JOC The Journal of Organic Chemistry

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Enantioresolution of 2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl Oxide Using Inclusion Complex with Chiral 2,2′-Dihydroxy-1,1′-binaphthyl

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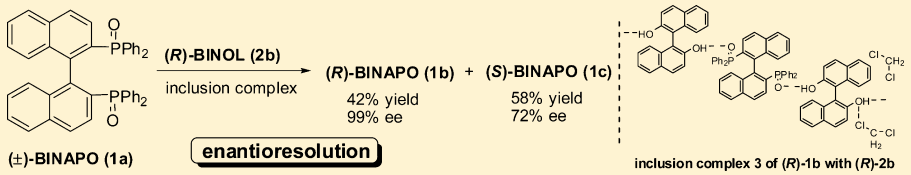
Supporting Information



ABSTRACT: An enantioresolution of 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl oxide (BINAPO) into its enantiomers was achieved using the inclusion complex with a commercially available chiral 2,2′-dihydroxy-1,1′-binaphthyl ((*R*)-BINOL), giving the two enantiomers with 99% ee and 72% ee, respectively.

The enantiomers of axially chiral phosphine oxide are frequently used in asymmetric synthesis. For example, chiral 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl oxide (BINAPO, **1**) is valuable as an organocatalyst and as a ligand of transition metal (Figure 1).[1,2]

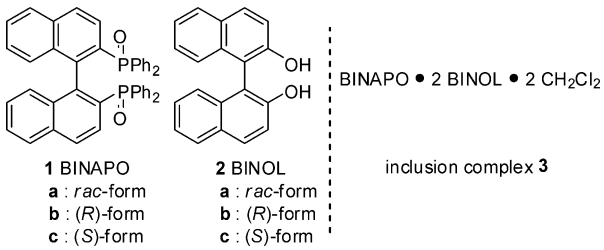


Figure 1. Structures related with enantioresolution.

However, there are a few reports of enantioresolution of **1** using inclusion complexes with tartaric acid or camphorsulfonic acid as a resolution reagent.[3−5] In our previous reports, we revealed that some phenols were useful for the formation of the inclusion complex of several compounds, such as 2-quinolone, quinoline, isoquinoline, and quinoline *N*-oxide, through a strong hydrogen-bonding network.[6] The application using a hydrogen-bonding network with phenol derivatives is of interest in the field of enantioresolution as well. Herein, we report an efficient enantioresolution of **1a** by the commercially available chiral (*R*)-2,2′-dihydroxy-1,1′-binaphthyl (BINOL, **2b**).[7] The formation of inclusion complex of **1b** proceeds smoothly in hexane−CH_2Cl_2 solution, giving a 1:2:2 inclusion complex **3** of **1b** with **2b** and CH_2Cl_2. From the isolated **3**, **1b** with 99% ee was obtained in 42% yield. On the other hand, **1c** with 72% ee was obtained in 58% yield from the filtrate left after separation of **3**. Intermolecular interactions shown in Figure 2 suggest prior growth up of **1b** to that of **1c**.

Table 1. Enantioresolution of 1a with 2b under Several Conditions

entry	solvent system	feed ratio (**1a**:**2b**)	inclusion ratio (**1b**:**2b**)[a]	yield of **3**[b] (%)	yield of **1b**[c,d] (%)	ee of **1b**[e] (%)
1	toluene−hexane	1:1	*f*			
2	$CHCl_3$−hexane	1:1	*f*			
3	AcOEt−hexane	1:1	*f*			
4	EtOH−hexane	1:1	*f*			
5	CH_2Cl_2−hexane	1:1	1:2	29	25	99
6	CH_2Cl_2−hexane	1:0.5	1:2	18	17	95
7	CH_2Cl_2−hexane	1:1.5	1:2	45	43	98
8	CH_2Cl_2−hexane	1:2	1:2	30	30	96

[a]The inclusion ratio was determined by ^{1}H NMR. [b]The yield of **3** was based on initially used **1a**. [c]The included **1b** was isolated after dissociation of inclusion complex **3**. [d]The presented yield was based on initially used **1a**. [e]The enantiomeric excess was determined by HPLC using a Chiralcel AD-H column. [f]Any inclusion complex was not detected, but crystalline **1a** was obtained.

At first, we demonstrated enantioresolution of **1a** with **2b** in several solvents and feed ratios as shown in Table 1. When **1a** (131 mg, 0.2 mmol) and **2b** (57 mg, 0.2 mmol) were dissolved in hot toluene−hexane (ca. 2 mL) and the mixture was kept at room temperature overnight, crystalline **1a** was recovered without any inclusion complex (entry 1). Similar results were

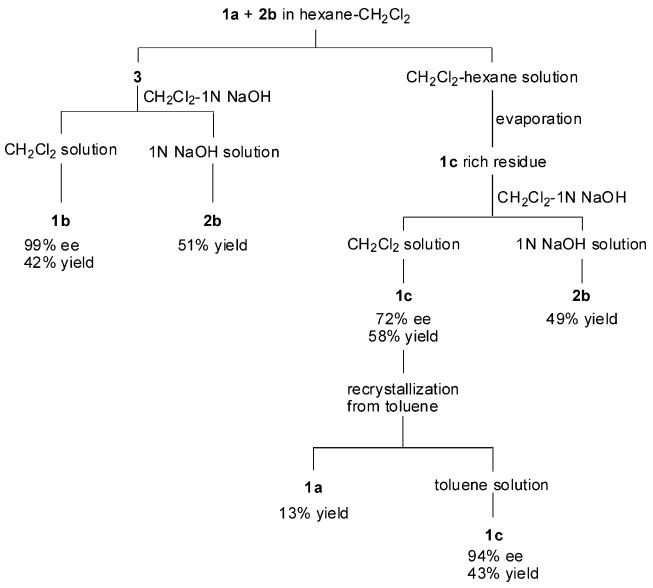
Received: December 26, 2011
Published: March 7, 2012

   dx.doi.org/10.1021/jo202630p | *J. Org. Chem.* 2012, 77, 3595−3597

observed in the solvent system using $CHCl_3$, AcOEt, and EtOH (entries 2–4). Surprisingly, the use of CH_2Cl_2–hexane was extremely effective for the formation of inclusion complex **3** of **1b** with **2b**; a 1:2:2 inclusion complex **3** of **1b** with **2b** and CH_2Cl_2 precipitated as colorless crystals in 29% yield. After dissociation of **3** using 1 N NaOH, **1b** with 99% ee was obtained in 25% yield based on initially used **1a** (entry 5). The feed ratio affected greater with the yield of **3** than the enantiomeric excess of **1b** (entries 6–8). From the viewpoint of both yield and enantiomeric excess, the best result was obtained using 1.5 equiv of **2b** against **1a** in feed (entry 7).

This method was applicable to large-scale enantioresolution of **1a** as shown in Scheme 1. When **1a** (10.0 g, 15.3 mmol) and

Scheme 1. Experimental Procedure of the Enantioresolution of 1a



2b (6.6 g, 23.0 mmol) were dissolved in hot hexane–CH_2Cl_2 (40 mL, 1:1 by volume), an inclusion complex **3** was obtained efficiently. From the inclusion complex **3**, **1b** with 99% ee was obtained in 42% yield. From the filtrate left after separation of **3**, **1c** with 72% ee was obtained in 58% yield, which gave high enantiomeric **1c** (94% ee) after **1a** crystallized out from toluene. On the other hand, the unchanged **2b** was quantitatively recovered. Enantioresolution of **1a** was also achieved by using **2c** instead of **2b**, giving **1c** with 99% ee in 43% yield from inclusion complex and **1b** with 67% ee in 56% yield from the filtrate.

In order to elucidate some aspects of the resolution procedures, an X-ray analysis of the inclusion complex **3** obtained from large scale enantioresolution was done.

As shown in Figure 2, the molecular **1b** is accommodated through two independent hydrogen bonds between phosphine oxide oxygens of **1b** and the hydroxyl groups of two molecular of **2b**, and the bond lengths are 2.584 Å (O1···O3) and 2.621 Å (O2···O6), respectively. Two molecules of **2b** also interact with each other through a hydrogen bond (O4···O5; 2.849 Å). Interestingly, two molecules of CH_2Cl_2 are included in this inclusion complex as crystal solvent, and they play an important role for the construction of inclusion complex and their mutual chiral recognition. One of the CH_2Cl_2 molecules would assist the hydrogen bond formed between two molecules of **2b** through the O···Cl short contact (O4···Cl4; 3.223 Å). Another CH_2Cl_2 molecule is accommodated in the cavity constructed by

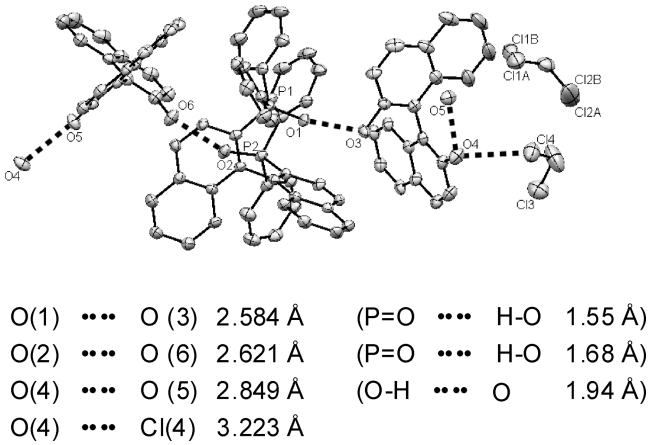


Figure 2. X-ray structure of **3**.

the inclusion crystal. These phenomena would contribute to the formation of the inclusion complex **3**, and thus, optically resolution of **1a** has been successfully achieved by preferential crystallization of one of the diastereomeric inclusion compounds using optically active **2b**. The absolute configuration of **1b** is also elucidated as the *R* enantiomer by being correlated with the known configuration of **2b**.

■ CONCLUSIONS

In conclusion, the efficient enantioresolution of **1a** into its enantiomers was achieved using chiral **2b**. The X-ray structural analysis revealed the molecular interactions between **1b** and **2b** in the inclusion complex **3**. This could be an important resolution technique in the future.

■ EXPERIMENTAL SECTION

Preparation of 2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl oxide (BINAPO, *rac*-1a).[8] To the solution of 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP, 3.0 g, 4.8 mmol) in CH_2Cl_2 (100 mL) was added 30 wt % H_2O_2 solution (10 mL, 88 mmol) at room temperature. The mixture was stirred for 5 h. After being stirred for 5 h at room temperature, H_2O (100 mL) was added. The organic layer was separated, washed with saturated Na_2SO_3 (50 mL), and dried over Na_2SO_4. After evaporation and recrystallization, the pure title compound was obtained in 97% yield (3.1 g, 4.7 mmol). **Spectral data for 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl oxide (*rac*-1a):** CAS 94041-16-4; white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.79 (d, 4H, J = 3.7 Hz), 7.21–7.24 (m, 8H), 7.32–7.37 (m, 6H), 7.38–7.45(m, 6H), 7.67–7.71 (m, 4H), 7.80–7.85 (m, 4H); ^{31}P NMR (200 MHz, $CDCl_3$) δ 29.4.

Procedure for the Enantioresolution of *rac*-1a Using Inclusion Complex 3 with (*R*)-2b. In a 100 mL Erlenmeyer flask were placed *rac*-**1a** (10.00 g, 15.3 mmol) and (*R*)-**2b** (6.60 g, 23.1 mmol), and to this was added CH_2Cl_2 (20 mL). The mixture was heated at 40 °C until a homogeneous solution was obtained. Hexane (20 mL) was added dropwise at the same temperature, and then the mixture was allowed to stand at room temperature and kept overnight. The precipitate was filtered off and washed with CH_2Cl_2 (7 mL), giving a 1:2:2 inclusion complex **3** of (*R*)-**1b** with (*R*)-**2b** and CH_2Cl_2 as colorless crystals (7.92 g). The complex obtained above was dissolved in CH_2Cl_2 (20 mL) and treated with 1 N NaOH solution (20 mL). The organic layer was separated, washed with 1 N NaOH solution (20 mL × 2), and dried over Na_2SO_4. After filtration and evaporation, (*R*)-**1b** was obtained in 42% yield (4.15 g, 6.34 mmol, 99% ee). The unchanged (*R*)-**2b** was recovered as follows: the combined aqueous layer was acidified with concd HCl to pH < 1 in an ice bath. The off-white precipitate of (*R*)-**2b** was collected by suction filtration and dried in air (3.36 g, 11.7 mmol, 51% yield). On the other hand, the hexane–CH_2Cl_2 solution left after separation of **3** was

dx.doi.org/10.1021/jo202630p | J. Org. Chem. 2012, 77, 3595–3597

evaporated, giving a residue rich in (*S*)-**1c**. Similar treatment of the residue gave (*S*)-**1c** in 58% yield (5.75 g, 8.78 mmol, 72% ee) and (*R*)-**2b** in 49% yield (3.24 g, 11.3 mmol). The high enantiomeric (*S*)-**1c** was obtained as follows: (*S*)-**1c** with 72% ee (2.80 g, 4.28 mmol) was dissolved in toluene (30 mL) at reflux, and the obtained homogeneous solution was allowed to cool to room temperature. After overnight, the precipitate of *rac*-**1a** was filtered off (610 mg, 0.93 mmol, 22% yield). The toluene solution left after separation of *rac*-**1a** was evaporated, giving the solid of (*S*)-**1c** with 94% ee in 74% yield (2.07 g, 3.16 mmol). Further enhancement of enantiopurity could not been achieved by recrystallization using (*S*)-**1c** with 94% ee. Enantioresolution of **1a** (2.00 g, 3.05 mmol) was also achieved by using **2c** (1.30 g, 4.54 mmol) instead of **2b**, giving **1c** with 99% ee in 43% yield (860 mg, 1.31 mmol) and **1b** with 67% ee in 56% yield (1.12 g, 1.71 mmol). Enantiomeric excess was determined by HPLC analysis with a Chiralcel AD-H column (hexane/2-propanol = 90:10), 1.0 mL/min, 280 nm. **Spectral data for inclusion complex 3:** white solid; mp 133.5−137.2 °C (from hexane−CH_2Cl_2); soluble in CH_2Cl_2, $CHCl_3$, EtOH, MeOH, and toluene; IR (KBr) 3477, 3406, 3053, 1507, 1339, 1286, 1185, 972 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.26 (CH_2Cl_2 as crystal solvent), 6.14 (br, 4H), 6.77 (d, 4H, J = 3.7 Hz), 7.08−7.11 (m, 8H), 7.18−7.37 (m, 28H), 7.59−7.67 (m, 8H), 7.81−7.84 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 53.4 (CH_2Cl_2 as crystal solvent), 112.1, 118.1, 123.4, 124.6, 125.9, 126.8, 126.9, 127.3, 127.8, 127.9, 127.9, 128.0, 128.1, 129.1, 130.5, 131.1, 131.3, 131.9, 132.0, 132.4, 132.5, 133.7, 134.0, 152.9; ^{31}P NMR (200 MHz, $CDCl_3$) δ 32.4. Anal. Calcd for $C_{86}H_{64}Cl_4O_6P_2$: C, 73.93; H, 4.62. Found: C, 74.40; H, 4.62.

Crystal data for inclusion complex 3: $C_{44}H_{32}O_2P_2 \cdot 2(C_{20}H_{14}O_2) \cdot 2(CH_2Cl_2)$, M = 1397.11, tetragonal, a = 11.2117(2) Å, ? >b = 11.2117(2) Å, c = 54.8735(10) Å, α = 90.00°, β = 90.00°, γ = 90.00°, V = 6897.7(2) Å^3, T = 93 K, space group $P4_1$, Z = 4, 130489 reflections measured, 12628 independent reflections (R_{int} = 0.0663). The final R_1 values were 0.0399 ($I > 2\sigma(I)$). The final w$R(F^2)$ values were 0.1032 ($I > 2\sigma(I)$). The final R_1 values were 0.0400 (all data). The final w$R(F^2)$ values were 0.1033 (all data).

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra of **1a** and **3**, CIF of **3**, and HPLC data for enantioresolution of **1a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by a Grant-in-Aid for Scientific Research (C) from the JSPS KAKENHI (No. 23550187).

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