Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 15 (2004) 1141–1143

A simple and efficient resolution of (±)-4,12-dihydroxy[2.2]paracyclophane

Biao Jiang* and Xiao-Long Zhao

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, PR China

Received 15 January 2004; accepted 10 February 2004

Abstract—The resolution of (±)-4,12-dihydroxy[2.2]paracyclophane [(±)-PHANOL] has been realized through the, simply separated by flash chromatography and reduced with $LiAlH_4$, diastereomeric esters of (1*S*)-(−)-camphanic acid. The (*R*)-(+)-PHANOL and (*S*)-(−)-PHANOL were obtained in an excellent yield (89%) with high enantiomeric excess (>99.8%).

1. Introduction

Chiral ligands play an important role in asymmetric synthesis. In comparison with tetrahedral chiral compounds, the axially chiral binaphthyl derivatives,[1] planar chiral ferrocene derivatives[2] and arene metal complexes,[3] less attention has been paid to the planar chiral [2.2]paracyclophane derivatives,[4] though it was first synthesized in 1949.[5] In fact, as a potential chiral ligand, [2.2]paracyclophane derivatives have their own advantages: highly rigid, chemically stable towards light, oxidation, acids and bases and racemisation only occurring at relatively high temperatures (>180 °C).[6]

Phanephos [4,12-bis(diphenylphosphino)[2.2]-paracyclophane], one of the excellent ligands used in asymmetric catalytic reactions, has been developed by Pye recently.[7] It was used in the asymmetric hydrogenation of dehydroamino acid methyl esters, tetrahydropyrazine[7a] and enantioenriched homoallylic alcohols,[8] the asymmetric hydrogenation of β-ketoesters,[9] or aromatic, heteroaromatic, unsaturated ketones,[10] and in the kinetic resolution of (±)-4,12-dibromo[2.2]paracyclophane.[11] [2.2]Paracyclophane and 1,1′-binaphthyl, the respective stereocontrolling skeleton of phanephos and BINAP, express in similar planar and axial chirality. Reasonably, PHANOL is supposed to act a similar role in asymmetric catalytic reactions as BINOL, an excellent ligand for asymmetric synthesis.

The preparation of racemic PHANOL [(±)-4,12-dihydroxy[2.2]paracyclophane] was first reported by Cram in 1969.[12] More than 30 years later, enantiomerically pure PHANOL was reported by Braddock.[13] However, to the best of our knowledge, PHANOL has never been used as a ligand in asymmetric catalytic reactions. This maybe because it was limited by the shortage of enantiomerically pure PHANOL. In Braddock's work, enantiomeric pure PHANOL was achieved through lipase-catalyzed enzymatic kinetic resolution of (±)-4,12-bisacetate[2.2]paracyclophane. However, this procedure is time consuming (more than 14 days) with low overall yield [(*R*)-(+)-PHANOL, 32%; (*S*)-(−)-PHANOL, 26%). Furthermore, the enzymatic resolution requires specialist equipment and skills meaning it to be inconvenient for most traditional organic chemists.

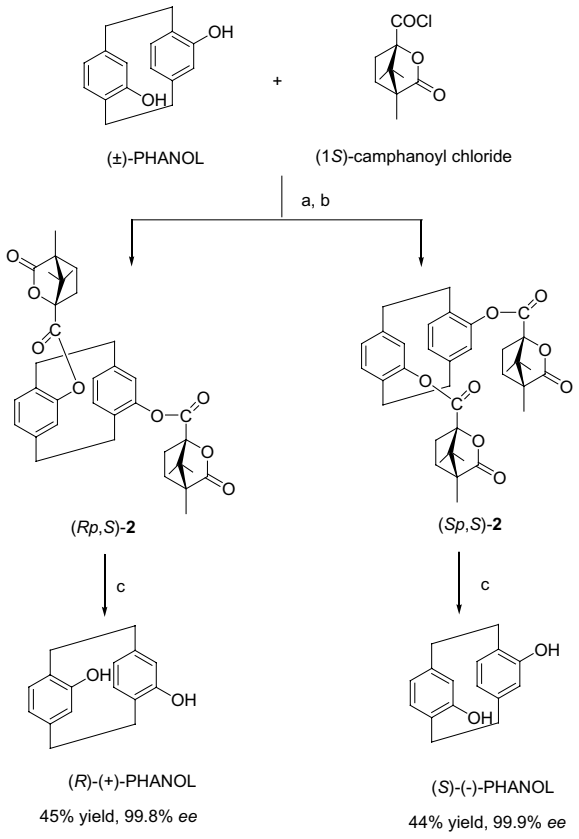
Herein, we report a simple and efficient resolution of (±)-PHANOL in excellent yield (89%) with high enatiomeric excess (>99.8%).

2. Results and discussion

(±)-PHANOL was synthesized according to the literature.[12] Initially, we tried to resolve (±)-PHANOL using methods commonly used for BINOL derivatives. (±)-PHANOL was subjected to the treatment of $POCl_3$ and NEt_3. However, our attempts to prepare the cyclic phosphoryl chloride proved unsuccessful. We then turned our attention to a chiral auxiliary reagent. Addition of L-menthyl chloroformate and NEt_3 to

* Corresponding author. Tel.: +86-21-64163300; fax: +86-21-64166128; e-mail: jiangb@pub.sioc.ac.cn

0957-4166/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2004.02.011



Scheme 1. Reagents and conditions: (a) pyridine, 25 °C; (b) flash chromatography; (c) $LiAlH_4$/THF, reflux.

(±)-PHANOL produced a mixture of diastereomeric esters, which were inseparable by recrystallization or flash chromatography.

An efficient resolution was finally achieved by treating (±)-PHANOL with (1*S*)-camphanoyl chloride[14] and pyridine.[15] The diastereoisomers were readily separated by flash chromatography on silical gel. The lower polarity portion (*S*ρ,*S*)-**2** {91% yield, >99% de determined by ^{1}H NMR, $[\alpha]_D^{20} = -55.9$ (*c* 1, $CHCl_3$)} and the higher polarity portion (*R*ρ,*S*)-**2** {91% yield, >99% de, $[\alpha]_D^{20} = +21.8$ (*c* 1, $CHCl_3$)} were reduced with $LiAlH_4$ produced (*S*)-(−)-PHANOL (44% yield, 99.9% ee) and (*R*)-(+)-PHANOL (45% yield, 99.8% ee), respectively (Scheme 1). The absolute configuration of (*S*)-(−)-PHANOL and (*R*)-(+)-PHANOL were determined by X-ray diffraction analysis of (*S*ρ,*S*)-**2**, which was identical to the data in the literature.[13] The results are shown in Figure 1.

3. Conclusion

In conclusion we have developed a simple and efficient resolution of (±)-PHANOL. Further extension of the use of these enantiomerically pure isomers in the generation of ligands for asymmetric catalytic reactions are currently being explored and will be reported separately.

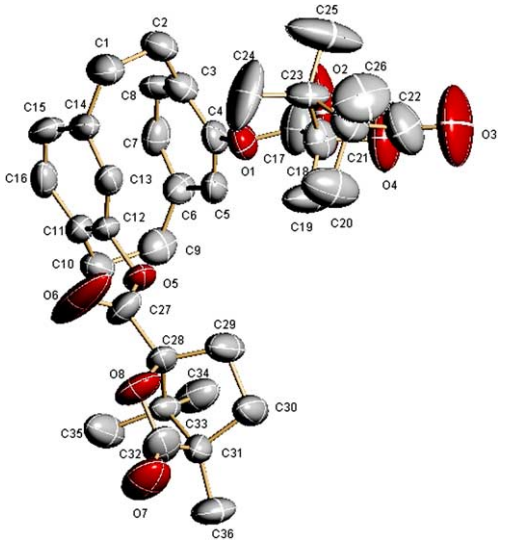


Figure 1. X-ray structures of (*S*ρ,*S*)-**2**.

4. Experimental

4.1. General

Melting points were measured on a WRS-1A digital melting point apparatus and are uncorrected. Optical rotations were recorded on Perkin–Elmer 341MC instrument. Infrared (IR) spectra were determined with a Shimadzu IR-440 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AMX-300. The chemical photo shifts are expressed in ppm and coupling constants are given in Hz. Low and high-resolution mass spectra were obtained, respectively, on a Finnigan 4021 GC MS/DC and Bruker APEXIII 7.0 TESLA FTMS. Chiral HPLC analyzes were performed on a Chiralpak® AD-H analytical column using 20% 2-propanol in hexane as an eluent (0.7 mL/min) detected at 254 nm. Flash chromatography was performed using silica gel H (10–40 μm). Standard reagents and solvents were purified according to known procedures.[16] (±)-PHANOL[13] and camphanoyl chloride[14] were synthesized followed the literature.

4.2. (*Sρ*,*S*)-2 and (*Rρ*,*S*)-2

Anhydrous pyridine (25 mL) was added to a mixture of (±)-PHANOL (120 mg, 0.5 mmol) and (1*S*)-camphanoyl chloride (260 mg, 1.2 mmol) at room temperature. The progress of the reaction was monitored by TLC. The reaction mixture was diluted with CH_2Cl_2 and washed successively with 2 M HCl, water and saturated $NaHCO_3$ aqueous. The organic solution was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain a mixture of diastereomeric esters **2** (274 mg, 91% yield), which were purified by flash chromatography on silica gel using petroleum ether–ethyl acetate (2:1) as the eluent.

(*S*ρ,*S*)-**2**, TLC $R_f = 0.45$ (petroleum ether–ethyl acetate 2:1), eluted first; 134 mg (44.6% yield); mp 242 °C;

$[\alpha]_D^{20} = -55.9$ (*c* 1, $CHCl_3$); IR (cm^{-1}) 1788, 1763; ^1H NMR ($CDCl_3$ 300 MHz) δ 1.13 (s, 6H), 1.15 (s, 6H), 1.18 (s, 6H), 1.78–1.82 (m, 2H), 1.96–2.04 (m, 2H), 2.17–2.20 (m, 2H), 2.52–2.60 (m, 2H), 2.70–2.75 (m, 2H), 3.02–3.12 (m, 6H), 6.48 (dd, $J = 7.8$ and 1.8 Hz, 2H), 6.55 (d, $J = 1.8$ Hz, 2H), 6.60 (d, $J = 7.8$ Hz, 2H); ^{13}C NMR ($CDCl_3$ 75 MHz) δ 9.7, 16.6, 16.9, 28.8, 30.9, 31.4, 33.3, 54.5, 55.0, 90.8, 124.4, 130.6, 130.9, 135.4, 142.0, 148.2, 165.5, 178.2; MS (EI) *m/z* 600 [M^+] (68); HRMS (ESI) calcd for $C_{36}H_{40}O_8Na$ 623.26153, found 623.26289.

(*R*ρ,*S*)-**2**, TLC $R_f = 0.37$ (petroleum ether–ethyl acetate 2:1), eluted next; 135 mg (45% yield); mp 235 °C; $[\alpha]_D^{20} = +21.8$ (*c* 1, $CHCl_3$); IR (cm^{-1}) 1793, 1759; ^1H NMR ($CDCl_3$ 300 MHz) δ 1.14 (s, 6H), 1.18 (s, 6H), 1.20 (s, 6H), 1.74–1.82 (m, 2H), 1.97–2.07 (m, 2H), 2.16–2.26 (m, 2H), 2.56–2.65 (m, 2H), 2.67–2.77 (m, 2H), 2.92–3.15 (m, 6H), 6.47 (dd, $J = 7.8$ and 1.8 Hz, 2H), 6.56 (d, $J = 1.8$ Hz, 2H), 6.59 (d, $J = 7.8$ Hz, 2H); ^{13}C NMR ($CDCl_3$ 75 MHz) δ 9.7, 16.8, 16.9, 28.9, 31.1, 31.3, 33.4, 54.4, 54.9, 90.8, 124.1, 130.5, 130.9, 135.5, 141.9, 148.3, 165.2, 178.0; MS (EI) *m/z* 600 [M^+] (100); HRMS (ESI) calcd for $C_{36}H_{40}O_8Na$ 623.26153, found 623.26144.

4.3. (*R*)-(+)-PHANOL

$LiAlH_4$ (328 mg, 8.6 mmol) was added in portions to a solution of (*R*ρ,*S*)-**2** (260 mg, 0.43 mmol) in anhydrous THF (20 mL). The mixture was heated under reflux for 6 h, with the progress of the reaction monitored by TLC. After aqueous work-up, the product mixture was purified by flash chromatography on silica gel using petroleum ether–ethyl acetate (4:1) to yield 103 mg (99%) (*R*)-(+)-PHANOL; 99.8% ee by HPLC analysis ($t_S = 7.89$, $t_R = 9.97$).

4.4. (*S*)-(−)-PHANOL

(*S*)-(−)-PHANOL was obtained by the same method from (*S*ρ,*S*)-2 in 97% yield; 99.9% ee by HPLC analysis.

4.5. Crystallographic analysis of (*Rρ*,*S*)-2

Colourless, needle-like crystals were grown from hexane–CH_2Cl_2 (10:1), $C_{36}H_{40}O_8$, $M = 600.38$, $a = 12.792$ (2) Å, $b = 6.9092$ (13) Å, $c = 18.758$ (4) Å, $v = 1603.0$ (5) $Å^3$, $T = 293(2)$ K, $Z = 4$, $D_{calcd} = 1.244$ mg/m^3. Final *R* indices [$I > 2\sigma(I)$], $R1 = 0.0775$, $wR2 = 0.1688$; *R* indices (all data), $R1 = 0.2231$, $wR2 = 0.2098$.

Crystallographic data (excluding structure factors) for (*S*ρ,*S*)-**2** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 228499. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

We thank the Shanghai Municipal Committee of Science and Technology and the National Natural Science Foundation of China for financial support.

References and notes

1. See, for example, (a) Kitamura, M.; Tsukamoto, M.; Bessho, Y.; Yoshimura, M.; Kobs, U.; Widhalm, M.; Noyori, R. *J. Am. Chem. Soc.* **2002**, *124*, 6649–6667; (b) Ohkuma, T.; Koizumi, M.; Muniz, K.; Hilt, G.; Kabuto, C.; Noyori, R. *J. Am. Chem. Soc.* **2002**, *124*, 6508–6509; (c) Li, X.; Lu, G.; Kwok, W.; Chan, A. S. C. *J. Am. Chem. Soc.* **2002**, *124*, 12636–12637; (d) Kumagai, N.; Matsunaga, S.; Kinoshita, T.; Harada, S.; Okada, S.; Sakamoto, S.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 2169–2178; (e) Matsunaga, S.; Kumagai, N.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 4712–4713.
2. See, for example, (a) Bolm, C.; Rudolph, J. *J. Am. Chem. Soc.* **2002**, *124*, 14850–14851; (b) Mermerian, A.; Fu, G. *J. Am. Chem. Soc.* **2003**, *125*, 4050–4051; (c) Matsumura, S.; Maeda, Y.; Nishimura, T.; Uemura, S. *J. Am. Chem. Soc.* **2003**, *125*, 8862–8869; (d) Dai, L. X.; Tu, T.; You, S. L.; Deng, W. P.; Hou, X. L. *Acc. Chem. Res.* **2003**, *36*, 659–667, and references cited therein.
3. See, for example, Gibson, S. E.; Ibrahim, H. *Chem. Commun.* **2002**, *21*, 2465–2473, and references cited therein.
4. See, for example, Gibson, S. E.; Knight, J. D. *Org. Biomol. Chem.* **2003**, *1*, 1256–1269, and references cited therein.
5. Brown, C. J.; Farthing, A. C. *Nature* **1949**, *164*, 915–916.
6. (a) Cram, D. J.; Allinger, N. *J. Am. Chem. Soc.* **1969**, *91*, 3517–3526; (b) Rozenberg, V.; Kharitonov, V.; Antonov, D.; Sergeeva, E.; Aleshkin, A.; Ikonnikov, N.; Orlova, S.; Belokon, Y. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 91–92, and references cited therein.
7. (a) Pye, P. J.; Rossen, K.; Reamer, R. A.; Tsou, N. N.; Volante, R. P.; Reider, P. J. *J. Am. Chem. Soc.* **1997**, *125*, 6207–6208; (b) Pye, P. J.; Rossen, K. *Tetrahedron: Asymmetry* **1998**, *9*, 539–541.
8. When, P. M.; Bois, J. D. *J. Am. Chem. Soc.* **2002**, *124*, 12950–12951.
9. Pye, P. J.; Rossen, K.; Reamer, R. A.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1998**, *39*, 4441–4444.
10. Burk, M. J.; Hems, W.; Herzberg, D.; Malan, C.; Zanotti-Gerosa, A. *Org. Lett.* **2000**, *2*, 4173–4176.
11. Rossen, K.; Pye, P. J.; Maliakal, A.; Volante, R. P. *J. Org. Chem.* **1997**, *62*, 6462–6463.
12. Reich, H. J.; Cram, D. J. *J. Am. Chem. Soc.* **1969**, *91*, 3527–3533.
13. Braddock, D. C.; MacGilp, I. D.; Perry, B. G. *J. Org. Chem.* **2002**, *67*, 8679–8681.
14. (a) Gerlach, H. *Helv. Chim. Acta.* **1968**, *51*, 1587; (b) Bhowmick, K. C.; Prasad, K. R. K.; Joshi, N. N. *Tetrahedron: Asymmetry* **2002**, *13*, 851–855.
15. Rozenberg V. and Hopf H. have resolved 4-hydroxy[2.2]paracyclophane using the same method: Rozenberg, V.; Danilova, T.; Sergeeva, E.; Vorontsov, E.; Starikova, Z.; Korlyukov, A.; Hopf, H. *Eur. J. Org. Chem.* **2002**, *1*, 468–477.
16. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon: Oxford, 1988.