Organocatalyzed Direct Asymmetric α–Hydroxymethylation of Aldehydes

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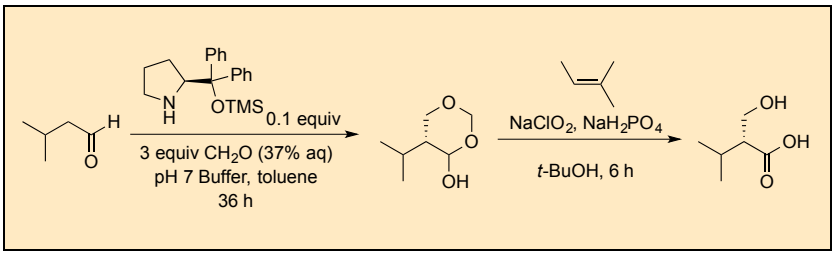

Procedure

*(R)-2-(Hydroxymethyl)-3-methylbutanoic acid (**1**).* A 250-mL 24/40 single-necked round-bottomed flask is equipped with a cylindrical Teflon-coated magnetic stir bar (7 x 25 mm). The flask is charged with *(S)*-1,1-diphenylprolinol trimethylsilyl ether (1.63 g, 5 mmol, 0.1 equiv) (Note 1), toluene (100 mL) (Note 2), pH 7 buffer (5 g) (Note 3), and 37% aqueous formaldehyde solution (11.2 mL, 12.2 g, 0.150 mol, 3.0 equiv) (Note 4). Vigorous stirring is initiated (Note 5), and isovaleraldehyde (5.49 mL, 4.31 g, 0.050 mol, 1.0 equiv) (Note 6) is added in one portion to the flask. The flask is capped with a yellow hard plastic Caplug® (Note 7), which is sealed with parafilm. The flask is allowed to stir at ambient temperature for 36 h (Note 8). The mixture is transferred to a 500 mL separatory funnel, the flask is rinsed with a minimum of toluene (~ 15 mL) and the rinsate added to the separatory funnel. The phases are separated and the aqueous phase is extracted with 30 mL toluene. The combined organic phases are added to a 24/40 1-L single-necked round-bottomed flask and concentrated by rotary evaporation (30 mmHg) in a 30 °C water bath to a clear colorless oil.

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The 1-L flask containing the residue is equipped with a cylindrical Teflon-coated magnetic stir bar (7 x 25 mm) and a 250-mL pressure equalizing addition funnel caped with a septum and a nitrogen inlet (Figure 1). *tert*-Butanol (250 mL) (Note 9) is added to the flask, followed by 2-methyl-2-butene (53.0 mL, 35.0 g, 0.50 mol, 10 equiv) (Note 10). The flask is then submerged in an ice water bath and cooled to 0 °C. A solution of sodium chlorite (18.1 g, 0.20 mol, 4 equiv) (Note 11) and sodium monobasic hydrogen phosphate monohydrate (27.6 g, 0.20 mol, 4 equiv) (Note 12) in 125 mL water is prepared by stirring until all solids dissolve. This yellow solution is then added via addition funnel to the cooled flask over 6 min, resulting in a slight exotherm. The reaction mixture turns dark yellow. The reaction mixture is allowed to warm to ambient temperature and stirred over a 6 h period. During this time, the color of the reaction mixture fades to a light yellow. The reaction mixture is then evaporated via rotary evaporator (30 mmHg) in a 50 °C water bath to remove *tert*-butanol. The resulting aqueous phase (approx. 140 mL) is diluted with 200 mL of ethyl acetate, 75 mL of sat aq sodium chloride solution, and 75 mL of 2.7 M aq hydrochloric acid, and transferred to a 1-L separatory funnel and mixed. After phase separation, the phases are separated and the aq phase is extracted with ethyl acetate (3 x 200 mL). The combined organic phases are dried over anhydrous sodium sulfate (15 g), gravity filtered through a powder funnel equipped with conical shaped medium porosity filter paper and concentrated via rotary evaporation (30 mmHg) in a 50 °C water bath to a yellow oil. Column chromatography provided the 6.06–6.32 g (92–96%, 93.0–93.5% ee) of *(R)-2-(hydroxymethyl)-3-methylbutanoic acid* (**1**) (Notes 13 and 14) as a white crystalline solid.

Figure 1. Reaction Set up

Notes

1. *(S)*-1,1-Diphenylprolinol trimethylsilyl ether was prepared using the procedure outlined in the preceding article.[2]
2. Toluene (99.9%, Certified ACS) was obtained from Fisher Scientific and used as received.
3. A stock bottle of pH 7 buffer was prepared by mixing potassium dibasic hydrogen phosphate, which was obtained from Spectrum Chemical and used as received, (64.9 g, 0.477 mol, 1 equiv) and potassium monobasic hydrogen phosphate, which was obtained from Spectrum Chemical and used as received, (91.1 g, 0.523 mol, 1.10 equiv) in a grinder and processing until a free flowing uniform solid formed. The solid is added directly to the reaction vessel.
4. Formaldehyde (36.5–38% aqueous formaldehyde) was obtained from EMD and used as received.
5. Vigorous stirring is required for efficient mixing of the phases. Stirring is sufficiently vigorous if the reaction appears homogenous, such that no distinct phases or phase boundary can be observed.
6. Isovaleraldehyde (≥97%) was obtained from Sigma-Aldrich and was distilled and stored under nitrogen prior to use. The presence of even trace amounts of isovaleric acid was found to catalyze elimination during the hydroxymethylation.
7. The Caplug® (part number WW12) is comprised of low density polyethylene. When rubber septa were used on this apparatus, a decrease in yield was noted, presumably due to septum leaching.
8. Reaction monitored by ^{1}H NMR. An aliquot (~0.20 mL) is taken from the toluene layer, diluted in 0.8 mL $CDCl_3$, then examined by NMR. The reaction is judged complete by disappearance of the aldehyde triplet of isovaleraldehyde at 9.75 ppm.
9. *tert*-Butyl alcohol (>99%, ACS Reagent) was obtained from EMD and was typically melted by submerging in warm water (bath temp ≈ 35 °C) for 15 min prior to use.
10. 2-Methyl-2-butene (>90.0%, remainder mainly 2-methyl-1-butene) was obtained from TCI and used as received.
11. Sodium chlorite (80%) was obtained from Alfa Aesar and used as received.
12. Sodium phosphate monobasic monohydrate (Baker analyzed ACS Reagent) was obtained from Spectrum Chemical and used as received.

13. Acid **1** is purified on a column (3.5 x 40 cm) packed with 75 g of silica (obtained from EMD Millipore, 60Å pore size, 230 - 400 mesh) packed in dichloromethane. Fraction collection (25 mL fractions) begins immediately; the column is eluted with 200 mL 1% methanol/dichloromethane, 200 mL 2% methanol/dichloromethane, 300 mL 3% methanol/dichloromethane, 200 mL 5% methanol/dichloromethane, 200 mL 7.5% methanol/dichloromethane, then flushed with 200 mL of 10% methanol/dichloromethane. Fractions 21-52 are pooled and contain the desired product. The product has an R_f of 0.28 in 10% methanol/dichloromethane. Physical properties of *(R)-2-(hydroxymethyl)-3-methylbutanoic acid* (**1**) are: ^{1}H NMR (600 MHz, $CDCl_3$) δ: 0.99 (t, *J* = 6.9 Hz, 6H), 2.02 (h, *J* = 6.9 Hz, 1H), 2.42 (ddd, *J* = 8.7, 7.2, 4.0 Hz, 1H), 3.79 (dd, *J* = 11.2, 4.0 Hz, 1H), 3.87 (dd, *J* = 11.2, 8.7 Hz, 1H), 6.76 (bs, 1H). ^{13}C NMR (150 MHz, $CDCl_3$) δ: 20.3, 20.7, 27.8, 54.4, 61.6, 180.1. $[\alpha]_D^{20}$ –5.50 (c 5.50, $CHCl_3$). IR (neat) 3371, 2964, 2879, 1707, 1468, 1392, 1270, 1198, 1065, 1014 cm^{-1}. mp 71–73 °C; HRMS (ESI) calcd for $C_6H_{11}O_3$ [M – H$^+$] 131.0714, Found 131.0713. Anal. calcd for $C_6H_{12}O_3$: C, 54.53, H, 9.15. Found: C, 54.68, H, 9.05.
14. Enantiomeric excess determined chiral CG of the methyl ester of the acid. Esterification procedure as follows: A small sample of the acid (50 mg, 0.38 mmol, 1 equiv) is added to a 5-mL single-necked round-bottomed flask equipped with cylindrical Teflon-coated magnetic stir bar (3.5 x 12 mm) capped with a rubber septum. DMF (1 mL) is added, followed by K_2CO_3 (105 mg, 0.76 mmol, 2 equiv). Stirring is initiated, and methyl iodide (26 μL, 0.42 mmol, 1.1 equiv) is added. The flask is let stir at ambient temperature 14 h. The reaction diluted with water (1 mL), transferred to a 25 mL separatory funnel, and extracted with diethyl ether (1 mL). The ether extract can be directly injected on the GC. A racemate for comparison was synthesized by substituting pyrrolidine for *(S)-1,1-diphenylprolinol trimethylsilyl ether* in the procedure discussed above. GC conditions: Column: Agilent CycloSil-B, 30 m, 0.25 mm, 0.25 μm, 112-6632 Agilent part # 19091J. GC: Agilent Technologies 7820A. Injector temp: 250 °C. Detector temp: 275 °C. Flow: 2 mL/min. Initial temp: 40 °C. Final Temp: 200 °C. Initial time: 1 min. Rate: 4 °C/min. T_{minor}: 21.186 min. T_{major}: 21.462 min.

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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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Discussion

α-Substituted β-hydroxy aldehydes and carboxylic acids are an important class of chiral building blocks that have proven useful in the synthesis of many biologically relevant molecules.[3] Current methods for the synthesis of such intermediates typically rely on the use of chiral auxiliaries as pioneered by Evans.[4] These methods can provide good stereoselectivity

but requires multiple manipulations and recycling of stoichiometric auxiliary, therefore, limiting scalability.

Direct asymmetric α-hydroxymethylation of aldehydes would provide one-step access to chiral α-substituded β-hydroxy aldehydes. Current methods to affect a direct asymmetric α-hydroxymethylation of an aldehyde rely on gaseous formaldehyde.[5] Other attempts at direct organocatalyzed hydroxymethylation have led to formation of elimination products owing to the unrecognized need to control the pH during the process and avoid the presence of acid.[6] Initial studies by our group indicated (*S*)-1,1-diphenylprolinol trimethylsilyl ether can catalyze the direct asymmetric α-hydroxymethylation of aldehydes.[7] Herein we report the direct asymmetric α-hydroxymethylation of isovaleraldehyde catalyzed by (*S*)-1,1-diphenylprolinol trimethylsilyl ether. Our method is mild, and tolerates a variety of functional groups including alkynes, aromatics, silylated alcohols and esters. The method uses easily handled aqueous formaldehyde, and employs a catalytic amount of a chiral catalyst, affording in one step a synthetically versatile chiral intermediate for further elaboration.

References

1. Department of Chemistry, University of Rochester, Rochester, NY 14627, email rkb@rkbmac.chem.rochester.edu.
2. Boeckman, Jr., R. K.; Tusch, D. J.; Biegasiewicz, K. F. *Org. Synth.* **2015**, *92*, 309-319.
3. For select examples, see: a) Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290–5313; b) Crimmins, M. T.; Carroll, C. A.; King, B. W. *Org. Lett.* **2000**, *2*, 597–599; c) Evans, D. A.; Connell, B. T. *J. Am. Chem. Soc.* **2003**, *125*, 10899–10905; d) Lister, T.; Perkins, M. V. *Angew. Chem., Int. Ed.* **2006**, *45*, 2560–2564.
4. a) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737–1739; b) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215–8216.
5. Casas, J.; Sundén, H.; Córdova, A. *Tetrahedron Lett.* **2004**, *45*, 6117–6119.
6. a) Erkkilä, A.; Pihko, P. M. *Eur. J. Org. Chem.* **2007**, 4205-4216.; b) Benohoud, M.; Erkkilä, A; Pihko, P. M. *Org. Synth.* **2010**, *87*, 201-208.
7. Boeckman, R. K.; Miller, J. R. *Org. Lett.* **2009,** *11* (20), 4544-4547.

Appendix
Chemical Abstracts Nomenclature (Registry Number)

(S)-1,1-Diphenylprolinol trimethylsilyl ether: (S)-(–)-α, α-Diphenyl-2-pyrrolidinemethanol trimethylsilyl ether; (848821-58-9)
pH 7 buffer: potassium phosphate dibasic and potassium phosphate monobasic; (7558-11-4) and (7778-77-0)
37% Aqueous formaldehyde solution; (50-00-0)
Isovaleraldehyde: 3-Methylbutyraldeyde; (590-86-3)
2-Methyl-2-butene: 2-methylbut-2-ene; (513-35-9)
Sodium chlorite; (7758-19-2)
Sodium phosphate, monobasic, monohydrate; (10049-21-5)
(R)-2-(Hydroxymethyl)-3-methylbutanoic acid; (72604-80-9)

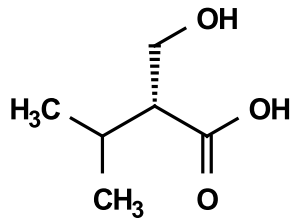
Robert K. Boeckman, Jr. received his Bachelors of Science degree in Chemistry in 1966 from Carnegie Institute of Technology (now Carnegie Mellon University). He moved on to Brandeis University where he received the Ph.D. degree under the supervision of James B. Hendrickson and Ernest Grunwald in 1971. He joined the research group of Gilbert Stork in 1970 as an NIH postdoctoral fellow. He began his academic career at Wayne State University in 1972, where he rose to the rank of Professor in 1979. In 1980, he joined the faculty of the University of Rochester where he is currently Marshall D. Gates Jr. Professor of Chemistry. His research interests lie primarily in the area of synthetic organic chemistry, both the development of new synthetic methodology and the total synthesis of complex substances of biological interest.

Douglas J. Tusch received his Bachelors of Science degree in Biochemistry from the Rochester Institute of Technology in 2010 where he researched alkaloid natural product synthesis under the guidance of Professor Jeremy Cody. He then joined the group of Professor Robert Boeckman at the University of Rochester and earned his M.S. in chemistry in 2012. He is currently pursuing a Ph.D. in Professor Boeckman's group studying the areas of total synthesis and organocatalysis.

Kyle F. Biegasiewicz received his Bachelors of Science in Chemistry from Niagara University in 2010, completing undergraduate research with Professor Ronny Priefer. He is currently a chemistry graduate student at the University of Rochester working under the tutelage of Professor Robert K. Boeckman, Jr. His graduate research areas include the total synthesis of natural products and organocatalysis.

Eduardo V. Mercado-Marin received his Bachelors of Science in Chemistry from the University of California, Santa Barbara in 2011, completing undergraduate research under the guidance of Professor Thomas R. R. Pettus. He is currently a chemistry graduate student at the University of California, Berkeley working with Professor Richmond Sarpong. His graduate research is focused on a unified approach to the total syntheses of prenylated indole alkaloid natural products.

AV-600 ZBO proton starting parameters 11/16/08 RN



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