Organic Syntheses

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.

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.

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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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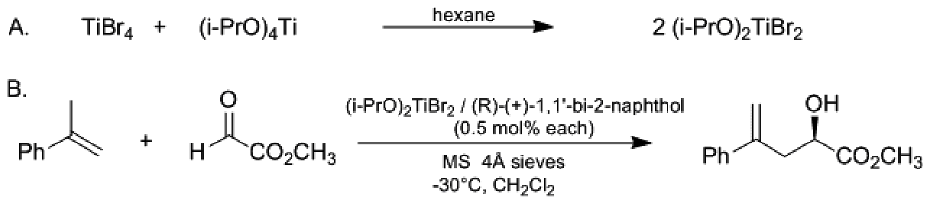
ASYMMETRIC CATALYTIC GLYOXYLATE-ENE REACTION: METHYL (2R)-2-HYDROXY-4-PHENYL-4-PENTENOATE

[Benzenebutanoic acid, α-hydroxy-γ-methylene, methyl ester, (R)-]



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Checked by Masami Okabe, Ruen-Chu Sun, and David L. Coffen.

1. Procedure

A. *Diisopropoxytitanium(IV) dibromide* (Note 1). A 50-mL, two-necked, round-bottomed pre-weighed flask equipped with a magnetic stirring bar, a rubber septum, and an argon inlet is charged with 20 mL of hexane (Note 2) and titanium(IV) bromide (7.3 g, 20 mmol) (Note 3). To the red-brown suspension is added titanium(IV) isopropoxide (5.9 mL, 20 mmol) (Note 4) slowly (~ 7 min) at ambient temperature from a syringe. The addition of titanium(IV) isopropoxide causes the mixture to warm to about 37°C. After stirring for 10 min, the now yellow solution is allowed to stand for 6 hr at room temperature, and the pale yellow precipitate that forms is isolated by removing the supernatant liquid with a syringe. The solid residue is then washed with hexane (5 mL × 2) and recrystallized from hexane (10 mL). Recrystallization is carried out in the same flask by heating the solution to reflux and then leaving it at room temperature overnight. Again the supernatant liquid is removed with a syringe and the crystalline residue is vacuum dried to give 5.7 g (44%) of yellow, *highly moisture sensitive* product. While still in the original flask, this product is dissolved in 88 mL of dry toluene to give a 0.2 M solution (Note 5).

B. *Methyl (2R)-2-hydroxy-4-phenyl-4-pentenoate*. A 100-mL, four-necked, round-bottomed flask equipped with a magnetic stirring bar, thermometer, two dropping funnels, and an argon inlet is charged with 20 mL of methylene chloride (Note 6) and (R)-(+)-1,1'-bi-naphthol (Note 7) (100 mg, 0.35 mmol). The suspension is stirred until the binaphthol is completely dissolved. Powdered molecular sieves 4 Å (2 g) (Note 8) are then added. To the resultant suspension is added a 0.2 M toluene solution of diisopropoxytitanium dibromide (1.75 mL, 0.35 mmol) by syringe at room temperature. After stirring for 1 hr at room temperature, the reaction mixture is cooled to −35°C. To the reaction mixture is added dropwise a mixture of α-methylstyrene (14 mL, 108 mmol) and methylene chloride (5 mL) followed by a solution of freshly distilled methyl glyoxylate (Note 9) (6.16 g, 70.0 mmol) in methylene chloride (20 mL) over 30 min. The mixture is stirred at −35° to −30°C (Note 10) for 6 hr. Progress of the reaction is monitored by thin layer chromatography (Note 11). Even after 6 hr, a small amount of unreacted methyl glyoxylate is detected. The solution is poured into saturated sodium hydrogen carbonate (30 mL). The molecular sieves are removed by filtration through a pad of Celite, and the filtrate is extracted with ethyl acetate (80 mL × 3). The combined organic layers are washed with brine (50 mL × 2). The extract is dried over magnesium sulfate and evaporated under reduced pressure. Fractional distillation gives 12.1 g (84%) of methyl 2-hydroxy-4-phenyl-4-pentenoate (Note 12) and (Note 13). The enantiomeric purity is 93–95% ee by HPLC analysis using a chiral column (Note 14) or by lanthanide induced shift (LIS) NMR measurement with (+)-Eu(dppm)$_3$ (Note 15) after conversion to the α-methoxy ester (Note 16).

2. Notes

1. Diisopropoxytitanium(IV) dibromide is prepared following the preparative procedure for diisopropoxytitanium(IV) dichloride.[2]

2. Hexane is freshly distilled from calcium hydride (CaH_2) or dried over 4 Å molecular sieves.
3. Titanium(IV) bromide is purchased from Aldrich Chemical Company, Inc. This material is very moisture sensitive and is therefore weighed and transferred under an argon blanket.
4. Titanium(IV) isopropoxide is purchased from Tokyo Kasei Co., Ltd. or Aldrich Chemical Company, Inc.
5. Storage of the solution in a refrigerator is recommended.
6. Methylene chloride is freshly distilled from CaH_2 or dried over 4 Å molecular sieves.
7. (R)-(+)-1,1'-Bi-2-naphthol is purchased from Wako Pure Chemical Industries Ltd. or Aldrich Chemical Company, Inc.
8. Molecular sieves 4 Å (activated powder) are purchased from Aldrich Chemical Company, Inc.
9. Methyl glyoxylate can be prepared following a literature procedure.[3] The checkers used commercial material supplied by Hoechst Celanese, Specialty Chemicals. Immediately before use, the material is depolymerized by vacuum distillation from phosphorus pentoxide (P_2O_5) (10% weight); bp 62°C/60 mm.
10. In order to achieve high chemical and optical yields, the reaction temperature must be kept in the range of −30 to −35°C.
11. E. Merck silica gel 60 F-254 plates are used, with 2:1 v/v hexane:ethyl acetate as eluent, $R_f = 0.4$ and iodine vapor for visualization.
12. The product has the following spectral and physical characteristics: IR (neat, KBr) cm^{-1}: 3450 (br,s), 2940 (s), 1730 (s), 1440 (m), 1030 (m), 910 (m), 780 (s), 710 (s); ^1H NMR (200 MHz, $CDCl_3$) δ: 2.76 (bs, 1 H, OH), 2.88 (dd, 1 H, J = 8.1, 13.5, CCH_2CH), 3.13 (dd, 1 H, J = 4.5, 13.5, CCH_2CH), 3.68 (s, 3 H, OCH_3), 4.33 (dd, 1 H, J = 4.5, 8.1, CHOH), 5.28 (m, 1 H, $C{=}CH_2$), 5.48 (m, 1 H, $C{=}CH_2$), 7.3–7.5 (m, 5 H, Ar); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 40.4 (t), 52.2 (q), 69.2 (d), 116.5 (t), 126.6 (d), 127.9 (d), 128.6 (d), 140.4 (s), 143.7 (s), 175.1 (s); $[\alpha]_D^{23}$ −30.55° ($CHCl_3$, *c* 4.83) for 97% ee R); m/z: Found M^+ 206.0936, $C_{12}H_{14}O_3$ requires M^+, 206.0943; mp 36–38°C.
13. Fractional distillation is carried out as follows: bp 105–106°C/0.2 mm; first fraction: 0.7 g, 5% (< 105°C); main fraction: 12.1 g, 84% (105–106°C); last fraction: 0.3 g, 2% (> 106°C).
14. SUMICHIRAL OA-2500I is available from Sumitomo Chemical Co., Ltd. The eluent was hexane/1,2-dichloroethane/ethanol, 200:40:1, with a flow rate of 0.5 mL/min, and detection by 254 nm light. The t_R of the (R)-isomer (16.8 min) is shorter than that of the (S)-isomer (18.3 min). The checkers used a CHIRACEL OC column supplied by Daicel Chemical Industries, Ltd., with 10% isopropyl alcohol/heptane as the mobile phase.
15. The shift reagent $Eu(dppm)_3$ (30 w/v% CCl_2FCClF_2 solution) is available from Daiichi Kagaku Yakuhin Co.[4]
A 10-μL sample of the α-methoxy ester is dissolved in 0.5 mL of $CDCl_3$ and transferred to an NMR tube. A 5-μL portion of (+)-$Eu(dppm)_3$ (30 w/v% CCl_2FCClF_2 solution) is added to the α-methoxy ester sample. The mixture is shaken well, and the ^1H NMR spectrum is recorded. Additional portions of the shift reagent solution are added in 5-μL portions until the methyl ether resonance shifts downfield beyond that of the methyl ester and shows baseline resolution of the methyl ester and methyl ether resonances from the two enantiomers. (Four singlets should be observed). In total 15–20 μL of the shift reagent solution should be required to achieve the desired shift. At that point, a chemical shift difference of the methyl esters (about 0.1 ppm) should be observed. The % ee is obtained by integration of the two methyl ester peaks. The chemical shifts of the α-methoxy groups of (R)-methoxy esters are lower than those of the (S)-isomers, and in contrast those of the methyl ester groups of (R)-methoxy esters are higher than those of the (S)-isomers.
16. The α-methoxy ester is prepared following a literature procedure:[5] To a mixture of methyl iodide (0.3 mL) and the ene product (104 mg, 0.50 mmol) in ether (1–2 mL) is added silver(I) oxide (0.23 g). The reaction mixture is stirred for 1 day at room temperature. The suspension is filtered through a pad of Celite and the filtrate is evaporated under reduced pressure. Chromatographic purification of the residue gives the α-methoxy ester in quantitative yield (110 mg).

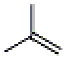
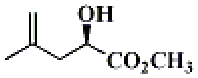
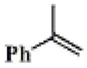
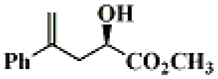
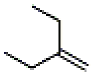
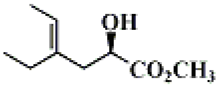
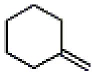
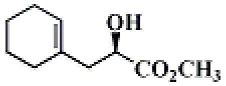
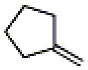
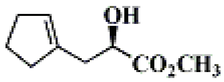
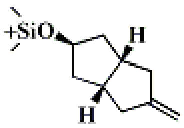
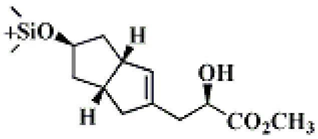
Waste Disposal Information

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

3. Discussion

A full account[5] describes the enantioselective carbonyl-ene reaction of glyoxylate esters catalyzed by a binaphthol-derived chiral titanium complex that is potentially useful for the asymmetric synthesis of α-hydroxy esters of biological and synthetic importance.[6,7,8,9] The present procedure is applicable to a variety of 1,1-disubstituted olefins to provide ene products in extremely high enantiomeric purity by the judicious choice of the dichloro or dibromo chiral catalyst (see Table). In certain glyoxylate-ene reactions involving removal of a methyl hydrogen, the dichloro catalyst is superior to the dibromo catalyst in enantioselectivity, although lower in reactivity (see Table, entries A and B). In reactions involving removal of a methylene hydrogen, the dibromo catalyst is superior in both enantioselectivity and reactivity (see Table, entries C, D, and E); the dibromo catalyst provides a higher % ee, while both catalysts provide equally high (ca. 90%) E selectivity (see Table, entry C). Since both (R)- and (S)-binaphthol are commercially available in optically pure form, the present asymmetric process allows the synthesis of both enantiomers of α-hydroxy esters and their derivatives.

TABLE
ASYMMETRIC CATALYTIC GLYOXYLATE-ENE REACTIONS WITH 1,1-DISUBSTITUTED OLEFINS[a]

Entry	Olefin	(i-PrO)$_2$TiX$_2$	Catalyst mol%	Time hr	Product	% Yield	%ee$_b$
A		Cl	10	8		72	95 R
						68	95 S[c]
		Br	10	3		87	94 R
B		Cl	1.0	8		97	97 (R)
		Br	1.0	3		98	95 (R)
C		Cl	10	8		68[d]	94[e](R)
		Br	5	3		73[f]	98[e](R)
D		Cl	10	8		82	97 (R)
		Br	5	3		89	98 (R)
E		Cl	10	8		93	88 (R)
		Br	5	3		92	89 (R)
F		Cl	10	3		77[g]	99[h](R)
		Br	10	3		100[g]	99[h](R)

[a] All reactions were run on

scale pf 1 mmol of methyl glyoxylate by the representative procedure described in the text. [b]Determined as described in (Note 14) and/or (Note 15). The configuration in parenthesis could be assigned by the similarity in shift pattern seen in the LIS-NMR spectra using (+)-Eu(dppm)$_3$ as a chiral shift reagent. [c] (S)-BINOL was used instead of the (R)-counterpart. [d]Combined yield of the (E)- and (Z)-isomer (E/Z = 89 : 11). [e]Refers to the optical purity of the major (E)-product. [f]Combined yield of the (E)- and (Z)-isomer (E/Z = 91 : 9). [g]Combined yield of the diastereomeric mixture (96 : 4). [h]Refers to the optical purity of the major isomer.

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

GLYOXYLATE-ENE

brine

methylene hydrogen

ethanol (64-17-5)

ethyl acetate (141-78-6)

ether (60-29-7)

sodium hydrogen carbonate (144-55-8)

silver(I) oxide (20667-12-3)

1,2-dichloroethane (107-06-2)

iodine (7553-56-2)

methyl hydrogen (7782-42-5)

toluene (108-88-3)

isopropyl alcohol (67-63-0)

Methyl iodide (74-88-4)

methylene chloride (75-09-2)

magnesium sulfate (7487-88-9)

heptane (142-82-5)

hexane (110-54-3)

α-methoxy (2143-68-2)

argon (7440-37-1)

calcium hydride (7789-78-8)

α-methylstyrene (98-83-9)

phosphorus pentoxide (1314-56-3)

titanium(IV) isopropoxide (546-68-9)

binaphthol

(R)-(+)-1,1'-Bi-2-naphthol (18531-99-2)

Methyl (2R)-2-hydroxy-4-phenyl-4-pentenoate,
Benzenebutanoic acid, α-hydroxy-γ-methylene, methyl ester, (R)- (119072-58-1)

Diisopropoxytitanium(IV) dibromide,
diisopropoxytitanium dibromide

titanium(IV) bromide (7789-68-6)

(R)-(+)-1,1'-bi-naphthol

methyl glyoxylate (922-68-9)

methyl 2-hydroxy-4-phenyl-4-pentenoate

diisopropoxytitanium(IV) dichloride