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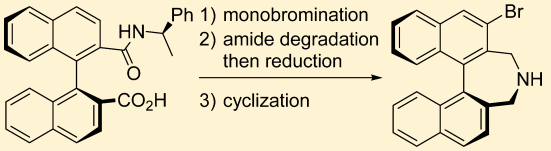
Synthesis of 3-Mono-Substituted Binaphthyl-Based Secondary Amine Catalysts via Monobromination of an Axially Chiral Dicarboxylic Acid Derivative

Taichi Kano, Momotaro Takeda, Ryu Sakamoto, and Keiji Maruoka*

Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan

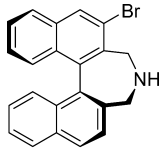
Supporting Information

ABSTRACT: A facile synthetic route to a 3-bromo binaphthyl-based secondary amine through the monobromination of an axially chiral dicarboxylic acid derivative has been developed. The combination of this new procedure with coupling reactions established an efficient synthetic approach to a series of binaphthyl-based secondary amine catalysts containing various functional groups in an efficient way.



In asymmetric catalysis, the design of a novel chiral motif is highly important for the development of new chiral ligands or catalysts providing unprecedented reactivity and selectivity. Among them, C_2-symmetric structures have been widely applied to various chiral ligands or catalysts, such as BINAP, BINOL, bisoxazoline (BOX), and salen complexes.[1] On the other hand, C_1-symmetric structures, such as 3-mono-substituted binaphthyl-based ligands or catalysts, frequently show unique reactivities and/or selectivities;[2] however, the utilizations of them in asymmetric reactions are relatively scarce to date.

We have previously designed C_1-symmetric binaphthyl-based secondary amine catalysts (*S*)-**1** and (*S*)-**2** containing an acid functional group at the 3-position for enamine catalysis.[3,4] These catalysts have been successfully utilized in several asymmetric reactions and have shown unique reactivity and selectivity in comparison with commonly used proline and its derivatives. 3-Mono-substituted binaphthyl-based secondary amine structures were also found in amine organocatalysts (*S*)-**3** and (*S*)-**4** as well as a phase-transfer catalyst (*S*)-**5** (Figure 1).[5,6] Despite their utility, however, the applications of 3-mono-substituted binaphthyl-based amines in asymmetric reactions are still rare due to their synthetic inefficiency. In the course of our research, we set out to investigate a novel procedure to effectively access the binaphthyl-based secondary amine (*S*)-**6** as a key intermediate for a series of binaphthyl-based secondary amine catalysts. Herein, we wish to report our result on this subject.



(*S*)-**6**

In our previous procedures for (*S*)-**1** and (*S*)-**2**, the deficit step was the monobromination by the *ortho*-magnesiation of the neopentyl ester (*S*)-**8** with magnesium bis(2,2,6,6-tetramethylpiperamide) [$Mg(tmp)_2$] prepared in THF, and subsequent bromination with bromine (Scheme 1a).[3] In this method, both mono- and dibrominated products, which are inseparable, were obtained simultaneously. To circumvent this synthetic issue, we examined the monolithiation and subsequent bromination of (*S*,*R*)-**9**, which could be easily obtained by the fractional recrystallization of the diastereomeric mixture of **9** prepared from racemic 1,1′-binaphthyl-2,2′-dicarboxylic acid (**7**) and (*R*)-1-phenylethylamine,[7] utilizing the amide group as an effective directing group for *ortho*-metalation (Scheme 1b).[8]

We first performed the bromination of (*S*,*R*)-**9** by using Br_2 as a brominating agent after the lithiation with *t*-butyllithium and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) (Scheme 2). However, the desired product (*S*,*R*)-**10** was obtained in only 24% yield along with substantial amounts of recovered starting material in 76% yield. Use of *N*-bromosuccinimide resulted in a slightly increased yield, giving (*S*,*R*)-**10** in 46% yield with the recovery of 47% of (*S*,*R*)-**9**. Fortunately, when 1,2-dibromotetrafluoroethane was used as a brominating agent, the starting material was completely consumed and (*S*,*R*)-**10** was obtained in 92% yield.[9] It is worth mentioning that, in the case of diastereomeric amide (*R*,*R*)-**9**, the desired brominated product was not obtained at all under the same reaction conditions, which implied that stereochemical combination of the amide and the binaphthyl moiety significantly affected the *ortho*-lithiation step (Scheme 3).

We then examined the transformation of (*S*,*R*)-**10** to the cyclic secondary amine (*S*)-**6** (Scheme 4). Refluxing in thionyl chloride transformed the amide to a nitrile through an imidoyl chloride (von Braun amide degradation),[10] and subsequent reduction with BH_3-THF gave the amino alcohol (*S*)-**11**. The obtained (*S*)-**11** was successfully cyclized with BBr_3 to the

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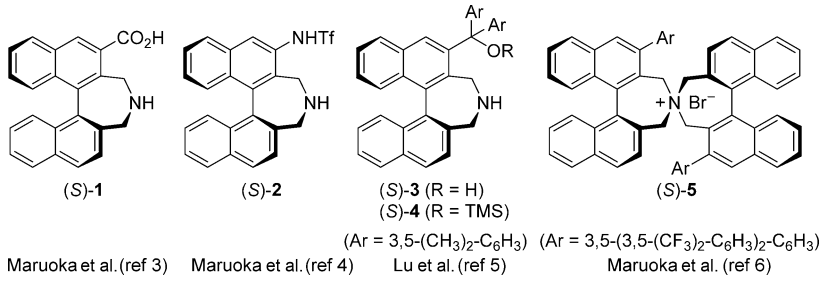
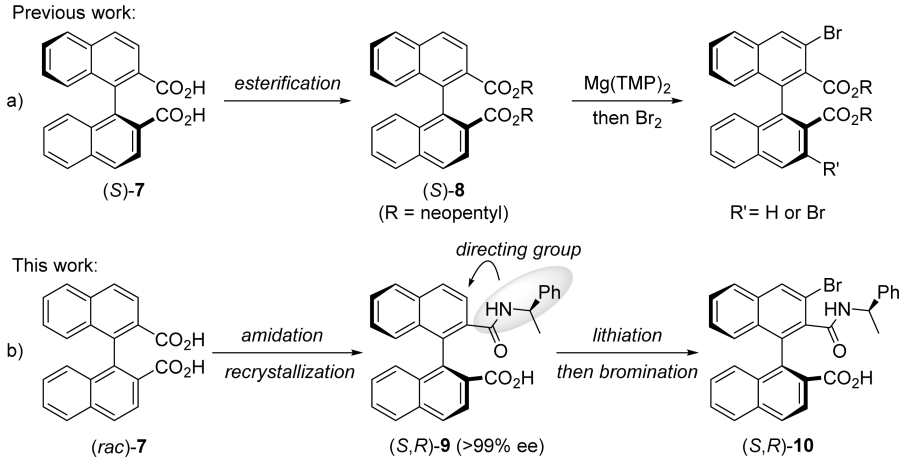
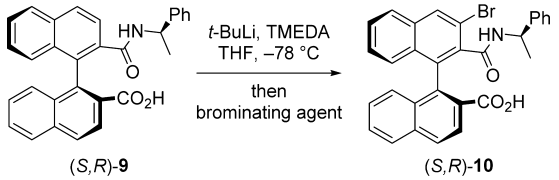


Figure 1. Binaphthyl-based organocatalysts.

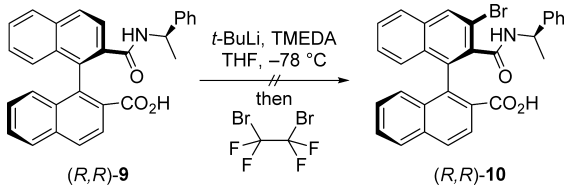
Scheme 1. Synthetic Approaches to 3-Bromo-binaphthyl Structures



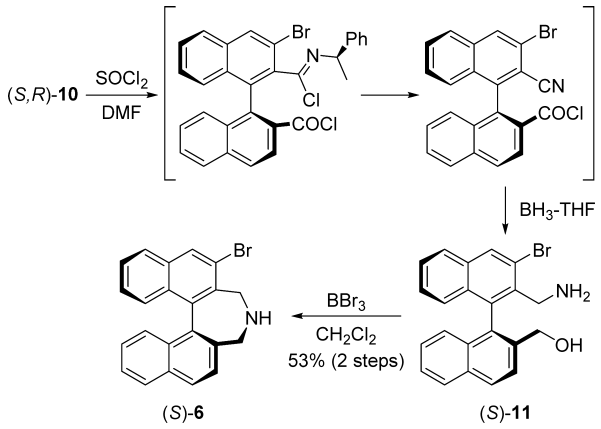
Scheme 2. Monobromination of (*S,R*)-9



Scheme 3. Monobromination of (*R,R*)-9



Scheme 4. Synthesis of Secondary Amine (*S*)-6



secondary amine (*S*)-**6** without either protection of the amino group or sulfonylation of the hydroxyl group.

With the key intermediate (*S*)-**6** in hand, various substituents could be introduced at the 3-position of the binaphthyl moiety by coupling reactions after the protection of the amino group by the benzyloxycarbonyl (Z) group (Scheme 5). For instance, benzyloxy carbonylation of (*S*)-**12** with CO in benzyl alcohol afforded the benzyl ester (*S*)-**13** in 87% yield. Then, hydrogenation of (*S*)-**13** gave the amino acid (*S*)-**1**, which could be easily isolated by the recrystallization instead of the purification by using an ion-exchange resin.[3] On the other hand, the palladium-catalyzed amination of (*S*)-**12** with benzophenone imine,[11] hydrolysis, and subsequent treatment with Tf_2O afforded trifluoromethanesulfonamide (*S*)-**14** in 88% yield. Subsequent hydrogenation of (*S*)-**14** gave the amino trifluoromethanesulfonamide (*S*)-**2**.

Finally, amino alcohol (*S*)-**16** as a new type of amine organocatalyst was successfully synthesized. The palladium-catalyzed borylation of (*S*)-**12** with bis(pinacolato)diboron ($B_2(pin)_2$) gave the boronic pinacol ester (*S*)-**15** in 90% yield. Following introduction of a hydroxyl group at the 3-position of (*S*)-**15** by oxidation with mCPBA,[12] deprotection of the Z group successfully afforded (*S*)-**16**. The obtained (*S*)-**16** was found to effectively catalyze the *anti*-selective Mannich reaction between 3-phenylpropanal and an α-imino ester to give the corresponding *anti*-Mannich adduct with excellent enantioselectivity (Scheme 6).[4a]

In summary, we have developed a new synthetic route to the 3-bromo binaphthyl-based secondary amine structure through the monobromination. This new procedure enabled us to

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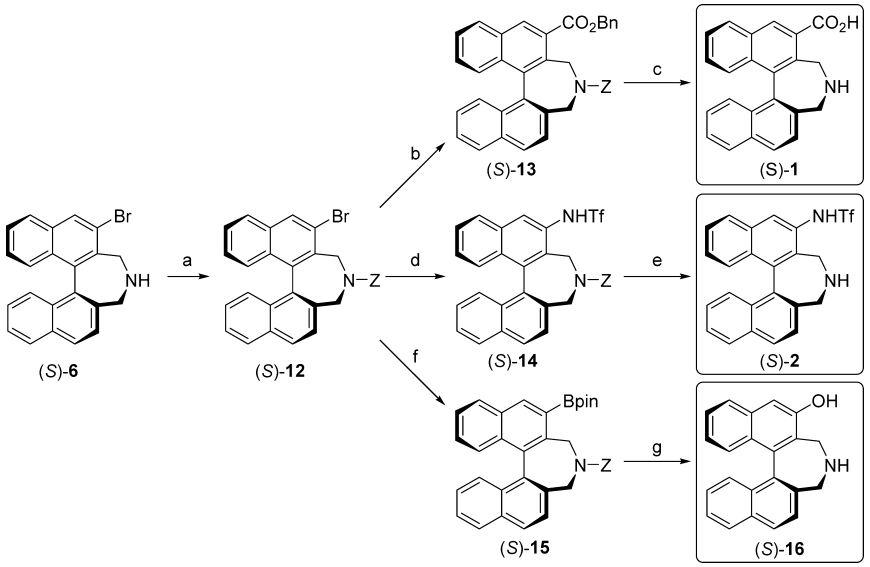
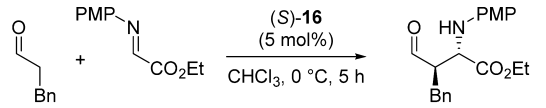
Scheme 5. Synthesis of a Series of Binaphthyl-Based Secondary Amine Catalysts[a]



[a]Reagents and conditions: (a) benzyl chloroformate (Z-Cl), Et_3N, THF, rt (88%); (b) CO, $Pd(OAc)_2$, dppp, EtN^iPr_2, DMSO/BnOH (87%); (c) H_2, Pd/C, MeOH, 40 °C (80%); (d) (i) benzophenone imine, $Pd_2(dba)_3$, BINAP, NaO^tBu, toluene, reflux, then 1 N HCl, THF, reflux; (ii) Tf_2O, *N*,*N*-dimethylaniline, CH_2Cl_2, rt (88% for three steps); (e) H_2, Pd/C, MeOH, 40 °C (93%); (f) $B_2(pin)_2$, $Pd(OAc)_2$, KOAc, DMF, 85 °C (90%); (g) (i) mCPBA, H_2O/EtOH, 0 °C; (ii) H_2, Pd/C, MeOH, 40 °C (45% for two steps).

Scheme 6. *anti*-Selective Mannich Reaction Catalyzed by (*S*)-16



66%, *anti*/*syn* = 7/1
98% ee (*anti*)

synthesize various types of amine organocatalysts containing acidic functionalities in an efficient way.

EXPERIMENTAL SECTION

General Information. Infrared (IR) spectra were recorded on an FT-IR spectrometer. ^1H NMR spectra were measured on 400 and 500 MHz spectrometers. Chemical shifts were reported in parts per million (ppm) from tetramethylsilane as an internal standard. Data were reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quintet, m = multiplet, br = broad, and app = apparent), coupling constants (Hz), and assignment. ^{13}C NMR spectra were recorded on 100 and 125 MHz spectrometers with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard. The high-resolution mass spectra (HRMS) were performed on an ESI-TOF mass spectrometer. Optical rotations were measured on a digital polarimeter.

In experiments requiring dry solvents, the dehydrated tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were purchased and used. *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine (TMEDA) was distilled from CaH_2 and was stored over 4 Å molecular sieves. The following products are all known: (*S*)-**1**,[3] (*S*)-**2**,[4] and (*S*,*R*)-**9**.[7]

Bromo Amide (*S*,*R*)-10. To a stirred solution of TMEDA (3 mL, 20 mmol) in THF (16 mL) was added a 1.67 M pentane solution of *t*-BuLi (12 mL, 20 mmol) at −78 °C. After stirring for 30 min at −78 °C, (*S*,*R*)-**9** (1.96 g, 4 mmol) in THF (24 mL) was added to the mixture at the same temperature. The reaction mixture was stirred for 30 min at −78 °C and then stirred for 1 h at 0 °C. To the mixture was added 1,2-dibromotetrafluoroethane (2.4 mL, 20 mmol) at −78 °C. The mixture was stirred for 30 min at −78 °C and then stirred for 2 h at room temperature. The reaction mixture was quenched with 1 N HCl and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 3/1 as eluent) to afford (*S*,*R*)-**10** (1.90 g, 3.68 mmol, 92% yield). Pale yellow solid. mp 149−150 °C. $[\alpha]_D^{24} = -175.3$ (*c* 1.05, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 8.25 (1H, s), 8.02 (1H, d, *J* = 8.5 Hz), 7.96 (1H, d, *J* = 8.2 Hz), 7.82 (2H, app t, *J* = 8.1 Hz), 7.55−7.50 (2H, m), 7.30 (1H, t, *J* = 7.7 Hz), 7.22 (1H, t, *J* = 7.7 Hz), 7.10−6.94 (5H, m), 6.45−6.43 (2H, br), 6.24 (1H, br), 4.93−4.86 (1H, m), 1.37 (3H, d, *J* = 5.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 168.6, 140.7, 135.5, 134.5, 134.2, 133.9, 132.4, 131.9, 131.3, 129.4, 128.3, 128.0, 127.6, 127.5, 127.2, 127.1, 126.5, 126.3, 125.5, 125.0, 115.2, 49.2, 20.2 (The several signals for aromatic carbons were not identified due to the overlap of peaks.); IR (neat) 2972, 1700, 1617, 1556, 1243, 908, 731 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{30}H_{22}BrNNaO_3$: 546.0675 ($[M + Na]^+$), Found: 546.0679 ($[M + Na]^+$).

Bromo Amine (*S*)-6. A mixture of (*S*,*R*)-**10** (1.05 g, 2 mmol), thionyl chloride (10 mL), and one drop of DMF was refluxed for 3 h, and excess thionyl chloride was removed under reduced pressure. To a solution of the residue in THF (10 mL) was added a 0.95 M solution of BH_3-THF (9.6 mL) at 0 °C. After stirring for 1 h at 0 °C, the mixture was refluxed overnight. The resulting mixture was quenched with $NaHCO_3$ aq. at 0 °C and then extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was roughly purified by flash column chromatography on silica gel (hexane/ethyl acetate 1:1 to ethyl acetate only as eluent) to give (*S*)-**11**. To a solution of (*S*)-**11** in CH_2Cl_2 (25 mL) was added BBr_3 (500 μL, 5.3 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 3 h. The mixture was then quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (ethyl acetate as eluent) to afford (*S*)-**6** (397 mg, 1.06 mmol, 53% yield). Pale yellow solid. mp 118−119 °C. $[\alpha]_D^{24} = 485.0$ (*c* 1.19, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (1H, s), 7.99 (1H, d, *J* = 8.2 Hz), 7.95 (1H, d, *J* = 8.2 Hz), 7.84 (1H, d, *J* = 8.5 Hz), 7.59 (1H, d, *J* = 8.2 Hz), 7.46 (2H, app t, *J* = 7.5 Hz), 7.37 (1H, d, *J* = 14.2 Hz), 7.35 (1H, d, *J* = 14.2 Hz), 7.29−7.23 (2H, m), 4.46 (1H, d, *J* = 13.1 Hz), 3.88 (1H, d, *J* = 11.8 Hz), 3.42 (1H, d, *J* = 11.8

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Hz), 3.34 (1H, d, J = 13.1 Hz), 2.11 (1H, br); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.0, 134.9, 134.6, 134.0, 133.6, 133.0, 131.8, 131.1, 130.4, 129.4, 128.3, 127.6, 127.2, 127.1 (two peaks are overlapped), 126.4, 126.1, 125.9, 125.5, 121.9, 48.5, 47.4; IR (neat) 3053, 1554, 979, 909, 729 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{22}H_{17}BrN$: 374.0539 ([M + H]$^+$), Found: 374.0554 ([M + H]$^+$).

***N*-Z Protected Amine (*S*)-12.** To a solution of (*S*)-**6** (200 mg, 0.53 mmol) were added TEA (800 μL, 2.65 mmol) and benzyl chloroformate (Z-Cl) (350 μL, 2.65 mmol) at 0 °C. After stirring at room temperature overnight, the mixture was quenched with $NaHCO_3$ aq. at 0 °C and then extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate 7:1 as eluent) to give (*S*)-**12** (239 mg, 0.47 mmol, 88% yield). White solid. mp 98−100 °C. $[\alpha]_D^{26}$ = −28.2 (c 1.23, $CHCl_3$). ^{1}H NMR (500 MHz, 50 °C, $CDCl_3$) δ 8.26 (1H, s), 7.98 (1H, d, J = 8.2 Hz), 7.94 (1H, d, J = 8.2 Hz), 7.83 (1H, d, J = 7.9 Hz), 7.59 (1H, br), 7.47 (2H, app t, J = 7.5 Hz), 7.43−7.41 (2H, m), 7.37−7.23 (7H, m), 5.75 (1H, br), 5.26 (1H, d, J = 12.5 Hz), 5.18 (1H, d, J = 12.2 Hz), 5.07 (1H, br), 3.66 (1H, d, J = 13.0 Hz), 3.57 (1H, d, J = 13.3 Hz); ^{13}C NMR (125 MHz, 50 °C, $CDCl_3$) δ 154.6, 137.6, 136.8, 134.7, 134.0, 133.3, 132.8, 132.2, 132.0, 131.3, 130.6, 129.8, 128.4, 128.4, 128.4, 128.0, 127.9, 127.7, 127.3, 127.2, 127.0, 126.4, 126.3, 126.0, 122.0, 67.4, 48.0, 46.5; IR (neat) 1696, 1414, 1244, 1203, 1100, 750, 736 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{30}H_{22}BrNNaO_2$: 530.0726 ([M + Na]$^+$), Found: 530.0720 ([M + Na]$^+$).

Benzyl Ester (*S*)-13. Compound (*S*)-**12** (166 mg, 0.325 mmol), $Pd(OAc)_2$ (13.5 mg, 0.06 mmol), bis(diphenylphosphino)propane (dppp) (24.5 mg, 0.06 mmol), and iPr$_2$NEt (300 μL, 1.76 mmol) in DMSO (1 mL) and BnOH (1 mL) were charged into an autoclave under an argon atmosphere. After pressurized with CO (10 atm), the mixture was heated to 100 °C with stirring for 24 h. After cooling to room temperature, the reaction mixture was poured into water and extracted with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, and then concentrated. The residue was purified by flash column chromatography on silica gel (CH_2Cl_2 as eluent) to give (*S*)-**13** (160 mg, 0.284 mmol, 87% yield). Pale yellow solid. mp 70−72 °C. $[\alpha]_D^{25}$ = −1.9 (c 2.1, $CHCl_3$). ^{1}H NMR (400 MHz, 50 °C, $CDCl_3$) δ 8.41 (1H, s), 7.85 (2H, app d, J = 8.2 Hz), 7.81 (1H, d, J = 8.2 Hz), 7.46−7.12 (17H, m), 5.98 (1H, d, J = 13.5 Hz), 5.22 (2H, br), 5.05 (2H, br), 4.95 (1H, br), 3.61 (1H, d, J = 13.1 Hz), 3.44 (1H, d, J = 13.5 Hz); ^{13}C NMR (100 MHz, 50 °C, $CDCl_3$) δ 167.6, 154.9, 137.5, 137.0, 136.1, 134.7, 133.4, 133.0, 132.9, 132.1, 131.5, 131.2, 129.6, 129.2, 128.6, 128.41, 128.37, 128.2, 128.0, 127.9, 127.8, 127.5, 127.2, 127.2, 126.7, 126.2, 125.9, 67.3, 67.2, 48.2, 43.3 (The several signals for aromatic carbons were not identified due to the overlap of peaks.); IR (neat) 2926, 1695, 1416, 1236, 733 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{38}H_{30}NO_4$: 564.2169 ([M + H]$^+$), Found: 564.2154 ([M + H]$^+$).

Amino Acid (*S*)-1. To a stirred solution of (*S*)-**13** (102 mg, 0.18 mmol) in MeOH (15 mL) was added 10 mol % palladium on carbon (51 mg) at room temperature. The mixture was then hydrogenated under H_2 (balloon) at 40 °C for 12 h and filtered through Celite. After the removal of the solvent, (*S*)-**1** was recrystallized from MeOH and Et_2O (49.2 mg, 0.145 mmol, 80% yield). White solid. ^{1}H NMR, ^{13}C NMR, IR, and HRMS data were consistent with previously reported values.[3]

Trifluoromethanesulfonamide (*S*)-14. A mixture of (*S*)-**12** (829 mg, 1.63 mmol), benzophenone imine (354 mg, 1.96 mmol), BINAP (161 mg, 0.26 mmol), $Pd_2(dba)_3$ (74.3 mg, 0.08 mmol), and NaOBu^t (218 mg, 2.27 mmol) in toluene (29 mL) was heated at 110 °C and stirred for 16 h under an argon atmosphere. After cooling to room temperature, the reaction mixture was filtered through a Celite pad, and the filter cake was washed with ethyl acetate. The filtrate was concentrated in vacuo. The residue was dissolved in 1 N HCl (5 mL) and THF (45 mL). After refluxing for 1 h, the mixture was then quenched with $NaHCO_3$ and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was roughly purified by flash column chromatography on silica gel (hexane/ethyl acetate 3:1 as eluent) to give the corresponding aminated product. To a stirred solution of the produxt (ca. 1.53 mmol) in CH_2Cl_2 (95 mL) were added *N*,*N*-dimethylaniline (190 μL, 1.53 mmol) and Tf_2O (258 μL, 1.53 mmol) at 0 °C. The reaction mixture was stirred at room temperature overnight. The mixture was then quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were washed with brine, and dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 5/1) to afford (*S*)-**14** (828 mg, 1.43 mmol, 88% yield for 2 steps). White solid. mp 115−117 °C. $[\alpha]_D^{21}$ = 12.41 (c 0.98, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (1H, s), 8.00 (1H, d, J = 8.5 Hz), 7.96 (2H, app d, J = 8.2 Hz), 7.56 (1H, d, J = 8.5 Hz), 7.51 (2H, app t, J = 7.1 Hz), 7.42−7.24 (9H, m), 5.24 (2H, m), 5.10 (1H, d, J = 12.3 Hz), 4.73 (1H, d, J = 12.8 Hz), 3.78 (1H, d, J = 12.6 Hz), 3.67 (1H, d, J = 14.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.6, 135.7, 135.7, 135.3, 133.5, 133.3, 132.3, 131.6, 130.1, 129.7, 129.5, 128.7, 128.6, 128.4, 128.3, 128.1, 128.1, 127.8, 127.4, 127.4, 127.0, 126.7, 126.5, 126.4, 125.6, 120.1 (C−F, d, J = 323.1 Hz, CF_3), 68.4, 49.7, 41.8; IR (neat) 3064, 1668, 1420, 1218, 1194, 732 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{31}H_{23}F_3N_2NaO_4S$: 599.1223 ([M + Na]$^+$), Found: 599.1206 ([M + Na]$^+$).

Amino Trifluoromethanesulfonamide (*S*)-2. To a stirred solution of (*S*)-**14** (160 mg, 0.278 mmol) in MeOH (32 mL) was added 10% palladium on carbon (80 mg) at room temperature. The mixture was then hydrogenated under H_2 (balloon) at 40 °C overnight and filtered through Celite. After removal of the solvent under reduced pressure, the residue was purified by flash column chromatography (CH_2Cl_2/MeOH = 20:1 as eluent) to afford (*S*)-**2** (114 mg, 0.26 mmol, 93% yield). Pale yellowish solid. ^{1}H NMR, ^{13}C NMR, IR, and HRMS data were consistent with previously reported values.[4]

Boronic Pinacol Ester (*S*)-15. A mixture of (*S*)-**12** (102 mg, 0.20 mmol), bis(pinacolato)diboron (55 mg, 0.22 mmol), $Pd(OAc)_2$ (1.5 mg, 0.006 mmol), and KOAc (59 mg, 0.60 mmol) in DMF (1 mL) was heated at 85 °C and stirred for 5 h under an argon atmosphere. After cooling to room temperature, the mixture was then quenched with H_2O and extracted with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 5/1 as eluent) to afford (*S*)-**15** (100 mg, 0.18 mmol, 90% yield). White solid. mp 102−104 °C. $[\alpha]_D^{15}$ = −18.1 (c 0.48, $CHCl_3$). ^{1}H NMR (500 MHz, 60 °C, $CDCl_3$) δ 8.50 (1H, s), 7.96−7.90 (3H, m), 7.57 (1H, br), 7.43 (2H, app t, J = 7.5 Hz), 7.38−7.20 (9H, m), 5.96 (1H, d, J = 13.0 Hz), 5.24−5.12 (3H, m), 3.68 (1H, d, J = 13.3 Hz), 3.59 (1H, d, J = 13.0 Hz), 1.39−1.25 (12H, m); ^{13}C NMR (125 MHz, 60 °C, $CDCl_3$) δ 154.9, 138.3, 137.3, 136.6, 135.8, 135.2, 133.3, 132.9, 132.8, 132.4, 131.7, 129.1, 128.8, 128.4, 128.4, 128.3, 127.7, 127.7, 127.5, 127.4, 127.1, 127.0, 126.0, 125.8, 125.7, 84.2, 83.4, 67.1, 48.0, 45.6, 25.0, 24.9, 24.8, 24.7; IR (neat) 2978, 1695, 1415, 1345, 1243, 732 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{36}H_{34}BNNaO_4$: 578.2479 ([M + Na]$^+$), Found: 578.2491 ([M + Na]$^+$).

Amino Alcohol (S)-16. To a stirred solution of (*S*)-**16** (100 mg, 0.18 mmol) in H_2O (270 μL) and EtOH (1.2 mL) was added mCPBA (ca. 70%, 45 mg, 0.18 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. The mixture was then quenched with saturated Na_2CO_3 and extracted with AcOEt. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was roughly purified by flash column chromatography on silica gel (hexane/ethyl acetate = 4/1) to afford the 3-hydroxy *N*-Z protected secondary amine, which was used for the next step without further purification. To a stirred solution of the product in MeOH (12 mL) was added 10 mol % palladium on carbon (13 mg) at room temperature. The mixture was then hydrogenated under H_2 (balloon) at 40 °C for 1 h and filtered through Celite. After removal of the solvent under reduced pressure, the residue was purified by flash column chromatography (CH_2Cl_2/MeOH = 9:1 as eluent) to afford (*S*)-**16** (25 mg, 0.081 mmol, 45% yield for 2 steps). Pale brownish solid. mp 193−195 °C. $[\alpha]_D^{23}$ = 442.4 (c 1.1, MeOH). ^{1}H NMR (400 MHz, CD_3OD) δ 8.03 (1H, d, J = 8.0 Hz), 7.95 (1H, d, J = 8.2 Hz),

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7.73 (1H, d, J = 8.2 Hz), 7.63 (1H, d, J = 8.5 Hz), 7.47 (1H, t, J = 6.9 Hz), 7.37−7.34 (3H, m), 7.27 (1H, t, J = 7.6 Hz), 7.15 (1H, d, J = 8.0 Hz), 7.02 (1H, t, J = 6.5 Hz), 4.56 (1H, d, J = 12.6 Hz), 3.92 (1H, d, J = 12.3 Hz), 3.48 (1H, d, J = 12.1 Hz), 3.04 (1H, d, J = 12.8 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 153.9, 138.7, 136.9, 136.9, 135.5, 132.6, 130.9, 129.8, 129.6, 128.4, 128.2, 128.2, 128.2, 127.9 (two peaks are overlapped), 127.7, 127.4, 124.6, 121.5, 111.5, 47.3, 39.6; IR (neat) 1597, 1342, 1150, 1109, 822, 748 cm^{-1}; HRMS (ESI-TOF) Calcd for $C_{22}H_{18}NO$: 312.1383 ($[M + H]^+$), Found: 312.1370 ($[M + H]^+$).

The Mannich Reaction between 3-Phenylpropanal and *N*-PMP-Protected α-Imino Ester Catalyzed by (*S*)-16. To a solution of (*S*)-**16** (1.6 mg, 0.005 mmol) and 3-phenylpropanal (40 μL, 0.30 mmol) in $CHCl_3$ (200 μL) was added *N*-PMP-protected α-imino ester (21 mg, 0.10 mmol) at 0 °C. After 4 h of stirring at 0 °C, the reaction mixture was quenched with H_2O and extracted with ethyl acetate. The combined organic layer was washed with water, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel to afford a Mannich adduct (22.5 mg, 0.066 mmol, 66% yield, *anti*/*syn* = 7/1, 98% ee (*anti*)), which was then reduced with $LiAlH_4$ for determining the enantiomeric excess. ^{1}H NMR, ^{13}C NMR, IR, HRMS, HPLC, and [α] data were consistent with previously reported values.[4a,13]

■ ASSOCIATED CONTENT

Supporting Information

Copies of NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: maruoka@kuchem.kyoto-u.ac.jp.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Ojima, I., Ed. *Catalytic Asymmetric Synthesis*; Wiley-VCH: New York, 2000. (b) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH: Weinheim, 2005. (c) Dalko, P. I., Ed. *Enantioselective Organocatalysis*; Wiley-VCH: Weinheim, 2007.

(2) (a) Matsui, K.; Takizawa, S.; Sasai, H. *J. Am. Chem. Soc.* **2005**, *127*, 3680. (b) Reets, M. T.; Ma, J.-A.; Goddard, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 412. (c) Yoshida, T.; Morimoto, H.; Kumagai, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3470. (d) Ihori, Y.; Yamashita, Y.; Ishitani, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2005**, *127*, 15528. (e) H. Harada, T.; Kanda, K. *Org. Lett.* **2006**, *8*, 3817. (f) Harada, T.; Kanda, K. *Org. Lett.* **2006**, *8*, 3817. (g) Muramatsu, Y.; Harada, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 1088. (h) Endo, K.; Takayama, R.; Shibata, T. *Synlett* **2013**, *24*, 1155.

(3) Kano, T.; Tokuda, O.; Takai, J.; Maruoka, K. *Chem.—Asian. J.* **2006**, *1*, 210.

(4) (a) Kano, T.; Yamaguchi, Y.; Tokuda, O.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 16408. (b) Kano, T.; Yamaguchi, Y.; Tanaka, Y.; Maruoka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 1738. (c) Kano, T.; Yamaguchi, Y.; Maruoka, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 1838. (d) Kano, T.; Yamaguchi, Y.; Maruoka, K. *Chem.—Eur. J.* **2009**, *15*, 6678.

(5) Liang, D.-C.; Luo, R.-S.; Yin, L.-H.; Chan, A. S. C.; Lu, G. *Org. Biomol. Chem.* **2012**, *10*, 3071.

(6) (a) Kano, T.; Lan, Q.; Wang, X.; Maruoka, K. *Adv. Synth. Catal.* **2007**, *349*, 556. (b) Shirakawa, S.; Wu, X.; Maruoka, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 14200.

(7) Ôi, S.; Matsuzaka, Y.; Yamashita, J.; Miyano, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 956.

(8) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.

(9) The use of 1,2-dibromotetrachloroethane instead of 1,2-dibromotetrafluoroethane gave the desired product in 67% yield with the 3-chloro product in 18% yield.

(10) Vaughan, W. R.; Carlson, R. D. *J. Am. Chem. Soc.* **1962**, *84*, 769.

(11) Wolfe, J. P.; Åhman, J.; Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6367.

(12) Chen, D.-S.; Huang, J.-M. *Synlett* **2013**, *24*, 499.

(13) Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjærsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296.