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THE SYNTHESIS OF (+)- AND (—)-2,3-*O*-ISOPROPYLIDENE-2,3-DIHYDROXY-1,4-BIS(DIPHENYLARSINO)BUTANE AND THEIR USE IN ASYMMETRIC CATALYSIS

AUBREY D. CALHOUN, WALTER J. KOBOS, TERENCE A. NILE * and CRYSTAL A. SMITH

Chemistry Department, University of North Carolina at Greensboro, Greensboro, North Carolina, 27412 (U.S.A.)

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Summary

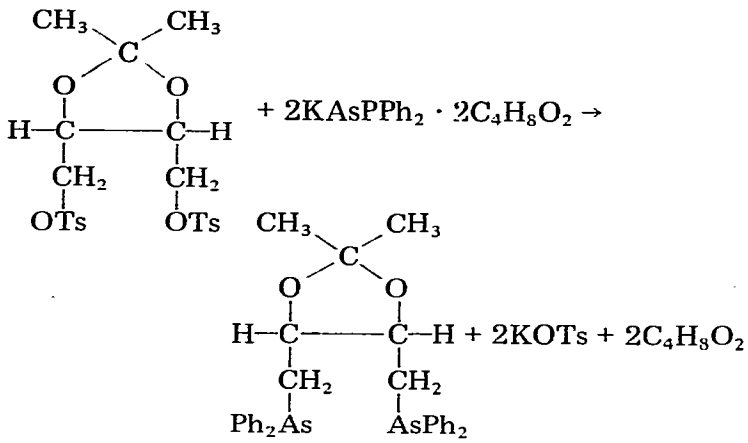
(+)- and (—)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylarsino)butane, the arsenic analogs of (+)- and (—)-diop have been synthesized in good yields. These ligands give similar optical yields to diop in the asymmetric hydrosilylation of ketones, but lower optical yields for the asymmetric hydrogenation of α-acetamidocinnamic acid, but, in this case, yield the isomer having the opposite configuration to diop.

Introduction

Asymmetric catalysis using transition metal complexes with chiral ligands is a synthetic technique showing great promise. Optical yields approaching 100% have been obtained with bidentate phosphines that are chiral at phosphorus [1], or with the chirality residing in the organic moiety attached to phosphorus [2]. We wish to report the synthesis of (+)- and (—)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylarsino)butane [(+)- and (—)-diarsop]. These ligands are the arsenic analogs of diop [3a] and dios [3b].

Synthesis of (+)- and (—)-diarsop

(+)-Diarsop was synthesized by the reaction of 1,4-ditosyl-2,3-*O*-isopropylidene-D-threitol [4] with potassium diphenylarsenide dioxanate [5] in a mixture of THF and dioxane at 5—15°C (eq. 1). The resultant oil was recrystallized with difficulty from hexane to yield white, air stable, crystals of (+)-diarsop (overall yield 58%, $[\alpha]_D^{20}$ + 31.6 (*c* 2.8, benzene), melting point 68—69°C). (—)-Diarsop was synthesized in a similar fashion from 1,4-ditosyl-2,3-*O*-isoprop-

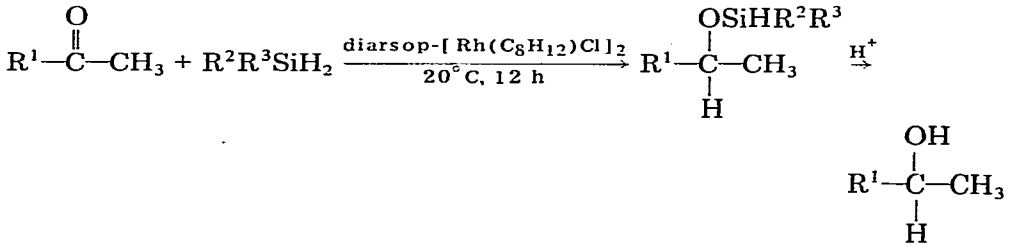


(1)

ylidene-L-threitol [4] as white, air stable, crystals (melting point 64—66°C, $[\alpha]_D^{20}$ —27.6 (*c* 2.8, benzene)).

Asymmetric reduction of ketones

The ligands were utilized in the asymmetric hydrogenation of ketones by means of hydrosilylation followed by acid cleavage of the silyl ether (eq. 2).

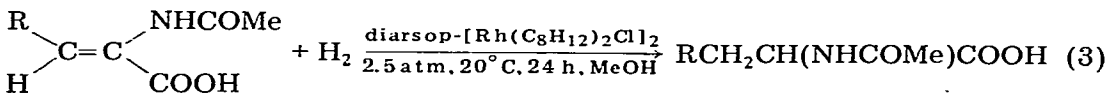


(2)

(R^1 = Ph, t-Bu, i-Bu; R^2 = R^3 = Ph, Et; R^2 = Ph, R^3 = Me)

Asymmetric hydrogenation of α,β-unsaturated acids

We have also utilized (+)- and (—)-diarsop to catalyze the hydrogenation of α,β-unsaturated acids, under mild conditions, using a catalyst generated in situ from $[Rh(1,5\text{-}C_8H_{12})_2Cl]_2$ and diarsop (Rh/diarsop/acid = 1/1/80) (eq. 3). The catalyst solution was prepared from diarsop and $[Rh(1,5\text{-}C_8H_{12})Cl]_2$ in benzene with a Rh/diarsop ratio of 1/1. The cleavage of the silyl ether was carried out using hydrochloric acid/acetone [6]. The alcohols were isolated in moderate to good chemical yield (35—80%). The optical yields are summarized in Table 1. Optical yields in the range 10—42% were obtained dependent on the ketone and silane used. The optical yields are comparable to those obtained with diop, and as with diop, (+)-diarsop yields *S*-alcohols and (—)-diarsop yields *R*-alcohols.



(3)

(R = Ph, H).

TABLE 1

ASYMMETRIC REDUCTION OF KETONES VIA HYDROSILYLATION USING diarsop-Rh [a]

Ketone	Silane	Ligand	Alcohol $[\alpha]_D^{20}$	Configuration	Optical [b] yield (%)
PhCOMe	$PhMeSiH_2$	(—)-Diarsop	+5.5° [c]	*R*	10
PhCOMe	$PhMeSiH_2$	(+)-Diarsop	—6.7° [c]	*S*	13
PhCOMe	Ph_2SiH_2	(—)-Diarsop	+10.4° [c]	*R*	20
PhCOMe	Ph_2SiH_2	(+)-Diarsop	—13.5° [c]	*S*	26
PhCOMe	Et_2SiH_2	(—)-Diarsop	+21.8° [c]	*R*	42
PhCOMe	Et_2SiH_2	(+)-Diarsop	—18.5° [c]	*S*	35
t-BuCOMe	Et_2SiH_2	(—)-Diarsop	—2.4° [c]	*R*	31
t-BuCOMe	Et_2SiH_2	(+)-Diarsop	+1.7° [c]	*S*	22
i-BuCOMe	Et_2SiH_2	(+)-Diarsop	+5.0° [c]	*S*	20

[a] Catalyst solution: $[Rh(C_8H_{12})Cl]_2$ (2.7×10^{-2} mmol) and diarsop (5.1×10^{-2} mmol) in 3 ml of benzene. Solution of 15 mmol ketone and 15 mmol silane added to catalyst solution cooled with an ice bath and allowed to warm to 20°C. [b] Optical yield calculated from the specific rotation of the pure enantiomer: *S*-PhMeCH(OH), $[\alpha]_D^{23}$ —52.50 (CH_2Cl_2, *c* 2.27) [8]; *S*-t-BuMeCH(OH), $[\alpha]_D^{20}$ + 7.84° (neat) [9]; *S*-i-BuMeCH(OH), $[\alpha]_D^{25}$ + 24.6° (neat) [10].

Using (—)-diarsop and *Z*-α-acetamidocinnamic acid (R = Ph), the product worked up in the normal manner [2], had a specific rotation $[\alpha]_D^{20}$ + 8.64 (*c* 1.0, CH_3OH) corresponding to an optical yield of 21% of *N*-acetyl-*S*-phenylalanine [2]. The chemical yield was moderate (37%) but could be made essentially quantitative by the addition of triethylamine (Et_3N/Rh = 14/1), with a slight increase in optical yield (27%). The optical yields are lower than those obtained with (—)-diop and the isomer formed has the opposite configuration; (—)-diop yielding *N*-acetyl-*R*-phenylalanine [3]. Hydrogenation of 2-acetamidoacrylic acid (R = H) using (—)-diarsop yields *N*-acetyl-*S*-alanine in good chemical, but disappointing optical yields (Table 2), whereas (—)-diop gives the *R*-derivative [7]. This is surprising as both (+)-diop [6] and (+)-diarsop give *S*-alcohols upon hydrogenation of ketones via hydrosilylation. Increasing the

TABLE 2

ASYMMETRIC HYDROGENEATION OF α, β, -UNSATURATED ACIDS [a]

α, β-Unsaturated acid	Ligand	Solvent	Molar ratio of Et_3N/Rh	Chemical yield (%) [b]	$[\alpha]_D^{20}$	Optical yield (%) [c]
α-Acetamidocinnamic acid	(—)-Diarsop	Methanol	0	37	+8.64	21
α-Acetamidocinnamic acid	(—)-Diarsop	Methanol	14	100	+10.7	27
α-Acetamidocinnamic acid	(—)-Diarsop	Methanol	80	50	+15.4	39
α-Acetamidocinnamic acid	(—)-Diarsop	Methanol	500	0	—	—
α-Acetamidocinnamic acid	(+)-Diarsop	Methanol	14	100	—5.0	12
α-Acetamidocinnamic acid	(+)-Diarsop	THF	14	0	—	—
2-Acetamidoacrylic acid	(—)-Diarsop	Ethanol	14	89	—5.2	8
2-Acetamidoacrylic acid	(+)-Diarsop	Ethanol	14	80	+2.9	4

[a] Catalyst solution: $[Rh(C_8H_{12})_2Cl]_2$ (13 mg, 2.6×10^{-2} mmol) and diarsop (30 mg, 5.1×10^{-2} mmol) in 3 ml of benzene, added to a hydrogenation flask containing 1.0 g of acid (α-acetamidocinnamic acid, 4.1 mmol; 2-acetamidoacrylic acid, 8.0 mmol) in solvent (25 ml), under H_2; pressurized to 2.5 atm for 24 h at room temperature. [b] Calculated by NMR. [c] Optical yield calculated from the specific rotation of the pure enantiomers [2].

ratio of Et_3N/Rh beyond 14/1 causes a slight increase in optical yield, but this is offset by a rapidly decreasing chemical yield (Table 2). The catalyst solutions in these cases becoming black, perhaps due to decomposition to metallic rhodium. Use of THF as a solvent also causes catalyst decomposition.

As would be expected, substitution of (+)-diarsop for (—)-diarsop causes formation of *N*-acetyl-*R*-phenylalanine and *N*-acetyl-*R*-alanine (Table 2).

Experimental

General procedures

All reactions were carried out under pure nitrogen or argon, using freshly distilled, dry liquids. The silanes were commercial samples or prepared by standard methods. The ketones, *Z*-α-acetamido cinnamic acid, and 2-acetamidoacrylic acid were commercial samples which were purified by distillation or recrystallization before use. ^{1}H NMR were recorded on a Varian Associates T60 spectrometer. Analytical gas chromatography was carried out on a Varian Autograph A-700 "Autoprep" Gas Chromatograph, using a 6 ft. column of 10% SE30 on Chromosorb G. Optical rotations were obtained with a Perkin—Elmer 241 polarimeter or a Rudolph polarimeter. Microanalyses were performed by Integral Microanalytical Laboratories, Inc. of Raleigh, North Carolina.

Preparation of (+)-2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylarsino)butane

A solution of 1,4-ditosyl-2,3-*O*-isopropylidene-D-threitol [4] (2.35 g, 5.00 mmol) in 6 ml of THF was added dropwise to a cooled solution (5—15°C) of potassium diphenylarsenide dioxanate [5] (4.85 g, 10.9 mmol) in 20 ml of dioxane and 15 ml THF, over a period of 45 minutes. The solution was allowed to warm to room temperature and stirred for a further 2 h. The white precipitate was filtered under nitrogen and washed with 25 ml of benzene. The washings were combined with the filtrate and the solvents removed under vacuum to leave an oil. The oil was recrystallized with difficulty from hexane to yield white crystals of (+)-diarsop (1.71 g, 2.91 mmol, yield 58%), m.p. 68—69°C, $[\alpha]_D^{20}$ + 31.6, (*c* 2.8, benzene). Found: C, 62.82; H, 5.41. $C_{31}H_{32}O_2As_2$ calcd.: C, 63.49; H, 5.50%. ^{1}H NMR ($CDCl_3$): τ(ppm) 8.72 [6 H, singlet, $C(CH_3)_2$], 7.80 (4 H, doublet, *J* 6 Hz, CH_2), 6.10 (2 H, broad multiplet, CH), 2.67 (20 H, broad singlet, C_6H_5).

Preparation of (—)-2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylarsino)butane

(—)-Diarsop was isolated from the reaction of 1,4-ditosyl-2,3-isopropylidene-L-threitol with potassium diphenylarsenide dioxanate using an analogous procedure, as white crystals, m.p. 64—66°C, $[\alpha]_D^{20}$ —27.6 (*c* 2.8, benzene). Found: C, 62.90; H, 5.35. $C_{31}H_{32}O_2As_2$ calcd.: C, 63.49; H, 5.50%. ^{1}H NMR ($CDCl_3$): τ(ppm) 8.60 [6 H, singlet, $C(CH_3)_2$], 7.55 (4 H, doublet, *J* 6 Hz, CH_2), 6.03 (2 H, broad multiplet, CH), 2.65 (20 H, broad singlet, C_6H_5).

Hydrosilylation of ketones

a. Preparation of catalyst solution. The catalyst solution was prepared by the

reaction of $[Rh(1,5\text{-}COD)Cl]_2$ with diarsop, using a standard procedure [11]. Typically, (+)- or (—)-diarsop (30 mg, 5.1×10^{-2} mmol) and $[Rh(C_8H_{12})Cl]_2$ (13 mg, 2.6×10^{-2} mmol) were dissolved in 3 ml of benzene and allowed to stir at room temperature for 15 minutes.

b. Hydrosilylation of acetophenone by diphenylsilane. A solution of diphenylsilane (2.7 g, 15 mmol) and acetophenone (1.8 g, 15 mmol) in 5 ml of benzene was added dropwise to the catalyst solution cooled in ice. The reaction mixture was allowed to warm to room temperature and stirred overnight. A solution of 4 ml of 10% hydrochloric acid in 20 ml of acetone was added to the reaction mixture to hydrolyze the silyl ether. The layers were separated, and the organic layer dried over calcium sulfate. Solvents were removed under vacuum and vacuum distillation yielded 1-phenylethanol (1.2 g, 67%), b.p. 50/1 mmHg, identified by its ^1H NMR spectrum, containing traces of acetophenone. The optical rotation was determined and is included in Table 1.

All other hydrosilylations were carried out in an analogous fashion with chemical yields of 35—80%. The optical yields are included in Table 1.

Hydrogenation of Z-α-acetamidocinnamic acid

Z-α-Acetamidocinnamic acid (1.00 g, 4.1 mmol) was placed in an hydrogenation flask, under hydrogen and 25 ml of methanol and triethylamine (73 mg, 0.72 mmol) added. The catalyst solution, prepared from (—)-diarsop (30 mg, 5.1×10^{-2} mmol) and $[Rh(C_8H_{12})Cl]_2$ (13 mg, 2.6×10^{-2} mmol) in 3 ml of benzene, was added, the flask pressurized with hydrogen to 2.5 atm, and left at room temperature overnight. The solvents were removed under vacuum, and the extent of reaction determined by ^1H NMR in dimethylsulfoxide-d_6. The optical rotation was determined by dissolving the product in methanol.

Hydrogenations of 2-acetamidoacrylic acid were carried out in a similar manner.

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