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.

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.

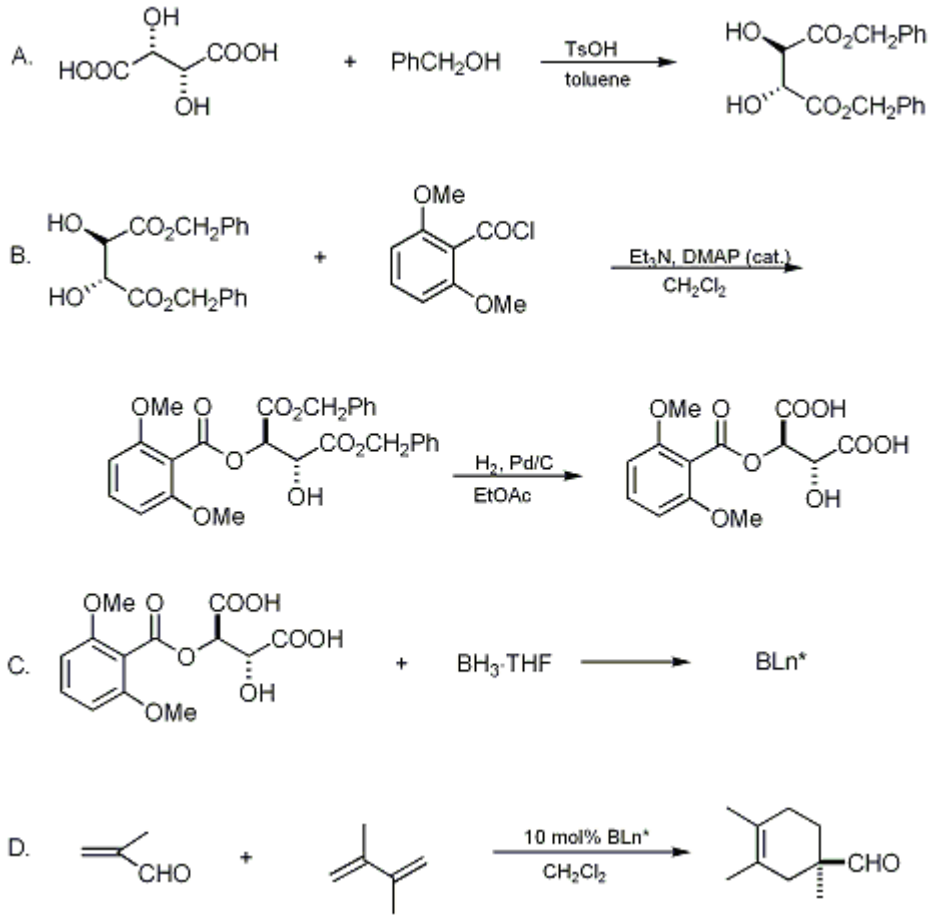
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.072.0086

Organic Syntheses, Coll. Vol. 9, p.722 (1998); Vol. 72, p.86 (1995).

CHIRAL (ACYLOXY)BORANE COMPLEX-CATALYZED ASYMMETRIC DIELS-ALDER REACTION: (1R)-1,3,4-TRIMETHYL-3-CYCLOHEXENE-1-CARBOXALDEHYDE

[3-Cyclohexene-1-carboxaldehyde, 1,3,4-trimethyl-, (−)-]



Submitted by Kyoji Furuta, Qing-Zhi Gao, and Hisashi Yamamoto[1].
Checked by Stephane Borrelly and Leo A. Paquette.

1. Procedure

A. *(−)-Dibenzyl tartrate*. A 300-mL, one-necked, round-bottomed flask is equipped with a magnetic stirrer, Dean-Stark trap, and a reflux condenser. The flask is charged with 3.0 g (20 mmol) of L-(+)-tartaric acid, 6.5 g (60 mmol) of benzyl alcohol, 47.5 mg (0.25 mmol) of p-toluenesulfonic acid monohydrate, and 40 mL of toluene (Note 1). The mixture is heated under reflux in an oil bath (about 130°C) for 13 hr. During this period the theoretical amount of water (0.62 mL) is collected. The mixture is allowed to cool to ambient temperature, diluted with ether, and poured into 50 mL of aqueous, saturated sodium bicarbonate. The organic phase is separated and the aqueous phase is extracted twice with 20 mL of ether. The combined organic phases are dried over sodium sulfate. The solvent is removed with a rotary evaporator, and the resulting crude product is triturated with hexane-ether (20:1, 210 mL) to give white crystals of (−)-dibenzyl tartrate. The precipitate is collected by filtration and washed with hexane-ether (20:1). The filtrate is further concentrated to give a second crop. The total yield is 6.2 g (94%), mp 49–50°C (Note 2).

B. *Mono(2,6-dimethoxybenzoyl)tartaric acid*. In a 250-mL, three-necked, round-bottomed flask,

equipped with a nitrogen inlet, a reflux condenser and a magnetic stirring bar are placed 6.1 g (18.5 mmol) of dibenzyl tartrate, 100 mL of dry dichloromethane, 4 mL (28.8 mmol) of triethylamine and 50 mg (0.4 mmol) of 4-(dimethylamino)pyridine. The stirred mixture is cooled to 0°C and 3.65 g (18.2 mmol) of 2,6-dimethoxybenozyl chloride (Note 3) is added portion-wise over 1 hr. The reaction mixture is then warmed to room temperature and refluxed for 12 to 18 hr (the reaction is easily monitored by TLC). The reaction mixture is then allowed to cool down to room temperature and poured in 100 mL of water, The aqueous phase is extracted with 2 × 75 mL of dichloromethane. The organic phases are combined, dried over sodium sulfate, filtered and concentrated to give a viscous oil. This is purified by column chromatography on silica gel using a mixture of hexane, ether and dichloromethane (3:1:5) as eluent (Note 4) to afford 7.1–7.5 g (78–82%) of a clear oil identified as dibenzyl mono(2,6-dimethoxybenzoyl)tartrate (Note 5). A 200-mL, pressure bottle is flushed with dry argon and charged with 5.8 g (11.7 mmol) of the above tartrate, 100 mL of ethyl acetate, and 580 mg of 10% palladium on charcoal (Note 6). The argon is then replaced by hydrogen and the reaction mixture is shaken on a Parr apparatus at 20 psi and room temperature for several hours (Note 7). The mixture is filtered through a pad of Celite and the filtrate is concentrated with a rotary evaporator, and dried completely under vacuum (80°C, ≤ 1 mm, overnight) (Note 8) to afford 3.5 g (97%) of mono(2,6-dimethoxybenozyl) tartaric acid as colorless solid, mp 184–186°C (Note 9). This material is practically pure and is used in Parts C, D without purification.

C. D. *(1R)-1,3,4-Trimethyl-3-cyclohexene-1-carboxaldehyde*. A 100-mL, three-necked, round-bottomed flask containing a magnetic stirring bar is equipped with a rubber septum and a three-way stopcock with an argon inlet. The air is displaced by repeated flushing with dry argon. The flask is charged with 1.57 g (5 mmol) of mono(2,6-dimethoxybenzoyl)tartaric acid obtained in Part B and 50 mL of dry dichloromethane (Note 10), and cooled in an ice bath. Through the septum, with a syringe, is added dropwise 3.57 mL (5 mmol) of borane-THF solution (1.40 M) at 0°C over a period of 30 min (Note 11). The reaction mixture is stirred for 15 min at 0°C and then cooled to −78°C in a dry ice-methanol bath. To this solution is added 4.14 mL (50 mmol) of freshly distilled methacrolein (Note 12) via a syringe dropwise. After the addition is complete, 8.49 mL (75 mmol) of 2,3-dimethyl-1,3-butadiene (Note 13) is introduced to the solution at the same temperature and the mixture is stirred for 12 hr. The cold reaction mixture is poured into 150 mL of ice-cold saturated sodium bicarbonate and the product is extracted with three 200-mL portions of hexane (Note 14). The combined organic phases are washed with brine (2 × 200 mL) (Note 15), dried over sodium sulfate, filtered, and concentrated at atmospheric pressure. The residue is distilled at reduced pressure to afford 6.53 g (86%) of (1R)-1,3,4-trimethyl-3-cyclohexene-1-carboxaldehyde as a colorless liquid, bp 92–93°C (23 mm) (Note 16).

2. Notes

1. L-(+)-Tartaric acid, benzyl alcohol, and p-toluenesulfonic acid monohydrate were purchased from Wako Pure Chemical Industries, Ltd. (Japan). Guaranteed-grade toluene was dried and stored over sodium metal.
2. The physical properties are as follows: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.15 (d, 2 H, J = 7.5), 4.6 (d, 2 H, J = 7.5), 5.27 (s, 4 H), 7.35 (s, 10 H); $[\alpha]_D^{24}$ −10.2° ($CHCl_3$, *c* 1.03).
3. 2,6-Dimethoxybenzoyl chloride was purchased from the Aldrich Chemical Company, Inc. and was used without purification.
4. The purity of the ligand depends largely on the purity of the dibenzyl ester. Flash chromatography was carried out with silica gel purchased from Merck (Kieselgel 60, Art. 9385). For TLC analysis, Merck silica gel F-254 TLC plates were used, with 3:1:5 hexane-ether-dichloromethane as eluent. Dibenzyl mono(2,6-dimethoxybenzoyl)tartrate has an R_f of ca. 0.35 in this solvent system.
5. The physical properties are as follows: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.24 (d, 1 H, J = 9), 3.7 (s, 6 H), 4.89 (dd, 1 H, J = 2.5 and 9), 5.08–5.34 (4 H), 5.99 (d, 1 H, J = 2.5), 6.53 (d, 2 H, J = 8.5), 7.25–7.4 (m, 11 H); $[\alpha]_D^{24}$ −60.1° ($CHCl_3$, *c*., 1.15).
6. Ethyl acetate was obtained from Wako Pure Chemical Industries and was used without purification. The 10% palladium on charcoal was purchased from Aldrich Chemical Company, Inc.
7. This requires 4–12 hr, depending on catalyst conditions. Progress of the reaction can be monitored by TLC.
8. Thorough drying is essential to obtain the % ee as described.
9. The physical properties are as follows: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 3.63 (s, 6 H), 4.61 (d, 1 H, J =

2), 5.61 (d, 1 H, J = 2), 6.38 (d, 2 H, J = 9), 7.13 (t, 1 H, J = 9); $[\alpha]_D^{24}$ −73.0° (EtOH, *c* 1.03).
10. Dichloromethane was purchased from Wako Pure Chemical Industries and was dried over Linde-type 4 Å molecular sieves.
11. Borane–THF complex was obtained from Toso-Akzo Chemical Company, Ltd. in Japan and should be titrated before use. Vigorous evolution of hydrogen is observed during addition of borane–THF solution to the reaction mixture.
12. Methacrolein from Tokyo Kasei Kogyo Company, Ltd. was dried with calcium sulfate and distilled through a 20-cm Vigreux column under argon prior to use.
13. 2,3-Dimethyl-1,3-butadiene was purchased from Tokyo Kasei Kogyo Company, Ltd. and was distilled before use.
14. The tartaric acid ligand can be recovered (1.52 g, 97%) from the aqueous phase by an acidification-extraction (4 N HCl-ethyl acetate) sequence. The material is essentially pure for future use.
15. Careful washing with brine is important to avoid foaming during distillation.
16. The physical properties are as follows: ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.99 (s, 3 H), 1.3–2.1 (m, 5 H), 1.56 (s, 3 H), 1.61 (s, 3 H), 2.23 (br d, 1 H, J = 17), 9.43 (s, 1 H); $[\alpha]_D^{23}$ −64.1° ($CHCl_3$, *c* 1.0). The optical purity of this adduct was 95% as determined by 200 MHz ^{1}H NMR spectroscopy and GC analysis (capillary column PEG, 0.25 mm × 25 m, purchased from Gaskuro Kogyo Company, Ltd. in Japan) after conversion to the corresponding chiral acetal as follows: A solution of the adduct, (2R,4R)-(−)-pentanediol (1.2 equiv, obtained from Wako Pure Chemical Industries), triethyl orthoformate (1.2 equiv), and p-toluenesulfonic acid monohydrate (as a 5 mM solution) in dry benzene is stirred at ambient temperature for 3 hr. The mixture is poured into saturated sodium bicarbonate and the product is extracted with ether. The combined organic phases are dried over sodium sulfate and concentrated on a rotary evaporator. The residue is purified by flash column chromatography on silica gel using hexane-ethyl acetate (25:1) as eluent to give the acetal quantitatively; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.83 (s, 3 H), 1.15 (d, 3 H, J = 6), 1.28 (d, 3 H J = 6.5), 1.56 (s, 6 H), 1.2–2.06 (m, 8 H), 3.86 (m, 1 H), 4.27 (m, 1 H), 4.42 (s, 1 H; diastereomer at 4.45).

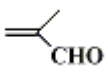
Waste Disposal Information

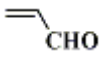
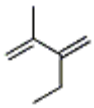
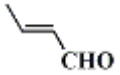
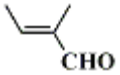
All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The procedure described here provides a simple and general method for the construction of optically active 3-cyclohexene-1-carboxaldehydes.[2,3] The reaction has been applied successfully to a series of α,β-unsaturated aldehydes with dienes (Table). Several methods are described in the literature for asymmetric Diels-Alder reactions of chiral α,β-unsaturated esters or amides;[4,5,6,7] little is reported, however, for the reaction of achiral, simple aldehydes.[8,9,10,11,12] The present method is characterized as a true catalytic process (only 10 mol % of chiral catalyst is needed), with good chemical and high optical yields, simple operation, preparation of both enantiomers with equal ease, and the ready availability of the starting materials.

TABLE
CHIRAL ACYLOXYBORANE CATALYZED ASYMMETRIC DIELS-ALDER REACTION

Dienophile	Diene	Temp (°C)	Yield (%)	Isomers endo/exo	ee (%)
		−78	85	11/89	96
		−78	84[a]	10/90	96
		−78	61	-	97
		−78	38	97/3[b]	93

		−40	65	98/2[b]	91
		−20	40	93/7	82
		−78	90	88/12	84
		−78	46	>99/1	80
		−78	53	-	84
		−78	53	90/10	2
		−78	91	3/97	90

[a](2S,3S)-Tartaric acid derivative was used as a chiral ligand.
[b]Ratio of regioisomers.

References and Notes

1. Department of Applied Chemistry, School of Engineering, Nagoya University, Chikusa, Nagoya 464–01, Japan.
2. Furuta, K.; Shimizu, S.; Miwa, Y.; Yamamoto, H. *J. Org. Chem.* **1989**, *54*, 1481;
3. Furuta, K.; Kanematsu, A.; Yamamoto, H.; Takaoka, S. *Tetrahedron Lett.* **1989**, *30*, 7231.
4. Paquette, L. A. In "Asymmetric Synthesis"; Morrison, J. D., Ed.; Academic Press: Orlando, 1984; Vol. 3;
5. Helmchen, G.; Karge, R.; Weetman, J. Mod. Synth. Methods **1986**, *4*, 261–306;
6. Bosnich, B., Ed. "Asymmetric Catalysis", Martinus Nijhoff Publishers: Dordrecht, Kluwer Academic Publishers: Boston; 1986;
7. Oppolzer, W. *Tetrahedron* **1987**, *43*, 1969.
8. Hashimoto, S.-i.; Komeshima, N.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1979**, 437;
9. Bir, G.; Kaufmann, D. *Tetrahedron Lett.* **1987**, *28*, 777;
10. Takemura, H.; Komeshima, N.; Takahashi, I.; Hashimoto, S-i.; Ikota, N.; Tomioka, K.; Koga, K. *Tetrahedron Lett.* **1987**, *28*, 5687;
11. Takasu, M.; Yamamoto, H. *Synlett* **1990**, 194;
12. Sartor, D.; Saffrich, J.; Helmchen, G. *Synlett* **1990**, 197.

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

brine

palladium on charcoal

3-Cyclohexene-1-carboxaldehyde, 1,3,4-trimethyl-, (−)-

(−)-Dibenzyl tartrate

2,6-dimethoxybenozyl chloride

mono(2,6-dimethoxybenozyl)tartaric acid

(2R,4R)-(−)-pentanediol

Benzene (71-43-2)

ethyl acetate (141-78-6)

ether (60-29-7)

hydrogen (1333-74-0)

sodium bicarbonate (144-55-8)

sodium sulfate (7757-82-6)

calcium sulfate (7778-18-9)

toluene (108-88-3)

sodium (13966-32-0)

Benzyl alcohol (100-51-6)

tartaric acid,
L-(+)-tartaric acid (87-69-4)

triethyl orthoformate (122-51-0)

dichloromethane (75-09-2)

borane (7440-42-8)

tartrate

THF (109-99-9)

2,3-DIMETHYL-1,3-BUTADIENE (513-81-5)

hexane (110-54-3)

triethylamine (121-44-8)

methacrolein (78-85-3)

argon (7440-37-1)

4-(dimethylamino)pyridine (1122-58-3)

p-toluenesulfonic acid monohydrate (6192-52-5)

dibenzyl tartrate (622-00-4)

Mono(2,6-dimethoxybenzoyl)tartaric acid (116212-44-3)

dibenzyl mono(2,6-dimethoxybenzoyl)tartrate (158732-36-6)

(1R)-1,3,4-Trimethyl-3-cyclohexene-1-carboxaldehyde (130881-20-8)

2,6-Dimethoxybenzoyl chloride (1989-53-3)

Mono(2,6-dimethoxybenzoyl)tartrate