

Development of a New Dimeric Cyclophane Ligand: Application to Enhanced Diastereo- and Enantioselectivity in the Catalytic Synthesis of β -Lactams

Harald Wack, Stefan France, Ahmed M. Hafez,
William J. Drury III, Anthony Weatherwax, and
Thomas Lectka*

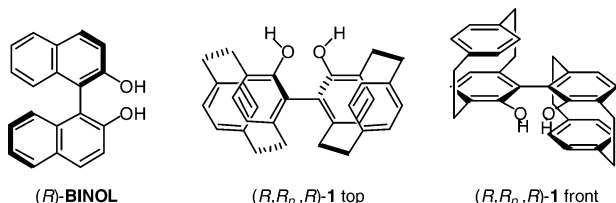
Department of Chemistry, New Chemistry Building,
Johns Hopkins University, 3400 North Charles Street,
Baltimore, Maryland 21218

lectka@jhu.edu

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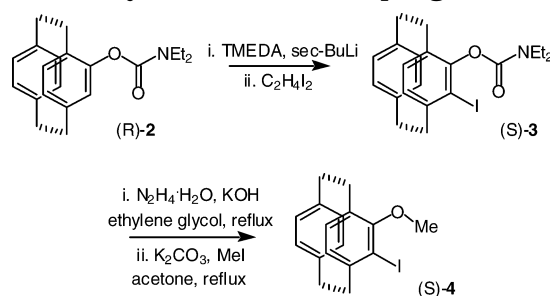
Abstract: We detail the synthesis of a new C_2 -symmetric bis(cyclophane) ligand system that can be thought of as electronically analogous to binol, but which possesses the added “third dimension” of cyclophane chirality. The ligand synthesis involves a spontaneous (but unexpected) atropisomerization to the desired product. We have employed this ligand to form a metal complex that is an effective cocatalyst for the highly enantio- and diastereoselective catalytic asymmetric synthesis of a β -lactam.

We thought it would be of interest to devise a new sterically bulky biaryl ligand system wherein the chiral bulk not only projects “horizontally” back from the metal center but also “vertically,” up and down from the site of catalysis, taking advantage of the added “third dimension” of cyclophane chirality,¹ in contrast to binol, which projects much less steric bulk in the vicinity of the metal. The result is a ligand system that possesses both planar and axial chirality and which may be appropriate for applications in which the use of binol is unsatisfactory. To demonstrate, in a preliminary fashion, the utility of this new ligand system, we apply an Al(III)-based complex of ligand **1** in the bifunctional, catalytic, asymmetric synthesis of β -lactams. The use of the ligand–metal complex in conjunction with a cinchona alkaloid cocatalyst provides enhanced yields of product in high diastereo- and enantioselectivity.



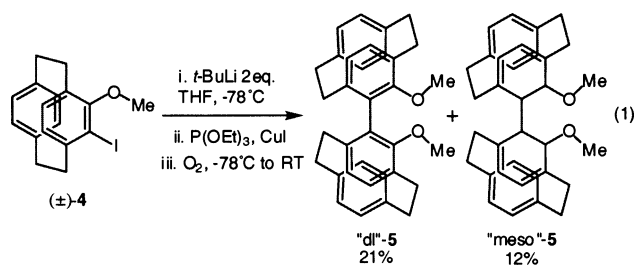
(1) For some examples of the use of cyclophanes as ligands, see: (a) Worsdorfer, U.; Vögtle, F.; Nieger, M.; Waletzke, M.; Grimme, S.; Glorius, F.; Pfaltz, A. *Synthesis* **1999**, 4, 597–602. (b) Hou, X.-L.; Wu, X.-W.; Dai, L.-X.; Cao, B.-X.; Sun, J. *Chem. Commun.* **2000**, 1195–1196. (c) Dahmen, S.; Brase, S. *Chem. Commun.* **2002**, 26–27. (d) Inoue, M. B.; Velazquez, E. F.; Medrano, F.; Ochoa, K. L.; Galvez, J. C.; Inoue, M.; Fernando, Q. *Inorg. Chem.* **1998**, 37, 4070–4075. (e) Pye, P. J.; Rossen, K.; Reamer, R. A.; Tsou, N. N.; Volante, R. P.; Reider, P. J. *J. Am. Chem. Soc.* **1997**, 119, 6207–6208.

SCHEME 1. Synthesis of Diol Coupling Precursor **4**



We envisioned the construction of ligand **1** from dimerization of a suitably functionalized cyclophane monomer, such as **4** (Scheme 1). The synthesis of **4** can be accomplished straightforwardly starting with the known carbamate **2**,² conveniently available in either racemic or optically pure forms as described by Pamperin et al. Iodination of either racemic or (*R*)-**2**, followed by deprotection by ethereal hydrazine and reprotection as the methyl ether, afforded the coupling precursor **4** in 87% overall yield from **2**.³

Formation of a di-(\pm)-copper(I)–ate complex from iodide (\pm)-**4** and its oxidation with molecular oxygen gave two new major products.⁴ These were shown to be both the “quasi-meso” (a racemic mixture of (*S,R_p*)-**5** and (*R,R_p*)-**5** in 12% yield) and the “quasi-dl” form of the dimer **5** ((*S,R_p*)-**5** and (*R,S_p*)-**5**, 21% yield) (eq 1). To our satisfaction, repeating the reaction with optically pure **4** produces one major dimeric product **5**. A single-crystal X-ray structure of **5** obtained from the coupling of (*R*)-**4** established its absolute configuration as (*S,R_p*)-**5**,⁶ the opposite of what we had desired.



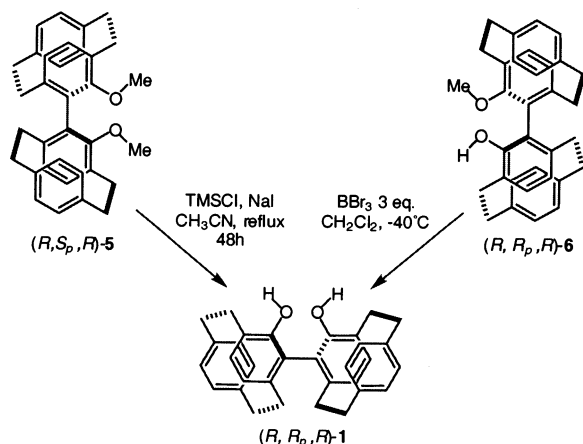
Surprisingly, treatment of (*R,S_p*)-**5** with BBr₃ at –40 °C not only resulted in the removal of one methyl ether but also initiated a concomitant atropisomerization to the desired (*R,R_p*)-**6** diastereomer (eq 2). Its configuration was also implied by the presence of an intramolecular hydrogen bond in the IR spectrum, necessitating proximity between the methoxy and hydroxyl groups. Depro-

(2) Hopf, H.; Grahn, W.; Barrett, D. G.; Gerdes, A.; Hillmer, J.; Hucker, J.; Y. O.; Kaida, Y. *Chem. Ber.* **1990**, 123, 841–845.

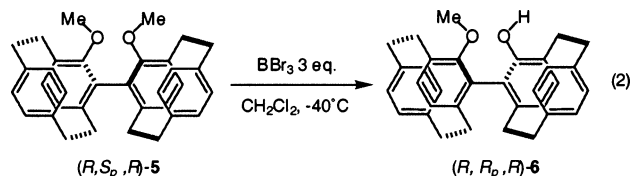
(3) Pamperin, D.; Schulz, C.; Hopf, H.; Syldatk, C.; Pietzsch, M. *Eur. J. Org. Chem.* **1998**, 7, 1441–1446.

(4) Whitesides, G. M.; SanFilippo, J. J.; Casy, C. P.; Panek, E. J. *J. Am. Chem. Soc.* **1967**, 89, 5302–5303.

(5) The stereochemical assignment for the coupled products adhere to the following denotation: (*A,B_p*, *C*): where *A* represents the absolute stereochemistry of the first cyclophane moiety; *B_p* represents the stereochemistry about the pivot bond (pivot or axial isomers); and *C* represents the configuration of the second cyclophane moiety.

SCHEME 2. Synthesis of (*R,R,p,R*)-Bis(cyclophane) Diol **1**


tection of either the (*R,S_p,R*)-isomer of diether **5** with *in situ* generated TMSI (83% yield) or the (*R,R_p,R*)-isomer of monoether **6** with BBr₃ resulted in the desired (*R,R_p,R*)-diol ligand **1** (Scheme 2).



Although diffractable crystals of the product **1** were not obtained, confirmation of its structure was achieved through the observation of a hydrogen bond in the IR spectrum analogous to that in (*R,R_p,R*)-**6** (the (*R,S_p,R*)-configuration of diol **1** would be unable to achieve this intramolecular H-bond for steric reasons), as well as the standard assortment of analytical data (NMR, MS). Also of note are the molecular mechanics calculations we performed on the cyclophane diol **1** and relevant intermediates. Monte Carlo calculations employing the MMFF force field predict that the (*R,R_p,R*)-diol **1** should be 9.1 kcal/mol more stable than the (*R,S_p,R*). Similarly, (*R,R_p,R*)-**6** is more stable than (*R,S_p,R*)-**6** by 8.6 kcal/mol, whereas (*R,S_p,R*)-**5** is more stable than (*R,R_p,R*)-**5** by 2.0 kcal/mol.⁷ These predictions are also mirrored in the DFT calculations (B3LYP/6-31G*) we performed that indicate a strong preference for (*R,R_p,R*)-diol **1** over (*R,S_p,R*)-diol **1** by 5.2 kcal/mol (see Figure 1 for DFT structure).⁸

To quantify the stabilization energy provided by the hydrogen bond, as a control, we modeled the difluorinated isostere **14**, in which the hydroxyl groups are replaced by fluorines (Figure 2). MMFF calculations predict that the (*R,R_p,R*)-**14** should be 6.7 kcal/mol more stable than its (*R,S_p,R*) counterpart. Thus, we can conclude that while hydrogen bonding accounts for almost 3 kcal/mol of stabilization for the (*R,R_p,R*) isomer according to MM

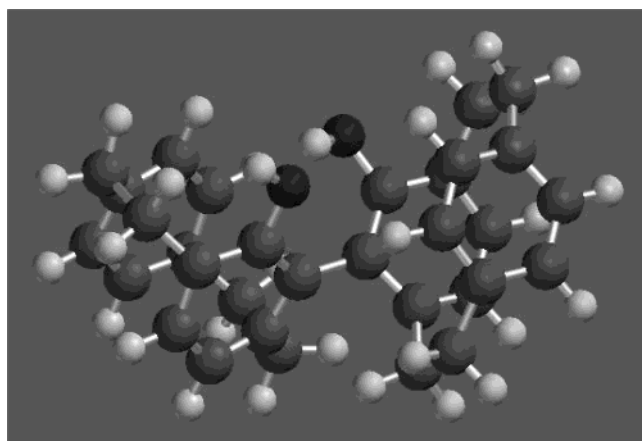


FIGURE 1. DFT structure of (*R,R_p,R*)-**1** (B3LYP/6-31G*).

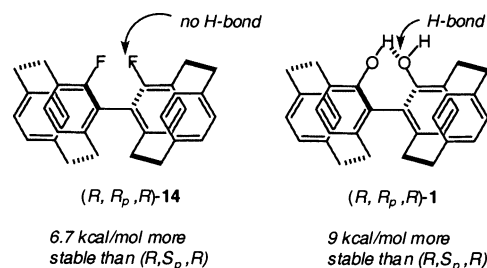
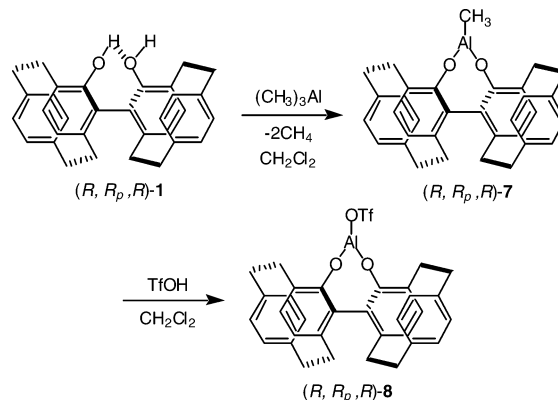


FIGURE 2. MMFF-calculated comparison of isomer stability for (*R,R_p,R*)-**14** and (*R,R_p,R*)-**1**.

SCHEME 3. Synthesis of the Putative Bis-(Cyclophanyl diol)AlOTf Complex


calculations, it is probably not solely responsible for the observed atropisomer equilibrium. Given the hydrocarbon based nature of the ligand system, both MM and DFT calculations should prove very reliable. In summary, these calculations explain the experimental data very well from a thermodynamic standpoint—namely, why (*R,S_p,R*)-**5** may be produced in the coupling reaction and why the atropisomerizations to (*R,R_p,R*)-**6** and (*R,R_p,R*)-**1** occur spontaneously upon deprotection. We can also conclude that on the basis of these calculations (*R,R_p,R*)-**1** must be formed in the deprotection.

Mixing (*R,R_p,R*)-**1** with either Zn(CH₃)₂ or Al(CH₃)₃ initiates immediate evolution of 2 equiv of CH₄ gas and loss of the phenolic protons (evidenced by ¹H NMR) (Scheme 3). Likewise, stirring (*R,R_p,R*)-**1** with TiCl₂-(^{*i*}PrO)₂ and molecular sieves causes the solution to turn

(6) Employing (*S*)-**4** in the coupling reaction provided the (*R,S_p,R*) enantiomer in identical yield.

(7) We used the program Macromodel (version 7.0) for the calculations (Schrodinger, Inc.).

(8) Calculations were performed using the Titan Program, version 2.0.

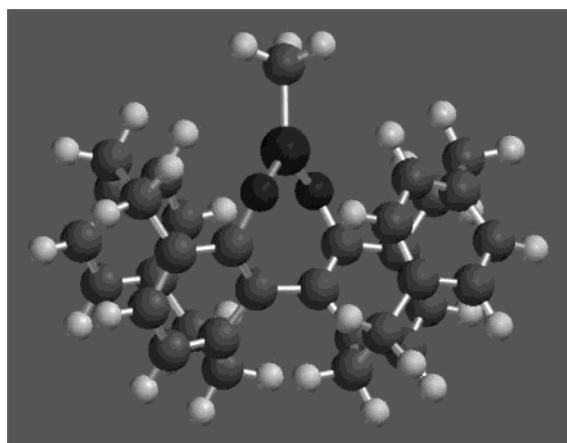
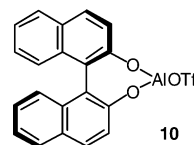


FIGURE 3. B3LYP/6-31G* structure of the putative bis-(cyclophanyl diol)AlCH₃ complex **7**.

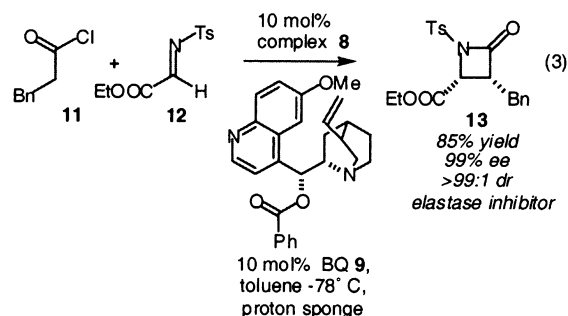
deep red, similar in color and appearance to the analogous complex obtained from binol. In contrast, the same experiments repeated with “quasi-meso” diol **1** resulted in reduced (or sporadic) gas evolution and with no apparent formation of a deep-red Ti(IV)-based complex. A DFT (B3LYP/6-31G*) structure of complex (*R,R,R*)-**7** is shown in Figure 3, revealing a metal surrounded by the considerable chiral bulk of the ligand. The methyl group of complex **7** could be burned off to form the corresponding triflate with 1 equiv of triflic acid to form **8**. Alternatively, *in situ* generation of complex **8** could be accomplished through treatment of diol **1** with Al(OTf)₃ and proton sponge base.

We immediately sought to establish the utility of the new ligand system in a Lewis acid-catalyzed asymmetric reaction as a test. An ideal candidate from our point of view is the bifunctional, Lewis acid/nucleophile-catalyzed synthesis of β -lactams recently developed in our laboratories.⁹ We discovered that Lewis acids (In(III), Zn(II), and Al(III), among others) work in tandem with cinchona alkaloid derivatives such as benzoylquinine (BQ, **9**) to produce β -lactams in high chemical yield and enantioselectivity in most cases. However, a side effect of some of our metal-cocatalyzed reactions is reduced diastereoselectivity (dr) and, in a few cases, enantioselectivity. We reasoned that the reactions could be brought to high levels of selectivity by the choice of an appropriate metal complex, perhaps one that was significantly bulkier than a bare metal salt. In earlier efforts, we screened a number of ligand–metal complexes, with limited success. For example, the team of Al–binol(OTf) **10** and BQ **9** (each 10 mol %) afforded product in moderate ee (80%), but only 8:1 dr.¹⁰ We were intrigued by the possibility that a

bulkier chiral diol ligand system could provide enhancements in selectivity and yield and thus afford the desired results.



We screened complex **8** (10 mol % BQ **9**, stoichiometric proton sponge as base) in the formation of β -lactam **13** (a potent inhibitor of human leukocyte elastase¹¹ that we need in large quantities for screening), under standard conditions (acid chloride **11**, imino ester **12**, toluene solvent, –78 °C), and found the diastereoselectivity of the reaction improved to 99:1. The enantioselectivity also improved to 99%, and the chemical yield increased to 85%, combining for a nearly ideal result. When the nonchelating “quasi-meso” diol **1** was examined as a control, the diastereoselectivity dropped to 6:1 cis/trans; the yield also dropped (70%). These results confirmed our original hypothesis that a bulky chiral diol ligand with appropriate stereochemistry attached to a metal could have positive effects on reaction selectivity and yield (eq 3).



In conclusion, further studies on ligand system **1** and its use as a ligand for chiral Lewis acid-catalyzed reactions are underway and will be reported in due course.

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Supporting Information Available: General procedures for the synthesis of ligand **1**, its precursors, its complexes, and β -lactam **13**. X-ray crystallographic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(10) When Al(OTf)₃ was used as the cocatalyst without BINOL ligand, lactam product was formed in 75% yield with 11:1 dr and 99% ee.

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