JOC*Note*

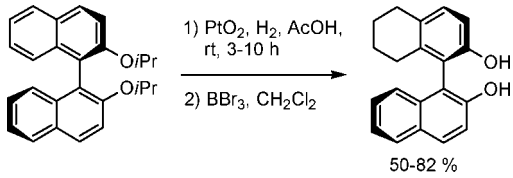
A New Method for the Synthesis of H_4-BINOL

Lars V. Heumann and Gary E. Keck*

Department of Chemistry, University of Utah, 315 South 1400 East, Room 2020, Salt Lake City, Utah 84112-0850

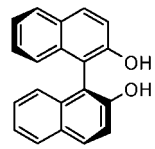
keck@chemistry.utah.edu

Received February 26, 2008

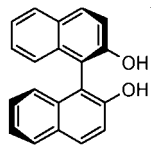


A method amenable to the gram scale synthesis of (*R*)-H_4-BINOL, a derivative of (*R*)-BINOL and ligand of interest in asymmetric catalysis, is described. The key step is the net partial hydrogenation of (*R*)-BINOL made possible by prior bis-etherification of the parent BINOL.

A versatile ligand that 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 (≥98:2 er), or as a racemic mixture followed by subsequent optical resolution.[1–3] 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 reactions[1] 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]

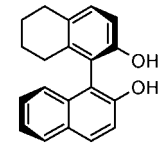


(*S*)-BINOL ((*S*)-1)

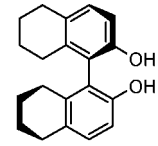


(*R*)-BINOL ((*R*)-1)

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 H_4-BINOL **2** and H_8-BINOL **3**.



(*R*)-H_4-BINOL ((*R*)-2)



(*R*)-H_8-BINOL ((*R*)-3)

Both the H_4-BINOL **2** and H_8-BINOL **3** ligands have been shown to work well in a number of catalytic asymmetric reactions[12] including the addition of alkylzinc and alkylaluminum reagents to aldehydes and the hetero-Diels−Alder addition with Danishefsky's diene.[13] In addition, the enantioselectivities obtained with these ligands surpassed those observed for reactions with the parent BINOL **1** as a ligand.

Recently, we were interested in examining the use of H_8-BINOL and H_4-BINOL in an asymmetric vinylogous Mukaiyama aldol reaction catalyzed by BINOL/Ti(OiPr)$_4$ (BITIP).[5a] While H_8-BINOL is commercially available, to our knowledge, H_4-BINOL is not. Moreover, the only published method for the preparation of H_4-BINOL involves heating a mixture of Ni/Al alloy, NaOH, H_2O, *i*PrOH, and MOM$_2$-BINOL to 80 °C for 24 h at a concentration of 3 μmol/L (ca. 1 L of solvent for 1 g 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 H_4-BINOL **3** led us to examine the development of an alternative procedure.

H_8-BINOL **3** has been accessed from BINOL **1** by using several different hydrogenation conditions;[15,16] among these, a

(1) (a) For a recent comprehensive review on the preparation and the use of BINOL as a ligand, see: Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857. (b) For a recent review on modified BINOL derivatives with some information on the parent BINOL, see: Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003**, *103*, 3155.

(2) (a) Brussee, J.; Groenendijk, J. L. G.; Koppele, J. M.; Jansen, A. C. A. *Tetrahedron* **1985**, *41*, 3313. (b) Brussee, J.; Jansen, A. C. A. *Tetrahedron Lett.* **1983**, *24*, 3261.

(3) For oxidative coupling of 2-naphthol, see: (a) Villemin, D.; Sauvaget, F. *Synlett* **1994**, 435. (b) Love, B. E.; Bills, R. A. *Synth. Commun.* **2002**, *32*, 2067. (c) Ji, S. J.; Lu, J.; Zhu, X.; Yang, J.; Lang, J. P.; Wu, L. *Synth. Commun.* **2002**, *32*, 3069. For the optical resolution of racemic BINOL, see: (d) Colonna, S.; Re, A.; Wynberg, H. *J. Chem. Soc., Perkin Trans.* **1981**, *1*, 547. (e) Cai, D.; Hughes, D. L.; Verhoeven, T. R.; Reider, P. *Tetrahedron Lett.* **1995**, *36*, 7991.

(4) (a) Keck, G. E.; Krishnamurthy, D.; Roush, W. R.; Reilly, M. L. *Org. Synth.* **1998**, *75*, 12. (b) Keck, G. E.; Geraci, L. S. *Tetrahedron Lett.* **1993**, *34*, 7827. (c) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467. (d) Keck, G. E.; Krishnamurthy, D.; Grier, M. C. *J. Org. Chem.* **1993**, *58*, 6543.

(5) (a) Heumann, L. V.; Keck, G. E. *Org. Lett.* **2007**, *9*, 4275. (b) Keck, G. E.; Krishnamurthy, D. *J. Am. Chem. Soc.* **1995**, *117*, 2363.

(6) (a) Terada, M.; Mikami, K.; Nakai, T. *Tetrahedron Lett.* **1991**, *32*, 935. (b) Mikami, K.; Terada, M.; Motoyama, Y.; Nakai, T. *Tetrahedron: Asymmetry* **1991**, *2*, 643.

(7) (a) Keck, G. E.; Krishnamurthy, D. *Synth. Commun.* **1996**, *26*, 367. (b) Keck, G. E.; Li, X.-Y.; Krishnamurthy, D. *J. Org. Chem.* **1995**, *60*, 5998.

(8) (a) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1989**, *111*, 1940. (b) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949.

(9) Keck, G. E.; Krishnamurthy, D. *J. Org. Chem.* **1996**, *61*, 7638.

(10) Imma, H.; Mori, M.; Nakai, T. *Synlett* **1996**, 1229.

(11) Komatsu, N.; Hashizume, M.; Sugita, T.; Uemura, S. *J. Org. Chem.* **1993**, *58*, 4529.

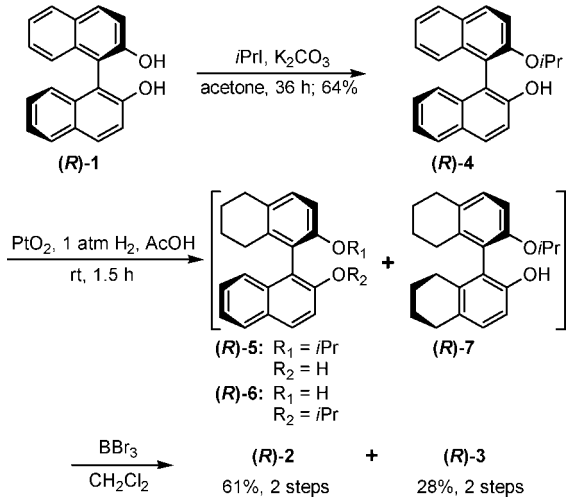
(12) (a) Iida, T.; Yamamoto, N.; Matsunaga, S.; Woo, H.-G.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2223. (b) Lin, Y.-M.; Fu, I.-P.; Uang, B.-J. *Tetrahedron: Asymmetry* **2001**, *12*, 3217. (c) Kim, J. G.; Camp, E. H.; Walsh, P. J. *Org. Lett.* **2006**, *8*, 4413.

(13) (a) Wang, B.; Feng, X.; Huang, Y.; Liu, H.; Cui, X.; Jiang, Y. *J. Org. Chem.* **2002**, *67*, 2175. (b) Chan, A. S. C.; Zhang, F.-Y.; Yip, C.-W. *J. Am. Chem. Soc.* **1997**, *119*, 4080. (c) Zhang, F.-Y.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 3651. (d) Long, J.; Hu, J.; Shen, X.; Ji, B.; Ding, K. *J. Am. Chem. Soc.* **2002**, *124*, 10.

(14) Shen, X.; Guo, H.; Ding, K. *Tetrahedron: Asymmetry* **2000**, *11*, 4321.

10.1021/jo8004556 CCC: $40.75
Published on Web 05/20/2008

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



straightforward procedure appeared to be the partial hydrogenation of either BINOL enantiomer **1** with Adam's catalyst ($PtO_2 \cdot (H_2O)_x$) in AcOH, under 3 atm of H_2, which provides enantiomerically pure H_8-BINOL.[17]

We initially hypothesized that H_4-BINOL **2** could be a possible intermediate in the hydrogenation of BINOL **1** with Adam's catalyst in AcOH. Therefore, we decided to perform this hydrogenation under only 1 atm of H_2 with the intention of intercepting H_4-BINOL **2**. However, in the event, only BINOL **1** and H_8-BINOL **3** could be detected by TLC or HPLC analysis.

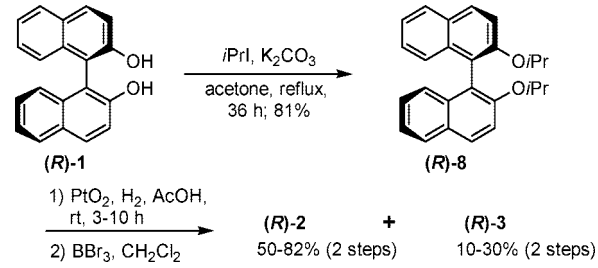
We next considered the use of a sterically demanding substituent on one of the two BINOL hydroxyls.

The "*i*Pr" group was selected as a bulky substituent and introduced to BINOL (***R***)-**1** with K_2CO_3 in dry acetone (Scheme 1). The hydrogenation was carried out in AcOH with use of Adam's catalyst and 1 atm of H_2. The ^1H NMR of the crude product revealed that, as expected, *i*Pr-H_8-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 with BBr_3 yielded H_4-BINOL (***R***)-**2** and H_8-BINOL (***R***)-**3**.[17]

The isolation of some H_4-BINOL (***R***)-**2** was encouraging, and we decided to investigate the influence of a second "*i*Pr" ether (Scheme 2). The hydrogenation of iPr_2-BINOL (***R***)-**8** with the same conditions was slower compared to the hydrogenation of *i*Pr-BINOL (***R***)-**4**. TLC analysis revealed the initial formation of iPr_2-H_4-BINOL; the appearance of iPr_2-H_4-BINOL was followed by the development of iPr_2-H_8-BINOL. The reaction was worked up and the crude material deprotected with BBr_3 yielding H_4-BINOL (***R***)-**2** as the major product together with some H_8-BINOL (***R***)-**3**. See Scheme 2.

The overreduction yielding H_8-BINOL (***R***)-**3** was undesired but appears to be inherent to this hydrogenation. The amount

SCHEME 2. Synthesis of H_4-BINOL (*R*)-2



of H_8-BINOL (***R***)-**3** could be kept low by monitoring the reaction progress and stopping the hydrogenation at the first appearance of iPr_2-H_8-BINOL. We were able to obtain yields of up to 82% of H_4-BINOL (***R***)-**2** following this hydrogenation–deprotection sequence (see the Experimental Section and the Supporting Information).[18] In practice, the reduction was monitored by HPLC with use of 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 iPr_2-BINOL (***R***)-**8**; however, an 8% yield of iPr_2-H_4-BINOL with 5% Rh/C was found to be the best result.[20]

The preparation of H_4-BINOL (***R***)-**2** with use of iPr_2-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 H_4-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 iPr_2-H_8-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 iPr_2-H_8-BINOL.

Experimental Section

Preparation of (*R*)-5,6,7,8-Tetrahydro-[1,1′]binaphthalenyl-2,2′-diol (*R*)-2.[15] and (*R*)-5,6,7,8,5′,6′,7′,8′-Octahydro-[1,1′]binaphthalenyl-2,2′-diol (*R*)-3.[16,17] To a 500 mL round-bottomed flask equipped with a stirbar at room temperature were added (*R*)-iPr_2-BINOL (***R***)-**8** (1.00 g, 2.70 mmol, 1.00 equiv), glacial acetic acid (27 mL, 0.10 M), and $PtO_2 \cdot (H_2O)_x$ (0.066 g, 0.27 mmol, 0.10 equiv). 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 that was generated in situ. After 5 h

(15) (a) Guo, H.; Ding, K. *Tetrahedron Lett.* **2000**, *41*, 10061. (b) Karam, O.; Martin-Mingot, A.; Jouannetaud, M.-P.; Jacquesy, J.-C.; Cousson, A. *Tetrahedron* **2004**, *60*, 6629. (c) Korostylev, A.; Tararov, V. I.; Fischer, C.; Monsees, A.; Boerner, A. *J. Org. Chem.* **2004**, *69*, 3220.

(16) (a) Cram, D. J.; Helgeson, R. C.; Peacock, S. C.; Kaplan, L. J.; Domeier, L. A.; Moreau, P.; Koga, K. M.; Mayer, J.; Chao, Y.; Siegel, M. G.; Hoffman, D. H.; Sogah, G. D. Y. *J. Org. Chem.* **1978**, *43*, 1930. (b) McDougal, N. T.; Trevellini, W. L.; Rodgen, S. A.; Kliman, L. T.; Schaus, S. E. *Adv. Synth. Catal.* **2004**, *346*, 1231. (c) Reetz, M.; Merk, C.; Naberfeld, G.; Rudolph, J.; Griebenow, N.; Goddard, R. *Tetrahedron Lett.* **1997**, *38*, 5273.

(17) Sala, T.; Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2593.

(18) With use of the same batch of Adam's catalyst, the activity of the reduced Adam's catalyst was found to be somewhat variable. Adam's catalyst is a precatalyst consisting of PtO_2, and its exposure to H_2 generates the active Pt(0)-catalyst in situ. As a rule of thumb, the generation of fine black particles resulted in a highly active catalyst whereas the reaction was found to be slow when the particles stuck to the wall of the flask or bonded together to form small spheres.

(19) *The Catalyst Technical Handbook–Be Selective*; Johnson Matthey Catalysts: West Deptford, NJ, 2005.

(20) The list of catalysts examined for the hydrogenation of iPr_2-BINOL (***R***)-**8** included 0.5% Pt/Al_2O_3 pellets (5% yield), 20% $Pd(OH)_2$/C (Pearlman's catalyst, 4% yield), 5% Rh/Al_2O_3 powder (3% yield), 5% Pd/C (1% yield), 5% Pt/C wet (2% yield), 5% Ru/C (NR), 0.5% Ru/MgO pellets (NR), 5% Pd/$BaSO_4$ unreduced (NR), 5% Pd/$BaSO_4$ reduced (NR), 5% Pd/C/Pb (Lindlar's catalyst, NR), Pd(IV) oxide (NR), Rh(IV) oxide (NR), and Pt black (NR) (yields determined by HPLC).

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 $NaHCO_3$ 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 was washed with water (50 and 100 mL) and brine (50 mL), dried over Na_2SO_4, then filtered and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL) and transferred into a 250-mL round-bottomed flask equipped with a stirbar, rubber septum, and nitrogen inlet. Boron tribromide (2.5 mL, 27 mmol, 10.0 equiv) 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 NH_4Cl solution (50 mL), water (50 and 100 mL), and brine (50 mL), then dried over Na_2SO_4, 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*)-H_4-BINOL (***R***)-**2** (0.644 g, 2.22 mmol, 82% yield) and (*R*)-H_8-BINOL (***R***)-**3** (127 mg, 0.431 mmol, 16% yield) as white solids. Analytical data for **2**: mp 128 °C (lit.[14] mp 131−133 °C); R_f 0.23 (25% EtOAc/hexanes); $[\alpha]^{20}_D$ +40.2 (*c* 1.01, THF) (lit.[14] $[\alpha]^{25}_D$ +40.4 (*c* 0.98, THF)); 300 MHz ^{1}H 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 $C_{20}H_{19}O_2$ *m*/*z* (M + H) 291.1385, found 291.1390. Only the (*R*) enantiomer was detected by HPLC analysis with use of a chiral column (see the Supporting Information).

Acknowledgment. Financial support was provided by the National Institutes of Health through grant GM-29861.

Supporting Information Available: General experimental procedures, compound characterization data, and copies of ^{1}H, ^{13}C, and DEPT NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO8004556