failed attempts to measure the ee values of their corresponding α-amino acid esters. [c]Performed at 25 °C instead of −40 °C.

(R^1 = Me) and **1u** (R^1 = $SiMe_3$), were further tested, and products **3ta** (79% yield, >20:1 dr, and 93% ee) and **3ua** (88% yield, >20:1 dr, and 98% ee) were afforded without a negative influence on the yield or stereoselectivity. In addition to the above exploration of *p*-QMs as acceptors, two glycine ester derivatives as donors were also evaluated, and it was found that the less bulky glycine esters, **2b** (R^3 = Me) and **2c** (R^3 = Ph), gave significant decreases of diastereoselectivity and/or enantioselectivity in **3ab** and **3ac**.

To further explore the influence of stereochemistry of exocyclic methylene substituents of *p*-QMs on the asymmetric control of 1,6-conjugate addition, as shown in Scheme 2, we

Scheme 2. Effect of Exocyclic Stereochemistry of *p*-QM

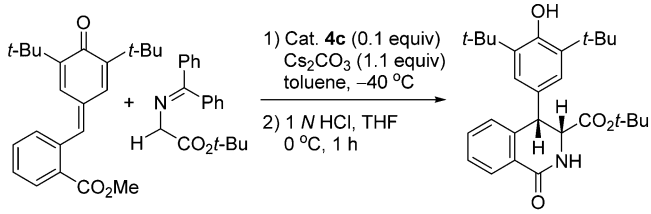


1v (1.4:1 dr) **2a** **3va** (>20:1 dr) (24 h, 96% yield, 99% ee)

conducted a control experiment using **1v** (1.4:1 dr). Importantly, the titled reaction smoothly delivered the corresponding α-amino acid ester **3va** with excellent yield (96% yield) and stereoselectivity (>20:1 dr, 99% ee). This result revealed the fact that the stereo discrimination to the prochiral face of **1v** was not affected by the configuration of the exocyclic methylene substituent of *p*-QM.

As an expansion of this methodology, as shown in Scheme 3, *p*-QM **1w** was designed and examined. Interestingly, the chiral

Scheme 3. Synthesis of the Core of Hyalachelin A



1w **2a** **3wa** (> 20:1 dr) (30 h, 96% yield, 96% ee)

1,2,3,4-tetrahydroisoquinoline-1-one **3wa**, constituting the core of the natural product Hyalachelin A (Figure 1),[1] was achieved with high yield (96% yield) and stereoselectivity (>20:1 dr, 96% ee) under the control conditions. For the synthetic potential of this protocol to be demonstrated further, as shown in Scheme 4, the effective construction of functionalized tetrahydroisoquinoline building blocks was alternatively exemplified by a Pictet–Spengler reaction of the adduct **3la** (90% ee), leading to the Cherylline analogue **5la** (96% yield, 90% ee) without erosion of optical purity.

In conclusion, a novel method for the chiral synthesis of unsymmetric β,β-diaryl-α-amino acid esters via catalytic enantioselective 1,6-conjugate addition of *p*-QMs and glycine derivatives under phase-transfer catalysis has been developed. A series of unnatural enantioenriched β,β-diaryl-α-amino acid esters with two vicinal tertiary stereocenters were achieved with good to high yields and enantioselectivities. This organocatalytic methodology also strategically provided an alternative approach to the synthetically important functionalized tetrahydroisoquinoline scaffolds, demonstrating its potential in asymmetric synthesis.

EXPERIMENTAL SECTION

General Methods. Unless otherwise noted, all moisture or oxygen-sensitive reactions were carried out under an argon atmosphere in oven or heat-dried flasks. All solvents were purified

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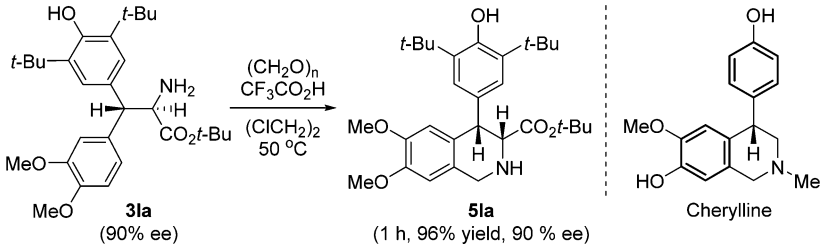
Scheme 4. Synthesis of Tetrahydroisoquinoline Building Block



and dried prior to use according to the literature.[23] Unless otherwise stated, all other commercial reagents were used as received without further purification. All reactions were monitored by thin-layer chromatography (TLC) on silica gel F_{254} plates using UV light as visualizing agent and a solution of ammonium molybdate tetrahydrate (50 g/L) in EtOH followed by heating as developing agents. The products were purified by flash column chromatography on silica gel (200−300 meshes). ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or acetone-d_6 solution at 400 MHz. Chemical shifts are denoted in ppm (δ) and calibrated by using residual undeuterated solvent ($CDCl_3$ (7.27 ppm), acetone-d_6 (2.05 ppm), or tetramethylsilane (0.00 ppm)) as internal reference for ^{1}H NMR and the deuterated solvent ($CDCl_3$ (77.00 ppm), acetone-d_6 (29.84 ppm), or tetramethylsilane (0.00 ppm)) as internal standard for ^{13}C NMR. Multiplicities are indicated as follows: s (singlet), d (doublet), t (triplet), and m (multiplet). The MS data were obtained with ESI technique, and the relative intensity (%) is given in brackets. High-resolution mass spectral analysis (HRMS) data were obtained using an Orbitrap instrument equipped with ESI source. Infrared spectra (IR) were recorded by means of the ATR technique. Optical rotations were measured using a 0.1 mL cell with a 1 cm path length on Autopol IV automatic polarimeter with a sodium lamp, and concentrations (c) were reported in g × 100 mL^{-1}. The chiral HPLC analyses were recorded on a HPLC machine equipped with a 1525 binary HPLC pump and a 2998 photodiode array detector and measured at the indicated wavelength (210−280 nm) using the indicated chiral column (Ø = 0.46 cm, length = 25.0 cm).

The *p*-quinone methides **1a−1w** were prepared according to reported literature procedures.[15a] Glycine derivatives **2a−2c** were prepared according to other known literature procedures.[24]

General Procedure for the Synthesis of Unnatural α-Amino Acid Esters. A mixture of *p*-quinone methides **1a−1w** (0.1 mmol), glycine derivatives **2a−2c** (0.11 mmol), and catalyst **4c** (6.0 mg, 0.01 mmol) in toluene (2.0 mL) was cooled to −40 °C, and then Cs_2CO_3 (35.8 mg, 0.11 mmol) was added. The resulting reaction mixture was kept under vigorous stirring until the consumption of *p*-QMs (monitored by TLC analysis). Then, the mixture was filtered through silica gel, and the filtrate was concentrated. The resulting residue was dissolved in THF (2.0 mL), and 1 N HCl (2.0 mL) was added at 0 °C. After stirring at 0 °C for 1 h, an aqueous saturated solution of $NaHCO_3$ (5 mL) was added dropwise to the reaction mixture. Following extraction with CH_2Cl_2 (3 × 10 mL), the combined extracts were dried over anhydrous Na_2SO_4. The solvent was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel using mixtures of petroleum ether/ethyl acetate as the eluent, giving products **3aa−3wa** and **3ab−3ac**.

*tert-Butyl (2R,3R)-2-Amino-3-(3,5-ditert-butyl-4-hydroxyphenyl)-3-phenylpropanoate (**3aa**).* Following the general procedure, the reaction gave product **3aa** (36 h, white solid, mp 146−148 °C, 41.0 mg, 96% yield, >20:1 dr, 96% ee, $[\alpha]_D^{20}$ −75 (*c* 1, $CHCl_3$)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 7.7 Hz, 2H), 7.27−7.24 (m, 2H), 7.18−7.14 (m, 3H), 5.12 (br, 1H), 4.06 (d, *J* = 9.4 Hz, 1H), 3.97 (d, *J* = 9.4 Hz, 1H), 1.41 (s, 20H), 1.17 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 152.6, 142.2, 136.0, 131.4, 128.4, 128.2, 126.4, 124.9, 80.8, 59.7, 57.6, 34.3, 30.3, 27.5. IR: $\bar{\nu}$ 2965, 1276, 1434, 1368, 1201, 1149, 844, 699 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $[C_{27}H_{39}NO_3 + H]^+$ 426.3003, found 426.2998. The dr and ee values were determined by chiral HPLC analysis (Chiralpak IA-3, *n*-hexane/2-propanol = 98:2, *v* = 0.5 mL/min^{-1}, λ = 280.0 nm; for the major diastereoisomer: t_{minor} = 12.0 min, t_{major} = 13.8 min).

*tert-Butyl (2R,3S)-2-Amino-3-(2-chlorophenyl)-3-(3,5-ditert-butyl-4-hydroxyphenyl)propanoate (**3ba**).* Following the general procedure, the reaction gave product **3ba** (14 h, light yellow solid, mp 193−196 °C, 44.0 mg, 96% yield, >20:1 dr, 98% ee, $[\alpha]_D^{22}$ −80 (*c* 1, $CHCl_3$)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.31 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.24−7.15 (m, 3H), 7.10 (td, *J* = 7.8, 1.5 Hz, 1H), 5.11 (s, 1H), 4.62 (d, *J* = 9.5 Hz, 1H), 4.11 (d, *J* = 9.4 Hz, 1H), 1.53 (br, 2H), 1.41 (s, 18H), 1.19 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 152.7, 140.0, 135.9, 133.9, 130.2, 129.6, 129.2, 127.4, 126.6, 125.2, 81.0, 59.2, 52.0, 34.3, 30.3, 27.5. IR: $\bar{\nu}$ 2925, 1728, 1433, 1368, 1291, 1151, 975, 760 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $[C_{27}H_{38}ClNO_3 + H]^+$ 460.2613, found 460.2619. The dr and ee values were determined by chiral HPLC analysis (Chiralpak IA-3, *n*-hexane/2-propanol = 98:2, *v* = 0.5 mL/min^{-1}, λ = 280.0 nm; for the major diastereoisomer: t_{minor} = 12.0 min, t_{major} = 13.1 min).

*tert-Butyl (2R,3S)-2-Amino-3-(2-bromophenyl)-3-(3,5-ditert-butyl-4-hydroxyphenyl)propanoate (**3ca**).* Following the general procedure, the reaction gave product **3ca** (23 h, white solid, mp 185−189 °C, 46.3 mg, 92% yield, >20:1 dr, 97% ee, $[\alpha]_D^{21}$ −80 (*c* 1, $CHCl_3$)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.50 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.31−7.23 (m, 1H), 7.22 (s, 2H), 7.02 (td, *J* = 7.9, 1.6 Hz, 1H), 5.10 (s, 1H), 4.60 (d, *J* = 9.5 Hz, 1H), 4.10 (d, *J* = 9.4 Hz, 1H), 1.53 (br, 2H), 1.41 (s, 18H), 1.19 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 152.7, 141.6, 135.9, 132.9, 130.2, 129.3, 127.8, 127.3, 125.2, 125.0, 81.0, 59.4, 54.7, 34.3, 30.3, 27.5. IR: $\bar{\nu}$ 2927, 1728, 1468, 1369, 1216, 1024, 758 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $[C_{27}H_{38}BrNO_3 + H]^+$ 504.2108, found 504.2113. The dr and ee values were determined by chiral HPLC analysis (Chiralpak IA-3, *n*-hexane/2-propanol = 98:2, *v* = 0.5 mL/min^{-1}, λ = 280.0 nm; for the major diastereoisomer: t_{minor} = 12.3 min, t_{major} = 13.2 min).

*tert-Butyl (2R,3S)-2-Amino-3-(3-bromophenyl)-3-(3,5-ditert-butyl-4-hydroxyphenyl)propanoate (**3da**).* Following the general procedure, the reaction gave product **3da** (23 h, white solid, mp 182−184 °C 48.4 mg, 96% yield, >20:1 dr, 97% ee, $[\alpha]_D^{21}$ −60 (*c* 1, $CHCl_3$)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.32−7.27 (m, 2H), 7.13 (t, *J* = 7.8 Hz, 1H), 7.09 (s, 2H), 5.13 (s, 1H), 4.00 (d, *J* = 9.3 Hz, 1H), 3.94 (d, *J* = 9.3 Hz, 1H), 1.50 (br, 2H), 1.41 (s, 18H), 1.21 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 152.9, 144.7, 136.2, 131.6, 130.5, 129.8, 129.5, 127.0, 125.0, 122.2, 81.2, 59.5, 57.1, 34.4, 30.3, 27.6. IR: $\bar{\nu}$ 2959, 1721, 1465, 1368, 1261, 1147, 992, 761 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $[C_{27}H_{38}BrNO_3 + H]^+$ 504.2108, found 504.2114. The dr and ee values were determined by chiral HPLC analysis (Chiralpak IA-3, *n*-hexane/2-propanol = 98:2, *v* = 0.5 mL/min^{-1}, λ = 280.0 nm; for the major diastereoisomer: t_{minor} = 12.1 min, t_{major} = 14.3 min).

*tert-Butyl (2R,3R)-2-Amino-3-(4-bromophenyl)-3-(3,5-ditert-butyl-4-hydroxyphenyl)propanoate (**3ea**).* Following the general procedure, the reaction gave product **3ea** (23 h, white solid, mp 150−153 °C, 48.3 mg, 96% yield, >20:1 dr, 93% ee, $[\alpha]_D^{21}$ −50 (*c* 1, $CHCl_3$)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 8.4 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 7.08 (s, 2H), 5.12 (s, 1H), 4.00, 3.97 (ABq, *J* = 9.3 Hz, 2H), 1.49 (br, 2H), 1.40 (s, 19H), 1.21 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 152.8, 141.5, 136.1, 131.3, 130.7, 130.2, 124.9, 120.2, 81.2, 59.5, 56.6, 34.3, 30.3, 27.7. IR: $\bar{\nu}$ 2958, 1724, 1461, 1377, 1261, 1148, 1012, 801 cm^{-1}. HRMS (ESI): *m*/*z* calcd for

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$[C_{27}H_{38}BrNO_3 + H]^+$ 504.2108, found 504.2115. The dr and ee values were determined by chiral HPLC analysis (Chiralpak IA-3, *n*-hexane/2-propanol = 98:2, v = 0.5 mL/min^{-1}, λ = 280.0 nm; for the major diastereoisomer: t_{minor} = 11.9 min, t_{major} = 14.4 min).

*tert-Butyl (2R,3R)-2-Amino-3-(4-chlorophenyl)-3-(3,5-ditert-butyl-4-hydroxyphenyl)propanoate (**3fa**).* Following the general procedure, the reaction gave product **3fa** (23 h, white solid, mp 145−148 °C, 44.0 mg, 96% yield, >20:1 dr, 93% ee, $[\alpha]_D^{21}$ −70 (*c* 1, $CHCl_3$)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 8.6 Hz, 2H), 7.23 (d, J = 8.5 Hz, 2H), 7.08 (s, 2H), 5.12 (s, 1H), 4.00, 3.98 (ABq, J = 9.3 Hz, 2H), 1.49 (br, 2H), 1.41 (s, 18H), 1.21 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 152.8, 140.9, 136.1, 132.2, 130.8, 129.8, 128.3, 124.9, 81.2, 59.5, 56.6, 34.3, 30.3, 27.7. IR: $\bar{\nu}$ 2926, 1275, 1460, 1369, 1216, 1155, 755 cm^{-1}. HRMS (ESI): m/z calcd for $[C_{27}H_{38}ClNO_3 + H]^+$ 460.2613, found 460.2620. The dr and ee values were determined by chiral HPLC analysis (Chiralpak IA-3, *n*-hexane/2-propanol = 98:2, v = 0.5 mL/min^{-1}, λ = 280.0 nm; for the major diastereoisomer: t_{minor} = 10.8 min, t_{major} = 13.0 min).

*tert-Butyl (2R,3R)-2-Amino-3-(3,5-ditert-butyl-4-hydroxyphenyl)-3-(4-fluorophenyl)propanoate (**3ga**).* Following the general procedure, the reaction gave product **3ga** (24 h, white solid, mp 128−130 °C, 40.3 mg, 91% yield, >20:1 dr, 95% ee, $[\alpha]_D^{20}$ −60 (*c* 1, $CHCl_3$)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.27 (m, 2H), 7.09 (s, 2H), 7.00−6.92 (m, 2H), 5.12 (s, 1H), 4.00, 3.98 (ABq, J = 9.3 Hz, 2H), 1.51 (br, 2H), 1.41 (s, 18H), 1.20 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 161.6 ($^1J_{C-F}$ = 243 Hz), 152.7, 138.1 ($^4J_{C-F}$ = 3 Hz), 136.1, 131.1, 129.9 ($^3J_{C-F}$ = 8 Hz), 124.9, 115.0 ($^2J_{C-F}$ = 21 Hz), 81.1, 59.8, 56.6, 34.4, 30.3, 27.6. IR: $\bar{\nu}$ 2957, 1720, 1543, 1460, 1217, 1159, 760, 668 cm^{-1}. HRMS (ESI): m/z calcd for $[C_{27}H_{38}FNO_3 + H]^+$ 444.2908, found 444.2917. The dr and ee values were determined by chiral HPLC analysis (Chiralpak IA-3, *n*-hexane/2-propanol = 98:2, v = 0.5 mL/min^{-1}, λ = 280.0 nm; for the major diastereoisomer: t_{minor} = 11.5 min, t_{major} = 14.0 min).

*tert-Butyl (2R,3R)-2-Amino-3-(3,5-ditert-butyl-4-hydroxyphenyl)-3-(4-nitrophenyl)propanoate (**3ha**).* Following the general procedure, the reaction gave product **3ha** (14 h, light yellow solid, mp 140−144 °C, 44.7 mg, 95% yield, >20:1 dr, 92% ee, $[\alpha]_D^{22}$ −50 (*c* 1, $CHCl_3$)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 8.8 Hz, 2H), 7.55 (d, J = 8.7 Hz, 2H), 7.08 (s, 2H), 5.18 (s, 1H), 4.18 (d, J = 8.6 Hz, 1H), 4.07 (d, J = 8.6 Hz, 1H), 1.53 (br, 2H), 1.41 (s, 18H), 1.23 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 153.1, 150.2, 146.5, 136.3, 129.6, 129.3, 125.0, 123.5, 81.6, 59.1, 56.4, 34.4, 30.2, 27.7. IR: $\bar{\nu}$ 2923, 1728, 1596, 1524, 1437, 1346, 1260, 1115, 796 cm^{-1}. HRMS (ESI): m/z calcd for $[C_{27}H_{38}N_2O_5 + H]^+$ 471.2853, found 471.2859. The dr and ee values were determined by chiral HPLC analysis (Chiralpak IA-3, *n*-hexane/2-propanol = 98:2, v = 0.5 mL/min^{-1}, λ = 280.0 nm; for the major diastereoisomer: t_{minor} = 6.5 min, t_{major} = 8.9 min).

*Methyl 4-((1R,2R)-2-Amino-3-(tert-butoxy)-1-(3,5-ditert-butyl-4-hydroxyphenyl)-3-oxopropyl)benzoate (**3ia**).* Following the general procedure, the reaction gave product **3ia** (24 h, white solid, mp 90−95 °C, 45.4 mg, 94% yield, >20:1 dr, 95% ee, $[\alpha]_D^{21}$ −50 (*c* 1, $CHCl_3$)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.3 Hz, 2H), 7.43 (d, J = 8.3 Hz, 2H), 7.10 (s, 2H), 5.14 (s, 1H), 4.06 (s, 2H), 3.88 (s, 3H), 1.53 (br, 2H), 1.40 (s, 18H), 1.19 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 166.9, 152.8, 147.7, 136.1, 130.5, 129.6, 128.4, 128.2, 125.0, 81.2, 59.3, 57.2, 52.0, 34.3, 30.2, 27.6. IR: $\bar{\nu}$ 2957, 1726, 1610, 1459, 1368, 1281, 1155, 1020, 760 cm^{-1}. HRMS (ESI): m/z calcd for $[C_{29}H_{41}NO_5 + H]^+$ 484.3057, found 484.3062. The dr and ee values were determined by chiral HPLC analysis (Chiralpak IA-3, *n*-hexane/2-propanol = 98:2, v = 0.5 mL/min^{-1}, λ = 280.0 nm; for the major diastereoisomer: t_{minor} = 16.8 min, t_{major} = 20.1 min).

*tert-Butyl (2R,3R)-2-Amino-3-(3,5-ditert-butyl-4-hydroxyphenyl)-3-(p-tolyl)propanoate (**3ja**).* Following the general procedure, the reaction gave product **3ja** (46 h, white solid, mp 141−144 °C, 42.2 mg, 96% yield, >20:1 dr, 96% ee, $[\alpha]_D^{22}$ −60 (*c* 1, $CHCl_3$)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, J = 8.0 Hz, 2H), 7.12 (s, 2H), 7.06 (d, J = 7.9 Hz, 2H), 5.07 (s, 1H), 4.03 (d, J = 9.4 Hz, 1H), 3.94 (d, J = 9.4 Hz, 1H), 2.28 (s, 3H), 1.47 (br, 2H), 1.40 (s, 18H), 1.18 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 152.6, 139.2, 135.91, 135.88, 131.6, 128.9, 128.2, 124.9, 80.8, 59.8, 57.2, 34.3, 30.3, 27.6, 20.9. IR: $\bar{\nu}$ 3421, 2923, 1718, 1460, 1366, 1220, 1159, 780 cm^{-1}. HRMS (ESI): m/z calcd for $[C_{28}H_{41}NO_3 + H]^+$ 440.3159, found 440.3164. The dr and ee values were determined by chiral HPLC analysis (Chiralpak IA-3, *n*-hexane/2-propanol = 98:2, v = 0.5 mL/min^{-1}, λ = 280.0 nm; for the major diastereoisomer: t_{minor} = 10.6 min, t_{major} = 12.2 min).

*tert-Butyl (2R,3R)-2-Amino-3-(3,5-ditert-butyl-4-hydroxyphenyl)-3-(4-methoxyphenyl)propanoate (**3ka**).* Following the general procedure, the reaction gave product **3ka** (48 h, white solid, mp 124−127 °C, 40.0 mg, 88% yield, >20:1 dr, 94% ee, $[\alpha]_D^{22}$ −60 (*c* 1, $CHCl_3$)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 8.7 Hz, 2H),7.11 (s, 2H), 6.81 (d, J = 8.7 Hz, 2H), 5.08 (s, 1H), 4.00 (d, J = 9.4 Hz, 1H), 3.93 (d, J = 9.4 Hz, 1H), 3.76 (s, 3H), 1.46 (br, 2H), 1.41 (s, 19H), 1.19 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 158.2, 152.6, 135.9, 134.5, 131.7, 129.4, 124.9, 113.6, 80.8, 59.9, 56.7, 55.2, 34.3, 30.3, 27.6. IR: $\bar{\nu}$ 2924, 2372, 1723, 1460, 1251, 1155, 1037, 767 cm^{-1}. HRMS (ESI): m/z calcd for $[C_{28}H_{41}NO_4 + H]^+$ 456.3108, found 456.3113. The dr and ee values were determined by chiral HPLC analysis (Chiralpak IA-3, *n*-hexane/2-propanol = 98:2, v = 0.5 mL/min^{-1}, λ = 280.0 nm; for the major diastereoisomer: t_{minor} = 13.2 min, t_{major} = 15.4 min).

*tert-Butyl (2R,3S)-2-Amino-3-(3,5-ditert-butyl-4-hydroxyphenyl)-3-(3,4-dimethoxyphenyl)propanoate (**3la**).* Following the general procedure, the reaction gave product **3la** (48h, light yellow gum, 35.4 mg, 73% yield, >20:1 dr, 90% ee, $[\alpha]_D^{22}$ −50 (*c* 1, $CHCl_3$)).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (s, 2H), 6.94−6.84 (m, 2H), 6.78 (d, J = 8.1 Hz, 1H), 5.09 (s, 1H), 3.99 (d, J = 9.2 Hz, 1H), 3.93 (d, J = 9.2 Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 1.49 (br, 2H), 1.41 (s, 18H), 1.21 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 152.6, 148.6, 147.7, 135.9, 134.9, 131.5, 124.9, 120.5, 111.8, 111.1, 80.9, 60.0, 57.0, 55.9, 55.7, 34.3, 30.3, 27.7. IR: $\bar{\nu}$ 2922, 1729, 1514, 1437, 1260, 1115, 1017, 791, 633 cm^{-1}. HRMS (ESI): m/z calcd for $[C_{29}H_{43}NO_5 + H]^+$ 486.3214, found 486.3218. The dr and ee values were determined by chiral HPLC analysis (Chiralpak IA-3, *n*-hexane/2-propanol = 98:2, v = 0.5 mL/min^{-1}, λ = 280.0 nm; for the major diastereoisomer: t_{minor} = 13.0 min, t_{major} = 14.4 min).

*tert-Butyl (2R,3S)-2-Amino-3-(3,5-ditert-butyl-4-hydroxyphenyl)-3-(3,4-dichlorophenyl)propanoate (**3ma**).* Following the general procedure, the reaction gave product **3ma** (23 h, white solid, mp 90−93 °C, 46.3 mg, 94% yield, >20:1 dr, 93% ee, $[\alpha]_D^{21}$ −50 (*c* 1, $CHCl_3$)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 2.0 Hz, 1H), 7.34 (d, J = 8.3 Hz, 1H), 7.20 (dd, J = 8.3, 2.0 Hz, 1H), 7.06 (s, 2H), 5.15 (s, 1H), 3.98 (s, 2H), 1.49 (br, 2H), 1.41 (s, 18H), 1.24 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 153.0, 142.8, 136.2, 132.1, 130.5, 130.3, 130.1, 127.8, 125.0, 81.4, 59.3, 56.0, 34.4, 30.3, 27.7. IR: $\bar{\nu}$ 2925, 1729, 1466, 1368, 1237, 1154, 1030, 760 cm^{-1}. HRMS (ESI): m/z calcd for $[C_{27}H_{37}Cl_2NO_3 + H]^+$ 494.2223, found 494.2230. The dr and ee values were determined by chiral HPLC analysis (Chiralpak IA-3, *n*-hexane/2-propanol = 98:2, v = 0.5 mL/min^{-1}, λ = 280.0 nm; for the major diastereoisomer: t_{minor} = 11.4 min, t_{major} = 13.5 min).

*tert-Butyl (2R,3S)-2-Amino-3-(benzo[d][1,3]dioxol-5-yl)-3-(3,5-ditert-butyl-4-hydroxyphenyl)propanoate (**3na**).* Following the general procedure, the reaction gave product **3na** (48 h, light yellow solid, mp 63−68 °C, 44.1 mg, 94% yield, >20:1 dr, 94% ee, $[\alpha]_D^{22}$ −50 (*c* 1, $CHCl_3$)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (s, 2H), 6.88−6.74 (m, 2H), 6.71 (d, J = 8.0 Hz, 1H), 5.88 (d, J = 1.2 Hz, 2H), 5.11 (br, 1H), 3.98 (d, J = 9.3 Hz, 1H), 3.92 (d, J = 9.4 Hz, 1H), 1.81 (br, 2H), 1.41 (s, 18H), 1.23 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 152.7, 147.4, 146.0, 136.2, 136.0, 131.4, 124.8, 121.4, 108.9, 108.0, 100.7, 81.0, 59.7, 57.0, 34.3, 30.3, 27.7. IR: $\bar{\nu}$ 2923, 1728, 1488, 1437, 1247, 1155, 1041, 760 cm^{-1}. HRMS (ESI): m/z calcd for $[C_{28}H_{39}NO_5 + H]^+$ 470.2901, found 470.2908. The dr and ee values were determined by chiral HPLC analysis (Chiralpak IA-3, *n*-hexane/2-propanol = 98:2, v = 0.5 mL/min^{-1}, λ = 280.0 nm; for the major diastereoisomer: t_{minor} = 17.7 min, t_{major} = 19.4 min).

*tert-Butyl (2R,3S)-2-Amino-3-(3,5-ditert-butyl-4-hydroxyphenyl)-3-(naphthalen-1-yl)propanoate (**3oa**).* Following the general procedure, the reaction gave product **3oa** (49 h, white solid, mp 152−156 °C, 44.7 mg, 94% yield, >20:1 dr, 98% ee, $[\alpha]_D^{22}$ −80 (*c* 1, $CHCl_3$)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 8.5 Hz, 1H), 7.81 (d, J = 7.8

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Hz, 1H), 7.70 (t, J = 7.0 Hz, 2H), 7.58−7.36 (m, 3H), 7.24 (s, 2H), 5.07 (s, 1H), 4.93 (d, J = 8.7 Hz, 1H), 4.22 (d, J = 8.6 Hz, 1H), 1.57 (br, 2H), 1.39 (s, 18H), 1.03 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 152.6, 138.4, 135.8, 133.9, 131.6, 131.0, 128.8, 127.0, 125.9, 125.33, 125.27, 125.2, 123.5, 80.9, 60.0, 50.7, 34.3, 30.3, 27.4. IR: $\bar{\upsilon}$ 2962, 1727, 1459, 1368, 1216, 1154, 1026, 756 cm^{-1}. HRMS (ESI): m/z calcd for $[C_{31}H_{41}NO_3 + H]^+$ 476.3159, found 476.3165. The dr and ee values were determined by chiral HPLC analysis (Chiralpak AD, n-hexane/2-propanol = 98:2, v = 0.5 mL/min^{-1}, λ = 280.0 nm; for the major diastereoisomer: t_{minor} = 23.5 min, t_{major} = 25.5 min).

*tert-Butyl (2R,3R)-2-Amino-3-(3,5-ditert-butyl-4-hydroxyphenyl)-3-(naphthalen-2-yl)propanoate (**3pa**).* Following the general procedure, the reaction gave product **3pa** (14 h, white solid, mp 129−132 °C, 45.6 mg, 96% yield, >20:1 dr, 93% ee, $[\alpha]_D^{22}$ −50 (c 1, $CHCl_3$)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85−7.70 (m, 4H), 7.52−7.34 (m, 3H), 7.18 (s, 2H), 5.10 (s, 1H), 4.18 (s, 2H), 1.56 (br, 2H), 1.41 (s, 18H), 1.08 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 152.7, 139.8, 136.0, 133.4, 132.2, 131.2, 127.73, 127.71, 127.4, 126.84, 126.79, 125.8, 125.4, 125.1, 81.0, 59.6, 57.5, 34.3, 30.3, 27.5. IR: $\bar{\upsilon}$ 2957, 1728, 1436, 1367, 1237, 1155, 746 cm^{-1}. HRMS (ESI): m/z calcd for $[C_{31}H_{41}NO_3 + H]^+$ 476.3159, found 476.3164. The dr and ee values were determined by chiral HPLC analysis (Chiralpak IA-3, n-hexane/2-propanol = 98:2, v = 0.5 mL/min^{-1}, λ = 280.0 nm; for the major diastereoisomer: t_{minor} = 13.7 min, t_{major} = 16.6 min).

*tert-Butyl (2R,3R)-2-Amino-3-(3,5-ditert-butyl-4-hydroxyphenyl)-3-(pyridin-2-yl)propanoate (**3qa**).* Following the general procedure, the reaction gave product **3qa** (20 h, white solid, mp 137−139 °C, 40.9 mg, 96% yield, >20:1 dr, 98% ee, $[\alpha]_D^{22}$ −70 (c 1, $CHCl_3$)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58−8.53 (m, 1H), 7.53 (td, J = 7.7, 1.7 Hz, 1H), 7.21−7.198 (m, 3H), 7.14−7.02 (m, 1H), 5.13 (br, 1H), 4.33 (d, J = 8.1 Hz, 1H), 4.22 (d, J = 8.1 Hz, 1H), 1.81 (br, 1H), 1.40 (s, 18H), 1.26 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 162.0, 152.9, 148.7, 136.1, 135.8, 129.9, 125.7, 123.7, 121.3, 80.7, 59.0, 57.8, 34.3, 30.3, 27.7. IR: $\bar{\upsilon}$ 2971, 1730, 1432, 1266, 1163, 975, 749 cm^{-1}. HRMS (ESI): m/z calcd for $[C_{26}H_{38}N_2O_3 + H]^+$ 427.2955, found 427.2947. The dr and ee values were determined by chiral HPLC analysis (Chiralpak IA-3, n-hexane/2-propanol = 98:2, v = 0.5 mL/min^{-1}, λ = 280.0 nm; for the major diastereoisomer: t_{minor} = 18.2 min, t_{major} = 31.6 min).

*tert-Butyl (2R,3R)-2-Amino-3-(3,5-ditert-butyl-4-hydroxyphenyl)-3-(thiophen-2-yl)propanoate (**3ra**).* Following the general procedure, the reaction gave product **3ra** (59 h, white solid, mp 116−119 °C, 18.5 mg, 43% yield, 9.7:1 dr, 90% ee, $[\alpha]_D^{22}$ −55 (c 1, $CHCl_3$)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18−7.10 (m, 3H), 6.95−6.88 (m, 2H), 5.12 (s, 1H), 4.36 (d, J = 8.2 Hz, 1H), 3.94 (d, J = 8.2 Hz, 1H), 1.51 (br, 2H), 1.42 (s, 18H), 1.28 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 153.0, 145.7, 135.9, 130.6, 126.2, 125.18, 125.16, 124.0, 81.2, 61.2, 52.2, 34.4, 30.3, 27.8. IR: $\bar{\upsilon}$ 2945, 1722, 1460, 1368, 1259, 1155, 703 cm^{-1}. HRMS (ESI): m/z calcd for $[C_{25}H_{37}NO_3S + H]^+$ 432.2567, found 432.2559. The dr and ee values were determined by chiral HPLC analysis (Chiralpak AD, n-hexane/2-propanol = 98:2, v = 0.5 mL/min^{-1}, λ = 280.0 nm; for the major diastereoisomer: t_{minor} = 15.0 min, t_{major} = 17.6 min; for the minor diastereoisomer: t_{minor} = 25.8 min, t_{major} = 23.3 min).

*tert-Butyl (2R,3R)-3-(3,5-Ditert-butyl-4-hydroxyphenyl)-2-((diphenylmethylene)amino)butanoate (**3sa**).* A mixture of p-quinone methide **1s** (23.2 mg, 0.10 mmol), glycine derivative **2a** (32.5 mg, 0.11 mmol), and catalyst **4c** (6 mg, 0.01 mmol) in toluene (2.0 mL) was cooled to −40 °C, and then Cs_2CO_3 (35.8 mg, 0.11 mmol) was added. After stirring at −40 °C for 25 h, the resulting mixture without further concentration was directly purified by flash column chromatography on silica gel using mixtures of petroleum ether/ethyl acetate as the eluent, giving unhydrolyzed product **3sa** (white solid, mp 52−57 °C, 46.4 mg, 88% yield, 1.5:1 dr, 92% ee (major), 96% ee (minor), $[\alpha]_D^{22}$ +90 (c 1, $CHCl_3$)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68−7.61 (m, 2H, major), 7.56−7.50 (m, 2H, minor), 7.39−7.20 (m, 11H, major + minor), 6.96 (s, 2H, minor), 6.88 (s, 2H, major), 6.62−6.56 (m, 3H, major + minor), 5.00 (s, 1H, major), 4.99 (s, 1H, minor), 3.97 (d, J = 5.1 Hz, 1H, major), 3.81 (d, J = 8.8 Hz, 1H, minor), 3.55−3.35 (m, 2H, major + minor), 1.44 (s, 9H, minor), 1.36 (s, 9H, major), 1.34 (s, 18H, minor), 1.31 (s, 18H, major). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0 (minor), 170.8 (major), 169.6 (major), 169.1 (minor), 152.1, 139.64, 139.61 136.6, 136.4, 135.2, 134.94, 134.1, 133.6, 133.0, 129.9, 128.8, 128.7, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 125.1, 124.8, 80.8 (minor), 80.6 (major), 73.8 (minor), 71.8 (major), 43.3 (major), 43.1 (minor), 34.23 (minor), 34.18 (major), 30.3 (minor), 30.2 (major), 28.1 (minor), 28.0 (major), 17.3 (minor), 16.0 (major). IR: $\bar{\upsilon}$ 2959, 1731, 1627, 1458, 1368, 1261, 1154, 1025, 804 cm^{-1}. HRMS (ESI): m/z calcd for $[C_{35}H_{45}NO_3 + H]^+$ 528.3472, found 528.3480. The dr and ee values were determined by chiral HPLC analysis (Chiralpak IE-3, n-hexane/2-propanol = 98:2, v = 0.5 mL/min^{-1}, λ = 254.0 nm; for the major diastereoisomer: t_{minor} = 16.1 min, t_{major} = 10.8 min; for the minor diastereoisomer: t_{minor} = 12.5 min, t_{major} = 9.9 min).

*tert-Butyl (2R,3R)-2-Amino-3-(4-hydroxy-3,5-dimethylphenyl)-3-phenylpropanoate (**3ta**).* To a mixture of p-quinone methide **1t** (21.0 mg, 0.10 mmol), glycine derivative **2a** (32.5 mg, 0.11 mmol), and catalyst **4c** (6.0 mg, 0.01 mmol) in toluene (2.0 mL) was added Cs_2CO_3 (35.8 mg, 0.11 mmol) at 25 °C. After stirring at 25 °C for 8 h, the mixture was filtered through silica gel, and the filtrate was concentrated. The resulting residue was dissolved in THF (2.0 mL), and 1 N HCl (2.0 mL) was added at 0 °C. After stirring at 0 °C for 1 h, an aqueous saturated solution of $NaHCO_3$ (5 mL) was added dropwise to the reaction mixture. Following extraction with CH_2Cl_2 (3 × 10 mL), the combined extracts were dried over anhydrous Na_2SO_4. The solvent was concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel using mixtures of petroleum ether/ethyl acetate as the eluent giving product **3ta** (white solid, mp 175−157 °C, 27.0 mg, 79% yield, >20:1 dr, 93% ee, $[\alpha]_D^{22}$ −70 (c 1, $CHCl_3$)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 7.4 Hz, 2H), 7.24 (t, J = 7.5 Hz, 2H), 7.15 (t, J = 7.3 Hz, 1H), 6.91 (s, 2H), 4.05 (d, J = 9.5 Hz, 1H), 3.93 (d, J = 9.5 Hz, 1H), 2.63 (br, 2H), 2.17 (s, 6H), 1.18 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 151.3, 142.0, 132.3, 128.5, 128.30, 128.26, 126.5, 123.6, 81.1, 59.3, 56.7, 27.6, 16.2. IR: $\bar{\upsilon}$ 3282, 2924, 1721, 1455, 1216, 1155, 1025, 761 cm^{-1}. HRMS (ESI): m/z calcd for $[C_{21}H_{27}NO_3 + H]^+$ 342.2064, found 342.2070. The dr and ee values were determined by chiral HPLC analysis (Chiralpak AD, n-hexane/2-propanol = 98:2, v = 0.5 mL/min^{-1}, λ = 280.0 nm; for the major diastereoisomer: t_{minor} = 9.2 min, t_{major} = 10.9 min).

*tert-Butyl (2R,3R)-2-Amino-3-(4-hydroxy-3,5-bis(trimethylsilyl)-phenyl)-3-phenylpropanoate (**3ua**).* Following the general procedure, the reaction gave product **3ua** (30 h, white solid, mp 128−130 °C, 40.2 mg, 88% yield, >20:1 dr, 98% ee, $[\alpha]_D^{22}$ −70 (c 1, $CHCl_3$)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.30 (m, 4H), 7.28−7.22 (m, 2H), 7.16 (t, J = 7.3 Hz, 1H), 4.91 (br, 1H), 4.06 (d, J = 9.5 Hz, 1H), 3.99 (d, J = 9.5 Hz, 1H), 1.48 (br, 2H), 1.17 (s, 9H), 0.31 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 164.3, 142.0, 136.6, 132.4, 128.4, 128.3, 126.5, 124.5, 81.0, 59.6, 57.0, 27.6, −0.6. IR: $\bar{\upsilon}$ 2925, 1726, 1459, 1246, 1147, 1110, 843, 699 cm^{-1}. HRMS (ESI): m/z calcd for $[C_{25}H_{39}NO_3Si_2 + H]^+$ 458.2541, found 458.2537. The dr and ee values were determined by chiral HPLC analysis (Chiralpak AD, n-hexane/2-propanol = 98:2, v = 0.5 mL/min^{-1}, λ = 280.0 nm; for the major diastereoisomer: t_{minor} = 6.0 min, t_{major} = 7.0 min).

*tert-Butyl (2R,3R)-2-Amino-3-(3-(tert-butyl)-4-hydroxy-5-methylphenyl)-3-phenylpropanoate (**3va**).* Following the general procedure, the reaction gave product **3va** (24 h, white solid, mp 185−187 °C, 36.8 mg, 96% yield, >20:1 dr, 99% ee, $[\alpha]_D^{22}$ −50 (c 1, $CHCl_3$)). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 7.3 Hz, 2H), 7.27−7.21 (m, 2H), 7.16 (t, J = 7.3 Hz, 1H), 7.08 (d, J = 2.0 Hz, 1H), 6.95 (d, J = 1.7 Hz, 1H), 4.05 (d, J = 9.5 Hz, 1H), 3.95 (d, J = 9.5 Hz, 1H), 2.17 (s, 3H), 1.38 (s, 9H), 1.17 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 151.7, 142.1, 135.9, 131.9, 128.3, 128.24, 128.20, 126.4, 125.2, 123.5, 81.0, 59.5, 57.2, 34.5, 29.7, 27.6, 16.3. IR: $\bar{\upsilon}$ 3277, 2925, 1724, 1459, 1216, 1159, 760 cm^{-1}. HRMS (ESI): m/z calcd for $[C_{24}H_{33}NO_3 + H]^+$ 384.2533, found 384.2527. The dr and ee values were determined by chiral HPLC analysis (Chiralpak IA-3, n-hexane/2-propanol = 98:2, v = 0.5 mL/min^{-1}, λ = 280.0 nm; for the major diastereoisomer: t_{minor} = 18.7 min, t_{major} = 20.2 min).

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*tert-Butyl (3R,4S)-4-(3,5-Ditert-butyl-4-hydroxyphenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**3wa**).* Following the general procedure, the reaction gave product **3wa** (30 h, white solid, mp 154−157 °C, 43.3 mg, 96% yield, >20:1 dr, 96% ee, $[\alpha]_D^{22}$ +180 (*c* 1, $CHCl_3$)). ^1H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 7.6 Hz, 1H), 7.43 (td, *J* = 7.5, 1.0 Hz, 1H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.28 (d, *J* = 6.3 Hz, 1H), 7.09 (s, 2H), 6.54 (s, 1H), 5.13 (s, 1H), 4.75 (d, *J* = 5.2 Hz, 1H), 4.40 (d, *J* = 5.1 Hz, 1H), 1.36 (s, 18H), 1.23 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 165.0, 153.2, 141.1, 135.7, 132.8, 129.4, 128.1, 128.0, 127.4, 127.3, 124.8, 82.8, 57.4, 46.2, 34.2, 30.1, 27.6. IR: $\bar{\nu}$ 3400, 2923, 1735, 1674, 1461, 1255, 1157, 1029, 777 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $[C_{28}H_{37}NO_4 + H]^+$ 452.2795, found 452.2802. The dr and ee values were determined by chiral HPLC analysis (Chiralpak IA-3, *n*-hexane/2-propanol = 98:2, v = 0.5 mL/min^{-1}, λ = 210.0 nm; for the major diastereoisomer: t_{minor} = 6.8 min, t_{major} = 8.0 min).

*Methyl (2R,3R)-3-(3,5-Ditert-butyl-4-hydroxyphenyl)-2-((diphenylmethylene)amino)-3-phenylpropanoate (**3ab**).* A mixture of *p*-quinone methide **1a** (29.4 mg, 0.10 mmol), glycine derivative **2b** (27.7 mg, 0.11 mmol), and catalyst **4c** (6 mg, 0.01 mmol) in toluene (2.0 mL) was cooled to −40 °C, and then Cs_2CO_3 (35.8 mg, 0.11 mmol) was added. After stirring at −40 °C for 29 h, the resulting mixture without further concentration was directly purified by flash column chromatography on silica gel using mixtures of petroleum ether/ethyl acetate as the eluent, giving unhydrolyzed product **3ab** (white solid, mp 75−78 °C, 52.5 mg, 96% yield, 1.9:1 dr, 90% ee (major), 64% ee (minor), $[\alpha]_D^{22}$ +155 (*c* 1, $CHCl_3$)). ^1H NMR (400 MHz, $CDCl_3$) δ 7.58−7.44 (m, 4H, major + minor), 7.41−7.10 (m, 17H, major + minor), 6.98 (s, 2H, major), 6.93 (s, 2H, minor), 6.54 (br, 3H, major + minor), 4.99 (s, 2H, major + minor), 4.76 (d, *J* = 9.7 Hz, 1H, major), 4.73−4.63 (m, 2H, major + minor), 3.52 (s, 3H, minor), 3.51 (s, 3H, major), 1.29 (s, 18H, minor), 1.27 (s, 18H, major). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8 (minor), 171.6 (major), 170.66 (major), 152.3, 152.2, 141.6, 141.2, 139.54, 139.51, 135.9, 135.3, 135.1, 131.8, 131.3, 130.2, 129.5, 128.91, 128.86, 128.6, 128.4, 128.2, 128.1, 128.0, 127.90, 127.85, 127.8, 126.4, 126.1, 126.0, 125.5, 71.4 (major), 70.8 (minor), 55.0 (major + minor), 51.9 (major), 34.19 (major), 34.17 (minor), 30.19 (minor), 30.17 (major). IR: $\bar{\nu}$ 2922, 1739, 1435, 1237, 1156, 1026, 759, 700 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $[C_{37}H_{41}NO_3 + H]^+$ 548.3159, found 548.3165. The dr and ee values were determined by chiral HPLC analysis (Chiralpak IA-3, *n*-hexane/2-propanol = 98:2, v = 0.5 mL/min^{-1}, λ = 210.0 nm; for the major diastereoisomer: t_{minor} = 4.2 min, t_{major} = 5.1 min; for the minor diastereoisomer: t_{minor} = 4.7 min, t_{major} = 6.9 min).

*Phenyl (2R,3R)-2-Amino-3-(3,5-ditert-butyl-4-hydroxyphenyl)-3-phenylpropanoate (**3ac**).* Following the general procedure, the reaction gave product **3ac** (10 h, white solid, mp 115−118 °C, 42.7 mg, 96% yield, 6.3:1 dr, 69% ee, $[\alpha]_D^{22}$ −80 (*c* 1, $CHCl_3$)). ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.3 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 2H), 7.29−7.21 (m, 4H), 7.19 (s, 2H), 7.15 (t, *J* = 7.4 Hz, 1H), 6.62−6.54 (m, 2H), 5.14 (s, 1H), 4.43 (d, *J* = 9.3 Hz, 1H), 4.19 (d, *J* = 9.3 Hz, 1H), 1.73 (br, 2H), 1.42 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 152.9, 150.3, 141.7, 136.2, 130.6, 129.3, 128.6, 128.4, 126.9, 125.9, 125.1, 121.3, 59.5, 57.5, 34.4, 30.3. IR: $\bar{\nu}$ 2953, 1756, 1593, 1436, 1236, 1163, 1025, 756 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $[C_{29}H_{35}NO_3 + H]^+$ 446.2690, found 446.2697. The dr and ee values were determined by chiral HPLC analysis (Chiralpak IA-3, *n*-hexane/2-propanol = 98:2, v = 0.5 mL/min^{-1}, λ = 280.0 nm; for the major diastereoisomer: t_{minor} = 25.9 min, t_{major} = 23.7 min; for the minor diastereoisomer: t_{minor} = 41.6 min, t_{major} = 32.7 min).

Synthesis of Tetrahydroisoquinoline Building Block. To a stirred solution of **3la** (32.7 mg, 0.068 mmol, 90% ee) in $ClCH_2CH_2Cl$ (2 mL) were added paraformaldehyde (10.1 mg, 0.34 mmol) and CF_3CO_2H (25.1 μmL, 0.34 mmol) at room temperature. After stirring for 1 h at 50 °C, the reaction mixture was cooled to room temperature and quenched with saturated aqueous $NaHCO_3$ solution. The mixture obtained was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic phase was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel eluting with petroleum ether/ethyl to afford compound **5la** (white solid, mp 119−122 °C, 32.5 mg, 96% yield, >20:1 dr, 90% ee, $[\alpha]_D^{22}$ +100 (*c* 1, $CHCl_3$)).

*tert-Butyl (3R,4S)-4-(3,5-Ditert-butyl-4-hydroxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**5la**).* ^1H NMR (400 MHz, $CDCl_3$) δ 7.00 (s, 2H), 6.57 (s, 1H), 6.50 (s, 1H), 5.02 (s, 1H), 4.22−4.04 (m, 3H), 3.86 (s, 4H), 3.77 (s, 3H), 1.95 (br, 1H), 1.38 (s, 18H), 1.23 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 152.6, 147.7, 147.5, 135.1, 132.5, 129.9, 126.6, 125.8, 112.8, 107.9, 80.8, 61.3, 55.9, 55.8, 47.3, 45.1, 34.2, 30.3, 27.9. IR: $\bar{\nu}$ 2923, 1731, 1515, 1367, 1226, 1158, 1113, 1027, 849, 762 cm^{-1}. HRMS (ESI): *m*/*z* calcd for $[C_{30}H_{43}NO_5 + H]^+$ 498.3214, found 498.3221. The dr and ee values were determined by chiral HPLC analysis (Chiralpak IA-3, *n*-hexane/2-propanol = 98:2, v = 0.5 mL/min^{-1}, λ = 280.0 nm; for the major diastereoisomer: t_{minor} = 18.9 min, t_{major} = 24.1 min).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00390.

X-ray crystallographic data for **3da** (CIF)

Details of the conditions optimization and copies of ^1H and ^{13}C NMR and HPLC spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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