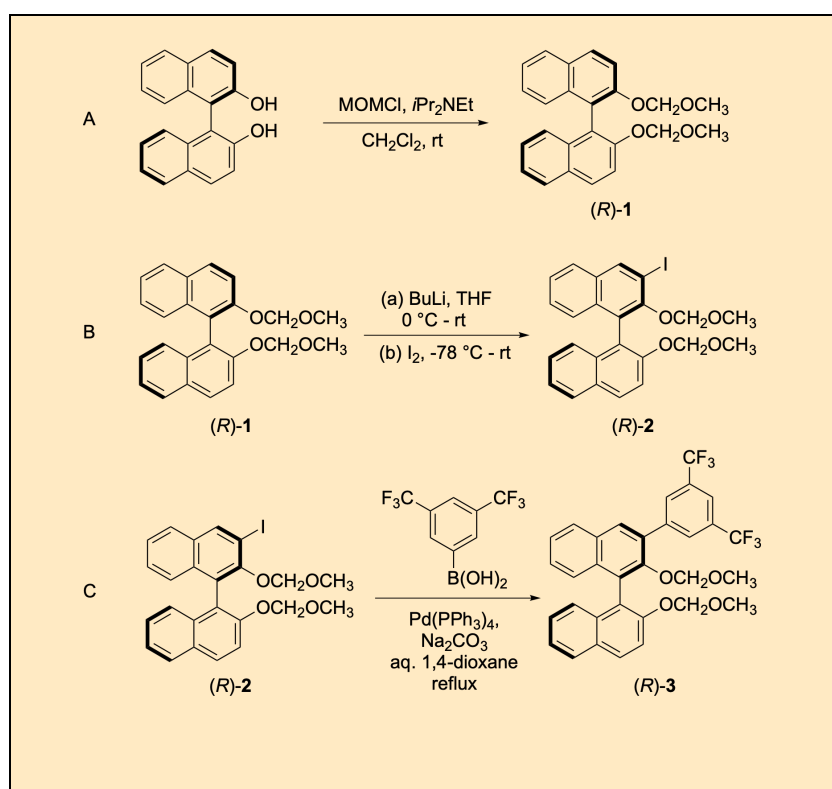


Preparation of (*R*)-3-(3,5-Bistrifluoromethylphenyl)-1,1'-bi-2-naphthol

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Checked by Andrew J. Neel and Kevin Campos



(25 mmHg) to give 15.8 g of a brown solid. The residue is placed in a 200-mL Erlenmeyer flask and dissolved in a 4:1 mixture of hexane and ethyl acetate (100 mL) with heating in Chem Glass Optitherm reaction block (70 °C) (Note 8). The solution is removed from heat and allowed to stand without stirring overnight. The flask is placed in an ice bath for 0.5 h and the solids are collected on a disposable 100-mL, 10 micron polyethylene fritted funnel (Note 9). The yellow crystals are washed with ice-cold hexane (2 x 5 mL) and dried in a vacuum oven (40 °C, 25 mmHg) to yield (R)-1 (13.6 g, 86%) (Notes 10 and 11).

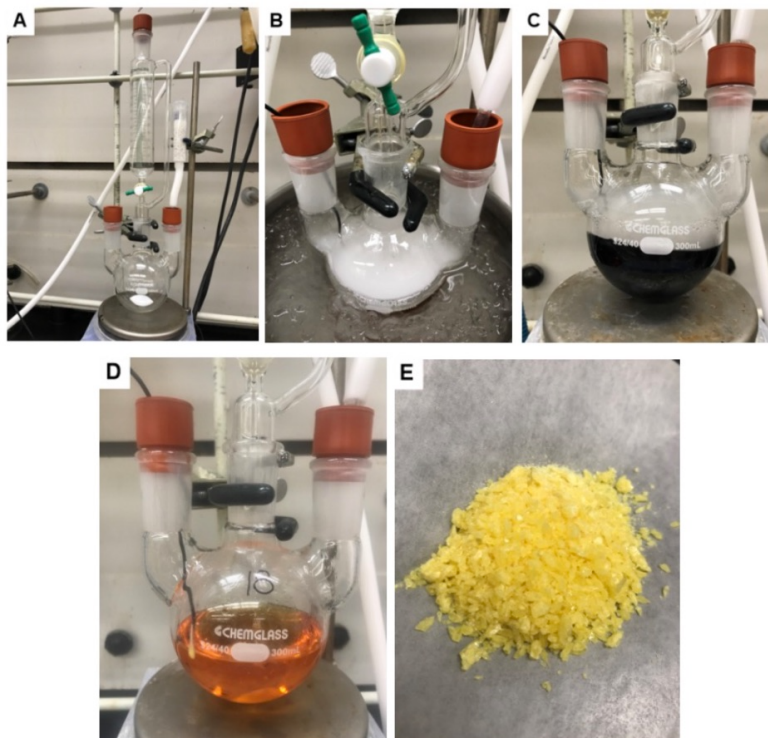


Figure 1. Step A photographs. A) Glassware setup; B) HCl evolution during dropwise addition of chloromethyl methyl ether; C) Color of reaction mixture immediately after ice bath removal; D) Color of reaction mixture after overnight agitation; E) Solids isolated from recrystallization; (all photos provided by checkers)

B. (*R*)-3-Iodo-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl ((*R*)-2) (Note 12). An oven-dried 300-mL, three-necked, round-bottomed flask is equipped with a Teflon-coated, magnetic stir bar (oval-shaped, 45 x 25 mm), two rubber septa and a 100-mL pressure equalizing dropping funnel fitted with a rubber septum. The flask is charged with (*R*)-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl ((*R*)-1) (10.0 g, 26.7 mmol) and anhydrous tetrahydrofuran (THF) (90 mL) (Note 13). The atmosphere is purged with N₂ for 5 min with stirring (400 rpm). The resulting solution is cooled in an ice water bath (internal temp = 3 °C). Butyllithium solution (18.3 mL, 1.60 M, 29.3 mmol, 1.1 equiv) (Note 14) is added to the dropping funnel *via* syringe and added dropwise to the reaction mixture at such a rate that the internal temperature did not exceed 5 °C (~10min). Additional anhydrous THF (6 mL) (Note 13) is added to the dropping funnel to rinse butyllithium solution into the reaction mixture. The resulting brown, homogeneous solution is stirred at 0 °C for 4 h, during which time a color change is observed from brown to dark green. A separate oven-dried 100 mL, round-bottomed flask equipped with a rubber septum is flushed with nitrogen and charged with iodine (11.6 g, 45.5 mmol, 1.7 equiv) (Note 15). Anhydrous THF (65 mL) (Note 4) is added *via* syringe and the flask is swirled to dissolve iodine. The solution of iodine is transferred to the dropping funnel *via* syringe and additional anhydrous THF (7 mL) (Note 4) is added to the flask to rinse iodine to the dropping funnel. The reaction flask is cooled in dry ice-acetone bath (internal temp = -72 °C) and the solution of iodine is added dropwise over 10 min, resulting in an increase in internal temperature to -64 °C. Stirring is continued for 10 min. The cooling bath is removed and the resulting orange suspension is allowed to warm to room temperature (22–23 °C) and stirred for 1.5 h. The reaction progress is monitored by TLC (Note 16). The reaction mixture is poured into brine (200 mL) in a 1-L separatory funnel. The reaction flask is rinsed with de-ionized water (50 mL) and ethyl acetate (150 mL) and the washings are added to the separatory funnel. The organic layer (top) is separated and the aqueous layer is extracted with ethyl acetate (2 x 100 mL). The combined organic layers are washed with aqueous sodium thiosulfate (10%, 100 mL), brine (100 mL), and dried over Na₂SO₄ (20 g). After filtration, the solution is concentrated under reduced pressure (40 mmHg) on a rotary evaporator at 40 °C and further dried under vacuum (25 mmHg) to give 13.6 g of a yellow solid. The crude solid is placed in a 200-mL Erlenmeyer flask and dissolved in ethyl acetate (35 mL) and hexane (70 mL) with heating using a Chem Glass Optitherm reaction block (70 °C) (Note 8). The solution is removed from heat allowed to stand at room temperature (22–23 °C) overnight. The solid is

collected on a disposable 100-mL 10 micron polyethylene fritted funnel (Note 9) and washed with ice-cold hexane (2 x 5 mL) to afford (*R*)-2 as yellow crystals (6.86 g, 51%) (Note 17). The mother liquor is concentrated and the residue is purified by flash chromatography on silica gel (Note 18) to give additional (*R*)-2 (2.5 g, 19 %) as a light yellow solid (Note 19).

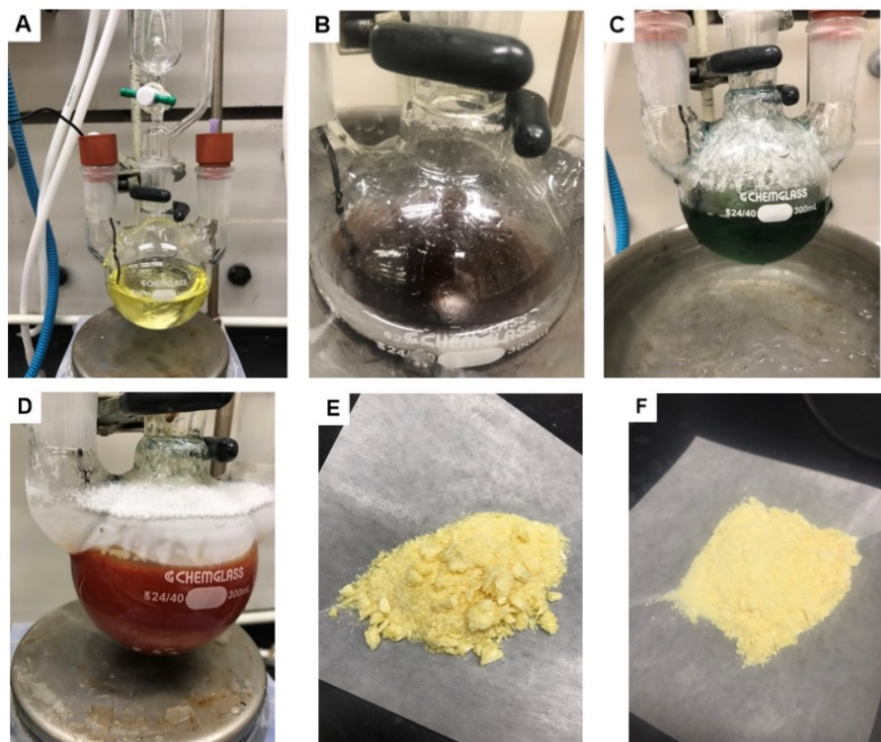


Figure 2. Step B photographs. A) Appearance of reaction mixture prior to addition of *n*-BuLi; B) Appearance of reaction mixture immediately following *n*-BuLi addition; C) Appearance of reaction mixture after aging 4 h; D) Appearance of reaction mixture after iodine addition; E) Solids obtained from recrystallization; F) Solids isolated from column chromatography (all photos provided by checkers)

C. (*R*)-3-(3,5-(Bistrifluoromethyl)phenyl)-2,2'-bis(methoxy(methoxy))-1,1'-binaphthyl ((*R*)-3). A 250-mL, three-necked, round-bottomed flask, equipped with a Teflon-coated, magnetic stir bar (cylindrical, 35 x 7 mm), a reflux condenser connected to a nitrogen line, and two rubber septa, is charged with

aqueous sodium carbonate (2 M, 8 mL) (Note 20) and 1,4-dioxane (60 mL) (Note 21). Nitrogen is bubbled through the resulting suspension for 0.5 h *via* a needle connected to the rubber septum. (*R*)-3-Iodo-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl ((*R*)-2) (2.00 g, 4.00 mmol), 3,5-bis(trifluoromethyl)phenylboronic acid (1.24 g, 4.81 mmol, 1.2 equiv) (Note 22), and tetrakis(triphenylphosphine)palladium(0) (0.231 g, 0.200 mmol, 5 mol%) (Note 23) are added. Stirring is started and the resulting yellow suspension is heated in a Chem Glass Optitherm reaction block (Note 7) at 100 °C for 5 h, monitoring the reaction's progress by TLC (Note 24). The reaction mixture is cooled at room temperature and poured into water (100 mL) in a 500-mL separatory funnel. The reaction flask is rinsed with water (100 mL) and ethyl acetate (75 mL), and the washings are added to the separatory funnel. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (2 x 75 mL). The combined organic layers are washed with brine (75 mL) and dried over Na₂SO₄ (15 g). After filtration, the solution is concentrated under reduced pressure (40 °C, 40 mmHg) on a rotary evaporator and further dried under vacuum (25 mmHg) to give 3.3 g of a brown residue, which is purified by flash chromatography on silica gel (Note 25) to give 2.03 g (87%) of (*R*)-3 as a white, amorphous solid (Notes 26, 27, and 28).

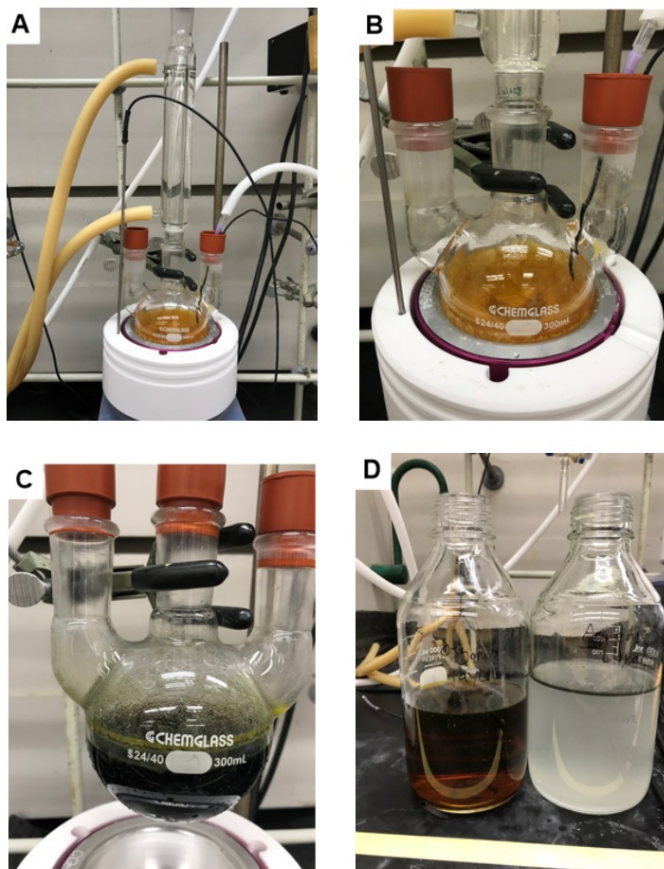


Figure 3. Step C photographs. A) Glassware setup; B) Color of reaction mixture prior to heating; C) color of mixture at end of reaction; D) Organic (left) and aqueous (right) layers after workup (all photos provided by checkers)

D. *(R)*-3-(3,5-Bistrifluoromethylphenyl)-1,1'-bi-2-naphthol (*(R)*-4). A 500-mL, round-bottomed flask equipped with a Teflon-coated, magnetic stir bar (cylindrical, 35 x 9 mm) is charged with *(R)*-3-(3,5-bistrifluoromethylphenyl)-2,2'-bis(methoxy(methoxy))-1,1'-binaphthyl (*(R)*-3) (2.13 g, 3.63 mmol), dichloromethane (60 mL)(Note 29), and ethanol (160 mL) (Note 30). Stirring (400 rpm) is started and conc. HCl (25 mL) (Note 31) is added. A reflux condenser is attached to the flask and the mixture is heated in a Chem Glass Optitherm reaction block (Note 7) at 60 °C for 5 h, monitoring the reaction's

progress by TLC (Note 32). The reaction mixture is cooled to room temperature and poured into water (500 mL) in a 1-L separatory funnel. The reaction flask is rinsed with water (50 mL) and ethyl acetate (100 mL) and the washings are added to the separatory funnel. The organic layer is separated and the aqueous layer is extracted with ethyl acetate (2 x 100 mL). The combined organic layers are washed with aqueous NaHCO₃ (5%, 100 mL), brine (50 mL) and dried over Na₂SO₄ (20 g). After filtration, the solution is concentrated under reduced pressure (40 °C, 40 mmHg) on a rotary evaporator and further dried under vacuum (25 mmHg) to give a crude white solid (1.81 g). The solid is charged into a 200-mL Erlenmeyer flask and dissolved in a 4:1 mixture of hexane and dichloromethane (100 mL) with heating in a Chem Glass Optitherm reaction block (50 °C) (Note 8). The solution is removed from heat and placed on the bench overnight (22–23 °C). The solid is collected on a disposable 100-mL 10 micron polyethylene fritted funnel (Note 9) and washed with ice-cold hexane (2 x 5 mL) to afford (*R*)-4 as colorless crystals (0.628 g, 35%) (Note 33). The mother liquor is concentrated and the residue is purified by flash chromatography on silica gel (Note 34) to give (*R*)-4 as a white solid (1.07 g, 59%) (Note 35).

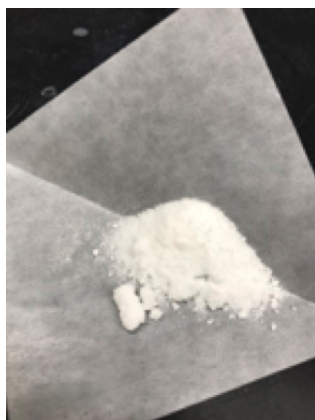


Figure 4. Final product isolated from recrystallization (photo provided by checkers)

Notes

1. Prior to performing each reaction, a thorough hazard analysis and risk assessment should be carried out with regard to each chemical substance and experimental operation on the scale planned and in the context of the laboratory where the procedures will be carried out. Guidelines for carrying out risk assessments and for analyzing the hazards associated with chemicals can be found in references such as Chapter 4 of "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at <https://www.nap.edu/catalog/12654/prudent-practices-in-the-laboratory-handling-and-management-of-chemical>). See also "Identifying and Evaluating Hazards in Research Laboratories" (American Chemical Society, 2015) which is available via the associated website "Hazard Assessment in Research Laboratories" at <https://www.acs.org/content/acs/en/about/governance/committees/chemicalsafety/hazard-assessment.html>. In the case of this procedure, the risk assessment should include (but not necessarily be limited to) an evaluation of the potential hazards associated with calcium chloride, (*R*)-1,1'-bi-2-naphthol, dichloromethane, *N,N*-diisopropylethylamine, chloromethyl methyl ether, aqueous HCl, sodium bicarbonate, sodium sulfate, hexanes, ethyl acetate, chloroform, tetrahydrofuran, butyllithium, iodine, sodium carbonate, 1,4-dioxane, 3,5-bis(trifluoromethyl)phenylboronic acid, tetrakis(triphenylphosphine)palladium(0), brine, ethanol, silica gel, toluene, 1,3,5-trimethoxybenzene, CDCl_3 , and dimethyl fumarate.
2. The compound is commercially available, for example, from Strem Chemicals, Inc.
3. (*R*)-1,1'-Bi-2-naphthol was purchased from Tokyo Chemical Industry Co., LTD. with >98% purity (submitters) and Chem-Impex Int'l Inc with 99.99 % purity (checkers).
4. Dichloromethane was purchased from Nacalai Tesque, Inc. and was dried over calcium hydride and distilled under argon atmosphere (submitters). Dichloromethane was purchased from Sigma-Aldrich in 100 mL Sure-Seal bottles containing 40-150 ppm amylene as stabilizer, and used as received (checkers).

- N,N*-Diisopropylethylamine was purchased from Nacalai Tesque, Inc. with $\geq 98\%$ purity (submitters) and Sigma-Aldrich with $\geq 99\%$ purity (checkers).
- Chloromethyl methyl ether was purchased from Tokyo Chemical Industry Co., LTD. with $>95\%$ purity and was used as received (submitters). Chloromethyl methyl ether was purchased from Sigma-Aldrich with $>95\%$ purity and was used as received (checkers).
- Thin layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) (submitters and checkers). UV light and phosphomolybdic acid stain were used to visualize the product. Thin layer chromatography is eluted with 5% ethyl acetate/toluene, and the observed R_f is 0.49 for (*R*)-1 and 0.24 for (*R*)-1,1'-bi-2-naphthol.



Figure 5. TLC analysis of Step A reaction progress at 18 h: Left lane = (*R*)-BINOL; Right lane = reaction mixture; Middle lane = cospot. Top spot in right lane corresponds to desired product, bottom spot corresponds to mono-methoxymethyl protected BINOL

- Reaction block purchased from Chem Glass (part number : CG-1992-50).
- Disposable 100-mL, 10 micron polyethylene fritted funnels purchased from OptiChem (part number: OP-6602-14).

10. The physical properties of (*R*)-1 are as follows: mp 100–101 °C; IR 1620, 1591, 1462, 1145, 1067, 1032, 1010, 920, 897, 809 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 3.19 (s, 6H), 5.02 (d, *J* = 6.8 Hz, 2H), 5.13 (d, *J* = 6.8 Hz, 2H), 7.20–7.23 (m, 2H), 7.24–7.32 (m, 2H), 7.34–7.44 (m, 2H), 7.63 (d, *J* = 9.0 Hz, 2H), 7.92 (d, *J* = 8.2 Hz, 2H), 8.00 (d, *J* = 9.0 Hz, 2H); ¹³C NMR (126 MHz, CDCl₃) δ: 55.8, 95.2, 117.3, 121.4, 124.1, 125.6, 126.3, 127.9, 129.4, 129.9, 134.1, 152.7; HRMS: [M + NH₄]⁺ calcd for C₂₄H₂₂O₄: 392.1861, found: 392.1859. Determined to be 99.1 wt% by ¹H NMR using 1,3,5-trimethoxybenzene as an internal standard.
11. A second run on identical scale provided 12.7 g (80%) of (*R*)-1.
12. The procedure is based on a previous report.²
13. THF was purchased from Wako Pure Chemical Industries, LTD. and distilled under argon atmosphere from sodium benzophenone ketyl (submitters). THF was purchased from Sigma-Aldrich in 100 mL Sure-Seal bottles and used as received (checkers).
14. Butyllithium solution (1.60 M in hexane) was purchased from KANTO CHEMICAL Co., Inc. (submitters). *n*-Butyllithium solution (1.6 M in hexanes) was purchased from Sigma-Aldrich in a 100 mL Sure-Seal bottle and used as received (checkers).
15. Iodine was purchased from Wako Pure Chemical Industries, LTD. with 99% purity and used as received.
16. Thin layer chromatography (TLC) was performed on pre-coated TLC-plates (Merck Co., Inc. TLC silica gel 60 F254, 25 mm). UV light and phosphomolybdic acid stain were used to visualize the product. Thin layer chromatography was eluted with toluene/ethyl acetate 19:1, and the observed *R_f* was 0.53 for (*R*)-2.

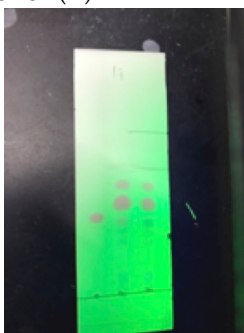


Figure 6. TLC analysis of Step B reaction progress 90 min after iodine addition. Left lane = starting material, right lane = reaction mixture, middle lane = cospot

17. The physical properties of (*R*)-**2** are as follows: mp 126–127 °C; $[\alpha]_D^{25} +82.8$ (*c* 5.0, CHCl₃); IR 1622, 1594, 1510, 1495, 1144, 1072, 1032, 915, 902, 758 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 2.76 (s, 3H), 3.23 (s, 3H), 4.74 (d, *J* = 5.3 Hz, 1H), 4.78 (d, *J* = 5.3 Hz, 1H), 5.08 (d, *J* = 7.0 Hz, 1H), 5.17 (d, *J* = 7.0 Hz, 1H), 7.16–7.22 (m, 2H), 7.25–7.35 (m, 2H), 7.36–7.46 (m, 2H), 7.62 (d, *J* = 9.1 Hz, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 8.00 (d, *J* = 9.1 Hz, 1H), 8.56 (s, 1H); ¹³C NMR (126 MHz, CDCl₃) δ: 56.0, 56.8, 92.9, 94.9, 99.2, 116.2, 120.1, 124.2, 125.5, 125.6, 126.1, 126.4, 126.8, 126.8, 126.9, 127.9, 129.5, 130.1, 132.5, 133.9, 133.9, 139.4, 151.6, 152.9. HRMS: $[M + NH_4]^+$ calcd for C₂₄H₂₁IO₄: 518.0828, found: 518.0842. Determined to be 97.4 wt% by ¹H NMR using 1,3,5-trimethoxybenzene as an internal standard.
18. Silica gel (45–75 μm) was purchased from Wako Pure Chemical Industries, LTD. Flash chromatography was performed using 130 g of silica gel (5 x 17 cm) and 70-mL fractions were collected. The compound was adsorbed onto silica and dry-loaded on the column. The column was eluted with hexane/toluene/ethyl acetate: 97:97:6 (840 mL). Compound (*R*)-**2** was obtained in fractions 4–8, which were combined and concentrated under reduced pressure (40 mmHg) on a rotary evaporator at 40 °C. The resulting solid was dried at 1–2 mmHg for 2 h (submitters). Flash chromatography was performed using a Teledyne ISCO Combi Flash R_f equipped with an 80 gram high performance Gold RediSep R_f silica cartridge (Teledyne Isco catalog no. 69-2203-348). The column was eluted with hexanes/toluene/ethyl acetate (97:97:6) using 25 x 150 mm test tubes. Compound (*R*)-**2** was obtained in fractions 15–17, which were combined and concentrated under reduced pressure (40 mmHg) on a rotary evaporator at 40 °C. The resulting solid was dried at 1–2 mmHg for 2 h (checkers).
19. A second run on identical scale provided 6.77 g (51 %) via crystallization. Purification of the mother liquor via chromatography provided an additional 2.3 g (17 %) of (*R*)-**2**.
20. Sodium carbonate was purchased from Nacalai Tesque, Inc. with 99.8% purity and used as received (submitters), and Fisher Chemical with >99.5% purity (checkers).
21. 1,4-Dioxane was purchased from Nacalai Tesque, Inc. with 99.5% purity and used as received (submitters). 1,4-Dioxane was purchased from Sigma-Aldrich in 100 mL Sure-Seal bottles with 99.8 % purity and used as received (checkers).

22. 3,5-Bis(trifluoromethyl)phenylboronic acid was purchased from Wako Pure Chemical Industries, LTD. with 97% purity and used as received (submitters), and from Combi-Blocks with 98 % purity and used as received (checkers).
23. Tetrakis(triphenylphosphine)palladium(0) was purchased from Nacalai Tesque, Inc. and used as received (submitters) and from Sigma-Aldrich in 99 % purity and used as received (checkers).
24. Thin layer chromatography (TLC) was performed on pre-coated TLC-plates (Merck Co., Inc. TLC silica gel 60 F254, 25 mm). UV light and phosphomolybdic acid stain were used to visualize the product. Thin layer chromatography is eluted with hexane/ethyl acetate 9:1, and the observed R_f is 0.41 for (*R*)-3.

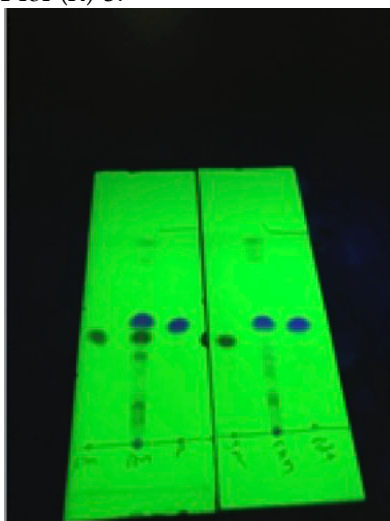


Figure 7. TLC analysis of Step C reaction progress. Left plate (2 h): left lane = starting material, right lane = product, middle lane = reaction mixture. Right plate (4.5 h): left lane = starting material, right lane = product, middle lane = reaction mixture

25. Silica gel (45–75 μm) was purchased from Wako Pure Chemical Industries, LTD. Flash chromatography was performed using 160 g of silica gel (5 x 20 cm) and 70-mL fractions were collected. The compound was adsorbed onto silica gel and dry-loaded on the column. The column was eluted with toluene (1.3 L). Compound (*R*)-3 was obtained in fractions 7-14, which were combined and concentrated under reduced pressure (40 mmHg) on a rotary evaporator at 40 °C. The resulting solid

- was dried at 1 mmHg for 5 h (submitters). Flash chromatography was performed using a Teledyne ISCO Combi Flash R_f equipped with a 40 gram high performance Gold RediSep R_f silica cartridge (Teledyne Isco catalog no. 69-2203-347). The column was eluted with toluene using 18 x 150 mm test tubes. Compound (*R*)-**3** was obtained in fractions 13 – 19, which were combined and concentrated under reduced pressure (40 mmHg) on a rotary evaporator at 40 °C. The resulting solid was dried 1 – 2 mmHg overnight (checkers).
26. The physical properties of (*R*)-**3** are as follows: $[\alpha]_{\text{D}}^{25} +54.2$ (*c* 5.0, CHCl₃); IR 1621, 1594, 1378, 1276, 1128, 1004, 963, 925, 754, 681 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 2.47 (s, 3H), 3.29 (s, 3H), 4.32 (d, *J* = 6.0 Hz, 1H), 4.42 (d, *J* = 6.0 Hz, 1H), 5.15 (d, *J* = 7.0 Hz, 1H), 5.21 (d, *J* = 7.0 Hz, 1H), 7.21–7.30 (m, 2H), 7.30–7.37 (m, 2H), 7.38–7.44 (m, 1H), 7.45–7.52 (m, 1H), 7.65 (d, *J* = 9.1 Hz, 1H), 7.89–7.94 (m, 2H), 7.97 (d, *J* = 8.2 Hz, 1H), 8.01 (s, 1H), 8.02 (d, *J* = 9.8 Hz, 1H), 8.24 (s, 2H); ¹³C NMR (126 MHz, CDCl₃) δ: 56.0, 56.2, 94.8, 99.3, 116.3, 120.8 (sept, *J* = 4 Hz), 123.5 (q, *J* = 273 Hz), 124.2, 125.4, 125.7, 126.0, 126.8, 126.9, 127.1, 128.0, 128.2, 129.7, 130.1, 130.1, 130.4, 130.9, 131.5 (q, *J* = 33 Hz), 132.8, 133.9, 134.1, 141.4, 151.0, 152.8; HRMS: $[M + \text{NH}_4]^+$ calcd for C₃₂H₂₄F₆O₄: 604.1923, found: 604.1934.
 27. The purity of (*R*)-**3** was determined to be 97% by ¹H NMR analysis using dimethyl fumarate as an internal standard (submitters). The purity of (*R*)-**3** was determined to be 98.5 wt% by ¹H NMR using 1,3,5-trimethoxybenzene as an internal standard (checkers).
 28. In addition to the 2 g scale reaction described in the text, the checkers conducted a second run on 4 g scale, which afforded 3.9 g (83 % yield) of (*R*)-**3** as a white solid.
 29. Dichloromethane was purchased from Nacalai Tesque with ≥98% purity and used as received (submitters). Dichloromethane was purchased from Sigma-Aldrich in 100 mL Sure-Seal bottles containing 40-150 ppm amylene as stabilizer, and used as received (checkers).
 30. Ethanol was purchased from Nacalai Tesque, Inc. with 95% purity and used as received (submitters). Ethanol was purchased from Sigma-Aldrich with ≥99.5 % purity and used as received (checkers).
 31. Concentrated hydrochloric acid was purchased from Nacalai Tesque, Inc. and used as received (submitters). Concentrated hydrochloric acid (fuming, 36.5 – 38 %) was purchased from Sigma-Aldrich and used as received (checkers).
 32. Thin layer chromatography (TLC) was performed on pre-coated TLC-plates (Merck Co., Inc. TLC silica gel 60 F254). UV light and

phosphomolybdic acid stain were used to visualize the product. Thin layer chromatography is eluted with hexane/ethyl acetate 4:1, and the observed R_f is 0.49 for (*R*)-4.

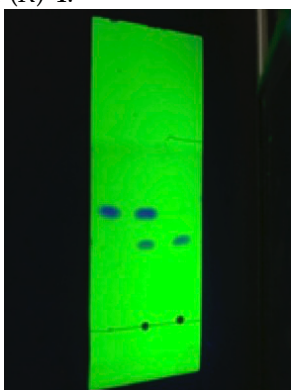


Figure 8. TLC analysis of Step D after 4.5 h. Left lane = starting material; right lane = reaction mixture; middle lane = cospot

33. The physical properties of (*R*)-4 are as follows: 229–231 °C; $[\alpha]_D^{25} +108.1$ (*c* 5.0, CHCl_3); IR 3476, 3398, 1619, 1593, 1275, 1139, 897, 822, 749, 704 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ : 5.08 (s, 1H), 5.39 (s, 1H), 7.17–7.27 (m, 2H), 7.32–7.52 (m, 5H), 7.91–7.96 (m, 2H), 8.01 (app t, $J = 9.3$ Hz, 2H), 8.10 (s, 1H), 8.26 (s, 2H); ^{13}C NMR (126 MHz, CDCl_3) δ : 110.2, 112.5, 117.8, 121.2 (sept, $J = 4$ Hz), 123.5 (q, $J = 272$ Hz), 124.0, 124.3, 124.3, 125.0, 127.6, 127.8, 128.3, 128.6, 128.7, 129.3, 129.6, 129.9, 129.9, 131.5 (q, $J = 34$ Hz), 131.8, 131.9, 133.3, 133.5, 139.8, 149.7, 152.9; $[\text{M} - \text{H}]^-$ calcd for $\text{C}_{28}\text{H}_{16}\text{F}_6\text{O}_2$: 497.0976, found: 497.1142. (*R*)-4 was determined to be 99.9 wt % by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.
34. Silica gel (45–75 μm) was purchased from Wako Pure Chemical Industries, LTD. Flash chromatography was performed using 10 g of silica gel (1.5 x 8 cm) and 30-mL fractions were collected. The column was eluted with toluene (330 mL). Compound (*R*)-4 was obtained in fractions 6–11, which were combined and concentrated under reduced pressure (40 mmHg) on a rotary evaporator at 40 °C. The resulting solid was dried at 1–2 mmHg for 3 h (submitters). Flash chromatography was performed using a Teledyne ISCO Combi Flash R_f equipped with a 12 gram high performance Gold RediSep R_f silica cartridge (Teledyne Isco catalog no. 69-2203-345). The column was eluted with ethyl acetate/hexanes using the following gradient program: 10 % ethyl acetate/hexanes for 5 min

- then gradient to 50 % ethyl acetate/hexanes over 10 min, then hold for 5 min. Fractions were collected using 13 x 100 mm test tubes. Compound (*R*)-**4** was obtained in fractions 10 – 20, which were combined and concentrated under reduced pressure (40 mmHg) on a rotary evaporator at 40 °C. The resulting solid was dried 1 – 2 mmHg overnight (checkers).
35. A second reaction performed on identical scale provided 0.686 g (38%) of the crystalline product. Chromatographic purification of the second reaction's mother liquor provided an additional 1.01 g (55 %) of (*R*)-**4**.

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

Discussion

Chiral titanium catalysts derived from 1,1'-bi-2-naphthol (BINOL) and its derivatives have been extensively used in the enantioselective carbonyl addition of organometallic reagents for the preparation of enantioenriched chiral alcohols.³ Recent reports from this laboratory revealed that the catalytic activity of the chiral titanium complexes is remarkably enhanced by the use of BINOL derivatives (*R*)-4–7 (Figure 9) bearing a sterically demanding aryl group at the 3-position of the parent BINOL or H₈-BINOL.⁴ The enhanced activity enabled us to expand the scope of organometallic nucleophiles, including organozinc,⁵ -boron,⁶ -aluminum,⁷ -magnesium,⁸ and -lithium reagents,^{9,10} and reduce the amount of the chiral ligands to a practical level (0.25–2 mol%) while maintaining high enantioselectivity (Scheme 1 and 2).

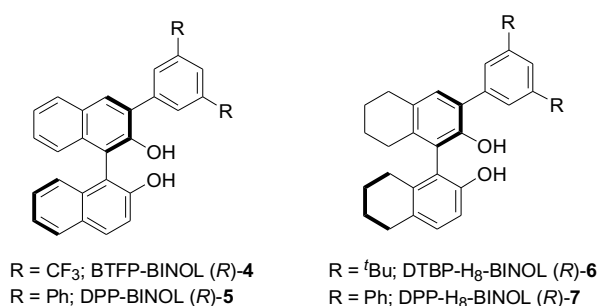
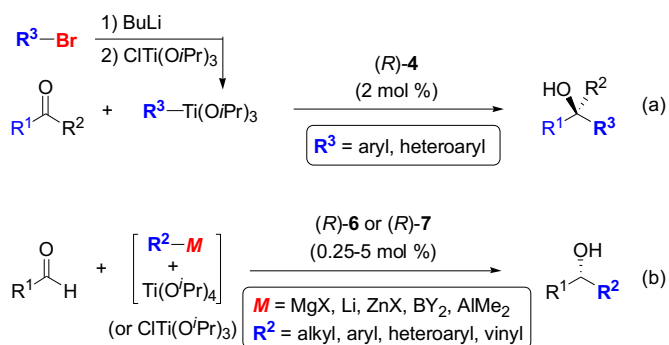


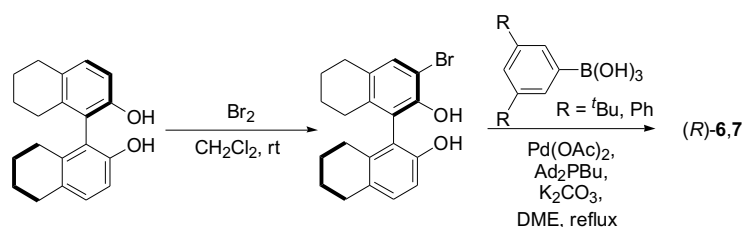
Figure 9. BINOL derivatives



Scheme 1. Enantioselective carbonyl addition catalyzed by chiral titanium complexes derived from 3-substituted BINOLs

The title compound, BTFP-BINOL (*R*)-**4**, is an excellent ligand for the enantioselective addition of aryl- and heteroaryl-titanium reagents to ketones (Scheme 1-a).¹⁰ For the phenylation of *p*-bromoacetophenone, for example, BTFP-BINOL exhibits 90% ee and 93% yield at 2 mol % catalyst loading, while the parent BINOL shows 82% ee and 50% yield under similar conditions. A detailed reaction procedure is described in the following procedure.¹¹

For the addition to aldehydes, H₈-BINOL derivatives (*R*)-**6** and (*R*)-**7** are better ligands. They can be synthesized in two steps from (*R*)-H₈-BINOL *via* regioselective mono-bromination and palladium-catalyzed cross-coupling with the corresponding arylboronic acids (Scheme 3).^{8e}



Scheme 2. Preparation of H₈-BINOL derivatives (*R*)-**6** and (*R*)-**7**

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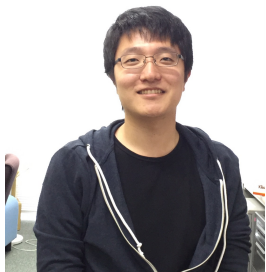
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Appendix

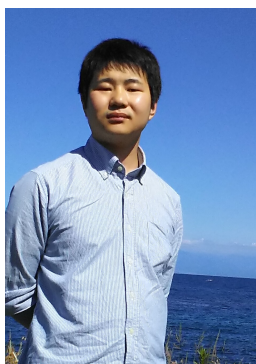
Chemical Abstracts Nomenclature (Registry Number)

- (*R*)-1,1'-Bi-2-naphthol: [1,1'-Binaphthalene]-2,2'-diol, (*1R*)-; (18531-94-7)
N,N-Diisopropylethylamine 2-Propanamine, *N*-ethyl-*N*-(1-methylethyl)-;
 (7087-68-5)
 Chloromethyl methyl ether: Methane, chloromethoxy-; (107-30-2)
 (*R*)-2,2'-Bis(methoxymethoxy)-1,1'-binaphthyl: 1,1'-Binaphthalene, 2,2'-
 bis(methoxymethoxy)-, (*1R*)-; (173831-50-0)
 (*R*)-3-Iodo-2,2'-bis(methoxymethoxy)-1,1'-binaphthyl: 1,1'-Binaphthalene, 3-
 iodo-2,2'-bis(methoxymethoxy)-, (*1R*)-; (389125-79-5)
 Butyllithium: Lithium, butyl-; (109-72-8)
 Iodine: Iodine; (7553-56-2)
 3,5-Bis(trifluoromethyl)phenylboronic acid: Boronic acid, *B*-[3,5-
 bis(trifluoromethyl)phenyl]-; (73852-19-4)
 Tetrakis(triphenylphosphine)palladium(0): Palladium,
 tetrakis(triphenylphosphine)-, (*T*-4)-; (14221-01-3)

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