Organic Syntheses

Catalytic Enantioselective Addition of an In-Situ Prepared Aryltitanium Reagent to *p*-Chloroacetophenone: (*R*)-(+)-1-(4-Chlorophenyl)-1-*m*-tolylethanol

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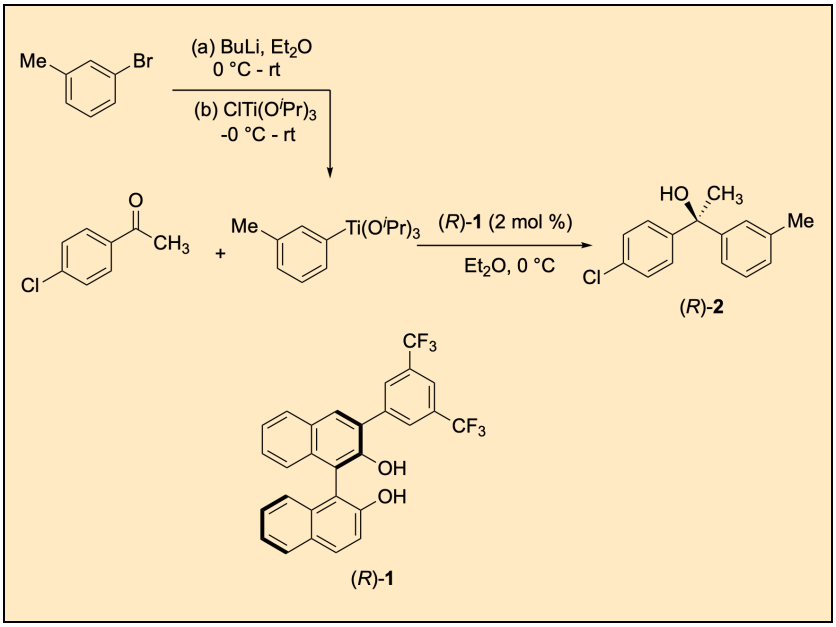

Procedure (Note 1)

*(R)-1-(4-Chlorophenyl)-1-m-tolylethanol ((R)-**2**).* An oven-dried, 100-mL three-necked, round-bottomed flask equipped with a Teflon-coated,

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magnetic stir bar (cylindrical, 8 x 30 mm) is loaded into a glove box under nitrogen atmosphere (Note 2). Titanium tetraisopropoxide (8.3 mL, 28 mmol, 1.1 equiv) (Note 3) is added, the flask is sealed with two rubber septa and a glass stopper and then removed from the glove box and connected to a nitrogen-filled Schlenk manifold. Anhydrous diethyl ether (34 mL) (Note 4) is added and the resulting solution is cooled in an ice-water bath (internal temp = 2 °C) (Note 5). While stirring, titanium tetrachloride (1.0 mL, 9.4 mmol, 0.4 equiv) (Note 6) (Figure 1) is added dropwise to the flask. The resulting solution is stirred in the ice-water bath for 10 min and then warmed to ambient temperature and stirred for an additional 30 min to give a colorless solution of chlorotitanium triisopropoxide (1.5 equiv).

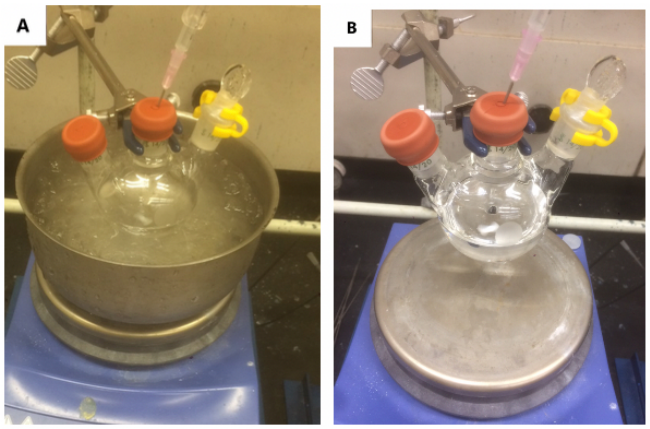


Figure 1. Chlorotitanium triisopropoxide preparation A) Solution immediately following the addition of titanium tetrachloride; B) Final chlorotitanium triisopropoxide solution (all photos provided by checkers)

An oven-dried, 300-mL, three-necked, round-bottomed flask equipped with a Teflon-coated, magnetic stir bar (cylindrical, 35 x 7 mm), a glass stopper and two rubber septa is attached to a Schlenk manifold and evacuated/back-filled with nitrogen (x3). The flask is charged with *m*-bromotoluene (5.0 mL, 40 mmol, 1.6 equiv) (Note 7) and anhydrous diethyl ether (Note 4) (77 mL). Stirring is started and the flask is cooled in an ice-water bath (internal temp = 2 °C). *n*-Butyllithium solution (23.4 mL, 1.6 M, 37.5 mmol, 1.5 equiv) (Note 8) is added dropwise *via* syringe pump over 15 min (internal temperature rose to 5 °C during the addition) (Figure 2) and

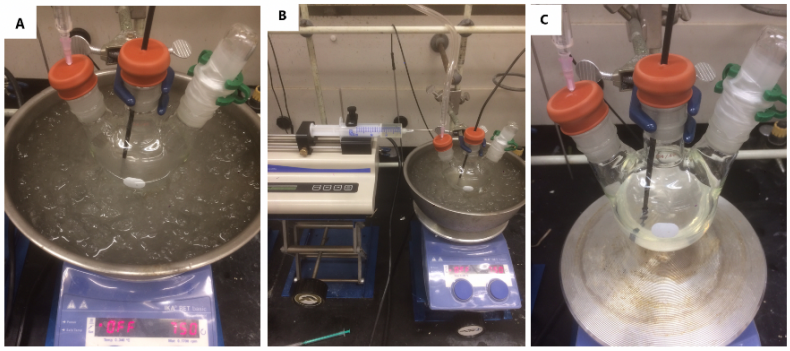


Figure 2. Aryllithium solution preparation A) Solution of *m*-bromotoluene; B) Syringe pump addition of *n*-butyllithium; C) Final aryllithium solution (all photos provided by checkers)

then the mixture is stirred for 10 min. The ice bath is removed and the reaction mixture is allowed to warm to ambient temperature, where it is stirred for 1 h. The flask is cooled again in the ice bath. The solution of chlorotitanium triisopropoxide is added dropwise *via* syringe pump over 10 min (internal temperature rose to 9 °C during the addition) (Figure 3) and then the reaction mixture is stirred for 30 min at 0 °C to give a light brown solution of *m*-tolyltitanium triisopropoxide in which lithium chloride is suspended. Stirring is stopped and the lithium chloride is allowed to settle for 15 min.

An oven-dried, 500-mL, three-necked, jacketed flask is equipped with a Teflon-coated, magnetic stir bar (cylindrical, 35 x 7 mm), a 500-mL pressure-equalizing addition funnel fitted with a rubber septum, a glass stopper, and a rubber septum. The flask is charged with (*R*)-3-(3,5-bistrifluoromethylphenyl)-1,1′-bi-2-naphthol ((*R*)-**1**) (0.27 g, 0.50 mmol, 2 mol%) (Note 9) and then the setup is attached to a Schlenk manifold and evacuated/back-filled with nitrogen (x3). Anhydrous diethyl ether (55 mL) (Note 4) and *p*-chloroacetophenone (3.2mL, 25 mmol) (Note 10) are added sequentially, stirring is started, and the flask is cooled to an internal

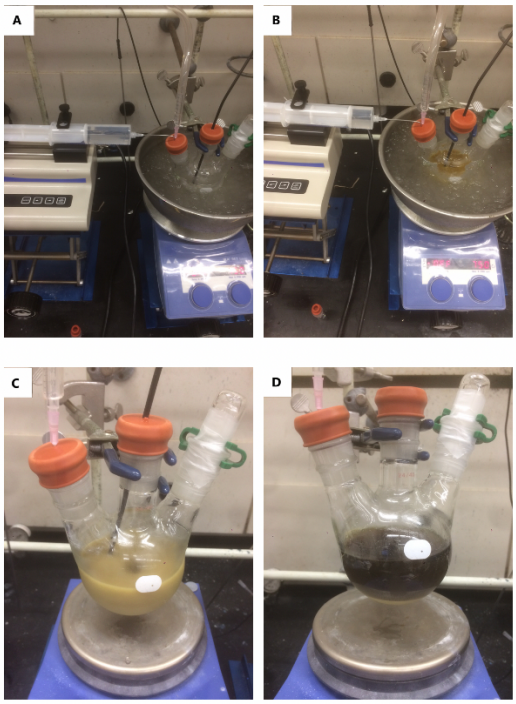


Figure 3. Aryltitanium triisopropoxide preparation. A) Syringe pump addition of chlorotitanium triisopropoxide; B) Syringe pump addition of chlorotitanium triisopropoxide midway through addition; C) Solution of aryltitanium triisopropoxide with a suspension of LiCl; D) Solution of aryltitanium triisopropoxide after LiCl has settled to the bottom of the flask (all photos provided by checkers)

temperature of 0 °C (Notes 11 and 12). The supernatant solution of the aryltitianium triisopropoxide is transferred to the dropping funnel *via* syringe and then added dropwise to the reaction flask over 3 h (Note 13) (Figure 4). The reaction mixture is then stirred at 0 °C (internal temperature) for an additional 40 h. The reaction progress is monitored by TLC (Note 14).

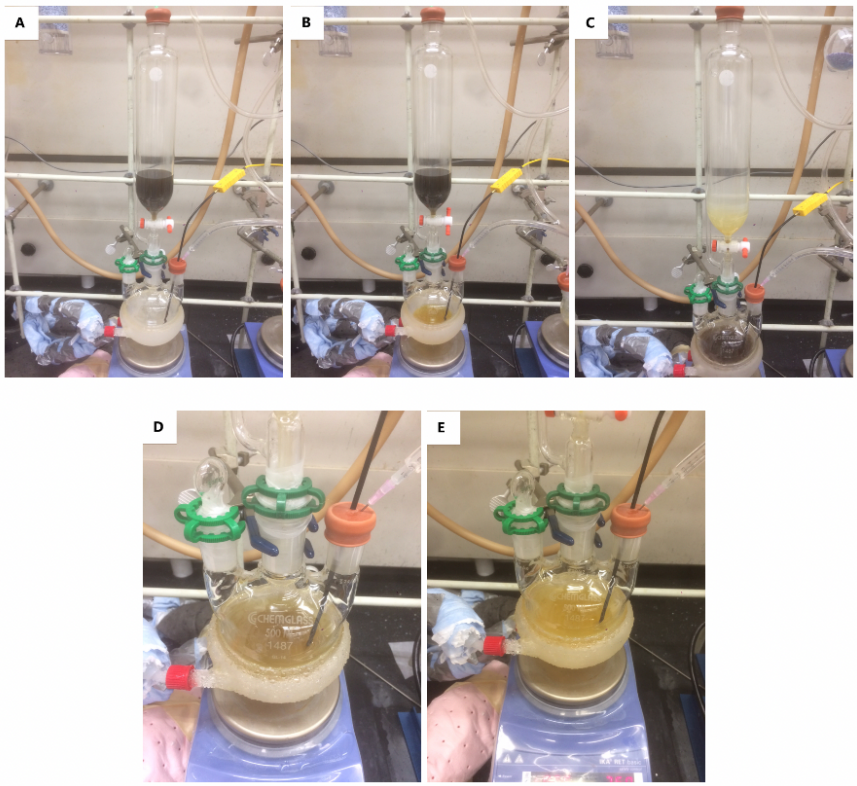


Figure 4. Aryltitanium addition to *p*-chloroacetophenone. A) Reaction setup; B) Reaction mixture during aryltitanium triisopropoxide addition; C) Reaction mixture immediately following the completion of aryltitanium addition; D) Reaction mixture 12 h after addition; E) Reaction mixture 40 h after addition (all photos provided by checkers)

The reaction mixture is quenched at 0 °C with aqueous ammonium chloride (10%, 150 mL). The resulting white slurry is stirred at room temperature for 10 min before being filtered through a pad of Celite (2 cm layer) (Note 15) (Figure 5) using a sintered-glass filter (7 cm), and washing with ethyl acetate

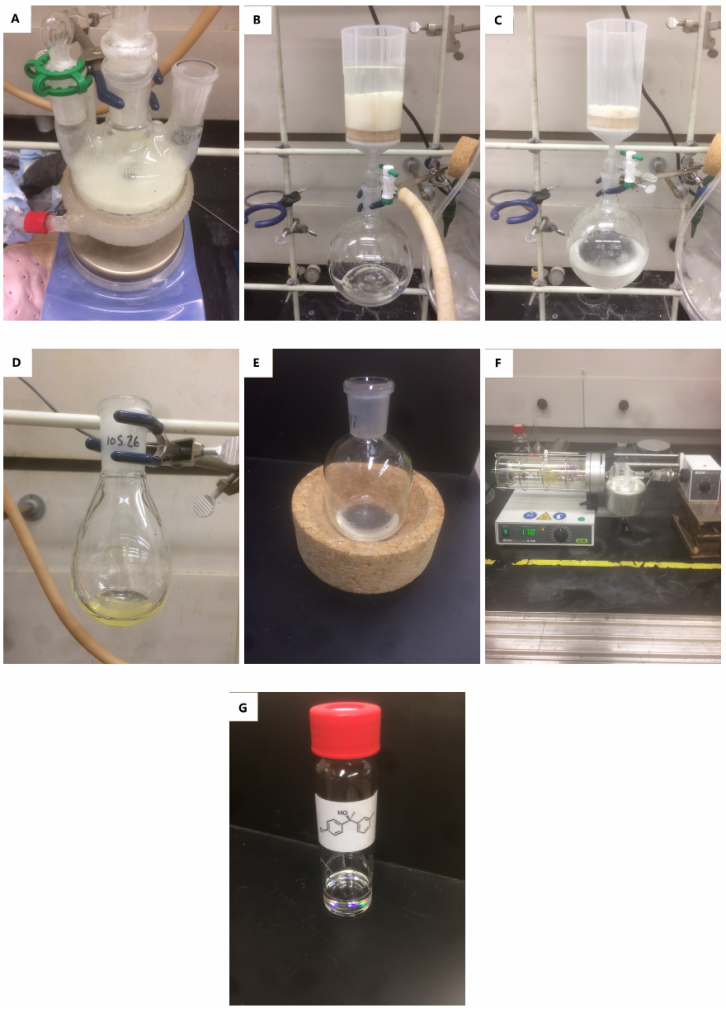


Figure 5. Work-up and purification of (*R*)-2 A) Reaction mixture after quenching with aqueous ammonium chloride; B) Filtration of quenched reaction mixture over Celite; C) The titanium salts sitting on the Celite; D) Crude oil; E) Mixture of compounds (*R*)-1 and (*R*)-2 following flash chromatography; F) Kugelrohr distillation; G) Purified (*R*)-2 (all photos provided by checkers)

(100 mL). The filtrate is transferred to a 1-L 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

$NaHCO_3$ (5%, 150 mL), brine (150 mL), and dried over Na_2SO_4 (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 (1–2 mmHg) to give 6.93 g of a yellow oil. Purification by flash chromatography on silica gel produced a mixture of compounds (*R*)-**1** and (*R*)-**2** (Note 16). The fractions containing (*R*)-**1** and (*R*)-**2** are concentrated under reduced pressure (40 mmHg) on a rotary evaporator at 40 °C and further dried under vacuum (1–2 mmHg) to give 6.18 g of a colorless oil. The title compound is distilled from this oil, in the presence of K_2CO_3 (0.2 g), under vacuum with a Kugelrohr apparatus (0.05 mmHg, 170 °C) to give (*R*)-**2** as a colorless liquid (5.72 g, 93%, 90% *ee*) (Notes 17 and 18).

The filtered titanium salts are scraped off of the Celite plug and placed in a 500-mL Erlenmeyer flask equipped with a Teflon-coated, magnetic stir bar (cylindrical, 35 x 7 mm). The flask is charged with aqueous HCl (1 N, 100 mL) and diethyl ether (100 mL), stirred for 2 h at room temperature (Figure 6), filtered, and washed with ethyl acetate (100 mL). The filtrate is transferred to a 500-mL 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 $NaHCO_3$ (5%, 100 mL) and dried over Na_2SO_4 (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 (1-2 mmHg) to give a residue. This residue is taken into CH_2Cl_2 (5 mL) and combined with the residue of the Kugelrohr distillation. The mixture is filtered to remove the K_2CO_3 and then the filtrate is concentrated under reduced pressure (40 mmHg) on a rotary evaporator at 40 °C and further dried under vacuum (1-2 mmHg) to give 0.44 g of a brown residue, which partially solidified upon standing. This residue is added to a 20 mL screw-cap vial equipped with a magnetic stir bar (cylindrical, 8 x 30 mm). Hexanes (2.2 mL) are added to the vial and the resulting slurry is stirred at ambient temperature for 16 h. The slurry is filtered under vacuum and the filter cake is washed with cold (*ca.* 5 °C) hexanes (2 x 2 mL) and then dried under vacuum (1-2 mmHg) overnight to give ligand (*R*)-**1** as a colorless, amorphous solid (0.159 g) (59% recovery).

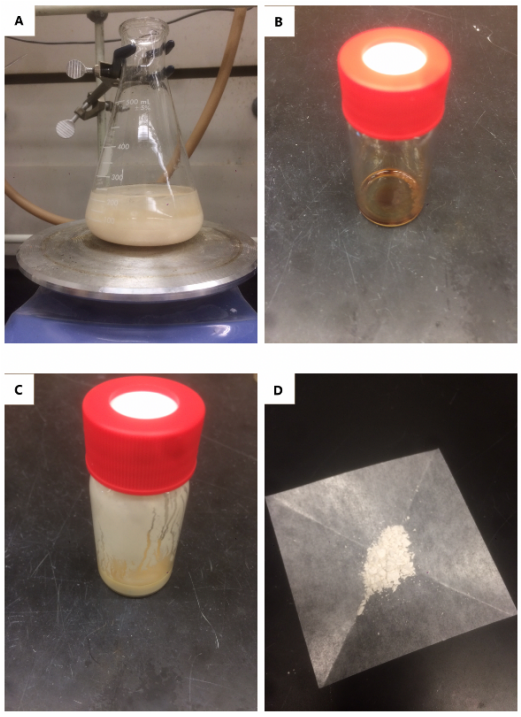


Figure 6. Recovery of (*R*)-1. A) Stirring solution of titanium salts in aqueous HCl and diethyl ether; B) Crude residue; C) Slurry of (*R*)-1 in hexanes; D) Recovered (*R*)-1 (all photos provided by checkers)

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 Titanium tetraisopropoxide, diethyl ether, titanium tetrachloride, nitrogen, *m*-bromotoluene, *n*-Butyllithium, lithium chloride, (*R*)-3-(3,5-bistrifluoromethylphenyl)-1,1'-bi-2-naphthol, *p*-chloroacetophenone, ammonium chloride, ethyl acetate, hydrochloric acid, Celite, sodium bicarbonate, brine, sodium sulfate, silica gel, hexanes, and potassium carbonate.

2. The use of a glove box is for simplicity of set up due to the moisture sensitive nature of the reagents. Alternatively, titanium tetraisopropoxide can be added *via* syringe.
3. Titanium tetraisopropoxide was purchased from Wako Pure Chemical Industries, LTD. with ≧95% purity and used as received. The checkers used titanium tetraisopropoxide (99.999% trace metals basis) that was purchased from Sigma-Aldrich and used as received.
4. Diethyl ether was purchased from Nacalai Tesque, Inc. and distilled under argon atmosphere from sodium benzophenone ketyl. The checkers used diethyl ether (>99.9%, inhibitor free) that was purchased from Sigma-Aldrich and used as received (water content = 21 ppm, determined by Karl Fischer titration).
5. The disproportionation reaction of titanium tetraisopropoxide and titanium tetrachloride is exothermic.
6. Titanium tetrachloride was purchased from Wako Pure Chemical Industries, LTD. with ≧99% purity and used as received. The checkers used titanium tetrachloride (>99.995% trace metals basis) that was purchased from Sigma-Aldrich and used as received.
7. *m*-Bromotoluene was purchased from Wako Pure Chemical Industries, LTD. with ≧97% purity and used as received. The checkers used *m*-bromotoluene (98%) that was purchased from Sigma-Aldrich and used as received.
8. *n*-Butyllithium solution (1.60 M in hexane) was purchased from KANTO CHEMICAL Co., Inc. The checkers used *n*-butyllithium solution (1.6 M in hexanes) that was purchased from Sigma-Aldrich and used as received.

9. See the preceding procedure[2] for the synthesis of (*R*)-3-(3,5-bistrifluoromethylphenyl)-1,1′-bi-2-naphthol ((*R*)-**1**). The wt. % of (*R*)-**1** was determined to be 93% based on quantitative NMR analysis, with 2,4,6-trimethoxybenzene as an internal standard.
10. *p*-Chloroacetophenone was purchased from Wako Pure Chemical Industries, LTD. with >95% purity and used as received. The checkers used *p*-chloroacetophenone (97%) that was purchased from Sigma Aldrich and used as received.
11. The jacketed flask was connected to a chiller and the indicated internal temperature was reached by continually passing a chilled mixture of ethylene glycol:water (1:1 v/v) through the flask jacket.
12. The checkers found that a sustained internal temperature of 0 °C, throughout the entirety of the 1,2-addition reaction, was crucial to obtaining reproducibly high enantiomeric excesses (*ee*).
13. Addition rate = *ca.* 1 drop/2-3 seconds. Longer addition times (e.g. 4 h) did not have an impact on the outcome on the product yield and *ee*.
14. Thin layer chromatography (TLC) was performed on pre-coated TLC-plates (Merck & Co., Inc. TLC silica gel 60 F254). UV light, phosphomolybdic acid stain, and cerium (IV) ammonium molybdate were used to visualize the product. Thin layer chromatography is conducted with a 1:1 CH_2Cl_2:hexanes mobile phase, and the observed R_f is 0.21 for (*R*)-**2**.

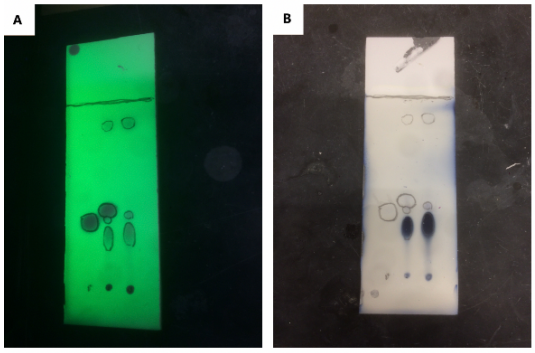


Figure 7. TLC Plates (1:1 CH_2Cl_2:hexanes) for reaction mixture at complete conversion. Left lane = *p*-chloroacetophenone; middle lane = co-spot; right lane = reaction mixture A) TLC plate visualized under UV light; B) TLC plate after developing with an acidic solution of cerium (IV) ammonium molybdate followed by heating (all photos provided by checkers)

15. Celite was purchased from Nacalai Tesque, Inc (submitters). The checkers used Celite purchased from Sigma Aldrich.
16. Flash chromatography was performed on a Teledyne Isco, using a pre-packed RediSep Rf GOLD silica gel column (330 g HP silica). The crude material was loaded onto the column with 10% EtOAc/hexanes (5 mL) and elution was conducted with 10% EtOAc/hexanes at a rate of 200 mL/min, collecting 50 mL per fraction. Compounds (*R*)-**1** and (*R*)-**2** co-eluted in fractions 21-34.
17. Enantioselectivity was determined by HPLC analysis using a Chiralcel OD-3R column, 1.5 mL/min, 50% MeCN:0.1% H_3PO_4; retention times: 8.09 min (major *R*-enantiomer) and 9.39 min (minor *S*-enantiomer). The submitters determined enantioselectivity by HPLC analysis using a Chiralcel OJ-H column, 1 mL/min, 6% ^{i}PrOH in hexane; retention times: 12.1 min (minor *S*-enantiomer) and 13.2 min (major *R*-enantiomer). Absolute configuration was determined by analogy. The physical properties of (*R*)-**2** are as follows: $[\alpha]_D^{25}$ +13.3 (*c* 1.0, $CHCl_3$); IR (film) 3384 (br), 2977, 1605, 1488, 1455, 1398, 1370, 1246, 1162, 1118, 1091, 1012, 973, 922, 877, 831, 779, 728, 704, 656 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.95 (s, 3H), 2.16 (s, 1H), 2.36 (s, 3H), 7.10 (d, *J* = 7.2 Hz, 1H), 7.18 – 7.26 (m, 3H), 7.28 – 7.32 (m, 2H), 7.35 – 7.40 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 21.6, 30.9, 75.9, 122.8, 126.5, 127.3, 128.0, 128.21, 128.23, 132.7, 138.0, 146.7, 147.4; HRMS (ESI) calcd for $C_{15}H_{13}{}^{35}Cl$ [$(M\text{-}OH)^+$] 229.0784, found 229.0793; The purity of (*R*)-**2** was determined to be 99.8% by quantitative NMR analysis, using 1,3,5-trimethoxybenzene as an internal standard.
18. A second reaction on full scale provided 5.67 g (92%) of (*R*)-**2** with 90% *ee*. This reaction also provided 0.160 g (60%) recovery of the ligand.

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 tertiary diaryl carbinols are key intermediates for the synthesis of pharmacologically active compounds.[3] For the enantioselective synthesis, much effort has been directed toward the development of the catalytic enantioselective arylation of alkyl aryl ketones.[4] Catalytic methods utilizing arylzinc,[5] -aluminum,[6] -titanium,[7] and -boron reagents[8] have been explored. However, reactions are generally carried out at relatively large catalyst loadings, making them less practical for scale-up applications. Availability of arylmetal reagents from inexpensive and easily handled aryl sources is another important issue in the practical use of the enantioselective arylation.

We have recently reported a catalytic enantioselective method that uses aryltitanium reagents, prepared *in situ* from inexpensive bromide precursors *via* organolithium intermediates[9] for reaction with ketones in the presence of chiral ligand BTFP-BINOL (*R*)-**1** (Figure 8) at 2 mol % loading (Scheme 1).[10]

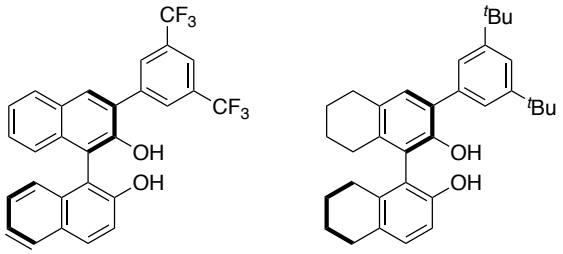
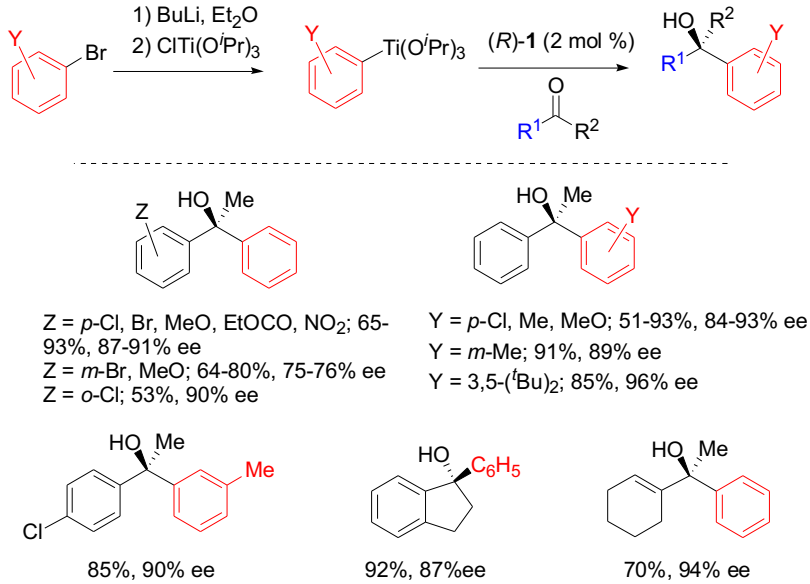
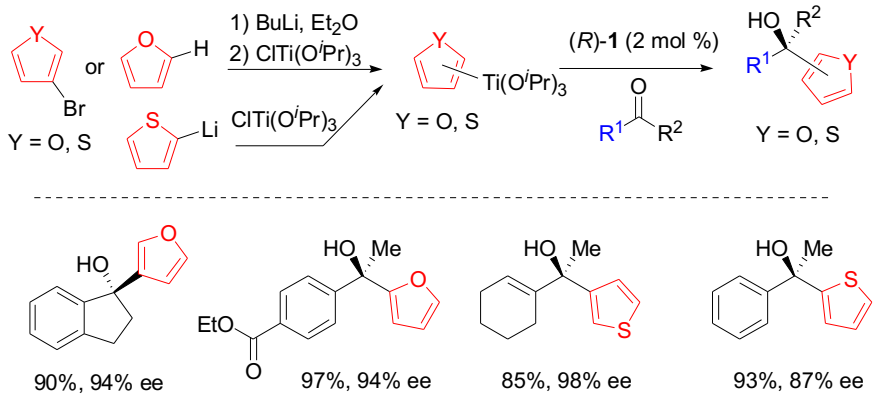


Figure 8. Catalysts (*R*)-**1** and (*R*)-**3**



Scheme 1. Catalytic enantioselective preparation of tertiary alcohols starting from aryl bromides and ketones

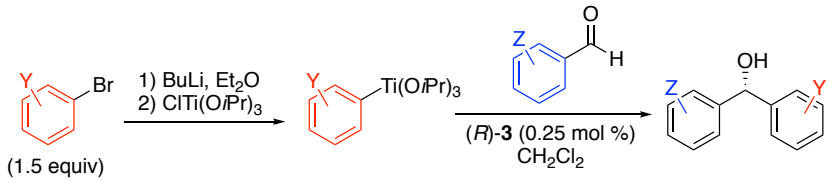
The ligand is prepared in a straightforward manner in three steps[11] and can be recovered after the arylation reaction. High enantioselectivity has been achieved in the preparation of various chiral tertiary diaryl carbinols by using this method. The reaction is also applicable to the heteroarylation of ketones (Scheme 2).



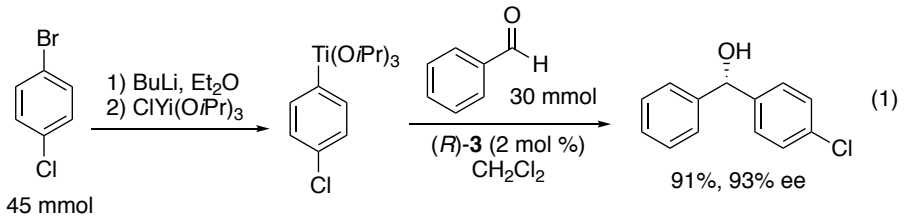
Scheme 2. Catalytic enantioselective preparation of tertiary 1-heteroarylethanols

Aryltitanium reagents, prepared *in situ* from the bromide precursors are also successfully employed in the enantioselective arylation of aldehydes using DTBP-H_8-BINOL (*R*)-**3** as a chiral ligand at 0.25 mol % loading for a 1 mmol-scale reaction (Table 1).[12] The reaction is carried out by adding a solution of the titanium reagents to a CH_2Cl_2 solution of aldehydes and the ligand at 0 °C for 3 h. As illustrated in the enantioselective synthesis of (*S*)-(4-chlorophenyl)phenylmethanol (eq 1), the reaction can be carried out at 30 mmol-scale with modification of the procedure reducing the amount of solvents and using a dropping funnel for the addition of the aryltitanium reagents.[13]

Table 1. Catalytic Enantioselective Arylation of Aldehydes



entry	Y	Z	yield (%)	ee (%)
1	*p*-Cl	H	96	94
2	*p*-F	H	87	93
3	*p*-Me	H	95	92
4	*p*-MeO	H	68	95
5	*m*-Cl	H	89	92
6	*m*-Me	H	93	91
7	H	*p*-Cl	96	89
8	H	*p*-CN	99	84
9	H	*m*-MeO	99	89
10	*p*-Cl	*o*-Cl	95	86



References

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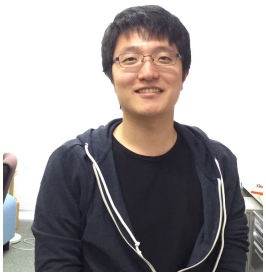
12. (a) Hayashi, Y.; Yamamura, N.; Kusukawa, T.; Harada, T. *Chem. Eur. J.* **2016**, *22*, 12095–12105. (b) See also, Uenishi, A.; Nakagawa, Y.; Osumi, H.; Harada, T. *Chem. Eur. J.* **2013**, *19*, 4896–4905.
13. *p*-$ClC_6H_4Ti(O^iPr)_3$ is prepared by treatment of 1-bromo-4-chlorobenzene (45 mmol, 1.5 equiv) with butyllithium (45 mmol, 1.5 equiv) in diethyl ether (90 mL), transmetallation of the resulting aryllithium intermediate with $ClTi(O^iPr)_3$ (0.5 M in CH_2Cl_2, 45 mmol, 1.5 equiv), and dilution with

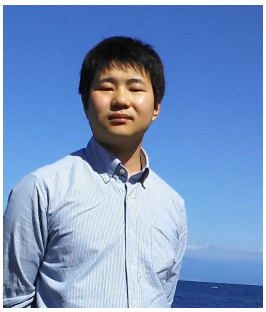
CH_2Cl_2 (150 mL). The titanium reagent is added dropwise to a well-stirred solution of benzaldehyde (30 mmol) and (*R*)-**3** (0.6 mmol, 2 mol %) in CH_2Cl_2 (150 mL) at 0 °C for 3 h.

Appendix
Chemical Abstracts Nomenclature (Registry Number)

(*S*)-1-(4-Chlorophenyl)-1-*m*-tolylethanol: Benzenemethanol, 4-chloro-α-methyl-α-phenyl-, (α*S*)-; (913383-13-8)
Titanium tetraisopropoxide; 2-Propanol, titanium(4+) salt (4:1); (546-68-9)
Titanium tetrachloride; Titanium chloride ($TiCl_4$) (*T*-4)-: (7550-45-0)
m-Bromotoluene; Benzene, 1-bromo-3-methyl-: (591-17-3)
Chlorotitanium tetraisopropoxide; Titanium, chlorotris(2-propanolato)-, (*T*-4)-: (20717-86-6)
p-Chloroacetophenone; Ethanone, 1-(4-chlorophenyl)-; (99-91-2)



Yusuke Kobayashi, was born in Hyogo, Japan. He received his B.Sc. in 2017 from Kyoto Institute of Technology. He is now an undergraduate researcher at Kyoto University, Faculty of Material Chemistry to pursue research in electrochemistry.

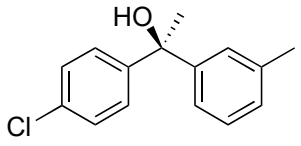


Atsushi Matsuda was born in Japan in 1991. He received his B.Sc. in 2015 and M.Sc. in 2017 from Kyoto Institute of Technology. He is now Research Associate at Tateyama Kasei Co., Ltd., Toyama, Japan.

Tomoya Ushimaru was born in Takayama, Japan. He received his B.Sc. in 2014 and M.Sc. in 2016 from Kyoto Institute of Technology. He is now Research Associate at Alps Pharmaceutic Industry, Co., Ltd., Hida, Japan.

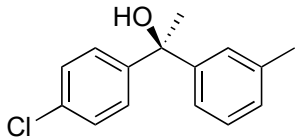
Toshiro Harada was born in Kyoto, Japan, in 1952. He graduated from Kyoto University in 1975. He received his Ph.D. from Kyoto University (1980) with Professor Zen-ichi Yoshida. Then he was appointed as a Research Associate in Kyoto Institute of Technology in 1981. He spent the year 1982–1983 as a postdoctoral fellow with Professor W. Clark Still at Columbia University. He was promoted to Full Professor in 2002 in Kyoto Institute of Technology. His research interests are in the development of catalytic enantioselective reactions and convergent carbon–carbon bond-forming reactions.

Jonathan Hughes was born in Regina, Saskatchewan, Canada and graduated with his B.Sc. in Chemistry from the University of Regina (2012). He then completed his Ph.D. studies at McGill University (2018), working with Professor James L. Gleason. He is now employed as a Senior Scientist in the Process Research & Development department at Merck & Co., Inc. in Rahway, NJ, USA.



(*R*)-**2**

^{1}H NMR (500 MHz, $CDCl_3$)



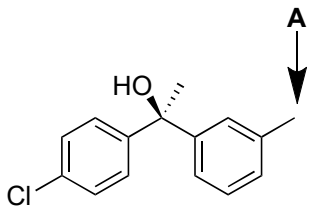
(*R*)-**2**

^{1}H NMR (126 MHz, $CDCl_3$)

147.44
146.71
137.98
132.70
128.23
128.21
128.00
127.32
126.49
122.84
77.28 CDCl3
77.03 CDCl3
76.77 CDCl3
75.87
30.87
21.60

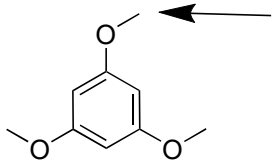
260 250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -6

f1 (ppm)



(*R*)-**2** (14.2 mg, 0.058 mmol)
wt% = 99.8%

^{1}H NMR (500 MHz, $CDCl_3$)



1,3,5-trimethoxybenzene (IS)
(5.7 mg, 0.034 mmol)