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A Convenient Synthesis of (*S*)-H_4-BINOL and Its Derivatives via Hydrogenation of Monoesters of BINOL

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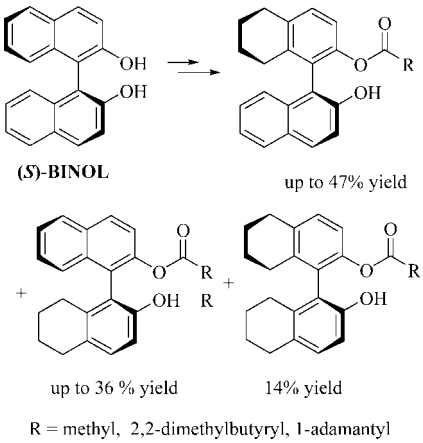
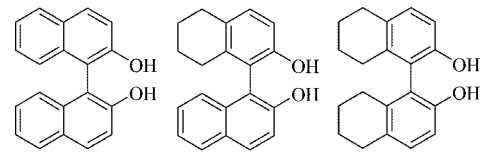


A new multigram synthesis of chiral (*S*)-H_4-BINOL and its derivatives in moderate to high yield (up to 83% total yield) via monoesterification of (*S*)-BINOL, hydrogenation, and saponification reaction was described. The two new monomethylated (*S*)-H_4-BINOL obtained may be useful materials in asymmetric catalysis.

1,1′-Bi-2-naphthol (BINOL) and its derivatives have been widely used in asymmetric synthesis.[1] Partially saturated BINOL derivatives, including H_4-BINOL and H_8-BINOL, exhibit higher efficiency and enantioselectivity in the alkylation of aldehydes or ketones, hydrogenation, and the hetero-Diels−Alder additions,[2] due to the steric and electronic modulations of the binaphthyl backbone. The convenient preparation of both H_8-BINOL enantiomers from commercially available BINOL with high optical purity and yield has already been achieved.[3] To our knowledge, there has been no satisfactory synthetic protocol for the preparation of H_4-BINOL and its derivatives. Ding et al. first reported the synthesis of H_4-BINOL by using Ni/Al alloy reduction of BINOL-MOM_2 in extremely dilute basic solvent of H_2O-*i*PrOH followed by removal of the protecting group.[4] To find a practical multigram scale synthesis of H_4-BINOL, we decided to explore the possibilities of developing an alternative procedure.



The C_2-symmetric BINOL can be converted to non-C_2-symmetric BINOL derivatives by a simple one-step reaction. It was hypothesized that this transformation led to the change of electronic effect and the steric action of the naphthalene ring, and the transformation will cause the naphthalene ring to possess a different hydrogenation ratio when non-C_2-symmetric BINOL derivatives are subjected to hydrogenation. The monoester of BINOL was first chosen as the reaction substrate due to ready preparation in high yield. During the preparation of this paper, Keck et al. reported the synthesis of H_4-BINOL by a three-step process: etherification of BINOL to BINOL-*i*Pr_2, hydrogenation, and deprotection.[5] Keck's method has some drawbacks including the use of high loading expensive PtO_2 catalyst (10% mol), poor duplication, and moderate yield (41−66% total yield). Herein we report the hydrogenation of the monoester of (*S*)-BINOL to synthesize (*S*)-H_4-BINOL and its new derivatives.

The acetate (*S*)-**1a** was first hydrogenated under different conditions to obtain the optimal ratio of (*S*)-**2a** and the process was tested by GC analysis (Scheme 1). As described in Table 1, solvents played an important role in the hydrogenation. Poor results were obtained when THF and cyclohexane were used as the reaction medium (Table 1, entries 2 and 3), while the best selectivity and yield were obtained when ethanol was employed as solvent at 50 °C under 50 atm for 4 h (Table 1, entry 1).[6] GC analysis showed that H_4-BINOL-Ac was the major product while H_8-BINOL-Ac was the minor product. The yield of H_4-BINOL-Ac under optimum conditions was 74% after

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(1) (a) McCarty, M.; Guiry, P. J. *Tetrahedron* **2001**, *57*, 3809. (b) Chen, Y.; Yekta, S.; Yudin, A. K. *Chem. Rev.* **2003**, *103*, 3155. (c) Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857. (d) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744.

(2) (a) Chan, A. S. C.; Zhang, F.-Y.; Yip, C.-W. *J. Am. Chem. Soc.* **1997**, *119*, 4080. (b) Zhang, F.-Y.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1997**, *8*, 3651. (c) Lin, Y.-M.; Fu, I.-P.; Uang, B.-J. *Tetrahedron: Asymmetry* **2001**, *12*, 3217. (d) Li, X.; Jia, X.; Lu, G.; Au-Yeung, T. T.-L.; Lam, K.-H.; Lo, T. W. H.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2003**, *14*, 2687. (e) Long, J.; Hu, J.; Shen, X.; Ji, B.; Ding, K. *J. Am. Chem. Soc.* **2002**, *124*, 10. (f) Wang, B.; Feng, X.; Huang, Y.; Liu, H.; Cui, X.; Jiang, Y. *J. Org. Chem.* **2002**, *67*, 2175. (g) Yuan, Y.; Long, J.; Sun, J.; Ding, K. *Chem. Eur. J.* **2002**, *8*, 5033.

(3) (a) Cram, D. J.; Helgeson, R. C.; Peacock, S. C.; Kaplan, L. J.; Domeier, L. A.; Moreau, P.; Koga, K.; Mayer, J. M.; Chao, Y.; Siegel, M. G.; Hoffman, D. H.; Sogah, G. D. Y. *J. Org. Chem.* **1978**, *43*, 1930. (b) Sugimura, T.; Yamada, H.; Inoue, S.; Tai, A. *Tetrahedron: Asymmetry* **1997**, *8*, 649. (c) Guo, H.; Ding, K. *Tetrahedron Lett.* **2000**, *41*, 10061. (d) Korostylev, A.; Tararov, V. I.; Fischer, C.; Monsees, A.; Börner, A. *J. Org. Chem.* **2004**, *69*, 3220. (e) Takasaki, M.; Motoyama, Y.; Yoon, S.-H.; Mochida, I.; Nagashima, H. *J. Org. Chem.* **2007**, *72*, 10291.

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

(5) Heumann, L. V.; Keck, G. E. *J. Org. Chem.* **2008**, *73*, 4725.

(6) Trace (*S*)-H_4-BINOL was determined when the (*S*)-BINOL was hydrogenated under the same conditions.

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SCHEME 1. Synthesis and Hydrogenation of (*S*)-1

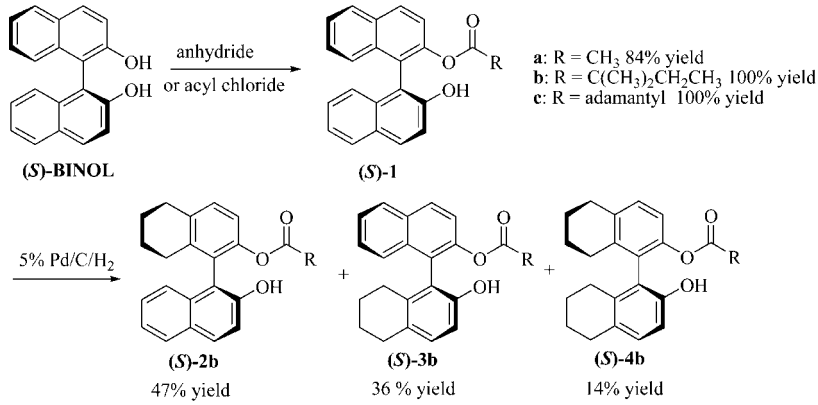


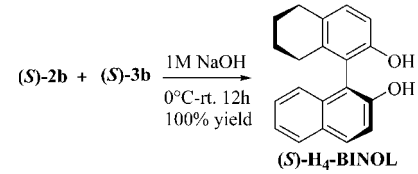
TABLE 1. Hydrogenation of the Monoester of (*S*)-BINOL[a]

					yield		
entry	sub.	catalyst	time (h)	conv[b]	**2**	**3**	**4**
1	**1a**	Pd/C	4	100	74		21
2[c]	**1a**	Pd/C	4	46	–		–
3[d]	**1a**	Pd/C	4	59	–		–
4	**1b**	Pd/C	4	100	47	36	14
5[e]	**1b**	Pd/C	5.5	99	44	33	18
6	**1c**	Pd/C	5	99	37	32	24
7	**1b**	$Pd/CaCO_3$	4	trace	–	–	–
8	**1b**	$Pd/BaSO_4$	4	trace	–	–	–
9[f]	**1b**	Rh/C	2	98	29	14	45
10	**1b**	Ru/C	5	99	34	17	39
11	**1b**	Rh/Al_2O_3	5	26	–	–	–
12	**1b**	Ru/Al_2O_3	2	100	32	13	41

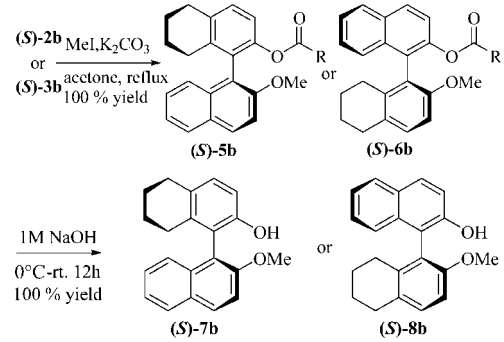
[a] All reactions were carried out with 2 mmol of (*S*)-**1**, 5% of metal/loading (0.2 g) in EtOH (15 mL) at 50 °C under H_2 (50 atm). [b] Determined by GC. [c] THF (15 mL) was used as solvent. [d] Cyclohexane (15 mL) was used as solvent. [e] (*S*)-**1b** (5.4 g, 14 mmol), 5% Pd/C (1 g), and EtOH (70 mL). [f] 5% Rh/C (0.23 g, 40 wt %).

purification with column chromatography. Though attempts at further purification to obtain pure (*S*)-**2a** and (*S*)-**3a** by chromatography were unsuccessful, the ratio of **2a** and **3a** (about 2.8:1) could be detected by GC.[7] GC analysis revealed that formation of 18% H_4-BINOL-Ac led to the formation of about 1% H_8-BINOL-Ac. The ratio of H_4-BINOL-Ac and H_8-BINOL-Ac was gradually reduced with prolonged hydrogenation time. This phenomenon indicated that overreduction, yielding much H_8-BINOL-Ac, was undesired and appears to be inherent to this hydrogenation. The results revealed our hypothesis was reasonable (Table 1). A bulky substituent, 2,2-dimethylbutyryl group, was introduced to BINOL for investigating steric and electronic effects. At the same time, we also hope to obtain a higher yield of the monoester of H_4-BINOL and separate (*S*)-**2** and (*S*)-**3**. Thus hydrogenation of (*S*)-**1b** was conducted under the optimum reaction conditions. Fortunately, compounds **2b** (47% yield) and **3b** (36% yield) could be separated by column chromatography (Table 1, entry 4). Hydrolysis of (*S*)-**2b** and (*S*)-**3b** gave the same (*S*)-H_4-BINOL in quantitative yield (Scheme 2). The structure of (*S*)-**2b** and (*S*)-**3b** could be determined by comparing the ^{1}H NMR of (*S*)-**1b**, (*S*)-**2b**, (*S*)-**3b**, and (*S*)-**4b**. The δ value of the terminal methyl group of (*S*)-**1b** is 0.51 ppm because it may be in the shielded region of the other naphthol ring, while the same methyl signals of (*S*)-**2b**, (*S*)-**3b**, and (*S*)-**4b** are 0.46, 0.69, and 0.64 ppm, respectively. This observation showed that the terminal methyl groups of (*S*)-**3b** and (*S*)-**4b** do not lie in the shielded region of the other naphthol ring. In other words, the naphthol ring is hydrogenated and the structure of (*S*)-**2b** and (*S*)-**3b** are reasonable. The ratio of the isolated (*S*)-**2b** and (*S*)-**3b** was 1.4:1. The compounds (*S*)-**2b** and (*S*)-**3b** were transformed to (*S*)-**7b** and (*S*)-**8b** by classic organic synthesis (Scheme 3). Attempts to characterize the structure of (*S*)-**7b** and (*S*)-**8b** by X-ray crystallographic analysis were unsuccessful.

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



SCHEME 3. Synthesis of (*S*)-7b and (*S*)-8b



The reaction was also carried out with other heterogeneous catalysts, such as $Pd/CaCO_3$, $Pd/BaSO_4$, Rh/Al_2O_3, and Ru/Al_2O_3. It was found that no reaction occurred in the presence of catalytic $Pd/CaCO_3$ or $Pd/BaSO_4$ and slow reaction rates were obtained with Ru/C and Rh/Al_2O_3 as catalyst (Table 1, entries 7, 8, 10, and 11). The more active catalysts Rh/C and Ru/Al_2O_3 provided poor selectivity (Table 1, entries 9 and 12).

To further improve the yield of (*S*)-**2**, compound (*S*)-**1c** with an adamantyl substituent was synthesized and hydrogenated. The result obtained was not superior to that of (*S*)-**1b** ((*S*)-**2c** (37%), (*S*)-**3c** (32%), and (*S*)-**4c** (24%)), and the compounds (*S*)-**3c** and (*S*)-**4c** were very difficult to separate.

To evaluate the capability of the new procedure for a mutigram scale synthesis, the hydrogenation of **1b** (5.4 g) was performed with 3.3 mol % of 5% Pd/C under the same

(7) The result was obtained by comparing with the products of the reaction of (*S*)-H_4-BINOL and acetic anhydride. Additionally, all (*S*)-**2** reveal red fluorescence under UV 254 nm and (*S*)-**3** does not have this property.

conditions for 5.5 h and (*S*)-**2b** (2.39 g, 44%), (*S*)-**3b** (1.79 g, 33%), and (*S*)-**4b** (1.0 g, 18%) were obtained (Table 1, entry 5).[8]

In summary, the results of this paper showed that the hydrogenation of the monoester of BINOL with 5% Pd/C is a more useful method for the practical synthesis of optically pure H_4-BINOL derivatives than other currently available methods. New derivatives of H_4-BINOL were obtained and characterized. The investigation of the derivative of H_4-BINOL as a novel asymmetric catalyst starting material is well underway in our laboratory, and the results will be reported in due course.

4. Experimental Section

General Procedure for the Partial Hydrogenation of (*S*)-1,1′-Binaphthyls (*S*)-1a−c. A mixture of (*S*)-1,1′-binaphthyls (*S*)-**1b** 0.77 g (2 mmol), 5% Pd/C (0.2 g, 5% mmol), and 15 mL of ethanol was placed into a 100 mL autoclave and stirred under 50 bar of hydrogen pressure at 50 °C for 4 h. The reaction mixture was cooled to rt. The catalyst was filtered off and washed with THF (3 × 5 mL). The combined filtrates were concentrated in vacuo to give a mixture of (*S*)-**2b**, (*S*)-**3b**, and (*S*)-**4b**, and column chromatographic separation on silica gel with hexane/ethyl acetate (15:1) as eluent afforded (*S*)-**2b** (365 mg, 47% yield), (*S*)-3**b** (280 mg, 36% yield), and (*S*)-**4b** (110 mg, 14% yield) with >99% ee (determined by HPLC on a Chiralcel AD-H column with 95:5 *n*-hexane:isopropanol as eluent, $t_{S\text{-}2b}$ = 11.66 min, $t_{R\text{-}2b}$ = 16.64 min; $t_{S\text{-}3b}$ = 14.50 min, $t_{R\text{-}3b}$ = 21.47 min; $t_{S\text{-}4b}$ = 10.82 min, $t_{R\text{-}4b}$ = 15.36 min).

(*S*)-2-(2,2-Dimethylbutyryl)oxy-2′-hydroxy-5,6,7,8-tetrahydro-1,1-binaphthyl ((*S*)-2b): [α] −25.9 (*c* 2.5, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.46 (t, *J* = 7.5 Hz, 3H), 0.57 (s, 3H), 0.68 (s, 3H), 1.09−1.24 (m, 2H), 1.54−1.62 (m, 2H), 1.64−1.78 (m, 2H), 2.03−2.11 (m, 1H), 2.35−2.43 (m, 1H), 2.85−2.88 (m, 2H), 5.28 (s, 1H), 6.92−6.95 (m, 1H), 7.20−7.31 (m, 5H), 7.75−7.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.6, 22.6, 22.7, 23.9, 24.0, 26.7, 29.6, 32.5, 42.4, 116.0, 118.2, 119.5, 123.6, 124.0, 126.4, 127.8, 129.0, 129.6, 130.8, 132.9, 136.0, 139.3, 148.1, 150.8, 177.6; HRMS (EI) calcd for $C_{26}H_{28}O_3$ 388.2038, found 388.2034. With >99% ee.

(*S*)-2-(2,2-Dimethylbutyryl)oxy-2′-hydroxy-5′,6′,7′,8′-tetrahydro-1,1-binaphthyl ((*S*)-3b): [α] +50.7 (*c* 1.8, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.68 (t, *J* = 7.5 Hz, 3H), 0.97 (s, 3H), 1.00 (s, 3H), 1.42−1.53 (m, 2H), 1.57−1.70 (m, 4H), 1.89−1.92 (m, 1H), 2.28−2.32 (m, 1H), 2.73−2.78 (m, 2H), 4.67 (s, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 7.04 (d, *J* = 8.3 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 7.41−7.43 (m, 1H), 7.47−7.51 (m, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.94 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.9, 23.1, 23.2, 24.2, 24.3, 27.1, 29.3, 32.8, 42.7, 114.0, 120.8, 121.5, 124.7, 125.2, 126.0, 127.2, 128.2, 129.5, 130.1, 130.3, 132.0, 132.9, 136.9, 147.1, 151.5, 177.4. HRMS (EI) calcd for $C_{26}H_{28}O_3$ 388.2038, found 388.2036.

(*S*)-2-(2,2-Dimethylbutyryl)oxy-2′-hydroxy-5,5′,6,6′,7,7′,8,8′-octahydro-1,1-binaphthyl ((*S*)-4b): [α] −17.4 (*c* 1.5, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.64 (t, *J* = 7.5 Hz, 3H), 0.88 (s, 3H), 0.91 (s, 3H), 1.33−1.47 (m, 2H), 1.59−1.76 (m, 8H), 1.98−2.05 (m, 1H), 2.10−2.17 (m, 1H), 2.30−2.45 (m, 2H), 2.68−2.72 (m, 2H), 2.80−2.83 (m, 2H), 4.80 (s, 1H), 6.74 (d, *J* = 8.2 Hz, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.94 (d, *J* = 8.3 Hz, 1H), 7.14 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.8, 22.6, 22.8, 23.1, 23.2, 24.1, 24.2, 26.8, 27.2, 29.3, 29.6, 32.8, 42.6, 114.1, 119.3, 122.5, 128.1, 129.4, 129.7, 130.2, 135.8, 135.9, 138.3, 147.1, 150.7, 177.7. HRMS (EI) calcd for $C_{26}H_{32}O_3$ 392.2351, found 392.2348.

Preparation of (*S*)-2-(2,2-Dimethylbutyryl)oxy-2′-methoxy-5′,6′,7′,8′-tetrahydro-1,1-binaphthyl ((*S*)-6b). A mixture of (*S*)-**3b** (338 mg, 1 mmol), MeI (284 mg, 2 mmol), K_2CO_3 (552 mg, 4 mmol), and acetone (5 mL) was refluxed for 15 h. AcOEt (30 mL) and H_2O (10 mL) were added to the cold reaction mixture. After phase separation, the organic phase was washed with water and dried over Na_2SO_4. After removal of the solvent, the residue was purified by flash column chromatography over silica gel with *n*-hexane−AcOEt (20:1) to provide (*S*)-**6b** as a colorless oil. [α] 44.2 (*c* 2.0, EtOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.68 (t, *J* = 7.5 Hz, 3H), 0.96 (s, 6H), 1.38−1.47 (m, 2H), 1.52−1.58 (m, 2H), 1.66−1.72 (m, 2H), 2.00−2.07 (m, 1H), 2.25−2.31 (m, 1H), 2.74−2.80 (m, 2H), 3.59 (s, 3H), 6.78 (d, *J* = 8.4 Hz, 1H), 7.10 (d, *J* = 8.4 Hz, 1H), 7.29−7.43 (m, 4H), 7.85−7.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.0, 23.1, 23.2, 24.3, 24.4, 27.0, 29.3, 33.0, 42.7, 55.9, 108.6, 121.8, 122.9, 125.2, 125.5, 126.3, 126.7, 128.1, 128.3, 129.4, 129.6, 131.6, 133.1, 137.9, 146.0, 155.6, 176.0. HRMS (EI) calcd for $C_{27}H_{30}O_3$ 402.2195, found 402.2191.

Preparation of (*S*)-2-Hydroxy-2′-methoxy-5′,6′,7′,8′-tetrahydro-1,1-binaphthyl ((*S*)-8b). A mixture of (*S*)-**6b** (0.7 g), 1 M NaOH (1 mL), and alcohol (5 mL) was stirred at room temperature for 12 h, then aqueous 10% HCl (5 mL) was added. The reaction mixture was extracted with AcOEt. After the extraction was dried with Na_2SO_4, the solvent was removed. The crude product was chromatographed on silica gel with hexane:AcOEt (10:1) to give a white sold in 100% yield. Mp 108−110 °C; [α] −35.3 (*c* 1.0, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55−1.61 (m, 2H), 1.70−1.75 (m, 2H), 2.09−2.15 (m, 1H), 2.19−2.23 (m, 1H), 2.80−2.82 (m, 2H), 3.62 (s, 3H), 4.90 (s, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 7.15−7.31 (m, 5H), 7.78−7.81 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 23.0, 26.9, 29.3, 55.9, 109.2, 116.5, 117.1, 120.5, 123.1, 124.2, 126.3, 128.1, 129.1, 129.2, 130.6, 130.7, 133.0, 139.2, 150.1, 156.3. HRMS (EI) calcd for $C_{21}H_{20}O_2$ 304.1463, found 304.1463.

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Supporting Information Available: Spectroscopic data for **1a−c**, **4a**, **2c**, **3c**, **4c**, and **5b−8b**, and copies of NMR spectra of **1a−c**, **2b−4b**, **2c−4c**, and **5b−8b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) The average total yield of (*S*)-**2b** and (*S*)-**3b** was 74% for three parallel experiments with this multigram scale.