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A New Method for the Synthesis of H₄-BINOL

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Abstract

A method amenable to the gram scale synthesis of (*R*)-H₄-BINOL, a derivative of (*R*)-BINOL and ligand of interest in asymmetric catalysis, is described. The key step is the net partial hydrogenation of (*R*)-BINOL made possible by prior bis-etherification of the parent BINOL.

A versatile ligand which has found widespread use in asymmetric catalysis is BINOL (*S*)-**1** and (*R*)-**1**.¹ Both BINOL enantiomers are commercially available or can be synthesized from inexpensive starting materials in enantioenriched form ($\geq 98:2$ *er*), or as a racemic mixture followed by subsequent optical resolution.^{1,2,3} The BINOL enantiomers have been extensively used as chiral ligands in catalysis, especially in combination with Ti(IV) salts. The BINOL/Ti(IV) system catalyzes a number of asymmetric reactions¹ including allyl and Mukaiyama aldol additions to aldehydes,^{4,5} hetero Diels-Alder reactions,^{6,7} ene-reactions,⁸ reduction of ketones and aldehydes,^{9,10} and oxidation of sulfides.¹¹

(S)-BINOL ((S)-1)

(R)-BINOL ((R)-1)

While the parent BINOL **1** works well as a ligand in a number of catalytic asymmetric systems, several modified versions of BINOL have been utilized in attempts to further improve such reactions.^{1b} One modification has been achieved by a formal partial hydrogenation of BINOL **1** to give H₄-BINOL **2** and H₈-BINOL **3**.

(*R*)-H₄-BINOL ((*R*)-2) **(*R*)-H₈-BINOL ((*R*)-3)**

Both the H₄-BINOL **2** and H₈-BINOL **3** ligands have been shown to work well in a number of catalytic asymmetric reactions¹² including the addition of alkylzinc and alkylaluminum reagents to aldehydes and the Hetero-Diels-Alder addition using Danishefsky's diene.¹³ In addition, the enantioselectivities obtained with these ligands surpassed those observed for reactions using the parent BINOL **1** as a ligand.

Recently, we were interested in examining the use of H₈-BINOL and H₄-BINOL in an asymmetric vinylogous Mukaiyama aldol reaction catalyzed by BINOL/Ti(OiPr)₄(BITIP).^{5a} While H₈-BINOL is commercially available, to our knowledge, H₄-BINOL is not. Moreover, the only published method for the preparation of H₄-BINOL involves heating a mixture of Ni/Al alloy, NaOH, H₂O, *i*PrOH and MOM₂-BINOL to 80 °C for 24 h at a concentration of 3 μmol/L (ca. 1L of solvent for 1g of substrate) followed by protective group removal, including chromatographic purification following each operation.¹⁴ The prospect of using the above process for a gram to multigram scale synthesis of H₄-BINOL **3** led us to examine the development of an alternative procedure.

H₈-BINOL **3** has been accessed from BINOL **1** using several different hydrogenation conditions;^{15,16} among these, a straightforward procedure appeared to be the partial hydrogenation of either BINOL enantiomer **1** using Adam's catalyst (PtO₂·(H₂O)_x) in AcOH, under three atmospheres of H₂, which provides enantiomerically pure H₈-BINOL.¹⁶

We initially hypothesized that H₄-BINOL **2** could be a possible intermediate in the hydrogenation of BINOL **1** using Adam's catalyst in AcOH. Therefore, we decided to perform this hydrogenation under only one atmosphere of H₂ with the intention of intercepting H₄-BINOL **2**. However, in the event, only BINOL **1** and H₈-BINOL **3** could be detected by TLC or HPLC analysis.

We next considered the use of a sterically demanding substituent on one of the two BINOL hydroxyls.

The '*i*Pr' group was selected as a bulky substituent and introduced to BINOL (**R**)-**1** with K₂CO₃ in dry acetone (Scheme 1). The hydrogenation was carried out in AcOH using Adam's catalyst and one atmosphere of H₂. The ¹H NMR of the crude product revealed that, as expected, *i*Pr-H₈-BINOL (**R**)-**7** had formed as a byproduct. In addition, two other isomers were present which were later identified as compounds **5** and **6**. Deprotection of the crude mixture using BBr₃ yielded H₄-BINOL (**R**)-**2** and H₈-BINOL (**R**)-**3**.¹⁷

The isolation of some H₄-BINOL (**R**)-**2** was encouraging, and we decided to investigate the influence of a second '*i*Pr' ether (Scheme 2). The hydrogenation of *i*Pr₂-BINOL (**R**)-**8** using the same conditions was slower compared to the hydrogenation of *i*Pr-BINOL (**R**)-**4**. TLC analysis revealed the initial formation of *i*Pr₂-H₄-BINOL; the appearance of *i*Pr₂-H₄-BINOL was followed by the development of *i*Pr₂-H₈-BINOL. The reaction was worked up and the

crude material deprotected with BBr₃ yielding H₄-BINOL (**R**)-**2** as the major product together with some H₈-BINOL (**R**)-**3**. See Scheme II.

The overreduction yielding H₈-BINOL (**R**)-**3** was undesired but appears to be inherent to this hydrogenation. The amount of H₈-BINOL (**R**)-**3** could be kept low by monitoring the reaction progress and stopping the hydrogenation at the first appearance of *i*Pr₂-H₈-BINOL. We were able to obtain yields of up to 82% of H₄-BINOL (**R**)-**2** following this hydrogenation-deprotection sequence (see Experimental Section and Supporting Information).¹⁸ In practice, the reduction was monitored by HPLC using small neutralized and filtered aliquots of the reaction mixture, and the reaction was terminated at 50% conversion.

Adam's catalyst appears to be unique in its ability to catalyze this hydrogenation.¹⁹ A number of other heterogeneous catalysts were tested for their ability to hydrogenate *i*Pr₂-BINOL (**R**)-**8**; however, an 8% yield of *i*Pr₂-H₄-BINOL using 5% Rh/C was found to be the best result.²⁰

The preparation of H₄-BINOL (**R**)-**2** using *i*Pr₂-BINOL (**R**)-**8** and Adam's catalyst represents a convenient method to access this interesting ligand. The hydrogenation is operationally simple and is amenable for gram-scale syntheses of H₄-BINOL (**R**)-**2**. This preparation uses a much higher substrate concentration (0.1 M vs 3 μM) than the only other available method, and only one final chromatographic purification is required, as opposed to two. The formation of *i*Pr₂-H₈-BINOL as a byproduct appears to be inherent to the reaction conditions; however, this side reaction can be suppressed by stopping the hydrogenation at the first appearance of *i*Pr₂-H₈-BINOL.

Experimental Section

Preparation of (*R*)-5,6,7,8-tetrahydro-[1,1']binaphthalenyl-2,2'-diol (*R*)-**2**¹⁴ and (*R*)-5,6,7,8,5',6',7',8'-octahydro-[1,1']binaphthalenyl-2,2'-diol (*R*)-**3**.^{15,16}

To a 500 mL round-bottom flask equipped with a stirbar at room temperature were added (*R*)-*i*Pr₂-BINOL (**R**)-**8** (1.00 g, 2.70 mmol, 1.00 eq), glacial acetic acid (27 mL, 0.10 M), and PtO₂·(H₂O)_x (0.066 g, 0.27 mmol, 0.10 eq). The flask was flushed with a stream of dry nitrogen and equipped with an adapter with a valve and a balloon filled with hydrogen. The valve was opened and the mixture exposed to a hydrogen atmosphere (balloon, ca. 1 atm). The progress of the reaction was closely monitored by TLC and/or HPLC since reaction time and composition were found to be strongly dependent on the activity of the active catalyst which was generated in situ. After 5 h the flask was flushed with a dry stream of nitrogen and the mixture diluted with a solution of saturated aqueous NaOH (14 mL) followed by slow addition of saturated aqueous NaHCO₃ solution (200 mL) until evolution of gas stopped. The mixture was extracted with 50% EtOAc/hexanes (100, 150 and 200 mL), and the organic phase washed with water (50 and 100 mL) and brine (50 mL), dried over Na₂SO₄, then filtered and concentrated under reduced pressure. The residue was dissolved in CH₂Cl₂ (50 mL) and transferred into a 250 mL round-bottom flask equipped with a stirbar, rubber septum, and nitrogen inlet. Boron tribromide (2.5 mL, 27 mmol, 10.0 eq) was added at room temperature followed after 10 min by slow addition of aqueous NaOH solution (0.75 M, 50 mL). The organic phase was washed with saturated aqueous NH₄Cl solution (50 mL), water (50 and 100 mL) and brine (50 mL), then dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on a 3 × 21 cm silica gel column eluting with a solvent gradient from 1% through 5% acetone/hexanes. The product containing fractions were concentrated to give (*R*)-H₄-BINOL (**R**)-**2** (0.644 g, 2.22 mmol, 82% yield) and (*R*)-H₈-BINOL (**R**)-**3** (127 mg, 0.431 mmol, 16% yield) as white solids. Analytical data for **2**: mp 128 °C (lit¹⁴ mp 131-133), R_f 0.23 (25% EtOAc/hexanes), [α]_D²⁰ +40.2 (c 1.01, THF), (lit¹⁴

$[\alpha]_D^{25} +40.4$, (c 0.98, THF)); 300 MHz ^1H NMR (CDCl_3) δ 7.90 - 7.83 (m, 2H), 7.42 - 7.23 (m, 4H), 7.12 (d, J = 8.3 Hz, 1H), 6.89 (d, J = 8.3 Hz, 1H), 5.23 (s, 1H), 4.54 (s, 1H), 2.84 - 2.72 (m, 2H), 2.33 - 2.05 (m, 2H), 1.79 - 1.55 (m, 4H); 75 MHz ^{13}C NMR (CDCl_3) δ 152.4, 152.0, 138.5, 133.1, 131.6, 131.0, 130.4, 129.5, 128.5, 127.5, 124.1, 123.9, 117.7, 117.5, 113.4, 112.6, 29.4, 27.2, 23.1, 23.1; 75 MHz DEPT (CDCl_3) δ CH_2 : 29.4, 27.2, 23.1 (2). CH: 131.6, 131.0, 128.6, 127.5, 124.1, 123.9, 117.7, 113.4. C: 152.4, 152.0, 138.5, 133.1, 130.4, 129.5, 117.5, 112.6; IR (neat) 3478, 3414, 3057, 2929, 2857, 1619, 1595, 1475, 1389, 1189, 1147, 817, 752 cm^{-1} ; HRMS (ESI/APCI) Calcd for $\text{C}_{20}\text{H}_{19}\text{O}_2$ m/z (M+H): 291.1385. Found: 291.1390. Only the (R) enantiomer was detected by HPLC analysis using a chiral column (see Supporting Information).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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SCHEME 1. Results with *i*Pr-BINOL (R)-4

SCHEME 2. Synthesis of H₄-BINOL (*R*)-2