Highly Efficient and Practical Resolution of 2,3:6,7-Dibenzobicyclo[3.3.1]nona-2,6-diene-4,8-dione and Stereoselective Synthesis of Its Chiral Diamine Derivatives

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Highly Efficient and Practical Resolution of 2,3:6,7-Dibenzobicyclo[3.3.1]nona-2,6-diene-4,8-dione and Stereoselective Synthesis of Its Chiral Diamine Derivatives

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Highly efficient and practical resolution of 2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene-4,8-dione by the inclusion complexation with commercially available enantiopure 1,1'-bi-2-naphthol is reported. The structure of the 1: 1 inclusion complex of the diketone and BINOL was confirmed by single crystal X-ray crystallography.

The rigid cleftlike molecules have attracted considerable attention in the area of molecular recongnition. One of the most prominent molecules is Tröger base **1** (Figure 1), which was first synthesized more than one hundred and twenty years ago.[1] The molecule has a dihedral angle of around 90° and the two phenyl rings are fused to the bicylic [3.3.1] framework to form a rigid V-shaped scaffold.[2] The Tröger base contains two chiral centers at nitrogen and it could be resolved by an optically active chiral acid.[3] However, in most of the host-guest studies with Tröger base,[4] enantiopure Tröger base has rarely been involved to discriminate chiral substrates.[5] One of the reasons is that Tröger base undergoes partial racemization under acidic conditions via ring-opening and ring-closing processes.[6,7] Studies were also carried out on a series of related systems, including the Kagan's ether **2**,[8] dibenzobicyclo[3.3.1]nona-2,6-diene **3**,[9] and 2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene-4,8-dione **4** (Figure 1).[10] We are insterested in this class of cleftlike molecules not only because of their utility in molecular recognition and self-assembly studies, but their potential applications in organic synthesis.[11]

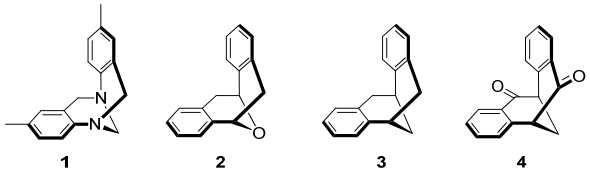
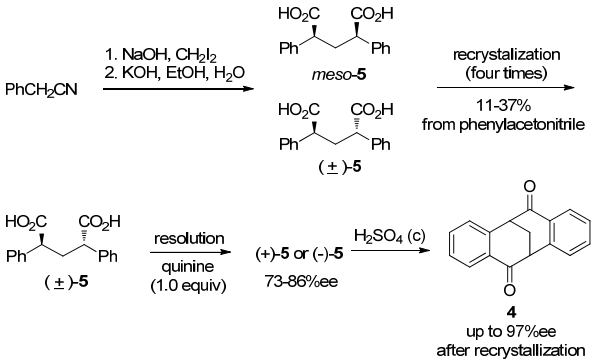


Fig. 1 Chiral Cleftlike Molecules

Our intial studies were focused on diketone **4** as the target molecule, which has the following two merits: 1) in comparison to Tröger base, the chirality of **4** is stable under either acidic or basic conditions; and 2) the carbonyl group in **4** provides opportunities for further functionalization of this V-shaped molecule. However, it has been difficult to obtain gram quantities of enantiopure **4** by the known procedures. For example, multiple recrystallizations of isomeric mixtures of diacids (±)-5 and *meso*-**5** were required to isolate pure (±)-**5** in a previous synthesis (Scheme 1).[10a, 12] Resolution of the (±)-**5** with 1.0 equiv of quinine afforded only moderate levels of enantioselectivity. Furthermore, the solid salt (+)-5 • quinine salt thus obtained was found to be thermally unstable under the conditions required for fractional recrystallization.[10a, 12] Double Friedel-Craft acylation of (+)-**5** or (–)-**5** provided **4** in good yield, for which the optical purity could be improved further by recrystallization.



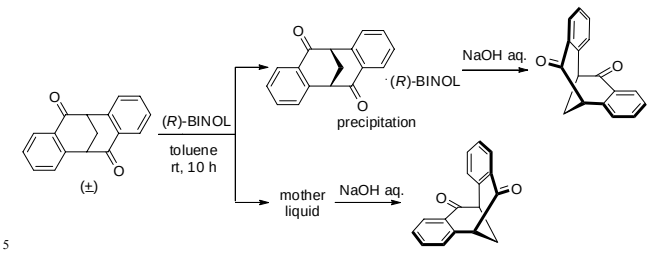
Scheme 1 Previous Synthesis of Enantiopure **4**[10a, 12]

The direct resolution of (±)-4 has advantages over the previous procedures for resolving diacid since the need for fractional recrystallization of **4** would be entirely bypassed. Ideally, **4** could be synthesized on multi-gram scale from 2-phenylacetonitrile in three steps without chromatography or recystallization (see Supporting Infromation for details).

The idea for direct resolution of the diketone by 1,1'-bi-2-naphthol (BINOL) came from an unexpected observation. Mixing a solution of (±)-**4** in toluene and a solution of (*R*)-BINOL in toluene resulted in the immediate formation of a white precipitate.[13,14] Thus, after stirring a mixture of (±)-**4** and 0.60 equiv of (*R*)-BINOL in toluene at rt for 5 min, a solid was collected by filtration and (*S*)-**4** was obtained in 91% ee by decomposition of the complex with aqueous NaOH (Table 1, entry 1). Both the yield and enantioselectivity were increased with the prolonged stirring time (entries 2 and 3). Various ratios of (±)-**4** and (*R*)-BINOL were investigated and it was found that the efficiency of the resolution gradually decreased when the

loading of (*R*)-BINOL was increased (entries 4 and 5). Varying the concentration did not provide better results (entries 6 and 7).

Table 1. Resolution of diketone (±)-**4** with (*R*)-BINOL[a]



entry	conc. (mol/L)	ratio **4**:BINOL	precipitation (*S*)-**4**		mother liquid (*R*)-**4**	
			yield/ %[b]	ee%	yield /%[b]	ee%
1[c]	0.20	1.0:0.60	36	91	63	-[f]
2[d]	0.20	1.0:0.60	44	93	55	-[f]
3	0.20	1.0:0.60	47	95	51	85
4	0.20	1.0:0.80	47	83	45	84
5	0.20	1.0:1.0	43	80	48	80
6	0.10	1.0:0.60	44	92	55	79
7	0.30	1.0:0.60	53	92	46	68
8[e]	0.20	1.0:0.65	(43)	(>99)	(42)	(>99)

[a] The reactions were conducted in 1.0 mmol scale of (±)-**4**. [b] Yields refer to the isolated yields after the decomposition with aqueous NaOH. [c] The mixture was stirred ar rt for 5 min. [d] The mixture was stirred ar rt for 1 h. [e] The reaction was carried out on 12.40 g (50.0 mmol) scale. The results in parenthesis are after one recystallization, for details see Supporting Information. [f] The ee% was not determined.

It is notable that the resolution performs very well for a multi-gram scale preparation of enantioenriched **4**. For example, stirring a mixture of (±)-**4** (12.40 g, 50.0 mmol) and (*R*)-BINOL (30.0 mmol) at room temperature for 10 h, followed by filtration and decomposition with aqueous NaOH, provides (*S*)-**4** and (*R*)-**4** in good yields and excellent enantiopurity after one recrystallization (Table 1, entry 8).

A single crystal of the complex suitable for X-ray analysis was obtained by slow evaporation of the solvent from a diluted solution containing 15 mg of the complex in 2.0 ml of toluene at room temperature. With (*R*)-BINOL being used as the resolution reagent, the absolute configuration of diketone in the complex was confirmed to be *S*. The ORTEP drawing of the complex (*S*)-**4**·(*R*)-BINOL are shown in Figure 2, which clearly showed the inclusion complex containing a 1:1 molar ratio of the diketone and BINOL.[15] Stronge hydrogen bonding was observed, where the nearest distance of two oxygen atoms [HO---O=C] is 2.827 Å, and the hydrgen bond OH---O=C is 2.096 Å (Figure 3).

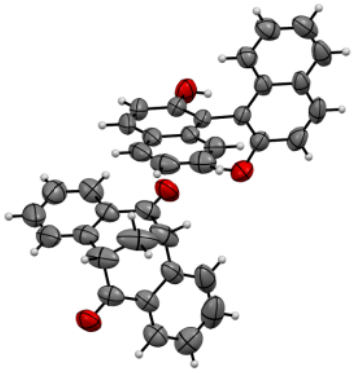


Fig. 2 ORTEP drawing of complex (*S*)-**4**·(*R*)-BINOL

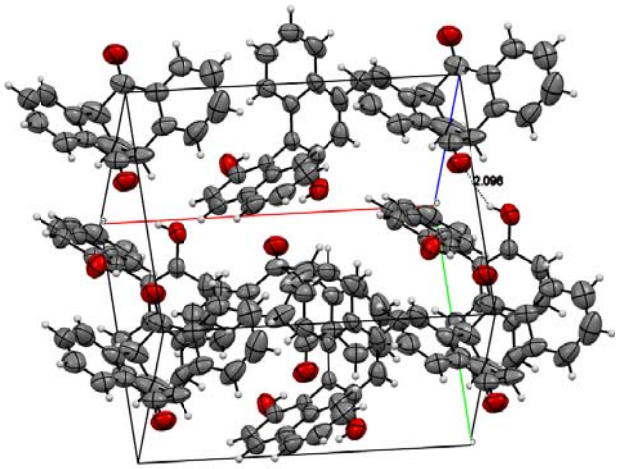


Fig. 3 Crystal packing of complex (*S*)-**4**·(*R*)-BINOL

The resolution in various solvents was also investigated. With CH_2Cl_2, ethyl acetate, or mixed PhMe/EtOAc as the solvent, the mass recovery after the precipitation was lower, and as a result the ee of (*R*)-**4** in the mother liquid was significantly decreased (Table 2, entries 1-3). Furthermore, the reaction gave only 22% yield after precipitation when the resolution was conducted in THF, even though the concentration was increased to 0.50 mol/L (entry 4). Due to the poor solubility of **4** in *t*-BuOMe, the resolution was conducted at a diluted condition, which gave a good yield and reasonably high enantioselectivity (entry 5).

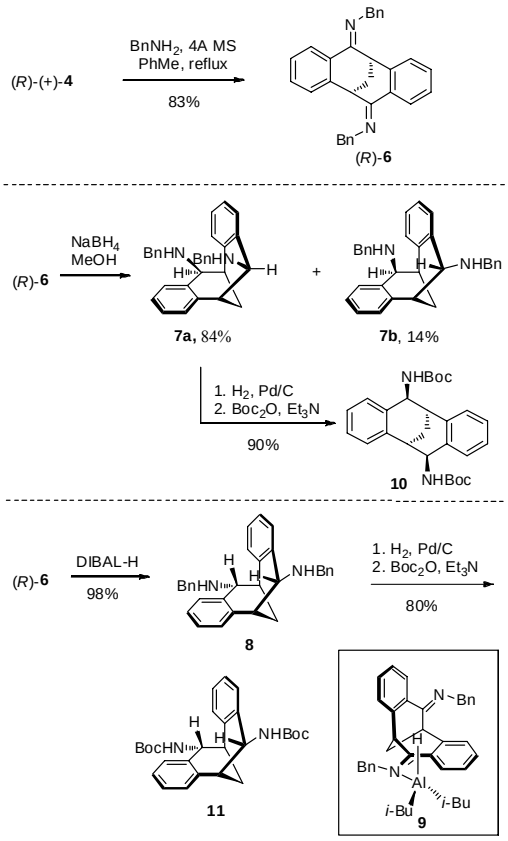
The carbonyl group in **4** provided opportunities for further transformations to other useful chiral compounds. Diketone (*R*)-(+)-**4** was advanced to *bis*-imine (*R*)-**6** as a single isomer in the presence of benzylamine and 4Å molecular sieve at reflux in toluene (Scheme 2).[16] Following the known procedure, reduction of the imine with $NaBH_4$ in MeOH gave *endo*-product **7a** in good yields, albeit a small amount of other isomers, such as **7b** were also detected.[12] The selectivity was presumably controlled by steric factors, where the reagent comes from the less hindered convex side of (*R*)-(+)-**4**. When diisobutylaluminium hydride

(DIBAL-H) was used, the reaction delivered *exo*-product **8** exclusively in excellent yield. This observation can possibly be explained by model **9** involving a tetrahedral aluminium complex. The sterically bulky isobutyl groups preferred to be at the convex side due to steric hindrance, and as a result the hydride was pushed to be at the concave position to give the *exo*-product. The related stereochemistry of both diamines **7a**[17] and **8** was unambiguously confirmed by X-ray crystallographic analysis (Figures 4 and 5).[18] The benzyl groups in **7a** and **8** could be de-protected under standard hydrogenation conditions with high selectivity. For the convenience of purification, the diamines were advanced to **10** and **11** in high overall yields.[19]

Table 2. Resolution of diketone (±)-**4** with (*R*)-BINOL in different solvents[a]

entry	solvent	Conc. (mol/L)	precipitation (*S*)-**4**		mother liquid (*R*)-**4**	
			yield/ %[b]	ee%	yield/ %[b]	ee %
1	CH_2Cl_2	0.20	31	94	67	56
2	EtOAc	0.20	33	90	56	48
3	Toluene/EtOAc(1:1)	0.20	40	92	49	58
4	THF	0.50	22	88	77	-[c]
5	*t*-BuOMe	0.07	44	89	54	-[c]

[a] The reactions were conducted in 1.0 mmol scale of (±)-**4**. [b] Yields refer to the isolated yields after the decomposition with aqueous NaOH. [c]The ee% was not determined.



Scheme 2 Synthesis of diamines **7a** and **8**

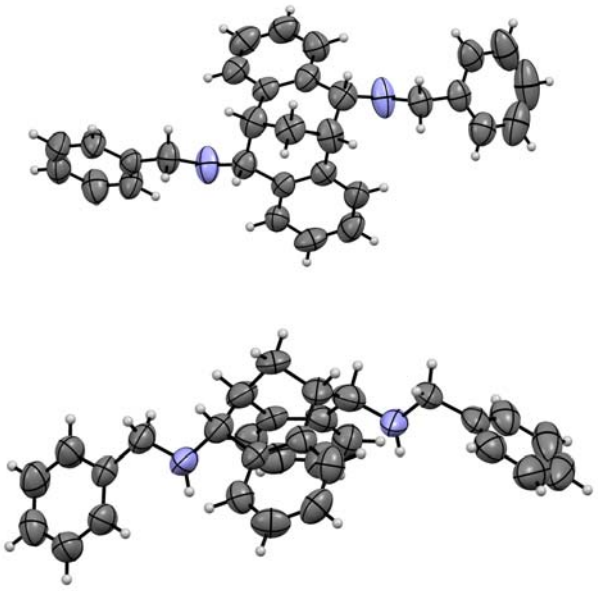


Fig. 4 ORTEP drawing of complex **7a** (up: top view; down: side view)

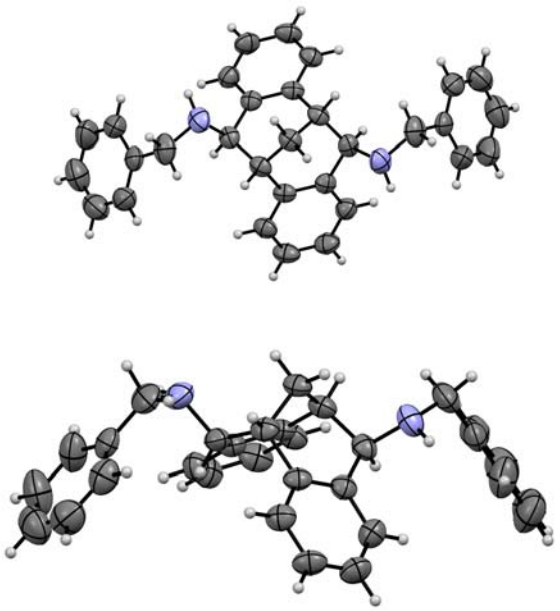


Fig. 5 ORTEP drawing of complex **11** (up: top view; down: side view)

In conclusion, we described a practical and efficient method for enantiomeric resolution of 2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene-4,8-dione (±)-**4**. Multi-gram quantities of both enantiopure (*S*)- and (*R*)-**4** could be synthesized from 2-phenylacetonitrile without a need for column chromatography. Further transformations of enantiopure **4** to its diamine derivatives **7a** and **8** were also performed. Synthetic applications, molecular recognition, and self-assembly studies of these V-shaped molecules are underway in our laboratory.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data, CIF files for (*S*)-**4**·(*R*)-BINOL, *rac*-**7a** and *rac*-**8**, ^{1}H and ^{13}C NMR spectra for all new compounds. See DOI: 10.1039/b000000x/

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15. CCDC 969970 contain the supplementary crystallographic data for complex (*S*)-**4**·(*R*)-BINOL. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.

16. The geometry of the bis-imine was confirmed by ^{1}H NMR and NOE studies, see Supporting Information for details.

17. CCDC 969971 contain the supplementary crystallographic data for compound *rac*-**7a**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.

18. CCDC 969972 contain the supplementary crystallographic data for compound *rac*-**8**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.

19. A pair of rotamers were observed by ^{1}H NMR at room temperature for both **10** and **11** probably due to the partially inhibited rotation of the amide functionalities. Clean NMR spectrscopies could be obtained by taking NMR at elevated temperature, see SI for details.