# Highly Efficient and Practical Optical Resolution of 2-Amino-2′-hydroxy-1,1′-binaphthyl by Molecular Complexation with *N*-Benzylcinchonidium Chloride: A Direct Transformation to Binaphthyl Amino Phosphine

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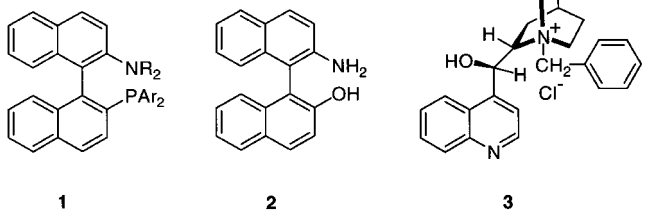
**Abstract:** A new type of N,P chiral ligand, binaphthyl amino phosphine **1** was synthesized through a simple and practical resolution of racemic 2-amino-2′-hydroxy-1,1′-binaphthyl by molecular complexation with 0.5 equivalents of *N*-benzylcinchonidium chloride in the solid state. The present procedure represents the first example of the optical resolution of amino alcohol with the use of a chiral ammonium salt as a resolving reagent. The resolution mechanism is discussed in terms of molecular recognition in solid state. The chlorine anion in *N*-benzylcinchonidium chloride provides the bridging link between two amino alcohol molecules [(+)-**2**] and the cinchonoid cation located in between, by hydrogen bonding with the surrounding moieties.

**Keywords:** amino alcohols · biaryls · molecular recognition · N,P ligands · optical resolution

## Introduction

Binaphthyl amino phosphine **1**, a new type of N,P chiral ligand, should be a very effective chiral inducer for asymmetric synthesis, because it possesses not only a rigid chiral 1,1′-binaphthyl scaffold but also effective P and N containing chelating groups for transition metals.[1] It is evident that the enantiomerically pure amino alcohol **2** is a direct precursor for the preparation of **1**. Since the amino alcohols themselves also represent the important chiral auxiliaries for asymmetric synthesis,[2–3] it is desirable to develop a facile method for the preparation of optically pure **2**.




**1** **2** **3**

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A homogenous preparative procedure of **2** was reported by Smrcina and Kocovsky.[4] However, a large excess of chiral amine (10 equiv) and a careful multistep crystallization are necessary in order to get the enantiomerically pure **2** because of the low optical enrichment (46 % *ee*) by diastereoselective crystallization. In our preliminary report, a novel two-phase oxidative cross-coupling procedure for large-scale preparation of racemic **2** by using $FeCl_3$ as the oxidant has been described;[5] this method has the advantages of environmental safety and simplicity for the workup of the product. Very recently, Cai et al. reported a kinetic resolution of **2**. However, the procedure is still less satisfactory in terms of yield and optical purity of the product.[6] We now wish to report the development of a highly efficient and practical optical resolution of **2** by molecular complexation with *N*-benzylcinchonidium chloride **4**; this represents the first example of the optical resolution of an amino alcohol by the use of a chiral ammonium salt as a resolving reagent. The resolution mechanism may be discussed in terms of molecular recognition in solid state. Further transformation of **2** to the new type of chiral aminophosphine ligand **1** is also achieved.

## Results and Discussion

Molecular complexation has proven to be one of the most effective methods for the resolution of chiral organic mole-

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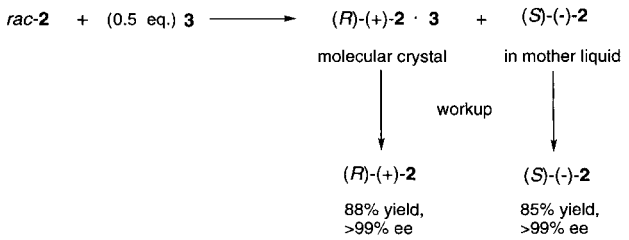
cules.[7] Toda et al. recently reported that chiral ammonium salts are excellent hosts for optical resolution of racemic phenol derivatives by selective complexation with one of the enantiomers.[8] In our first attempt, 2-amino-2′-hydroxy-1,1′-binaphthyl **2** was readily resolved by the use of 1/2 equivalent of *N*-benzylcinchonidium chloride (Scheme 1). In order to




Scheme 1. The resolution of *rac*-**2** by molecular complexation.

improve the efficiency of the resolution, several kinds of solvents, such as methanol, ethyl acetate, acetonitrile, and acetone, were examined and acetone was found to be an excellent solvent. A period of reflux is able to accelerate the formation of molecular crystals between (+)-**2** and **3**. The crystals precipitated were collected by filtration and washed with acetone; these were characterized as a 1:1 molecular crystal of (+)-**2** and **3**.[9] The opposite enantiomer of **2** is left in the filtrate. The filtrate was concentrated to dryness, redissolved in ethyl acetate, and washed with dilute HCl and brine. The organic layer was dried over anhydrous $Na_2SO_4$, filtered, and concentrated to a pale solid. Further recrystallization from benzene gives enantiomerically pure (−)-**2** in 85 % yield based on one enantiomer (> 99 % *ee*). The molecular crystals can be decomposed with dilute HCl and extracted with ethyl acetate. Following the same procedure for the workup of (−)-**2** as mentioned above, the enantiomerically pure (+)-**2** is obtained in 88 % yield based on the other enantiomer with > 99 % *ee*. The aqueous phase is neutralized with $Na_2CO_3$ and concentrated to give *N*-benzylcinchonidium chloride in almost quantitative recovery.

Thus, an efficient and practical resolution of an amino alcohol, 2-amino-2′-hydroxy-1,1′-binaphthyl (**2**), has been successfully achieved. It is generally considered that the ammonium salts form an inclusion complexes with alcohol or phenol through hydrogen bonding interactions between the counter anion of the ammonium salt host and the hydroxy group of the alcohol or phenol guest.[8, 10] However, how a chiral ammonium salt resolves amino alcohol has not yet been reported. In order to understand the resolution mechanism, the X-ray crystal structure of the molecular complex was determined.[11]

As shown in Figure 1, the structure of the molecular complex network between (+)-**2** and **3** can be described as continuous chains of interlinked species that are aligned in an alternating manner parallel to the (011) lattice plane of the crystal. The chloride anion provides the bridging link between two amino alcohol molecules (+)-**2** and the cinchonoid cation located in between, by hydrogen bonding with the surrounding moieties at OH···Cl distances of 3.10–3.11 Å and NH···Cl distance of 3.41 Å. The *N*,*N*-dimethyl derivative

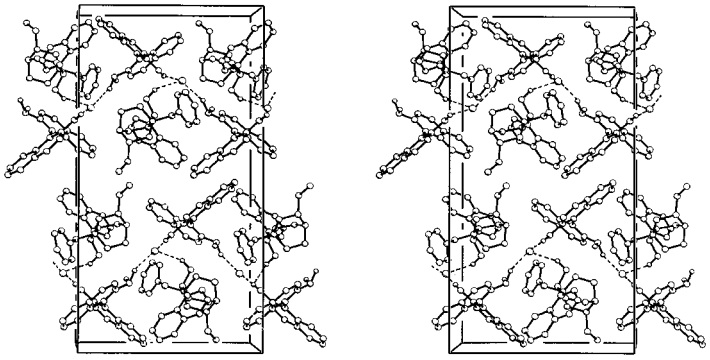


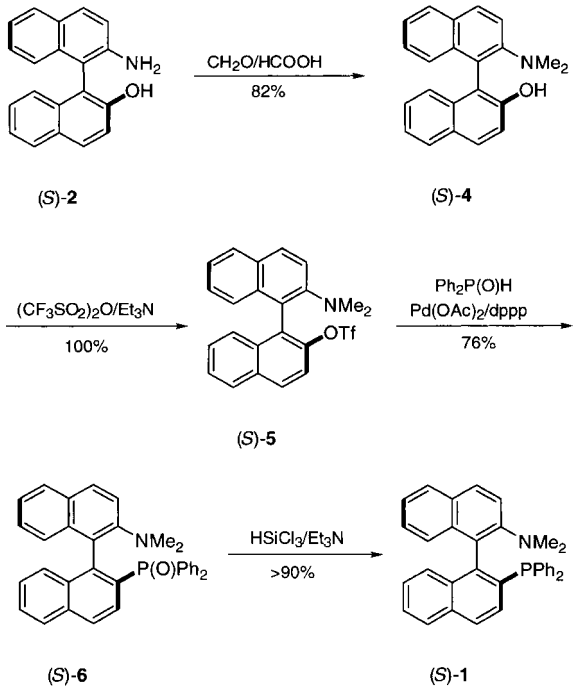
Figure 1. Stereoview of the crystal structure of (*R*)-(+)-**2**·**3**. Contents of one and one-half unit cell are shown to illustrate better the intermolecular interaction pattern.

(**4**) of racemic **2** does not form molecular crystal under various conditions; this illustrates that the alternative OH···Cl···HN hydrogen bonding pattern is very important for the formation of molecular crystal. There is no intramolecular hydrogen bonding between the $NH_2$ and OH of the amino alcohol moiety. The C–H π interaction between the benzyl substituent of the cinchonidium derivative and two naphthyl rings of amino alcohol is found to be an additional force for the formation of the molecular crystal. The shortest relevant nonbonding H···C distances are within the range of 2.79–3.02 Å. The dihedral angle of the binaphthyl unit is 103.8° and its absolute configuration is found to be *R* and is unambiguously related to the absolute configuration of cinchonidium moiety. The chirality of stereogenic carbon connected to OH group in the host molecule is found to be crucial for molecular recognition between **2** and **3**, because when epimeric benzylcinchonium chloride is used, under various conditions, for the complexation of **2**, no molecular crystal is formed.[12]

With the enantiopure **2** in hand, we extended its application to the synthesis of a new type of amino-phosphine chiral ligand **1**. As shown in Scheme 2, the enantiopure *N*,*N*-dimethyl derivative (**4**) of **2** can be obtained by methylation with $CH_2O$–HCOOH[13] in 82 % yield. Treatment of **4** with $(CF_3SO_2)_2O$ in the presence of $Et_3N$ gives its triflate derivative **5** quantitatively. We tried various procedures for the transformation of **5** to **1**.[14] Finally it was found that **5** undergoes coupling reaction with $Ph_2P(O)H$ effciently in the presence of $Pd(OAc)_2$/dppp (dppp = 1,3-bis(diphenylphosphino)propane) and diisopropylethylamine to give 2-(*N*,*N*-dimethylamino)-2′-(diphenylphosphinyl)-1,1′-binaphthyl **6** in 76 % yield. The chiral target ligand **1** can be easily obtained in > 90 % yield by the reduction of its oxide **6** with $HSiCl_3$ in the presence of $Et_3N$.

## Conclusion

A highly efficient and practical optical resolution of 2-amino-2′-hydroxy-1,1′-binaphthyl has been achieved. It was found that the chirality of the host molecule, hydrogen bonding, and C–H π interactions dominate the selective formation of molecular crystal between (*R*)-(+)-**2** and **3**. This protocol combined with a two-phase oxidative cross-coupling proce-




Scheme 2. Transformation of **2** to **1**.

dure for the large-scale preparation of racemic **2** provides a convenient route to enantiopure **2**. One of its phosphine derivatives **1** has been prepared from chiral **2** readily without racemization. Further application of **1** and **2** for asymmetric synthesis is under investigation.

## Experimental Section

**General**: $^1$H NMR and $^{13}$C NMR were measured on a Varian Gemini 300 (300 MHz) spectrometer. Chemical shifts of $^1$H NMR were expressed in ppm with tetramethylsilane as an internal standard ($\delta = 0$) in $CDCl_3$, unless otherwise noted. Chemical shift of $^{13}$C NMR were expressed in ppm with residual signal of $CDCl_3$ as an internal standard ($\delta = 77$), unless otherwise noted. IR spectra were measured with a JASCO FTIR-5000 spectrometer. Optical rotations were measured with a JASCO DIP-140 instrument. Mass spectra were obtained on a JEOL AUTO FAB. Liquid chromatographic analyses were conducted on a Shimadzu LC-6A instrument equipped with Model SPD 6A spectrometer as an ultra violet light (at 254 nm). The peak areas were calculated by a Shimadzu C-R6A as an automatic intergrator. Analytical thin-layer chromatography (TLC) was performed on Merck Kieselgel 60 $F_{254}$. Visualization was accomplished by UV light (254 nm) and phosphomolybidic acid. All experiments were carried out under an argon atomsphere. All of the solvents were dried and freshly distilled prior to use. Racemic 2-amino-2′-hydroxy-1,1′-binaphthyl (**2**) was prepared according to the reported procedure.[5]

**Optical resolution of 2-amino-2′-hydroxy-1,1′-binaphthyl (2)**: *N*-benzylcinchonidium chloride **3** (4.20g, 10 mmol) was added to the solution of (±)-**2** (5.70 g, 20 mmol) in acetone (100 mL). The mixture was heated to reflux for 4 h and then allowed to cool to room temperature. The resulting crystalline white solid was collected by filtration and washed with acetone (3 × 10 mL). The solid was characterized as a two-component molecular crystal of (*R*)-(+)-**2** and **3** in a 1:1 molar ratio.[9] The enriched (*S*)-(−)-**2** was left in the mother liquid. A suspension of molecular crystals in HCl (50 mL; 1N ) and ethyl acetate (100 mL) was stirred for 10 min until the white solids disappeared. The organic layer was separated and was washed with brine (20 mL) and then dried over $Na_2SO_4$. After removal of the solvent, the residue obtained from organic phase was recrystallized from benzene to afford (*R*)-(+)-**2** in 88% yield based on one enantiomer with >99% *ee* (determined by HPLC on a CHIRALCEL OD−H column with 90:10 hexane/isopropanol as eluent, 0.6 mL min$^{-1}$, *S*: 21.22 min; *R*: 25.04 min). M.p. 167–169 °C; $[\alpha]_D^{25} = +117.0$ ($c = 1.0$, THF); $^1$H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 3.72$(br s, 2H), 5.14(s, 1H), 7.05–7.39 (m, 8H), 7.74–7.92 (m, 4H); $^{13}$C NMR (125.7 MHz, $(CD_3)_2SO$): $\delta = 111.36$, 115.00, 118.53, 118.87, 120.89, 122.33, 122.66, 123.53, 124.20, 125.82, 126.26, 127.10, 127.91, 129.19, 128.54, 129.23, 133.73, 134.10, 144.00, 153.38; IR (KBr, cm$^{-1}$): $\tilde{\nu} = 3408$ (w), 3326 (m), 3225 (w), 1622 (vs), 1599 (s), 816 (vs), 756 cm$^{-1}$ (s); $C_{20}H_{15}NO$ (285.34): C 84.18, H 5.30, N 4.91%; found: C 84.50, H 5.31, N 4.77%. The mother liquid was concentrated to dryness, then redissolved in ethyl acetate (50 mL), and washed with HCl (10 mL; 1N) and brine (20 mL). The organic layer is dried over $Na_2SO_4$. Following the same procedure for the recrystallization of (*R*)-(+)-**2**, (*S*)-(−)-**2** was obtained in 85% yield based on the other enantiomer with >99% *ee*: $[\alpha]_D^{25} = -117.0$ ($c = 1$, THF).

**(*S*)-2-(*N*,*N*-dimethylamino)-2′-hydroxy-1,1′-binaphthyl (4)**: (*S*)-(−)-**2** (570 mg, 2 mmol) was added to a solution of HCOH (0.40 g) in HCOOH (2 mL). The mixture was heated to 100 °C and stired for 4 h. After cooling, the resulting solution was neutralized with NaOH solution (2N) to pH < 11. The product was extracted with ethylacetate (2 × 30 mL). The organic phase was washed with brine and dried over $MgSO_4$. After the removal of the solvent, the residue was submitted to column-chromatographic separation on silica gel with hexane/EtOAc (4:1) as eluent to give (*S*)-**4** in 82% yield (516 mg). M.p. 184–186 °C; $[\alpha]_D^{25} = -30.8$ ($c = 1.0$, THF); $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 2.46$ (s, 6H), 7.02–7.23 (m, 5H), 7.28–7.34 (m, 2H), 7.37 (d, $J = 9.0$ Hz, 1H), 7.84 (t, $J = 8.4$ Hz, 2H), 7.88 (d, $J = 8.7$ Hz, 1H), 7.95 (d, $J = 8.7$ Hz, 1H), [the proton of the OH group was not detected); $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta = 43.58$, 118.32, 118.43, 119.38, 122.07, 123.18, 124.17, 125.72, 125.89, 126.29, 126.48, 127.89, 128.12, 129.25, 129.66, 129.91, 130.06, 133.93, 134.10, 149.47, 151.58; IR(KBr): $\tilde{\nu} = 3070$ (w), 2956 (w), 1618 (s), 1595 (s), 818 (vs), 762 cm$^{-1}$ (s); HRMS calcd for $C_{22}H_{19}NO$ ($[M]^+$): 313.1467; found: 313.1466.

**(*S*)-2-(*N*,*N*-dimethylamino)-2′-(trifluoromethylsulfonyloxy)-1,1′-binaphthyl (5)**: $Et_3N$ (0.3 mL, 2.2 mmol) was added to a solution of (*S*)-**4** (313 mg, 1 mmol) in $CH_2Cl_2$ (3 mL). The resulting mixture was cooled to −78 °C and then $(CF_3SO_2)O$ (0.185 mL, 1.1 mmol) was added dropwise. After stirring for 3 h at −78 °C, the solution was warmed to room temperature. After the removal of the solvent, the resulting residue was submitted to column-chromatographic separation on silica gel with hexane/EtOAc (10:1) as eluent to give (*S*)-**5** in 100% yield (445 mg). M.p. 125–126 °C; $[\alpha]_D^{25} = +144.2$ ($c = 1.0$ in THF); $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 2.45$ (s, 6H), 6.92 (d, $J = 8.4$ Hz, 1H), 7.16 (t, $J = 8.4$ Hz, 1H), 7.27–7.44 (m, 3H), 7.48–7.58 (m, 3H), 7.83 (d, J = 7.8 Hz, 1H), 7.94–8.00 (m, 2H), 8.01 (d, $J = 8.7$ Hz, 1H); $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta = 43.53$, 116.08, 119.38, 119.85, 120.32, 123.69, 125.16, 126.26, 126.72, 127.29, 127.50, 127.89, 128.30, 129.53, 129.88, 130.21, 132.45, 133.67, 134.22, 145.36, 150.86; IR(KBr): $\tilde{\nu} =$ 3056 (m), 2940 (m), 1624 (s), 1595 (s), 818 (s), 748 (s); HRMS calcd for $C_{23}H_{18}F_3NO_3S$ ($[M]^+$): 445.0960; found: 445.0950.

**(*S*)-2-(*N*,*N*-dimethylamino)-2′-(diphenylphosphinyl)-1,1′-binaphthyl (6)**: Dimethylsulfoxide (5 mL) and diisopropylethylamine (0.87 mL, 5.0 mmol) were added to a mixture of (*S*)-**5** (445 mg, 1 mmol), diphenylphosphine oxide (404 mg, 2 mmol), palladium diacetate (22.4 mg, 0.1 mmol), and 1,3-bis(diphenylphosphino)propane (dppp; 61.8 mg, 0.15 mmol), and the mixture was heated with stirring at 100 °C for 20 h. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure to give a brown residue. The residue was diluted with EtOAc, washed with water, dried over $MgSO_4$, and concentrated again under reduced pressure. The residue was chromatographed on silica gel (elution with EtOAc) to give (*S*)-**6** as a yellow amorphous solid in 76% yield (380 mg). $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 2.37$ (s, 6H), 6.68 (d, $J = 8.4$ Hz, 1H), 6.92–7.04 (m, 3H), 7.10–7.19 (m, 10H), 7.48–7.58 (m, 5H), 7.79 (t, $J = 7.8$ Hz, 1H), 7.86–7.92 (m, 2H); $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta = 43.47$, 119.24, 122.97, 125.53, 125.68, 126.78, 127.08, 127.18, 127.34, 127.52, 127.76, 128.01, 128.98, 129.59, 129.66, 129.75, 130.37, 130.80, 131.03, 131.16, 131.55, 131.66, 134.09, 134.65, 150.31; $^{31}$P NMR (109.25 MHz): $\delta = 28.93$; IR(KBr): $\tilde{\nu} = 3058$ (m), 2940 (w), 1620 (s), 1597 (s), 1199 (vs), 818 (s), 748 (vs), 700 cm$^{-1}$ (vs); HRMS calcd for $C_{34}H_{29}NOP$ ($[M+H]^+$): 498.1987; found: 498.1992.

**(*S*)-2-(*N*,*N*-dimethylamino)-2′-(diphenylphosphino)-1,1′-binaphthyl (1)**: $Cl_3SiH$ (1 mL) was added to a mixture of (*S*)-**6** (498 mg, 1 mmol) and $Et_3N$ (3 mL) in toluene (10 mL) at 0 °C. The reaction mixture was stirred at 100 °C for 6 h. After being cooled to room temperature, the mixture was



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diluted with ether and quenched with small amount of saturated $NaHCO_3$ solution. The resulting suspension was filtered through Celite, and the solid was washed with ether. The combined organic phase was dried over $MgSO_4$ and concentrated to solvent free under reduced pressure. The crude aminophosphine was purified by silica gel column chromatography with hexane/EtOAc (10:1) as eluent to give (*S*)-**1** as an amorphous solid in 90% yield (432 mg). $[\alpha]_D^{25} = +26.6$ ($c = 1.0$, THF); $ee > 98\%$ (determined by HPLC on a CHIRALPAK AD column with 99:1 hexane/isopropanol as eluent, 0.8 mL min$^{-1}$, *R*: 5.41 min, *S*: 8.88 min). $^1$H NMR (300 MHz, $CDCl_3$): $\delta = 2.22$ (s, 6H), 6.70 (d, $J = 9.3$ Hz, 1H), 6.92–7.15 (m, 6H), 7.20–7.36 (m, 7H), 7.38 (d, $J = 9.0$ Hz, 1H), 7.41(d, $J = 9.0$ Hz, 1H), 7.45–7.50 (m, 2H), 7.80–7.89 (m, 3H), 7.94 (d, $J = 8.7$ Hz, 1H); $^{13}$C NMR (75.5 MHz, $CDCl_3$): $\delta = 43.07$, 119.08, 123.36, 125.68, 125.84, 126.29, 126.57, 127.46, 127.50, 127.75, 127.88, 127.96, 127.99, 128.04, 129.17, 129.40, 131.65, 132.79, 132.96, 133.04, 133.23, 133.55, 133.73, 134.10, 150.36; $^{31}$P NMR (109.25 MHz): $\delta = -12.72$; IR(KBr): $\tilde{\nu} = 3056$ (m), 2938 (w), 1620 (m), 1595 (m), 816 (s), 745 (s), 696 cm$^{-1}$ (vs); HR-MS calcd for $C_{34}H_{28}NP$ ($[M]^+$): 481.1959; found:481.1978.

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[9] (*R*)-(+)-**2**·**3**: m.p. > 250 °C (decomp); $C_{46}H_{44}ClN_3O_2$ (706.32): C 78.22, H 6.28, N 5.95%; found: C 78.15, H 6.30, N 6.04%.

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[11] The single crystal growth was carried out in a 1:1 acetone-acetonitrile mixed solvent at room temperature. X-ray crystallographic analysis was performed with a Rigaku AFC7R diffractometer (graphite monochromator, $Mo_{K\alpha}$ radiation, $\lambda = 0.71069$ Å) The structutre was solved by direct methods and expanded by means of Fourier techniques. Crystal data for (*R*)-(+)-**2**·**4**: $C_{46}H_{44}ClN_3O_2$, colorless, crystal dimensions $0.35 \times 0.20 \times 0.20$ mm, orthorhombic, space group $P2_12_12_1$ (No.19), $a = 13.710(6)$, $b = 26.471(5)$, $c = 10.49(1)$ Å, $V = 3805(3)$ Å$^3$, $Z = 4$, $\rho_{calcd} = 1.233$ g cm$^{-3}$, $\mu(Mo_{K\alpha}) = 1.43$ cm$^{-1}$, $T = 223$ K, 4908 reflections were independent and unique, and 2781 with $I > 3.00\sigma(I)$ ($2\theta_{max} = 55.0°$) were used for the solution of the structure. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. $R = 0.075$, $wR = 0.092$. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-102753. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[12] In a similar manner, racemic BINOL can be effectively resolved by using 0.5 equiv of *N*-benzylcinchonidium chloride (**3**) as resolving agent. The BINOL included in the molecular crystal was found to have an (*R*)-(+) configuration.

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