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Design, Synthesis and Optical Resolution of New Bifunctional Ligand: 1,1′-Dimethyl-octahydro-8,8′-Biquinoline-7,7′-diol

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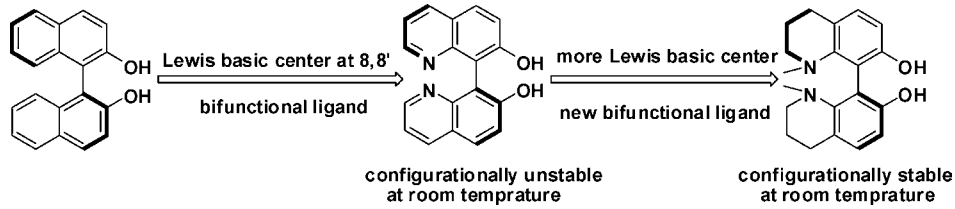
ABSTRACT



The design, synthesis and optical resolution of a new bifunctional ligand, 1,1′-dimethyl-octahydro-8,8′-biquinoline-7,7′-diol, is described. This new aza analogue of BINOL exhibits different properties as compared to BINOL.

Development of a new effective chiral ligand continues to be an important endeavor in the field of organic chemistry. This is because novel classes of chiral ligands not only offer additional synthetic opportunities but also provide new insights into fundamental chemical processes and new applications. Of all the widely employed chiral ligands, 1,1′-binaphthyl-2,2′-diol (BINOL) has emerged as one of the most powerful ligands in asymmetric catalysis.[1] Furthermore, BINOL-based synthons are also attractive molecular modules for applications in many fields such as chiral supramolecular recognition, crystal engineering and electronic materials.[2] Therefore, modification of the BINOL backbone is highly valuable in terms of tuning its steric and electronic properties for exploring new chiral ligands and new applications.

Efforts to modify the BINOL backbone were mainly focused on varying substituents at the C-3, C-4, C-6 and C-7 positions.[1c] Notably, the rotational barrier of peri C−H bonds contributed significantly to the configurational stability of BINOL, hence direct modification of this special moiety provides another important strategy to change its scaffold. In addition, the chiral core defined by the two naphthyl rings provides an ideal chiral environment for the transfer of stereoinformation. The functionalization of the 8, 8′-positions is also believed to have interesting implications in asymmetric induction. For example, F_8−BINOL,[3] H_8−BINOL[4] and H_4−BINOL[5] has been used to facilitate some asymmetric reactions with better enantioselectivities than BINOL itself.[6]

The axially chiral heterocyclic biaryl ligands have been explored in asymmetric synthesis and present many amazing properties for the discovery of new asymmetric catalytic methods.[7] In connection with our interest to explore new chiral ligand for asymmetric catalysis, we become interested

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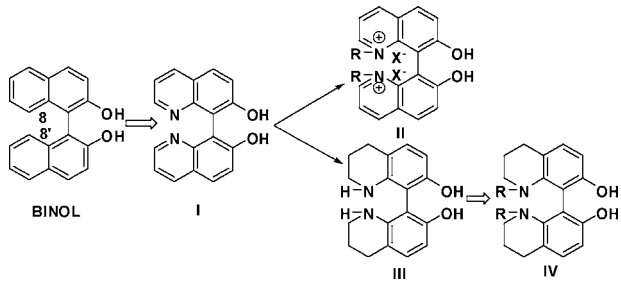
in introducing heteroatom into the 8,8′-positions of BINOL. However, upon replacement of 8-C by a sp^2-hybridized N-atom, the resulting bifunctional 7,7′-dihydroxy-8,8′-biquinolyl **I** was found to be configurationally unstable at room temperature to serve as a useful chiral ligand.[8] Furthermore, its high polarity and insolubility in common organic solvents and tedious resolution limited its application in asymmetric catalysis.

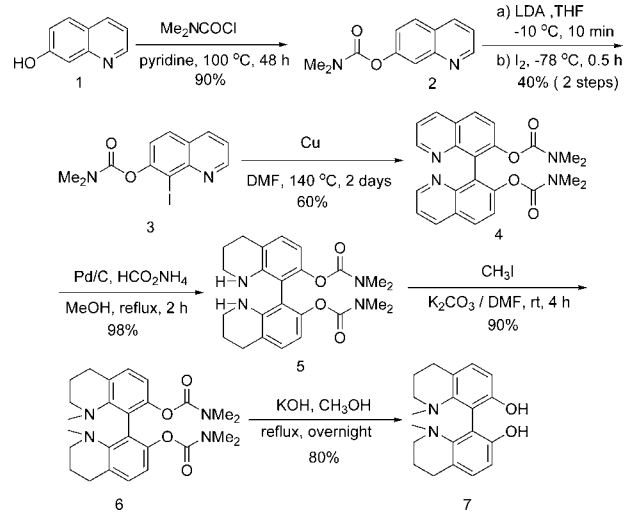
To resolve this problem, we envisaged that ligands **II** and **IV** should be configurationally stable and could serve as chiral ligand for asymmetric synthesis at room temperature. Preliminary results showed that alkylation of the sp^2-hybridized groove N-atom was difficult.[9] However, alkylation of sp^3 hybridized groove N-atom should be easier. Herein we report the synthesis and chiral resolution of the new bifunctional ligand **IV**, which is configurationally stable at room temperature to serve as a new chiral ligand for asymmetric catalysis. The octahydro biquinolyl part of **IV** should considerably induce electronic perturbation and steric tuning as an aza analogue of BINOL (Scheme 1).

Scheme 1. Design of New Bifunctional Ligand: Aza Analogue of BINOL



Initial attempts to synthesize the target molecules **III** or **IV** by various direct oxidative coupling reactions of 7-tetrahydroquinolinol or 1-methyl-7-tetrahydroquinolinol were unsuccessful.[10] Failure of the coupling reactions probably arises from the poisoning of the metal by the basic nitrogen atom. Finally, the established ullmann coupling strategy was found to be successful for the construction of the biaryl system.[8a] Starting from the 7-hydoxyquinoline, under the protection of dimethylaminocarbonyl chloride, carbamate **2** was obtained in 90% yield. Direct ortho metalation of carbamate **2** was carried out with LDA in THF at −78 °C, after which a solution of iodine in THF was added to the resulting metalate at −78 °C to afford 8-iodoquinoline **3** in 40% yield. Ullmann coupling of iodide **3** with copper catalyst proceeded in 60% yield to produce biaryl **4**. The quinoline part of **4** was effectively reduced to give biquinolyl **5** quantitatively in the presence of ammonium formate and Pd/C. Methylation of the amine was accomplished using potassium carbonate as base, and finally culminating at basic methanolysis of the carbamate groups of **6** to afford the target molecule **7** in good yield (Scheme 2). Compound **7** was

Scheme 2. Synthesis of Bifunctional Chiral Ligand: 1,1′-Dimethyl-octahydro-8,8′-biquinoline-7,7′-diol



observed to be less polar than **I** and exhibited good solubility in a wide range of common organic solvents such as CH_2Cl_2, $CHCl_3$ and THF which evaded the solubility problem for future application. An X-ray crystallographic analysis of **7** provided definitive proof of structure and revealed a preferred transoid conformation with the angle between the two aromatic ring planes being 124.97°.[11] N···H−O contact distances for intramolecular hydrogen bonds are 1.84 and 0.9 Å.

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(8) (a) Blakemore, P. R.; Kilner, C.; Milicevic, S. D. *J. Org. Chem.* **2005**, *70*, 373. (b) Blakemore, P. R.; Kilner, C.; Milicevic, S. D. *J. Org. Chem.* **2006**, *71*, 8212. (c) Blakemore, P. R.; Milicevic, S. D.; Zakharov, L. N. *J. Org. Chem.* **2007**, *72*, 9368.

(9) When MeI was used to conduct methylation of **4**, only trace of mono methylation product was observed. Further work is in progress.

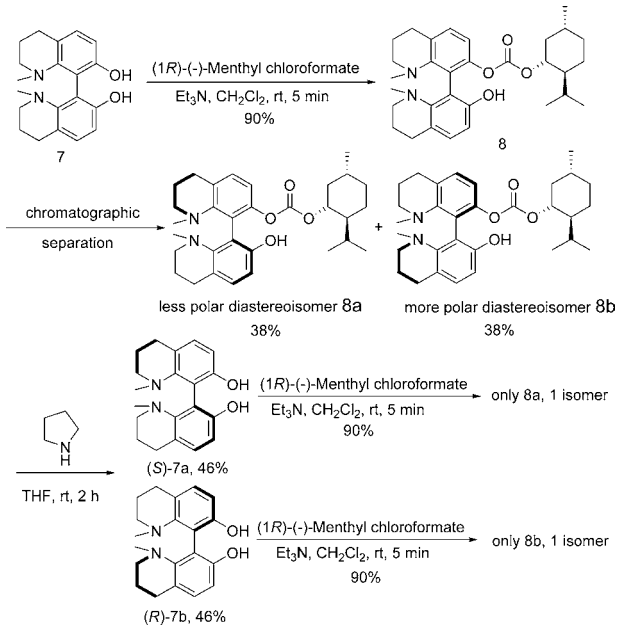
(10) The common single-electron oxidants methods tested are as follows. CuCl(OH)•TMEDA: (a) Noji, M.; Nakajima, M.; Koga, K. *Tetrahedron Lett.* **1994**, *35*, 7983. $CuCl_2BnNH_2$: (b) Vyskocil, S.; Smrcina, M.; Lorenc, M.; Tislerova, I.; Brooks, R. D.; Kulagowski, J. J.; Langer, V.; Farrugia, L. J.; Kocovsky, P. *J. Org. Chem.* **2001**, *66*, 1359. $FeCl_3$: (c) Ding, K.; Wang, Y.; Zhang, L.; Wu, Y.; Matsuura, T. *Tetrahedron* **1996**, *52*, 1005. $(NH_4)_2Ce(NO_3)_6$: (d) Jiang, P.; Lu, S. *Synth. Commun.* **2001**, *31*, 131.

(11) The angle between the two quinolyl ring planes of racemic **II** as its dimethanol solvate is 104.5° and racemic BINOL is only slightly transoid in the solid state (angle between naphthyl ring planes is 91.4°).

With an efficient synthesis of **7** established, its resolution was explored next. We found that the general methods using fractional crystallization of diastereomeric mixtures of salts or complexes formed with various chiral complexation reagents such as *N*-benzylcinchonidinium chloride or *trans*-1,2-diaminocyclohexane were unsuccessful.[12] This initial failure implied that lower acidity of phenol groups rendered hydrogen bonding formation with chiral reagents more difficult as the piperidine unit made the aromatic rings more electron-rich.

Among the chromatographic resolution methods of BINOL, the chromatographic separation of diastereomeric bismenthyl carbonate derivatives has proven to be particularly useful.[13] When excess of (−)-menthyl chloroformate was employed in the presence of triethylamine at room temperature, bismenthyl carbonates and monocarbonate were obtained simultaneously. However, different from the previous report,[13] the bismenthyl carbonate could not be resolved by fractional recrystallization or column chromatography. To our delight, the monomenthyl carbonate **8** could be separated by column chromatography (Scheme 3). Significant chemical

Scheme 3. Resolution of New Chiral Ligands and Configuration Determination



shift differences were observed in the ^{1}H NMR (Figure 3). For the menthyl moiety in **8a** and **8b**, the C-22 proton appears as a triplet at δ 4.37 ppm and 4.28 ppm respectively. The C-25 methyl group also showed significant difference as a doublet at δ 0.63 and 0.70 ppm correspondingly. The

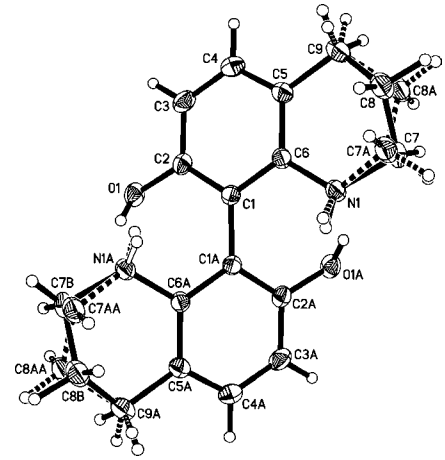


Figure 1. X-ray crystal structure of **7**.

less polar diastereoisomer **8a** was determined by X-ray crystallographic analysis (Figure 2) and it was assigned to

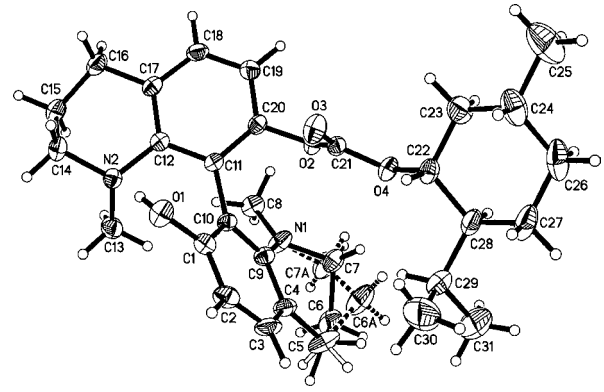


Figure 2. X-ray crystal structure of **8a**.

possess an (*S*)-configuration relating it to the configuration of (1*R*,2*S*,5*R*)-menthyl moiety. Clean removal of chiral auxiliary groups from **8a** and **8b** was achieved with pyrrolidine in THF at room temperature. (*S*)-**7a** and (*R*)-**7b** were obtained in good yields respectively. To determine the enantiomeric excess, reinstallation of menthyl carbonate units to freshly prepared enantioenriched (*S*)-**7a** or (*R*)-**7b** gave the corresponding **8a** or **8b** as single diastereoisomer which confirmed the optical purity of each enantiomer (≥99% ee, Figure 3). This issue was further confirmed by chiral HPLC (Chiralpak OD-H column, hexane/2-propanol 95:5, 1 mL/min) to afford a single peak in each case for (*S*)-**7a** or (*R*)-**7b** with retention times of 18.4 and 20.8 min respectively. Each enantiomer has been stored at room temperature for several months without any drop on its enantiopurity.

In summary, we have developed a new bifunctional ligand 1,1′-dimethyl-octahydro-8,8′-biquinoline-7,7′-diol as an aza analogue of BINOL. Both the enantiomers of 1,1′-dimethyl-octahydro-8,8′-biquinoline-7,7′-diol **7** could be easily ob-

(12) (a) Wang, Y.; Sun, J.; Ding, K. *Tetrahedron* **2000**, *56*, 4447. (b) Schanz, H. J.; Linseis, M. A.; Gilheany, D. G. *Tetrahedron: Asymmetry* **2003**, *14*, 2763.

(13) For resolution of BINOL through separation of the bis[(−)-menthoxycarbonyl] derivatives, see: Fabbri, D.; Delogu, G.; Lucchi, D. O. *J. Org. Chem.* **1995**, *60*, 6599. For bismenthyl carbonate resolution of aza BINOL I, see ref 8b.

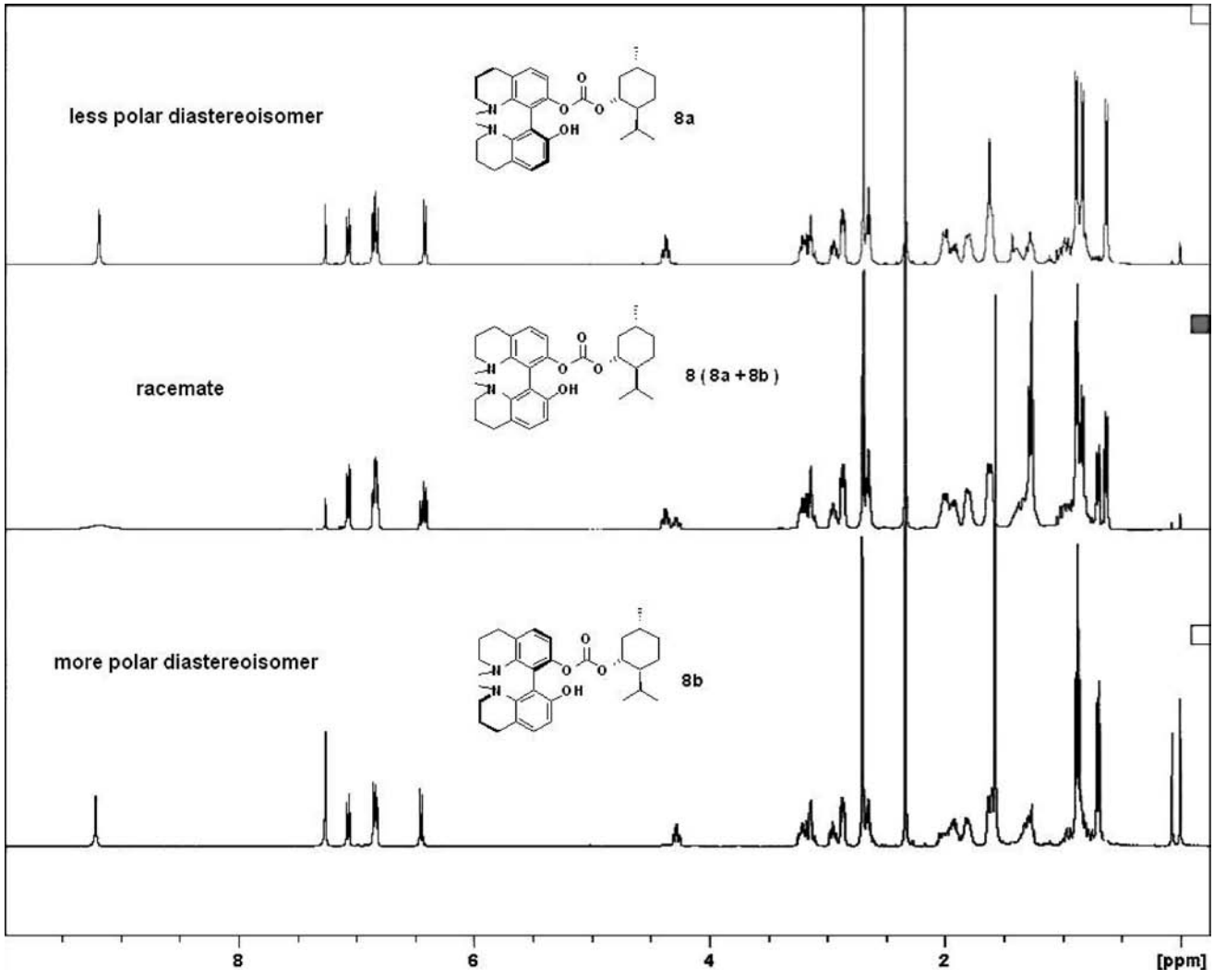


Figure 3. ^{1}H NMR of **8**, **8a** and **8b**.

tained via short steps. Its application in asymmetric catalysis is highly anticipated. This new member of the aza BINOL family will open up new catalyst design and provide synthetic material in many fields such as chiral supramolecular recognition and crystal engineering.

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Supporting Information Available: Additional experiment procedures, spectrum data for reactions products, and two CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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