First Example of a Highly Enantioselective Catalytic Diels−Alder Reaction of an Achiral C_{2v}-Symmetric Dienophile and an Achiral Diene

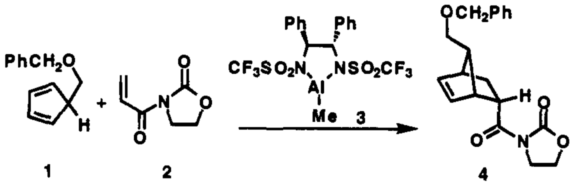
E. J. Corey,* Sepehr Sarshar, and Duck-Hyung Lee

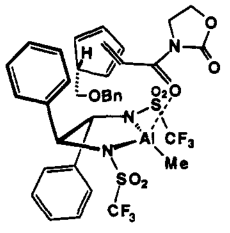
Department of Chemistry, Harvard University
Cambridge, Massachusetts 02138

Received August 29, 1994

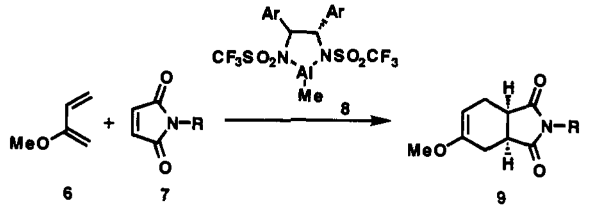
The recent development of highly enantioselective catalytic Diels−Alder reactions of achiral components has been one of the most gratifying advances in synthetic chemistry.[1,2] The reactants have been mainly relatively simple dienes, e.g., cyclopentadiene and monosubstituted butadienes, and unsymmetrical dienophiles, e.g., acrylic or substituted acrylic derivatives. Reported herein is a new type of system, involving an effectively C_{2v}-symmetric *Z*-dienophile, in which enantioselectivity requires dissymmetry in the diene moiety. The origin of enantioselectivity and the variation of enantioselectivity with catalyst and dienophile structure are also described.

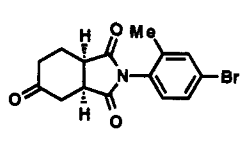
The present study sprang from earlier findings involving Diels−Alder reactions such as the addition of **1** to **2** under catalysis by the diazaluminolidine **3** (10 mol %, −78 °C, in CH_2Cl_2), which affords the adduct **4** in 93% yield and 94% enantiomeric excess (ee) by way of the experimentally suggested transition-state assembly **5**.[3] From this starting point, a highly enantioselective reaction has been developed which is exemplified by the addition of 2-methoxybutadiene (**6**) to *N*-*o*-tolylmaleimide (**7**, R = *o*-tolyl) in the presence of catalyst **8**, Ar = 3,5-dimethylphenyl (20 mol %, −78 °C, in C_7H_8), to give the adduct **9**, R = *o*-tolyl, in 98% yield and 93% ee;[4] one recrystallization from *i*-PrOH−hexane furnished the enantiomerically pure compound. The absolute configuration of the adduct **9** was determined by carrying out a parallel experiment with *N*-(*p*-bromo-*o*-tolyl)maleimide, which produced the adduct **9**, R = 4-bromo-2-methylphenyl, in 96% yield and >97% ee,[4] purification of this product to 100% ee by recrystallization from *i*-PrOH−hexane, acid-catalyzed hydrolysis of the enol ether function to give ketone **10**, and absolute structure determination of **10** by X-ray crystallography (anomalous dispersion analysis).[5,6]



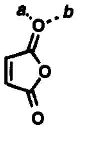


5

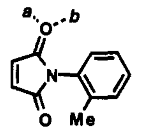




10



11



12

The *m*-methyl substituents in catalyst **8**, Ar = 3,5-dimethylphenyl, are crucial for the realization of high enantioselectivity, as is shown by the fact that the use of catalyst **8**, Ar = phenyl, with 2-methoxybutadiene and **7**, R = *o*-tolyl, affords adduct **9**, R = *o*-tolyl, in only 58% ee. The ortho substituent in the *N*-aryl group of dienophile **9** is also critical to enantioselective Diels−Alder reaction with 2-methoxybutadiene, as is shown by the ee values observed for catalyst **8**, Ar = phenyl, as a function of R in **9** (R = Ph, 30% ee; R = *o*-FC_6H_4, 48% ee; R = *o*-$CH_3C_6H_4$, 58% ee; R = *o*-*t*-BuC_6H_4, 52% ee), as well as for catalyst **8**, Ar = 3,5-dimethylphenyl, as is shown by the ee values as a function of R in **9** (R = Ph, 62% ee; R = *o*-$CH_3C_6H_4$, 93% ee; R = *o*-*t*-BuC_6H_4, 95% ee; R = *o*-IC_6H_4, 93% ee).

The Diels−Alder reaction of 2-methoxybutadiene with maleic anhydride and catalyst **8**, Ar = C_6H_5 (10 mol %, −78 °C, in CH_2Cl_2), proceeds rapidly, *but produces completely racemic adduct.* This fact and the contrast between the enantioselectivity of the catalyzed Diels−Alder reactions of maleic anhydride and the *N*-arylmaleimides **7** can readily be understood if the coordination of catalyst **8** to maleic anhydride occurs at lone pair b rather than lone pair a in **11**. Coordination of **8** at lone pair b in **11** places the dienophilic α,β-double bond so far from the chiral catalyst that no enantioselection can be expected. In the case of the *N*-arylmaleimides such as **12**, coordination of catalyst **8** to lone pair b is effectively blocked by the bulky aryl group.

Several lines of evidence support the proposition that the highly enantioselective maleimide Diels−Alder reactions described above proceed by a transition-state assembly analogous to **5**. X-ray studies in the crystalline state[5] and ^1H and ^{13}C NMR studies in solution demonstrate that catalyst **8**, Ar = 3,5-dimethylphenyl, is structurally analogous to **8**, Ar = phenyl,[3a] and exists under these conditions as a diazaluminolidine which is dimeric due to coordination between sulfonamide oxygen and aluminum. In the presence of 1 equiv of *N*-(*o*-*tert*-butylphenyl)maleimide per Al in CD_2Cl_2 solution at −73 °C, a 1:1 diazaluminolidine−maleimide complex is formed whose structure is clearly evident from ^1H NMR experiments which show the NOE enhancements summarized in formula **13**. The proton spectrum reveals that the 3,5-dimethylphenyl groups are rotating rapidly so that, for example, Me_1 and Me_2 are equivalent. The data clearly indicate the proximity of H_1 (4.4 ppm) to H_α (6.82 ppm), Me_1 (2.3 ppm) to H_β (7.08 ppm), and Me_3 of *tert*-butyl at 1.33 ppm to Me_1 (2.3 ppm). An alternative stereographic view of the *o*-tolyl analog of complex **13**, which shows more clearly

---

[1] For early studies, see: (a) Hashimoto, S.; Komeshima, M.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1979**, 437. (b) Narasaka, K.; Inoue, M.; Okada, N. *Chem. Lett.* **1986**, 1109.

[2] For recent reviews, see: (a) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007. (b) Togni, A.; Venanzi, L. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 497. (c) Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* **1993**, *93*, 741. (d) Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763.

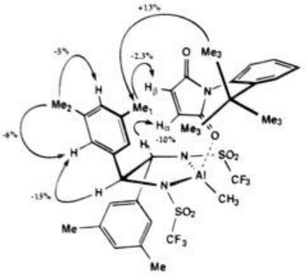
[3] (a) Corey, E. J.; Sarshar, S.; Bordner, J. *J. Am. Chem. Soc.* **1992**, *114*, 7938. (b) Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, X. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493. (c) Corey, E. J.; Imai, N.; Pikul, S. *Tetrahedron Lett.* **1991**, *32*, 7517.

[4] Enantiomeric purity of the Diels−Alder adducts with *N*-arylmaleimides was determined by HPLC analysis using a Chiralpak AD column (Chiral Technologies Inc.) with *i*-PrOH−hexane for elution.

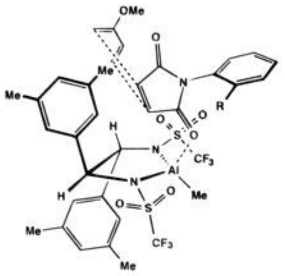
[5] Detailed X-ray crystallographic data are available from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, U.K.

[6] Empirical formula $C_{15}H_{14}O_3NBr$; $[\alpha]^{23}{}_D$ −36° (c = 1.6, CH_2Cl_2); mp 167−168 °C; space group $P2_1,2_1,2_1$; a = 7.206(1) Å, b = 13.426(2) Å, c = 15.290(4) Å; V = 1479.2(5) Å^3; Z = 4; Mo Kα radiation (296 K); 2236 independent reflections (R_{int} = 2.54%); 1592 observed reflections ($F_o > 4\sigma(F_o)$); absolute configuration (η) 1.04(4); R_w = 5.41%; GOF = 1.14.

0002-7863/94/1516-12089$04.50/0

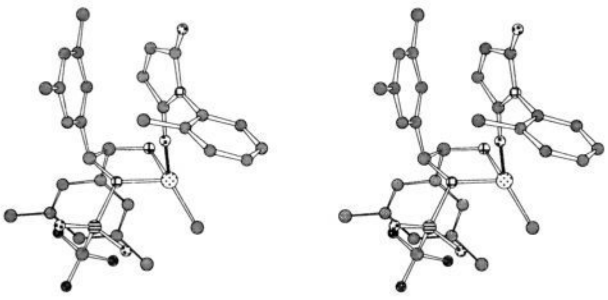


13



15

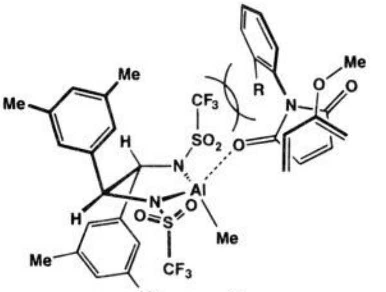
the obstruction of one face of the dienophile by the aromatic group of the catalyst, is given in formula **14**. In this depiction an O−Al−C angle at 150° has been used since the literature of X-ray crystal structures of complexes of carbonyl compounds with Lewis-acidic aluminum suggests that this angle should fall in the range 140−160°.[7,8] If complex **13** were to react as such with 2-methoxybutadiene, the diene would have to approach from the rearward direction, as shown in **15**, since attack from the foreground is prevented by the 3,5-dimethylphenyl group which is blocking the front face of the dienophile.



14 (one CF_3SO_2 omitted for clarity)

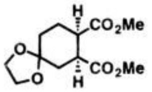
⊕ O ◌ Al ⊕ N ● F ⊜ S ● C

It is important to note not only that the transition-state assembly **15** leads to the observed sterochemistry of the Diels−Alder product but also that the diene must add to the complexed dienophile in the relative orientation which is shown in **15**. This is obviously a more favorable orientation with regard to the matching of diene HOMO and dienophile LUMO coefficients than the opposite relative positioning of diene and dienophile components which would lead to the enantiomeric (very minor) product.[9] In complex **13/14** all the ring substituents can be accommodated without unfavorable steric repulsion, even the *tert*-butyl group. The beneficial effects of the methyl groups in the 3,5-dimethylphenyl moiety of the catalyst and the ortho substituent in the phenylmaleimide moiety can be readily explained in terms of **13/14**, because these groups contribute to steric shielding at the front face of the dienophile. Indeed, inspection of molecular models suggests that there may be van der Waals attraction between the aromatic methyl substituents in the catalyst part of **13** and the *tert*-butyl (or other ortho group) of the *N*-arylmaleimide partner which can favor the organization of the catalyst−dienophile complex as shown in **13**. Another way in which these substituents can serve to channel the catalytic Diels−Alder addition in the observed absolute stereochemical direction is to disfavor an alternative transition-state assembly, **16** which is the result of a rotation of *ca.* 180° about the Al−O bond of complex **13/14**. In **16** there is quite serious steric repulsion between the ortho substituent of the phenylmaleimide component and one of the (trifluoromethyl)sulfonyl groups of the catalyst, as indicated in the drawing. Another strong argument against reaction *via* **16** derives from the fact that this transition-state assembly does not lead to an explanation of the superiority of catalyst **8**, Ar = 3,5-dimethylphenyl, over **8**, Ar = phenyl.

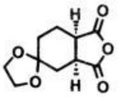


16

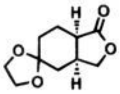
To the best of our knowledge, the Diels−Alder processes described herein represent the *first instances of highly enantioselective (>20:1) addition of two carbons to an effectively C_{2v}-symmetric olefin.* The basis of the observed enantioselection has been clarified by the stereomechanistic data presented above, which clearly favor transition-state assembly **15** over other possibilities (e.g., **16**). These new insights provide an excellent basis for the design of new catalytic enantioselective reaction systems. We have converted these enantiomerically pure adducts of 2-methoxybutadiene into a number of useful synthetic intermediates, for example **17**-**20**, using known transformations.[10]



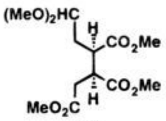
17



18



19



20

The enantioselective Diels−Alder reactions of *N*-arylmaleimides are potentially useful for the synthesis of complex natural products, for instance gracilin B.[11−14]

Supplementary Material Available: Experimental procedures for Diels−Alder reactions and catalyst synthesis (14 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

---

[7] Unfortunately, we have been unable to grow X-ray quality crystals of any 1:1 complex of catalyst **8**, Ar = 3,5-dimethylphenyl, with various N-ortho-substituted phenylmaleimides. X-ray data reported for carbonyl complexes with Al Lewis acids indicate a variation of Al−O−C angle from 133° to 174°, the largest angles being observed with very bulky Lewis acids. See: (a) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 256. (b) Power, M. M.; Bott, S. G.; Clark, D. L.; Atwood, J. L.; Barron, A. R. *Organometallics* **1990**, *9*, 3086. (c) Healy, M. D.; Mason, M. R.; Gravelle, P. W.; Bott, S. G.; Barron, A. R. *J. Chem. Soc., Dalton Trans.* **1993**, 441.

[8] If the Al−O−C angle were 170−180°, no NOE proximity effects should be observed between the *tert*-butyl and H_β protons of the dienophile and Me_1 of the catalyst, as can be verified by inspection of molecular models, since these groups would not be in sufficient proximity. If the Al−O−C angle were 130−140°, the arguments used for the 150° angle could be used with equal force, although the smaller angle seems less likely on steric grounds as well as from literature data.

[9] In this connection, it is noteworthy that the reaction of isoprene with *N*-(2-methyl-4-nitrophenyl)maleimide in the presence of catalyst **8**, Ar = 3,5-dimethylphenyl (20 mol %, −78 °C, in toluene for 36 h), affords the Diels−Alder adduct in 74% yield and 67% ee, whereas the corresponding reaction with 2-methoxybutadiene is faster and produces the Diels−Alder adduct in 97% yield and >95% ee.

[10] Manuscript in preparation.

[11] (a) Mayol, L.; Piccialli, V.; Sica, D. *Tetrahedron Lett.* **1985**, *26*, 1253. (b) Mayol, L.; Piccialli, V.; Sica, D. *J. Nat. Prod.* **1986**, *49*, 823.

[12] The advantages of the Diels−Alder methodology described herein include readily available starting materials, efficiently recoverable catalytic ligand, and high yields of enantiomerically pure Diels−Alder adduct after recrystallization. The catalytic ligand and catalyst are available from tetramethylbenzil as previously described for **8**, Ar = C_6H_5; see: Corey, E. J.; Pikul, S. *Org. Synth.* **1992**, *71*, 22. See also the supplementary material for the present paper.

[13] For studies of diastereoselective Diels−Alder reactions between a chiral 1,3-diene and maleic anhydride or maleimides, see: (a) Tripathy, R.; Carroll, P. J.; Thornton, E. *J. Am. Chem. Soc.* **1991**, *113*, 7630. (b) Menezes, R. F.; Zezza, C. A.; Sheu, J.; Smith, M. B. *Tetrahedron Lett.* **1989**, *30*, 3295.

[14] This research was assisted financially by the National Institutes of Health and the National Science Foundation.