A Solid-to-Solid Asymmetric Dihydroxylation Procedure for Kilogram-Scale Preparation of Enantiopure Hydrobenzoin

Zhi-Min Wang and K. Barry Sharpless*

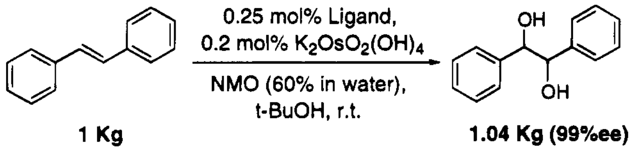
Department of Chemistry, The Scripps Research Institute, 10666 N. Torrey Pines Road, La Jolla, California 92037

Received September 8, 1994

The enantiopure threo hydrobenzoins and their derivatives have found a variety of uses in asymmetric synthesis as chiral ligands,[1] as chiral building blocks,[2] and as chiral auxiliaries.[3] At present the applications for these enantiopure diols are limited by their high price.

Previous routes to enantiopure hydrobenzoins include: enzymatic methods,[4-7] reduction of benzil and benzoin,[8] resolution of hydrobenzoin[9] and its monoester,[10] and asymmetric dihydroxylation (AD) of *trans*-stilbene.[11] Since our original AD procedure for stilbene,[11a] much better ligands [$(DHQD)_2$-PHAL and $(DHQ)_2$-PHAL] have been developed.[12] These ligands are especially effective for stilbene and we describe here a dramatically improved procedure for the AD of this olefin.

As in the original procedure,[11a] *N*-methylmorpholine *N*-oxide (NMO) was employed as the cooxidant, for it allows the reaction to be run at a very high concentration. By using the new $(DHQD)_2$–PHAL ligand we found that only 0.25 mol % of ligand was adequate to achieve 99% ee. This should be compared to the 90% ee realized in the original procedure using 20 times as much of the first-generation *p*-chlorobenzoate ligand. In addition only half the amount of osmium catalyst (cf. 0.2 mol % here and 0.4 mol % in ref 11a) was necessary to realize an efficient and complete reaction. The optimal stilbene concentration was 2–2.5 M.[13] If the stilbene concentration is more than 2.5 M, there is a drop in ee (for example, at 10 M the ee of the diol is only 90%). The solvent selection was also optimized. Acetone was replaced with t-BuOH to further lower the solubility of stilbene, thus approximating the "slow addition" conditions for high ee.[14] The use of t-BuOH also decreases the solubility of hydrobenzoin making workup easier.



With these modifications, we successfully conducted a kilogram-scale AD of stilbene in a 5 L flask. The reaction was carried out by stirring at room temperature a suspension of 1 kg of *trans*-stilbene, NMO, 0.25 mol % of ligand, and 0.2 mol % of potassium osmate in a solvent system of t-BuOH and H_2O (the H_2O enters with the technical grade aqueous NMO solution). After 14 h, the crystalline stilbene had been completely digested and transformed to the powdery hydrobenzoin. The workup merely consists of adding Tiron (4,5-dihydroxy-1,3-benzenedisulfonic acid, disodium salt monohydrate from Aldrich, to sequester the osmium) and water (to further decrease the solubility of the diol) followed by filtration. This produces enantiopure hydrobenzoin in 76% yield (910 g) and 99% ee. Following acidic extraction of the ligand, concentration affords an additional 130 g of 99% ee hydrobenzoin, for a combined yield of 1.04 kg (87% yield and 99% ee).[15]

In conclusion, 1 kg of stilbene was converted to 1.04 kg of enantiopure hydrobenzoin in a process requiring little more than stirring and filtration. This simple and

---

(1) (a) Tomioka, K.; Shindo, M.; Koga, K. *J. Am. Chem. Soc.* **1989**, *111*, 8266. (b) Rosini, C.; Franzini, L.; Pini, D.; Salvadori, P. P. *Tetrahedron Asymmetry* **1990**, *1*, 587. (c) Cucciolito, M. E.; Francesco, R.; Vitagliano, A. *Tetrahedron Lett.* **1994**, *35*, 169. (d) Oh, T.; Devine, P. N. *J. Org. Chem.* **1992**, *57*, 396. (e) Corey, E. J.; Yu, C.-M.; Lee, D.-H. *J. Am. Chem. Soc.* **1990**, *112*, 878. (f) Gamez, P.; Fache, F.; Mangeney, P.; Lemaire, M. *Tetrahedron Lett.* **1993**, *34*, 6897. (g) Mikami, K.; Terada, M.; Nahai, T. *Chem. Express* **1989**, *4*, 589. (h) Quallich, G. T.; Woodall, T. M. *Tetrahedron Lett.* **1993**, *34*, 4145. (i) Joshi, N. N.; Srebnik, M.; Brown, H. C. *Tetrahedron Lett.* **1989**, *30*, 5551. (j) Pfaltz, A.; Zhou, Q.-L. *Tetrahedron Lett.* **1993**, *34*, 7725. (k) Alexakis, A.; Fruto, J.; Mangeney, P. *Tetrahedron Asymmetry* **1993**, *4*, 2427.

(2) (a) Crosby, J.; Stoddart, J. F.; Sun, X.; Venner, M. P. W. *Synthesis* **1993**, 141. (b) Sasak, H.; Irie, R.; Katsuki, T. *Synlett* **1993**, 300. (c) D'Accolti, L.; Detomaso, A.; Fusco, C.; Rosa, A.; Curci, R. *J. Org. Chem.* **1993**, *58*, 3600. (d) Wink, D. J.; Kwok. T. J.; Yee, A. *Inorg. Chem.* **1990**, *29*, 5006. (e) Aube, J.; Mossman, C. J.; Dickey, S. *Tetrahedron* **1992**, *48*, 9819. (f) Kikuchi, Y.; Kobayashi, K.; Aoyama, Y. *J. Am. Chem. Soc.* **1992**, *114*, 1351. (g) Imuta, M.; Ziffer, H. *J. Org. Chem.* **1979**, *44*, 2505. (h) Crosby, J.; Fakley, M. E.; Gemmell, C.; Martin, K.; Quick, A.; Slawin, A. M. Z.; Shahriar-Zavareh, H.; Stoddart, J. F.; William, D. *Tetrahedron Lett.* **1989**, *30,* 3849. (i) Konopelski, J. P.; Boehler, M. A.; Tarasow, T. M. *J. Org. Chem.* **1989**, *54*, 4966. (j) Mukaiyama, T.; Yamada, T.; Nagata, T.; Imagawa, K. *Chem. Lett.* **1993**, 327. (k) Corey, E. J.; Imwinkelried, R.; Pikul, S.; Yiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493. (l) Nishimura, K.; Yamaguchi, T.; Shinho, T. *Jpn Kokai Tokkyo Koho* JP 87-30614 87 1203, **1989**. (m) Pini, D.; Inliano, A.; Rosini, C.; Salvadori, P. *Synthesis* **1990**, 1023.

(3) (a) Brugidou, J.; Christol, H.; Sales, R. *Bull. Soc. Chim. Fr.* **1974**, 2027. (b) Eid, C. N., Jr.; Konopelski, J. P. *Tetrahedron Lett.* **1991**, *32*, 461. (c) Jung, M. E.; Lew, W. *Tetrahedron Lett.* **1990**, *31*, 623. (d) Deluchi, O.; Fabris, F. *Synlett* **1993**, 275. (e) Konopelski, J. P. *Tetrahedron Lett.* **1991**, *32*, 465. (f) Eid, C. N.; Konopelski, J. P. *Tetrahedron* **1991**, *47,* 975. (g) Konopelski, J. P.; Boehler, M. A. *J. Am. Chem. Soc.* **1989**, *111*, 4515. (h) Konopelski, J. P.; Boehler, M. A. *Tetrahedron* **1991**, *47*, 4519. (i) William, R. M.; Fegley, G. J. *J. Org. Chem.* **1993**, *58*, 6933. (j) Ditrich, K.; Bube, T.; Stumer, R.; Hoffmann, R. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 1028. (k) Andersen, M. W.; Hildebrandt, B.; Hoffmann, R. W. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 97. (l) Matteson, D. S.; Man, H.-W. *J. Org. Chem.* **1993**, *58*, 6545.

(4) Buisson, D.; El Baba, S.; Azerad, R. *Tetrahedron Lett.* **1986**, *27*, 4453.

(5) Imute, M.; Ziffer, H. *J. Org. Chem.* **1978**, *43*, 3319.

(6) Bellucci, G.; Berti, G.; Chiappe, C.; Fari, F.; Marioni, F. *J. Org. Chem.* **1989**, *54*, 968.

(7) Basavaiah, D.; Krishna, P. R. Indian *J. Chem., Sect. B.* **1993**, *32B*, 131.

(8) Yamashita, J.; Kawahara, H.; Ohashi, S.; Honda, Y.; Kenmotsu, T.; Hashimoto, H. *Technol. Rep. Tohoku Univ.* **1983**, *48*, 211.

(9) Kawashima, M.; Hirayama, A. *Chem. Lett.* **1991**, 763.

(10) Brienne, M. J.; Collet, A. *J. Chem. Research (s),* **1978**, 60.

(11) (a) Mckee, B. H.; Gilheany, D. G.; Sharpless, K. B. *Org. Synth.* **1992**, *70*, 47. (b) Hirama, M.; Oishi, T.; Ito, S. *J. Chem. Soc., Chem. Commun.* **1989**, 665. (c) Oishi, T.; Hirama, M. *J. Org. Chem.* **1989**, *54*, 5834. (d) Erdik, E.; Matteson, D. S. *J. Org. Chem.* **1989**, *54*, 2742. (e) Tomioka, K.; Nakajima, M.; Koga, K. *J. Am. Chem. Soc.* **1988**, *110*, 988. (f) Tomioka, K.; Shinmi, Y.; Shiina, K.; Nakajima, M.; Koga, K. *Chem. Pharm. Bull.* **1990**, *38*, 2133. (g) Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroeder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 1968. (h) Yamada, T.; Narasaka, K. *Chem. Lett.* **1986**, 131. (i) Tokles, M.; Snyder, J. K. *Tetrahedron Lett.* **1986**, *27*, 3951. (j) Corey, E. J.; Jardine, P. D.; Virgil, S.; Yuen, P.; Commell, R. D. *J. Am. Chem. Soc.* **1989**, *111*, 9243. (k) Pini, D.; Petri, A.; Nardi, A.; Rosini, C.; Savadori, P. *Tetrahedron Lett.* **1991**, *32*, 5175.

(12) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768.

(13) Please note this use of the term "concentration" is nontraditional, since the bulk of the stilbene is present as a solid slurry and only a small fraction is dissolved in the *tert*-butyl alcohol/water mixture.

(14) Wai, S. M.; Marko, I.; Svendsen, J. S.; Finn, M. G.; Jacobsen, E. N.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 1123.

0022-3263/94/1959-8302$04.50/0

efficient solid-to-solid procedure should prove to be practical on an industrial scale and will hopefully make the enantiopure hydrobenzoins more available.

Experimental Section

General. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AMX 400 instrument.

(*R*,*R*)-(+)-1,2-Diphenyl-1,2-ethanediol. A 5 L round-bottomed flask, equipped with a large magnetic stir bar, was charged with 10.89 g (0.25 mol %) of $(DHQD)_2$-PHAL, 1 kg (5.6 mol) of *trans*-stilbene, 1.4 L of 60% aqueous *N*-methylmorpholine *N*-oxide (aqueous NMO, Aldrich), and 2.24 L of *tert*-butyl alcohol. The flask was placed in a water bath (initially at about 20 °C and no further efforts were made to control the temperature). Under stirring, 4.12 g (0.2 mol %) of potassium osmate(VI) dihydrate was added (caution, see footnote 16). The reaction mixture was then stirred until all the stilbene was consumed (about 14 h, monitored by TLC[17]). The reaction was quenched by the addition of 10 g of 4,5-dihydroxy-1,3−benzenedisulfonic acid, disodium salt monohydrate (Tiron, Aldrich) followed by stirring at rt for 3 h. The resulting mixture was poured into 3 L of water and stirred for another 3 h. The crude product was collected by filtration and washed with water until colorless. After drying under vacuum, 910 g of (*R*,*R*)-1,2-diphenyl-1,2−ethanediol was obtained as a white powder (76% yield, 99% ee). To recover the ligand, the largely aqueous filtrate was stirred with 2 L of ethyl acetate for 1 h. The resulting organic phase was separated and then washed with 0.5 M sulfuric acid (2 × 250 mL). To these combined acidic extracts was added 500 mL of CH_2Cl_2, and this mixture was stirred while sodium carbonate was added until the pH of the aqueous phase had been raised to ca. 10 or 11. The CH_2Cl_2 phase was washed with water, dried over $MgSO_4$, and concentrated to give 10 g of $(DHQD)_2$-PHAL (95% recovery). Meanwhile, another 130 g of (*R*,*R*)-1,2-diphenyl-1,2-ethanediol was obtained from the ethyl acetate phase after evaporation of the solvent (11% yield, 99% ee), for an overall yield of 87% (1.04 kg). The enantiomeric excess was determined by HPLC analysis of the bis-MTPA ester of diol on Chiralcel OD column. Mp 148−150 °C; $[\alpha]_D$ +95° (*c* 0.87, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.22 (m, 6H), 7.11 (m, 4H), 4.67 (s, 2H), 3.00 (br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 139.79, 128.09, 127.89, 126.92, 79.07.

(*S*,*S*)-(−)-1,2-Diphenyl-1,2-ethanediol: Mp 148−150 °C. $[\alpha]_D$ +95.2° (*c* 1.28, EtOH).[15]

Acknowledgment. Financial support was provided by the National Institutes of Health (GM-28384).

---

[15] The detailed procedure is only given for (*R*,*R*)-hydrobenzoin, but (*S*,*S*)-hydrobenzoin was also made on a kilogram scale following the identical procedure (but using $(DHQ)_2$-PHAL as ligand) and with essentially the same yield and ee.

[16] On one occasion at this kilogram scale, the osmium catalyst was added as osmium tetraoxide which led to a too rapid reaction and an exotherm to ca. 50 °C. Being mild and limited, this self-heating excursion was not dangerous but did substantially reduce the ee and the yield. Therefore we recommend using only the potassium osmate salt for these large scale applications employing concentrated conditions and NMO as oxidant. Another implication of this result is that for reactions above the 1 kg scale it may become necessary to add even the salt form of the catalyst in portions over a period of time, and/or provide for heat removal other than the passive, ambient temperature water bath utilized here.

[17] Excessive reaction times will result in some overoxidation, with benzaldehyde and benzoin as the byproducts.