Organic Syntheses

A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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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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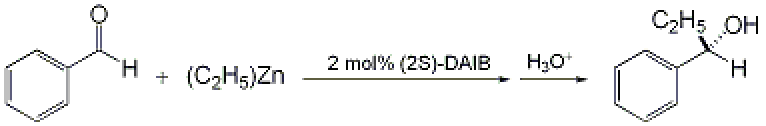
CATALYTIC ENANTIOSELECTIVE ADDITION OF DIALKYLZINCS TO ALDEHYDES USING (2S)-(−)-3-exo-(DIMETHYLAMINO)ISOBORNEOL [(2S)-DAIB]: (S)-1-PHENYL-1-PROPANOL

[Benzenemethanol, α-ethyl-, (S)-]



Submitted by Masato Kitamura, Hiromasa Oka, Seiji Suga, and Ryoji Noyori[1] .
Checked by David E. Kaelin, Stephen F. Martin, Gregory L. Beutner, and Scott E. Denmark.

1. Procedure

Caution! Since DAIB deteriorates in air, bottles of DAIB should be flushed with N_2 or Ar and kept tightly closed for storage over long periods. Diethylzinc easily catches fire upon contact with air or moisture and addition to benzaldehyde should be performed under anaerobic conditions using degassed solvent.

A dry, 500-mL Schlenk tube, equipped with a rubber septum and a Teflon-coated stirring bar and filled with argon (Note 1) is charged with (2S)-(−)-3-exo-(dimethylamino)isoborneol [(2S)-DAIB] (371 mg, 1.88 mmol) (Note 2), dry toluene (200 mL) (Note 3), and a 4.45 M toluene solution of diethylzinc (25.4 mL, 113 mmol) through a rubber septum using hypodermic syringes at 20°C (Notes 4 and 5). The mixture is stirred for 15 min and then cooled to −78°C with a dry ice-methanol bath. To this is added benzaldehyde (10.0 g, 94.2 mol) (Note 6) in one portion (Note 7). The bath is replaced by an ice bath, and the septum is replaced by a glass stopper. The reaction mixture is stirred at 0°C for 6 hr in a closed system. The glass stopper is removed under an argon stream, and saturated aqueous ammonium chloride solution (40 mL) is carefully added (Note 5), resulting in the formation of a white precipitate. The liquid layer and the solid phase are roughly separated by decantation. The precipitate is washed with ether (100 mL), and the combined liquid layers and 2 M aqueous hydrochloric acid solution (100 mL) are transferred to a 1-L separatory funnel. The aqueous layer is separated and extracted twice with ether (100 mL) (Note 8). The combined organic layers (ca. 550 mL) are washed with water (50 mL) and brine (50 mL), dried over anhydrous sodium sulfate , and concentrated under reduced pressure. The crude residue is distilled at 150-155°C and 20 mm Hg using a Kugelrohr apparatus to give 12.4 g of (S)-1-phenyl-1-propanol (97% yield) in 95.4% ee as a colorless oil (Notes 9 and 10).

2. Notes

1. Argon gas (99.998%) is used without further purification. The Schlenk tube and syringes are dried overnight at 150°C.
2. Supplied by Professor James D.White Oregon State University;[2] see previous procedure, p.130.
3. Toluene is first distilled from sodium benzophenone ketyl under argon. Prior to the reaction, the toluene is degassed by performing two freeze-pump-thaw cycles, then the flask is backfilled with argon.
4. A stock solution of diethylzinc is prepared in an 80-mL Schlenk tube equipped with a Young's tap by mixing toluene and 99% diethylzinc [(16.5 g, 134 mmol) in a lecture bottle, which is purchased from Aldrich Chemical Company, Inc.] to make a total volume of 30 mL.
5. Ethane gas evolution is observed.
6. Benzaldehyde, which is purchased from Aldrich Chemical Company, Inc., is purified by distillation from 4 Å molecular sieves (70.5-71.5°C/20 mmHg) and kept in a Schlenk tube equipped with a Young's

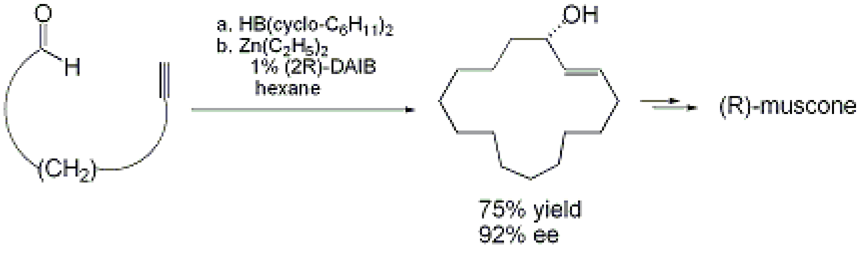
tap.
7. The solution becomes a pale yellow color; the color fades after 6 hr.
8. (2S)-DAIB (312 mg) is recovered in 77–84% yield from the aqueous layer. To the aqueous layer (pH <2), cooled with an ice bath, is added 6 M aqueous sodium hydroxide solution (60 mL). The mixture, which has a pH of >12, is extracted three times with ether (50 mL). The combined organic layers are washed with water (20 mL) and brine (20 mL), dried over anhydrous sodium sulfate , and concentrated under reduced pressure to give a colorless oil.
9. The product, which contains 2-3% of benzyl alcohol and 2-3% of propiophenone , has the following physical properties: $[\alpha]_D{}^{21}$ −45.6° $CHCl_3$, c 5.55); ^1H NMR (400 MHz, $CDCl_3$) δ: 0.91 (t, 3, J = 7.3, CH_3), 1.68-1.88 (m, 2, CH_2), 1.90-1.95 (m, 1, OH), 4.58 (td, 1, J = 6.4, 3.4, OCH), 7.21-7.38 (5, aromatic protons) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 10.1, 31.9, 76.0, 125.9, 127.5, 128.4, 144.6 .
10. The enantiomeric purity is determined by chiral stationary phase, supercritical fluid chromatographic (CSP-SFC) analysis (Berger Instruments, Daicel Co. CHIRALCEL OD column; 4% methanol , 180 psi, 3.0 mL/min flow rate; detection at 220 nm). Racemic 1-phenylpropanol exhibited base-line separation of peaks of equal intensity arising from the R-isomer (t_R 2.74 min) and the S-isomer (t_R 3.10 min) whereas the synthetic alcohol showed these peaks in the ratio 97.7 / 2.3. This chromatographic method allowed for identification of the trace contaminants propiophenone (t_R 1.63 min) and benzyl alcohol (t_R 3.40 min).
11. The submitters used HPLC analysis to determine the enantiomeric purity (Daicel Co. CHIRALCEL OB column; 99.5/0.5 hexane/2-propanol mixture, 1.0 mL/min flow rate; detection at 254-nmS-isomer t_R 19.2 min, R-isomer t_R 24.6 min)). Under these conditions, however, the propiophenone contaminant is coincident with the S-enantiomer thus affording unreliable enantiomeric analysis.

Waste Disposal Information

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

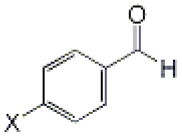
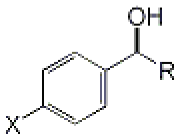
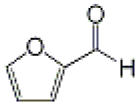
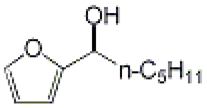
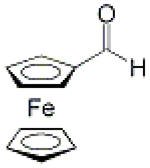
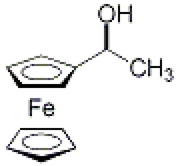
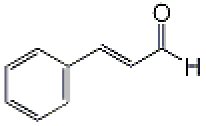
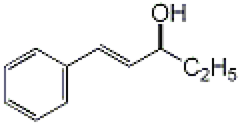
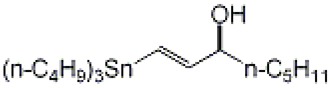
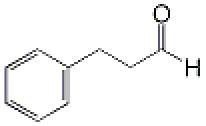
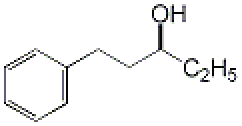
3. Discussion

(2S)-DAIB, a chiral β-dialkylamino alcohol, serves as an efficient catalyst for enantioselective addition of diethylzinc to benzaldehyde in toluene , hexane , ether , or their mixtures, giving (S)-1-phenyl-1-propanol in up to 99% ee.[3] [4] This catalytic enantioselective alkylation can be extended to a range of alkylating agents and aldehyde substrates, as illustrated in the Table. Dimethyl-, diethyl-, and other simple dialkylzinc agents can be used as alkylating agents. p-Substituted benzaldehydes give the corresponding secondary alcohols with consistently high enantioselectivity. 2-Furaldehyde is alkylated with di-n-pentylzinc in the presence of (2S)-DAIB to give (1S)-1-(2-furyl)hexan-1-ol , a versatile compound in organic synthesis, with >95% ee. Optically active 1-ferrocenylethanol , a key compound for the synthesis of a wide variety of chiral ferrocene derivatives, is obtained in 81% optical yield by methylation of ferrocenecarboxaldehyde . Certain α,β-unsaturated and aliphatic aldehydes can also be alkylated in moderate to high optical yield. The (2S)-DAIB-catalyzed addition of di-n-pentylzinc to (E)-3-tributylstannylpropenal proceeded with an S:R selectivity of 93:7 to afford a key chiral building block that was used in the three-component coupling step of a prostaglandin synthesis. The DAIB-catalyzed reaction of (1-alkenyl)ethylzincs, prepared by transmetalation of (1-alkenyl)dicyclohexylboranes with diethylzinc , plays a key role in the asymmetric syntheses of muscone and aspicilin.[5] Polystyrene-anchored DAIB can also be used as a chiral auxiliary for enantioselective reactions.[6]



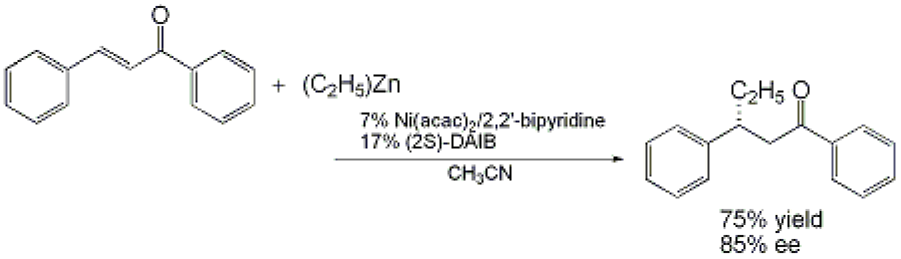
TABLE

(2S)-DAIB-PROMOTED ENANTIOSELECTIVE ADDITION OF DIORGANOZINCS TO ALDEHYDES[3,4]

Aldehyde	Diorganozinc	Product	% Yield	% ee
 X = H	$(CH_3)_2Zn$	 R = CH_3	95	95
	$(C_2H_5)_2Zn$	R = C_2H_5	97	98
	$(n\text{-}C_4H_9)_2Zn$	R = $n\text{-}C_4H_9$	88	95
X = Cl	$(C_2H_5)_2Zn$	R = C_2H_5	86	93
X = CH_3O	$(C_2H_5)_2Zn$	R = C_2H_5	96	93
	$(n\text{-}C_5H_{11})_2Zn$		80	>95
	$(CH_3)_2Zn$		60	81
	$(C_2H_5)_2Zn$		81	96
	$(n\text{-}C_5H_{11})_2Zn$		84	85
	$(C_2H_5)_2Zn$		80	90

Dramatic chiral amplification is observed in alkylations catalyzed by partially resolved DAIB.[7] Reaction of benzaldehyde and diethylzinc in toluene containing 8 mol% of (2S)-DAIB of 15% ee leads to (S)-1-phenyl-1-propanol in 95% ee, a value close to the 98% ee obtained with enantiomerically pure (2S)-DAIB.

A combined system consisting of a Ni(II) complex and (2S)-DAIB effects the conjugate addition of diethylzinc to chalcone , resulting in the formation of (R)-1,3-diphenylpentan-1-one in 85% ee.[8]



This preparation is referenced from:

- Org. Syn. Coll. Vol. 10, 305

References and Notes

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

(2S)-3-exo-Aminoisoborneol:
Bicyclo[2.2.1]heptan-2-ol, 3-amino-1,7,7-trimethyl-, [1R-(exo,exo)]; (41719-73-7)

(2S)-3-exo-(Dimethylamino)isoborneol:
Bicyclo[2.2.1]heptan-2-ol, 3-(dimethylamino)-

1,7,7-trimethyl-, [1R-(exo,exo)]; (103729-96-0)

(S)-1-Phenyl-1-propanol:
Benzenemethanol, .alpha.-ethyl-, (S)-; (613-87-6)

(R)-1-Phenyl-1-propanol:
Benzenemethanol, .alpha.-ethyl-, (R)-; (1565-74-8)

(±)-1-Phenyl-1-propanol:
Benzenemethanol, .alpha.-ethyl-, (93-54-9)

Benzaldehyde:
Benzaldehyde; (100-52-7)