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A New Cationic, Chiral Catalyst for Highly Enantioselective Diels–Alder Reactions

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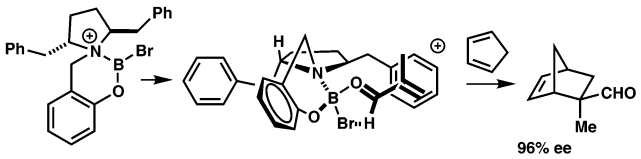
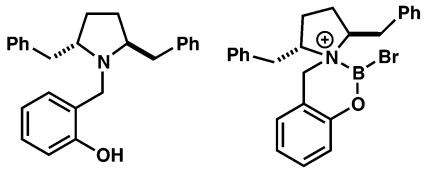
ABSTRACT

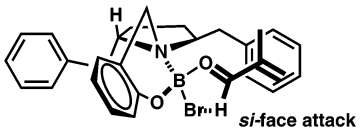


The Diels–Alder reaction of cyclopentadiene and 2-methacrolein is catalyzed by a chiral Lewis acid to form the exo adduct in 96% yield and 96% ee.

The use of chiral Lewis acids as catalysts for Diels−Alder reactions has transformed the classical thermal cycloaddition, already one of the most versatile and useful processes in the repertoire of synthetic chemistry, into even more powerful enantioselective versions in recent years.[1] The impact of research in this area has been multifaceted. The use of catalytic enantioselective Diels−Alder reactions to generate a chiral adduct from achiral starting materials greatly facilitates the synthesis of complex molecules.[1a] In addition, mechanistic studies have provided a remarkably detailed understanding of the organizing factors and pre-transition-state assemblies which give rise to high enantioselectivity.[1a,b,2] Further, the understanding of these structural and mechanistic principles provides a foundation for the prediction of the absolute stereochemical course of many new reactions and for the design of new catalysts. In this paper, we describe the successful design of a new catalytic system and its application to Diels−Alder reactions of α,β-enals as dienophiles. Because of the very high degree of Lewis acidity that can be achieved through the use of cationic Lewis acids,[3] we chose to design this type of catalyst. Specifically, the chiral bidentate amino phenol **1** was selected as a ligand for boron in Lewis acid **2**. The expectation was that Lewis acid **2** could catalyze enantioselective Diels−Alder additions with α,β-enals such as 2-methacrolein and direct the addition to the *si* face of the dieneophile via the pre-transition-state assembly **3**. The selection of a phenolic subunit in ligand **1** was made in order to preclude heterolytic C−O bond dissociation in the complex **2**. Such cleavage reactions have been found to limit the thermal stability of strong chiral Lewis acids.[1a,3] The choice of the C_2-symmetric pyrrolidine subunit in **1** was made on the basis of synthetic accessibility and the presence of a suitably placed π-rich aromatic neighboring group.[1]



1 **2**



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(1) For recent reviews, see: (a) Corey, E. J. *Angew.* Chem., *Int. Ed.* **2002**, *41*, 1650. (b) Evans, D. A.; Johnson, J. S. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 3, p 1177. (c) Diaz, L. C. *J. Braz. Chem. Soc.* **1997**, *2*, 289. (d) Corey, E. J.; Guzman-Perez, A. *Angew.* Chem., *Int. Ed.* **1998**, *37*, 488. (e) Ishihara, K.; Yamamoto, H. *Eur. J. Chem.* **1999**, 527.

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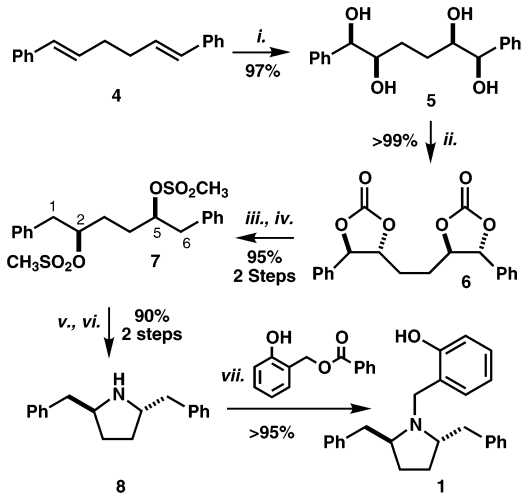
The synthetic route devised for the synthesis of **1** is outlined in Scheme 1. (*E*,*E*)-1,6-Diphenyl-1,5-hexadiene (**4**)[4]

Scheme 1. Synthesis of Ligand **1**[a]



[a] Reagents: (i) $K_3Fe(CN)_6$, $K_2OsO_4 \cdot 2H_2O$, $(DHQD)_2PHAL$, K_2CO_3, H_2O, *t*-BuOH, hexanes; (ii) triphosgene, Et_3N, CH_2Cl_2; (iii) Raney-Ni, H_2, EtOH; (iv) MsCl, Et_3N, CH_2Cl_2; (v) $BnNH_2$; (vi) Pd/C, H_2, EtOH; (vii) toluene.

(mp 78−80 °C) was synthesized from cinnamyl bromide by stirring with zinc powder and iodine in ether at −45 °C and purified to homogeneity on a 60 g scale by recrystallization from methanol. Enantioselective double bishydroxylation of **4** using the Sharpless catalytic system with the ligand $(DHQD)_2PHAL$ (2 mol %) and K_2OsO_4 (2 mol %) together with K_2CO_3, $K_3Fe(CN)_6$, and $CH_3SO_2NH_2$ in *t*-BuOH−H_2O−hexanes (1:1:0.6 by volume) at 4 °C for ca. 64 h gave tetraol **5**, mp 123−125 °C, in 97% yield and >99% ee as determined by HPLC analysis.[5−7] This enantiomerically pure tetraol was converted in >99% yield to the corresponding bis cyclic carbonate **6**, mp 131−133 °C, by reaction with triphosgene and Et_3N in CH_2Cl_2. Hydrogenolysis of **6** (1 atm H_2, Raney Ni, 23 °C, EtOH, Me_2CO) proceeded smoothly to form enantiomerically pure (*R*,*R*)-1,6-diphenylhexane-2,5-diol, mp 66−68 °C, $[\alpha]^{22}_D$ −12.5 (*c* = 2.4, $CHCl_3$). Addition of methanesulfonyl chloride to this diol and Et_3N in CH_2Cl_2 at −30 °C gave the crystalline bismesylate **7** (mp 99−101 °C) in 95% overall yield from the biscarbonate **6**. Reaction of **7** with 5 equiv of neat benzylamine at 80 °C for 10 h furnished *N*-benzyl-(*S*,*S*)-2,5-dibenzylpyrrolidine. A small amount (ca. 5%) of *cis*-*N*-benzyl-2,5-dibenzylpyrrolidine was formed in this reaction which is most conveniently removed after the next step.[8] *N*-Debenzylation of *N*-benzyl-(*S*,*S*)-2,5-dibenzylpyrrolidine was accomplished by stirring under 1 atm of H_2 with Pd−C catalyst in EtOH at 23 °C to form (*S*,*S*)-2,5-dibenzylpyrrolidine (**8**) in 90% overall yield from dimesylate **7**. Pure **8** was readily obtained by recrystallization of the hydrochloride salt from EtOAc. The final step in the synthesis of ligand **1** was effected in >95% yield by the reaction of **8** with 2-hydroxybenzyl benzoate in toluene at reflux for 1 h. This useful procedure involves the base-catalyzed elimination of benzoic acid from 2-hydroxybenzyl benzoate to form an intermediate orthoquinone methide which then serves as a Michael acceptor for **8**.

A simple procedure was devised for the synthesis of oxazaborolidine **2** from the chiral aminophenol **1**. ^1H and ^{11}B NMR studies demonstrated that boron tribromide does not coordinate with 2,6-di-*tert*-butylpyridine in $CDCl_3$ solution at room temperature or below since mixtures showed the same spectra as the sum of the component spectra. This finding led to the following method for generating catalyst **2** from **1** for use in situ. Ligand **1** (dried azeotropically with benzene or toluene) in CH_2Cl_2 at 10 °C was treated with 1 equiv of 2,6-di-*tert*-butylpyridine and subsequently with 1 equiv of boron tribromide to produce a colorless precipitate. The mixture was allowed to warm to room temperature (23 °C) leading to a colorless, clear solution. After a further 15 min at 23 °C, formation of **2** had proceeded to completion and the catalyst solution was cooled to −94 °C or −78 °C for the subsequent Diels−Alder reaction. A number of Diels−Alder reactions were performed with **2** (10 mol %) that had been prepared in this way with excellent results using 2-substituted α,β-enals as dienophiles. These results and also the result of one test with a quinone as dienophile are summarized in Table 1 for reactions in CH_2Cl_2 with cyclopentadiene (5 equiv) as test diene and catalyst **2** (10 mol %). It is evident from the rapidity of these Diels−Alder reactions at −78 to −94 °C that catalyst **2** is a powerful Lewis acid. The absolute configurations of the products were assigned from comparison of optical rotation with known values, and ee determinations were made by GC or ^1H NMR

(2) Corey, E. J.; Lee, T. W. *J. Chem. Soc., Chem. Commun.* **2001**, 1321.

(3) See: (a) Hayashi, Y.; Rohde, J. J.; Corey, E. J. *J. Am. Chem. Soc.* **1996**, *118*, 5502. (b) Corey E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, *124*, 3808. (c) Ryu, D. H.; Lee, T. W.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 9992. (d) Bruin, M. E.; Kündig, E. P. *J. Chem. Soc., Chem. Commun.* **1998**, 2635. (e) Kündig, E. P.; Saudan, C. M.; Bernardinelli, G. *Angew.* Chem., *Int. Ed.* **1999**, *38*, 1220.

(4) For previous syntheses, see: (a) Clive, D. L. J.; Anderson, P. C.; Moss, N.; Singh, A. *J. Org. Chem.* **1982**, *47*, 1641. (b) De Meijere, A.; Stecker, B.; Kourdioukov, A.; Williams, C. M. *Synthesis* **2000**, 929. (c) Doering, W. v. E.; Birladeanu, L.; Sarma, K.; Teles, J. H.; Klärner, F. G.; Gehrke, J.-S. *J. Am. Chem. Soc.* **1994**, *116*, 4289. (d) Ishiyama, T.; Ahiko, T.-A.; Miyaura, N. *Tetrahedron Lett.* **1996**, *37*, 6889. (e) Lutz, R. P.; Berg, H. A. J. *J. Org. Chem.* **1980**, *45*, 3915. (f) Orita, A.; Watanabe, A.; Tsuchiya, H.; Otera, J. *Tetrahedron* **1999**, *55*, 2889. (g) Pasto, D. J.; L'Hermine, G. *Tetrahedron* **1993**, *49*, 3259. (h) Sasaoka, S.; Yamamoto, T.; Kinoshita, H.; Inomata, K.; Kotake, H. *Chem. Lett.* **1985**, 315. (i) Sjoholm, R.; Rairama, R.; Ahonen, M. *J. Chem. Soc., Chem. Commun.* **1994**, 1217. (j) Yanagisawa, A.; Hibino, H.; Habaue, S.; Hisada, Y.; Yasue, K.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 1263.

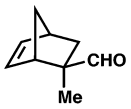
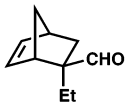
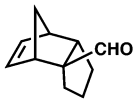
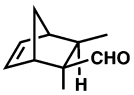
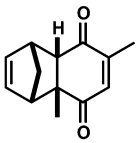
(5) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768.

(6) The use of hexanes as cosolvent and the addition of a solution of the substrate **4** in hexanes to the well-stirred reaction mixture are essential to efficient bis-dihydroxylation.

(7) The enantiomeric purity of the tetraol **5** was determined by HPLC analysis at 23 °C using a Chiracel AD column with 1% isopropyl alcohol in hexanes (retention time for **5** 16.7 min; retention times for the corresponding racemate 18.3 and 16.7 min; retention times for the corresponding 5,6-diastereomeric racemate 19.9 and 21.7 min).

(8) The formation of *cis*-*N*-benzyl-2,5-dibenzylpyrrolidine in small amounts from the reaction of benzylamine with the bis-mesylate **7** may be due to π-neighboring group participation by phenyl to form a phenonium ion which then reacts with benzylamine to give a benzylamino mesylate with overall retention. Cyclization by an internal S_N2 reaction of this amino mesylate would then lead to *cis*-*N*-benzyl-2,5-dibenzylpyrrolidine.

Table 1. Diels−Alder Reactions of α,β-Enals and Cyclopentadiene with Catalyst **2** (10 mol %)

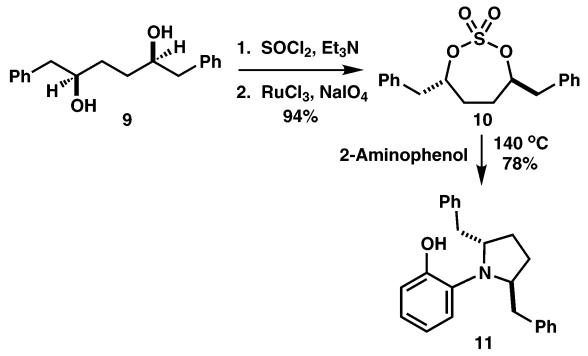
product	t [°C], time	yield	*exo:endo*	*ee*
	–94 ºC, 1 h	96%	>99:1	96%
	–94 ºC, 1 h	94%	>99:1	94%
	–78 ºC, 10 h	90%	>99:1	90%
	–78 ºC, 1 h	92%	>99:1	86%
	–78 ºC, 6 h	76%	1:>99	86%

analysis of Mosher derivatives as previously described.[3a−c,9] The isolation of pure Diels−Alder adducts and recovery of ligand **1** (>99%) was accomplished simply by flash chromatography on silica gel using either ether-pentane or EtOAc−hexanes for elution. The quantitative recovery of ligand **1** for reuse together with its synthetic accessibility and the high enantioselectivities shown in Table 1 combine to make this new catalytic methodology an attractive option. The effectiveness of catalyst **2** for the quinone Diels−Alder subtype indicates a wider potential for catalyst **2** in synthesis. The simplicity of the methodology can be seen from an illustrative example.[10]

The absolute configurations of the adducts listed in Table 1 are in accord with the predictions made on the basis of the pre-transition-state assembly **3**, thus supporting the general mechanistic model for enantioselective catalytic Diels−Alder reactions which has been developed.[1a,2,3a−c] The results obtained so far indicate that the replacement of the two phenyl groups in ligand **1** and catalyst **2** by 3,5-dimethylphenyl could lead to an even more effective catalytic Diels−Alder system due to the greater π-electron basicity of the 3,5-dimethylphenyl group as compared to phenyl.[1,3a−c]

An interesting observation was made on the reaction of cyclopentadiene and catalyst **2** with 2-bromoacrolein and 2-chloroacrolein. We were surprised to find that, although these reactions were very fast (complete within ca. 20 min at −94 °C) and gave >97% yields of exo adduct, the enantioselectivities were distinctly lower than for the other α,β-enals listed in Table 1; 65% ee for bromoacrolein and 71% ee for chloroacrolein. In previous work, ee's of Diels−Alder adducts from 2-bromo- and 2-chloroacrolein were found to be at least as high as with 2-methacrolein.[1a,2,3a] Additional research will be required to understand the basis for the divergent behavior of catalyst **3**.

We believe that there are numerous other useful applications of the readily available chiral diol **9**. For example, it can be used to prepare the cyclic sulfate **10** and the novel amino phenol **11** as shown below.



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Supporting Information Available: Experimental procedures for the synthesis of **4**−**11** and for the Diels−Alder reactions summarized in Table 1 and characterization data for the products shown in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388.

(10) **Illustrative Procedure for Catalyst Preparation and Diels−Alder Reaction.** Ligand **1** was dried by azeotropic distillation from toluene or benzene, and all volatiles were removed under vacuum (<0.5 mm) for 2 h with magnetic stirring. Ligand **1** (21.2 mg, 0.059 mmol) was dissolved in CH_2Cl_2 (1.5 mL) under N_2 and cooled to 10 °C, and 2,6-di-*tert*-butylpyridine (13.3 μL, 0.059 mmol) was added. Boron tribromide (59 μL, 0.059 mmol, as a 1.0 M solution in CH_2Cl_2) was added slowly to the reaction mixture, and a colorless precipitate formed. The cold bath was removed, and the reaction mixture was allowed to warm to room temperature over 4−5 min during which time the precipitate had dissolved. Fifteen minutes after dissolution of the solid, the colorless, clear reaction mixture was cooled to −94 °C (liquid N_2, hexanes), and methacrolein (49 μL, 0.59 mmol) was added directly to the stirred reaction mixture. A precooled solution (−94 °C) of 1,3-cyclopentadiene (247 μL, 2.95 mmol, in 494 μL of CH_2Cl_2) was added by cannula along the cold flask wall to the reaction mixture over a 10 min period. The reaction was monitored by TLC, and quenched with Et_3N (ca.. 100 μL) upon completion. The reaction mixture was carefully concentrated (volatile product) under reduced pressure, and the slurry was subjected to flash chromatography on silica gel (Et_2O−pentane; for less volatile products, EtOAc−hexanes) to furnish (1*S*,2*R*,4*S*)-bicyclo[2.2.1]hept-5-ene-2-methyl-2-carboxaldehyde (77.2 mg, 96%) and ligand **1** (21.2 mg, >99%). Product R_f values were as follows (10% EtOAc−hexanes): 2,6-di-*tert*-butylpyridine, R_f = 0.78. (1*S*,2*R*,4*S*)-bicyclo[2.2.1]hept-5-ene-2-methyl-2-carboxaldehyde, R_f = 0.46; ligand **1**, R_f = 0.28.