A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

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.

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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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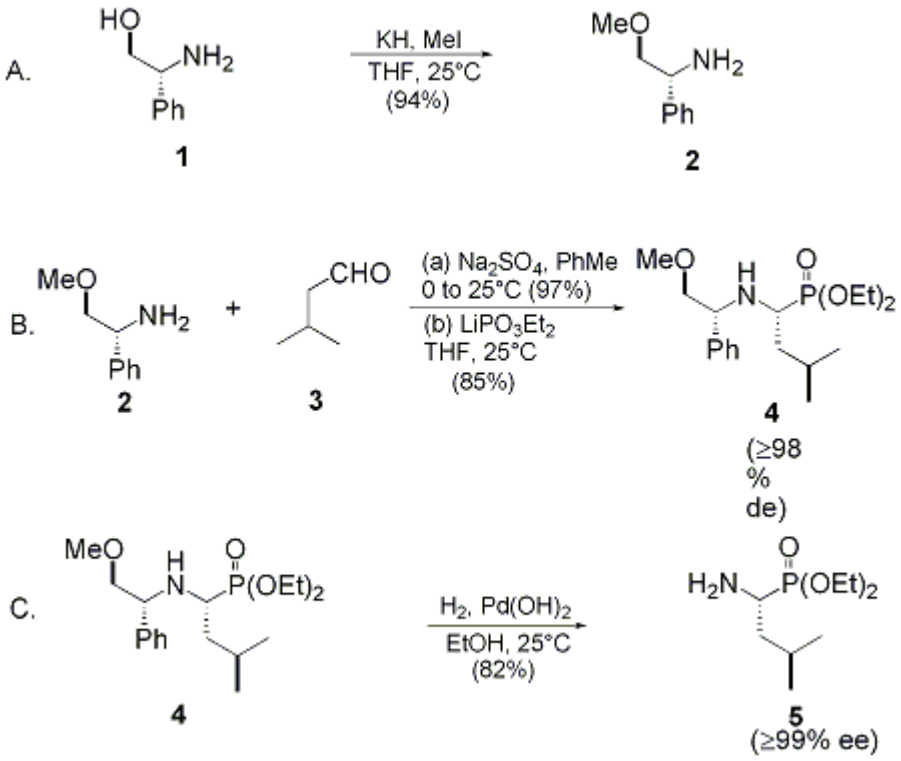
ASYMMETRIC SYNTHESIS OF DIETHYL (R)-(−)-(1-AMINO-3-METHYLBUTYL)PHOSPHONATE

[Phosphonic acid, (1-amino-3-methylbutyl)-, diethyl ester, (R)-]



Submitted by Amos B. Smith, III, Kraig M. Yager, Barton W. Phillips, and Carol M. Taylor[1] .
Checked by Martha Huntington, Edward G. Corley, Andrew S. Thompson, and Ichiro Shinkai.

1. Procedure

A. *(R)-(−)-1-Amino-1-phenyl-2-methoxyethane* **(2)** .[2] A solution of (R)-(−)-2-phenylglycinol **(1)** (25.0 g, 182.2 mmol) (Note 1) in anhydrous tetrahydrofuran (THF) (370 mL) (Note 2) is added dropwise via an oven-dried, 500-mL, pressure-equalizing addition funnel to an oven-dried, 2-L, round-bottomed flask containing a stirred (Note 3) suspension of potassium hydride (7.82 g, 195 mmol) (Note 4) in anhydrous THF (150 mL) at 25°C under an argon atmosphere. The resultant pale yellow mixture is stirred overnight and then treated dropwise with a solution of methyl iodide (25.2 g, 177.6 mmol) (Note 5) in THF (220 mL) over 2 hr at room temperature. The resultant mixture is stirred for an additional 3 hr, poured into cold (~5°C) saturated aqueous sodium chloride solution (1.5 L) and extracted with anhydrous diethyl ether (4 × 250 mL); the combined organic extracts are dried over anhydrous sodium sulfate (Note 6). Filtration and rotary evaporation gives 39.2 g of yellow oil that is purified by vacuum distillation (bp 47-50°C, 0.2 mm) to yield 25.3 g (94%) of **2** as a colorless oil (Note 7).

B. *Diethyl (R)-(−)-[1-((N-(R)-(1-phenyl-2-methoxyethyl)amino)-3-methylbutyl)]phosphonate* **(4)** . To an oven-dried, 1-L, round-bottomed flask containing a magnetic stirring bar (Note 3) are added isovaleraldehyde **(3)** (9.4 g, 109 mmol) (Note 8) and dry toluene (100 mL) (Note 9) under an argon atmosphere. The solution is cooled to 0°C (ice bath) and a solution of (R)-(−)-1-amino-1-phenyl-2-methoxyethane **(2)** (16.5 g, 109 mmol) in dry toluene (160 mL) is introduced dropwise over 45 min via a 250-mL, pressure-equalizing addition funnel. The cooling bath is removed and the mixture is allowed to warm to room temperature. The resultant turbid solution is treated with anhydrous sodium sulfate (125 g, 0.88 mol), stirred for 1 hr, and then filtered through a fritted glass funnel, washing the residue

with toluene (150 mL). The filtrate is concentrated, first by rotary evaporation and then at ≤1 mm for 1 hr, yielding 23.3 g of the imine as a slightly yellow oil.

To the 1-L, round-bottomed flask containing the above imine are added a magnetic stirring bar and dry THF (180 mL) under an argon atmosphere. To this stirring solution is added lithium diethyl phosphite (Note 10) via a 12-gauge cannula. After 20 hr at ambient temperature the reaction mixture is quenched by addition of water (200 mL) and most of the THF is removed by rotary evaporation. The aqueous layer is then saturated with sodium chloride and extracted with ethyl acetate (3 × 300 mL) (Note 11), and the combined organic phases are dried over anhydrous sodium sulfate. Filtration and rotary evaporation furnish 39-45 g of a pale yellow oil that is dissolved in 50% ethyl acetate-hexane (50 mL) and purified by flash chromatography [9-cm column, 800 g of Silica Gel 60 (Note 12), eluting with 1.2 L of 50% ethyl acetate-hexane followed by 6 L of 60% ethyl acetate-hexane , 35 mL/min, 125-mL fractions after a 2-L forerun; product R_f = 0.5, 2:1 ethyl acetate-hexane]. Concentration via rotary evaporation furnishes 30.5 g (85%) of **4** as a colorless oil (Note 13) and (Note 14).

C. *Diethyl (R)-(−)-(1-amino-3-methylbutyl)phosphonate* **(5)** . A 1-L, round-bottomed flask is equipped with a magnetic stirring bar and charged with **4** (30.5 g, 85.4 mmol) and absolute ethanol (600 mL). To this solution is added 20% palladium hydroxide on carbon (35.5 g) (Note 15), and the flask is connected to an atmospheric-pressure hydrogenation apparatus equipped with a graduated burette containing water or mercury to monitor uptake of hydrogen (Note 16). The suspension is thoroughly degassed (aspirator pressure), backfilled twice, with hydrogen and stirred vigorously for 16 hr. The mixture is then degassed (aspirator pressure) and filtered through a pad of Celite (Note 17). The filter pad is washed with absolute ethanol (3 × 75 mL), the filtrate concentrated under reduced pressure, and the residual oil purified by flash chromatography (9-cm column, 580 g of Silica Gel 60, eluting with 150 mL of dichloromethane , 1.5 L of 2% methanol-dichloromethane and 2 L of 5% methanol-dichloromethane , 50 mL/min, 125-mL fractions; product R_f = 0.25, 5% methanol-dichloromethane). Concentration of the fractions gives 15.5 g (82%) of **5** as a pale yellow oil (Note 18) and (Note 19).

2. Notes

1. (R)-(−)-2-Phenylglycinol (≥98% ee), purchased from Aldrich Chemical Company, Inc. , was used as received.
2. Tetrahydrofuran was distilled from sodium/benzophenone ketyl at atmospheric pressure under an argon atmosphere.
3. A large (7 cm long, 4 cm diameter) football-shaped magnetic stirring bar was required to ensure efficient mixing of the heterogeneous mixture.
4. Potassium hydride, 35% by weight in mineral oil, was purchased from Aldrich Chemical Company, Inc. , and washed with dry pentane prior to use. *Note that potassium hydride is a pyrophoric solid and must be handled with extreme care*.
5. Methyl iodide was purchased from Aldrich Chemical Company, Inc. , and used as received.
6. Anhydrous, powdered sodium sulfate, purchased from Aldrich Chemical Company, Inc. , was used as received.
7. Analytical data for **2** are as follows: $[\alpha]_D^{25}$ −49.4° (benzene , *c* 6.3); IR ($CHCl_3$) cm^{-1}: 3380 (w), 3040 (w), 3000 (w), 2900 (m), 2240 (m), 1580 (m), 1460 (m), 1200 (m), 1120 (s), 905 (s), 700 (s) ; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.75 (br s, 2 H), 3.39 (t, 1 H, J = 9.1), 3.41 (s, 3 H), 3.53 (dd, 1 H, J = 9.3, 3.9), 4.21 (dd, 1 H, J = 8.7, 3.9), 7.30 (m, 1 H), 7.35 (t, 2 H, J = 7.3), 7.40 (dd, 2 H, J = 8.7, 1.6) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 55.4, 58.8, 78.9, 126.7, 127.3 (2 C), 128.3, 142.6 (2 C) ; high resolution mass spectrum (CI, CH_4) m/z 152.1069 [$(M+H)^+$; calcd for $C_9H_{14}NO$: 152.1075].
8. Isovaleraldehyde was purchased from Aldrich Chemical Company, Inc. , and distilled at atmospheric pressure before use.
9. Toluene was distilled from sodium spheres at atmospheric pressure under an argon atmosphere. The checkers report that reagent grade toluene stored over 4 Å molecular sieves proved satisfactory.
10. An oven-dried, 250-mL, conical flask is charged with freshly distilled diethyl phosphite (29.3 g, 212.1 mmol) (Note 20) and dry THF (110 mL) under an argon atmosphere. The solution is cooled to 0° C (ice bath) and treated dropwise over 20 min with a solution of butyllithium (1.6 M in hexane; 63.0 mL, 100.8 mmol) (Note 21). After an additional 0.5 hr the mixture is warmed to room temperature and used immediately.

11. Reagent-grade ethyl acetate and hexanes were purchased from commercial sources and distilled before use.
12. EM Science Silica Gel 60 (230-400 mesh ASTM) was purchased from Bodman Industries (Aston, PA) . The checkers recommend 36 g of silica gel/1 g of crude product.
13. Analytical data for **4** are as follows: $[\alpha]_D^{25}$ −118.4° ($CHCl_3$, *c* 2.07); IR ($CHCl_3$) cm^{-1}: 3340 (br, w), 2985 (s), 2960 (s), 2940 (s), 1460 (m), 1390 (w), 1370 (w), 1230 (s), 1050 (s), 1030 (s), 970 (s), 700 (m) ; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.51 (d, 3 H, J = 6.5), 0.88 (d, 3 H, J = 6.8), 1.37 (m, 6 H, J = 7.0), 1.41 (q, 2 H, J = 7.6), 1.95 (m, 1 H), 2.12 (br s, 1 H), 2.69 (ddd, 1 H, J_{HP} = 9.1, J_{HH} = 7.9, 6.7), 3.38 (t, 1 H, J = 3.9), 3.40 (s, 3 H), 3.46 (t, 1 H, J = 9.6), 4.09-4.19 (m, 4 H), 4.54 (dt, 1 H, J = 9.4, 3.9), 7.27 (m, 1 H), 7.30 (t, 2 H, J = 7.6), 7.40 (d, 2 H, J = 7.2) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 16.5 (d, J_{CP} = 6), 16.6, 20.7 (d, J_{CP} = 6), 23.6 (d, J_{CP} = 5), 23.7, 40.5 (d, J_{CP} = 7), 49.4, 58.4, 59.5 (d, J_{CP} = 138), 61.4 (d, J_{CP} = 7), 61.8, 77.7, 127.6 (d, J_{CP} = 7), 128.2 (2 C), 128.3, 140.3 (2 C) ; high resolution mass spectrum (CI, CH_4) m/z 358.2132 [$(M+H)^+$; calcd for $C_{18}H_{33}NO_4P$: 358.2147]. Anal. Calcd for $C_{18}H_{32}NO_4P$: C, 60.49; H, 9.02; N, 3.92. Found: C, 60.70; H, 9.21; N, 3.80.
14. The minor (R,S) diastereomer is present in the crude reaction mixture to the extent of approximately 0.9% as determined by capillary gas-liquid chromatographic analysis performed on a Hewlett-Packard 5790A gas chromatograph equipped with a Hewlett-Packard 3390A integrator and HP-1 methylsilicone gum column (25 m × 0.2 mm × 0.33 μm film thickness). The checkers found that HPLC analysis (Zorbax SB-Phenyl column 25 cm × 4.6 mm, 40:60 MeCN/0.1% aqueous phosphoric acid, 1.5 mL/min, 250 nm detection) provided satisfactory resolution of the R,R- and R,S-diastereomers. The minor diastereomer is hardly discernible by ^1H NMR (500 MHz) after purification by flash chromatography.
15. Palladium hydroxide on carbon (moist, Pd content 20%, dry weight basis, moisture content ≤50%) was purchased from Aldrich Chemical Company, Inc. , and used as received.
16. The checkers found the use of a Parr shaker (2 PSIG hydrogen, 16 hr, ambient temperatures) satisfactory for the hydrogenolysis step, and distillation (bp 108°C/2.5 mm, 89.9-91% yield) for purification.
17. The filter pad was prepared by compressing Celite (4 cm) onto a layer of sand (1.5 cm) in a fritted glass funnel (10-cm diameter).
18. Analytical data for **5** are as follows: $[\alpha]_D^{25}$ −20.8° ($CHCl_3$, *c* 1.6); IR ($CHCl_3$) cm^{-1}: 3690 (br, w), 3000 (s), 2940 (m), 1470 (w), 1390 (m), 1230 (s), 1040 (s), 965 (s), 780 (m) ; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.90 (d, 3 H, J = 6.7), 0.96 (d, 3 H, J = 6.7), 1.34 (td, 6 H, J_{HH} = 7.0, J_{HP} = 1.8), 1.50 (m, 2 H), 1.56 (br s, 2 H), 1.91 (m, 1 H, J = 1.4), 3.04 (ddd, 1 H, J_{HP} = 10.8, J_{HH} = 10.8, 3.7), 4.16 (m, 4 H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 16.5, 21.0, 23.5 (d, 2 C, J_{CP} = 5), 24.1, 39.9 (d, J_{CP} = 13), 46.7 (d, J_{CP} = 148), 62.0 (d, J_{CP} = 7), 62.1 (d, J_{CP} = 7) ; high resolution mass spectrum (CI, CH_4) m/z 224.1419 [$(M+H)^+$; calcd for $C_9H_{23}NO_3P$: 224.1415]. Anal. Calcd for $C_9H_{22}NO_3P$: C, 48.42; H, 9.93; N, 6.28. Found: C, 48.60; H, 9.93; N, 6.23.
19. α-Aminophosphonate **5** is obtained in >99% enantiomeric excess as determined by ^1H NMR (500 MHz) analysis of the derived S-Mosher amide.[3]
20. Diethyl phosphite, purchased from Aldrich Chemical Company, Inc. , was vacuum distilled just prior to use (bp 50-51°C, 2 mm).
21. Butyllithium, purchased from Aldrich Chemical Company, Inc. , was standardized by titration with diphenylacetic acid . Butyllithium solutions with concentrations less than 1.5 M may result in drastically reduced diastereomeric excesses and should be avoided.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

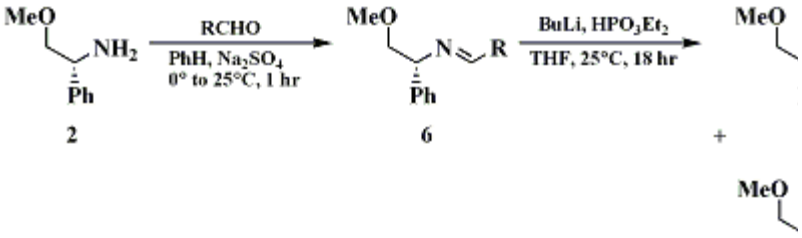
α-Aminophosphonic acids and esters, also referred to as α-aminophosphonates, represent an important class of organic compounds by virtue of their analogy to α-aminocarboxylic acids. Several synthetic derivatives of α-aminophosphonates have significant biological activities including inhibition of proteolytic enzymes[4 5 6] and of bacterial growth,[7 8 9 10] and they have also been found in nature as components of hypertensive tripeptides.[11] Currently, α-aminophosphonates are also serving as transition-state mimics in haptens for catalytic antibody research.[12] It is not surprising that their

biological properties are strongly influenced by the absolute configuration at the α carbon.[7,8,9,10]

Several methods have been devised for the preparation of racemic α-aminophosphonates; in 1972 the first optically active example was synthesized.[13] Since then, optically active α-aminophosphonates have been obtained by a variety of methods including resolution, asymmetric phosphite additions to imine double bonds and sugar-based nitrones, condensation of optically active ureas with phosphites and aldehydes, catalytic asymmetric hydrogenation, and 1,3-dipolar cycloadditions. These approaches have been discussed in a comprehensive review by Dhawan and Redmore.[14] More recent protocols involve electrophilic amination of homochiral dioxane acetals,[15] alkylation of homochiral imines derived from pinanone [16] and ketopinic acid ,[17] and alkylation of homochiral, bicyclic phosphonamides.[18]

The method described here takes advantage of the chelating ability of homochiral imines typified by **6** to achieve high levels of asymmetric induction during the addition of phosphite anion to the C-N double bond.[19] Coordination of the lithium counterion by the ether oxygen and imine nitrogen is believed to generate a rigid, five-membered-ring transition state; addition occurs anti to the phenyl ring, leading predominantly to the R,R-diastereomers with de values typically exceeding 96%. The α-aminophosphonates are then generated with ee values of 71 to 99% by catalytic hydrogenolysis of the chiral directing group. As illustrated in Table I, this strategy is widely applicable. Moreover, the enantiomer of **1** is also commercially available, providing ready access to the corresponding S-α-aminophosphonates.[20,21,22,23]

TABLE I
PREPARATION OF α-AMINOPH



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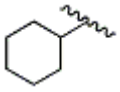
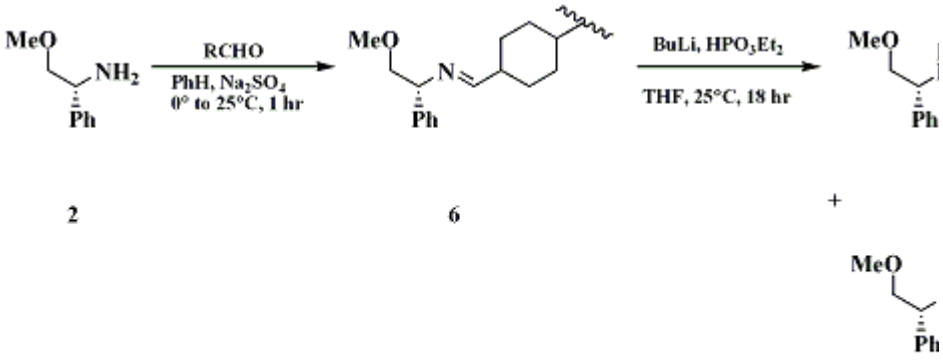
a		



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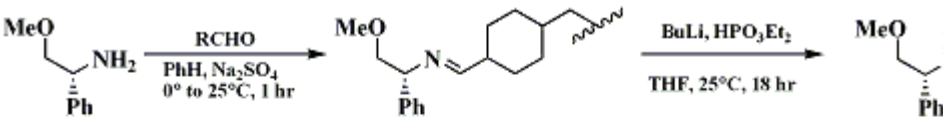

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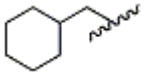
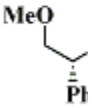
b 



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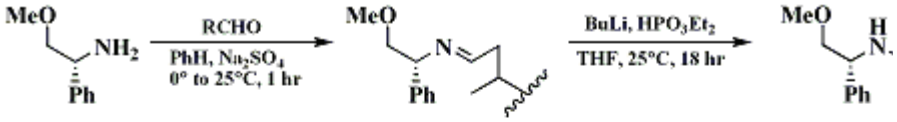

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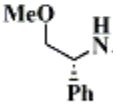

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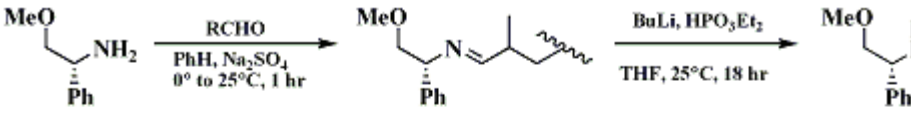

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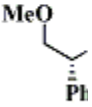

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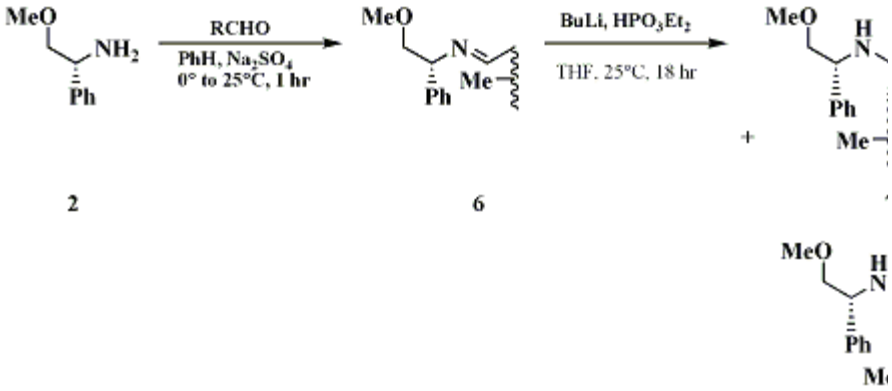

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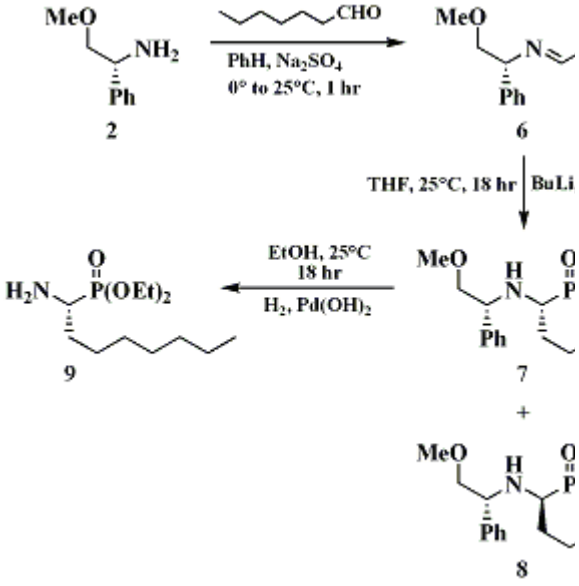

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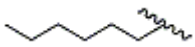
f 

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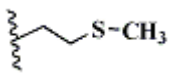
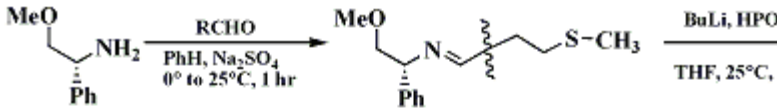
g 



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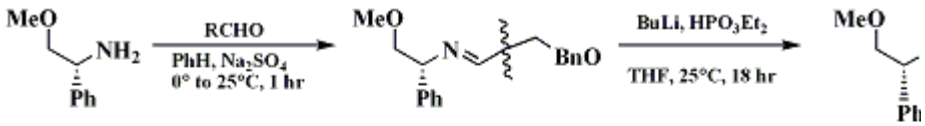

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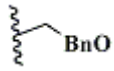
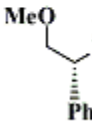
h[21] 



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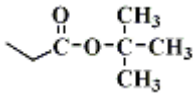
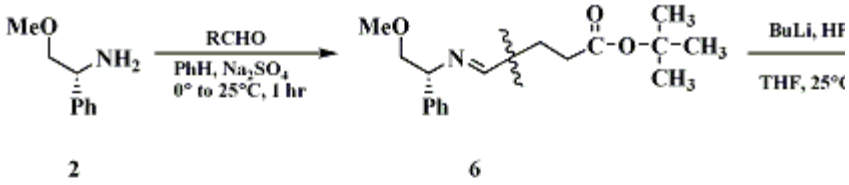
i[22] 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RCHO
PhH, Na2SO4
0° to 25°C, 1 hr
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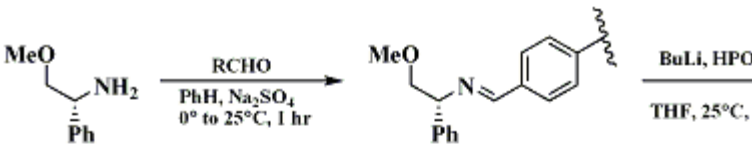
N
O
C
O
C
CH3
CH3
CH3
Ph
BuLi, HF
THF, 25°C

2 6

95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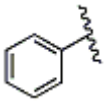
Ph
BuLi, HPO
THF, 25°C,

2 6

j 

[a]Crude yield. [b]After chromatography. [c]Determined by 500 MHz ^{1}H NMR analysis of the derive material. [e]Determined by capillary gas-liquid chromatographic analysis of crude material. [f]Trace AcOH, 48 hr. [i]R = CH_2OH. [j]Reactic

References and Notes

1. Department of Chemistry, University of Pennsylvania, Philadelphia, PA 19104.
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Diethyl (R)-(−)-(1-amino-3-methylbutyl)phosphonate:
Phosphonic acid, (1-amino-3-methylbutyl)-, diethyl ester, (R)- (13); (159171-46-7)

(R)-(−)-1-Amino-1-phenyl-2-methoxyethane:
Benzenemethanamine, α-(methoxymethyl)-, (R)- (10); (64715-85-1)

(R)-(−)-2-Phenylglycinol:
Benzeneethanol, β-amino-, (R)- (9); (56613-80-0)

Potassium hydride (8,9); (7693-26-7)

Methyl iodide:
Methane, iodo- (8,9); (74-88-4)

Diethyl (R)-(−)-[1-((N-(R)-(1-phenyl-2-methoxyethyl)amino)-3-methylbutyl)]phosphonate:
Phosphonic acid, [1-(2-methoxy-1-phenylethyl)amino]-3-methylbutyl]-, diethyl ester, [R-(R*,R*)]- (13); (159117-09-6)

Isovaleraldehyde (8);
Butanal, 3-methyl- (9); (590-86-3)

Diethyl phosphite:
Phosphonic acid, diethyl ester (8,9); (762-04-9)

Butyllithium:
Lithium, butyl- (8,9); (109-72-8)