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π-Facial Stereoselectivity in Diels−Alder Cycloadditions to 1-Oxaspiro[4.5]deca-6,9-dien-8-one. The Strong Directive Effect of Ether Oxygen in a Cross-Conjugated Ketone Setting

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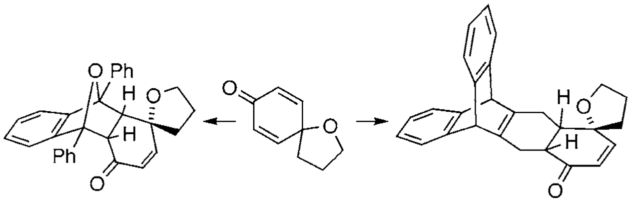
ABSTRACT



The title compound 1, prepared from 1,4-cyclohexanedione monoethylene ketal, was treated with several reactive dienes, including diphenylisobenzofuran and 9,10-dihydro-11,12-dimethylene-9,10-ethanoanthracene. These [4 + 2] cycloadditions proceed with a strong kinetic bias for bonding to the dienophile from the direction syn to the tetrahydrofuranyl oxygen and consequently hold value in stereoselective synthesis.

The facial stereoselectivity intrinsic to the $(4 + 2)\pi$ addition of dienes to a double bond desymmetrized by virtue of nearby substitution holds the potential for providing fundamental insight into a subtle means for gaining high-level diastereoselectivity. Past exploration of this aspect of stereoelectronic control has been most intensively pursued from the perspective of reactions involving functionalized semicyclic dienes,[1] cyclopentadienes,[2] and 1,3-cyclohexadienes[3] with π-facially symmetric dienophiles. The consequences of positioning allylic substituents into relatively rigid cyclic dienophiles on directed Diels−Alder capture have been accorded more limited attention.[4] The available data reveal that the stereogenic centers being established come under the control of steric, orbital, and electrostatic influences.[5] The relative importance of these factors is the subject of continuing discussion and analysis. The explanations have

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(1) For example: (a) Fisher, M. J.; Hehre, W. J.; Kahn, S. D.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 4625. (b) Datta, S. C.; Franck, R. W.; Tripathy, R.; Quigley, G. J.; Huang, L.; Chen, S.; Sihaed, A. *J. Am. Chem. Soc.* **1990**, *112*, 8472. (c) Kawamata, T.; Harimaya, K.; Iitaka, Y.; Inayama, S. *Chem. Pharm. Bull.* **1989**, *37*, 2307. (d) Giuliano, R. M.; Buzby, J. H.; Marcopulos, N.; Springer, J. P. *J. Org. Chem.* **1990**, *55*, 3555. (e) Burnouf, C.; Lopez, J. C.; Calvo-Flores, F. G.; Laborde, M. A.; Olesker, A.; Lukacs, G. *J. Chem. Soc., Chem. Commun.* **1990**, 823. (f) Grabby, S.; Kluge, H.; Hoppe, H.-U. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 664.

(2) For example: (a) Breslow, R.; Hoffman, J. M., Jr. *J. Am. Chem. Soc.* **1972**, *94*, 2110. (b) Franck-Neumann, M.; Sedrati, M. *Tetrahedron Lett.* **1983**, *24*, 1391. (c) Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675. (d) Paquette, L. A.; Vanucci, C.; Rogers, R. D. *J. Am. Chem. Soc.* **1989**, *111*, 5792. (e) Ishida, M.; Beniya, Y.; Inagaki, S.; Kato, S. *J. Am. Chem. Soc.* **1990**, *112*, 8980.

(3) For example: (a) Auksi, H.; Yates, P. *Can. J. Chem.* **1981**, *59*, 2510. (b) Holmberg, K.; Kirudd, H.; Westin, G. *Acta Chem. Scand., Ser. B* **1974**, *28*, 913. (c) Yates, P.; Gomes, A.; Burnell, D. J.; Cong, D. D.; Sawyer, J. F. *Can. J. Chem.* **1989**, *67*, 37. (d) Gillard, J. R.; Burnell, D. J. *J. Chem. Soc., Chem. Commun.* **1989**, 1439. (e) Gillard, J. R.; Newlands, M. J.; Bridson, J. N.; Burnell, D. J. *Can. J. Chem.* **1991**, *69*, 1337.

(4) (a) Dâu, M.-E. T.-H.; Wartchow, R.; Winterfeldt, E.; Wong, Y.-S. *Chem. Eur. J.* **2001**, *7*, 2349. (b) Jeroncic, L. O.; Cabal, M.-O.; Danishefsky, S. J.; Shulte, G. M. *J. Org. Chem.* **1991**, *56*, 387. (c) Dauben, W. G.; Kowalczyk, B. A.; Lichtenthaler, F. W. *J. Org. Chem.* **1990**, *55*, 2391.

(5) Reviews: (a) Fallis, A. G.; Lu, Y.-F. In *Advances in Cycloaddition*; Curran, D. P., Ed.; Jai Press: Greenwich, CT, 1993; Vol. 3, pp 1−66. (b) Mehta, G.; Uma, R. *Acc. Chem. Res.* **2000**, *33*, 278. (c) Cieplak, A. S. *Chem. Rev.* **1999**, *99*, 1265. (d) Ohwada, T. *Chem. Rev.* **1999**, *99*, 1337.

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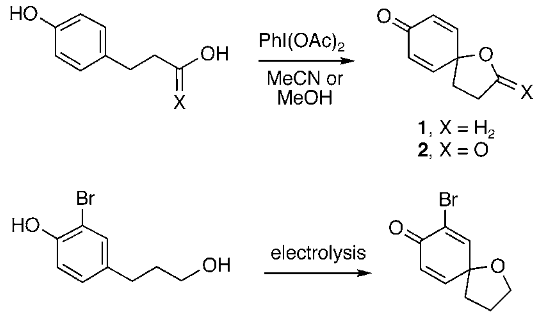
focused on ground-state as well as transition-state properties. When the level of diastereoselection is high, as is often the case, the transformation holds particular attraction for adaptation in stereodirected synthesis.

In continuation of our long-standing interest in the utilitarian potential of spirotetrahydrofurans,[6,7] we have now probed the dienophilic behavior of **1**, a cyclohexadienone in which the two surfaces of its π-network differ as a direct consequence of their syn or anti relationship to the flanking C−O bond. At issue is the extent to which incoming dienes recognize this structural feature, which has previously been shown to exert a significant effect on nucleophilic additions to the carbonyl group of **1**, **2**, and related compounds.[8,9] Also, during the late stages of the present investigation, Ohkata and co-workers reported as part of a synthetic effort directed toward scyphostatin their discovery of the significant preference of cyclopentadiene for addition predominantly syn to the lactone oxygen of **2**.[10]

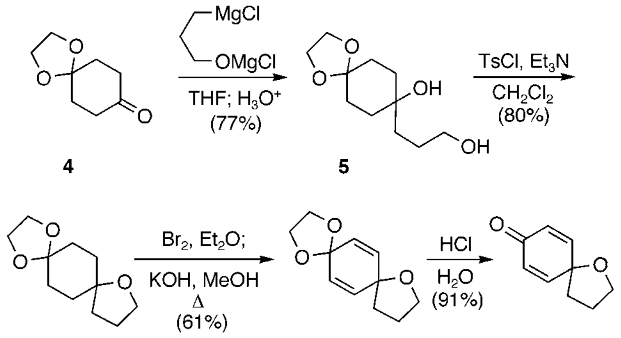


1, X = H$_2$
2, X = O

3

The spiro oxygenation pattern resident in **1** and **2** can be introduced directly in modest yield by oxidative cyclization of 3-(4-hydroxyphenyl)propanol or its carboxylic acid congener.[8] Constant current electrolysis of the *o*-bromo derivative similarly leads to **3**.[11] Despite this precedent, we chose to advance on **1** via the route defined by Scheme 1 because of the generality offered for modification of the size of the oxygenated ring on demand.[12] This versatile, four-step pathway commenced with the addition of the Normant reagent[13] to commercially available 1,4-cyclohexanedione monoethylene ketal (**4**). Generation of the spirotetrahydrofuran ring was realized spontaneously following monotosylation.[14] Bromination−dehydrobromination of **6** according to the Garbisch protocol[15] provided a reliable means for the introduction of a pair of double bonds as in **7**. The title ketone **1** was obtained following exposure of this acetal to aqueous acid.

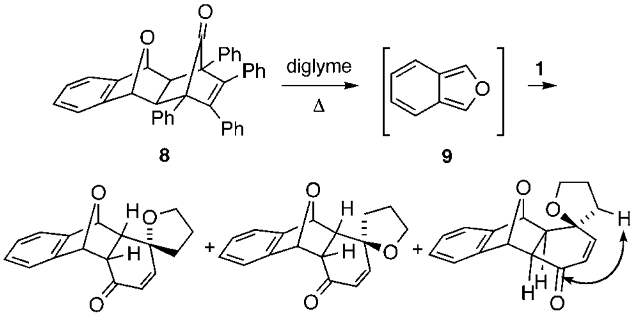
Scheme 1



4 **5** **6** **7** **1**

In order that Lewis acid catalysis could be avoided to simplify mechanistic considerations, attention was directed to highly reactive dienes as reactants. In the first instance, heating **8** with **1** in diglyme to allow for trapping of in situ-generated isobenzofuran (**9**) as it was formed[16] afforded three adducts that were amenable to chromatographic separation (Scheme 2).

Scheme 2



10 (63%) **11** (10%) **12** (6%)

The two less polar bridged ethers **10** and **11** were readily identified as the end products of endo addition on the basis of the magnitude of the *J* values between the bridgehead and fused-ring protons (5.9, 4.8 Hz).[17] The coupling constant between the pair of fused-ring protons is 9.0 Hz. In contrast, no coupling between the fused-ring and bridgehead protons is seen in the ^{1}H NMR spectrum of **12**, thereby defining it

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(6) Overview: Paquette, L. A. In *Chemistry for the 21st Century*; Keinan, E., Schechter, I., Eds.; Wiley-VCH: Weinheim, 2001; pp 37−53.

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to be an exo adduct. The relative stereochemistry of the spirotetrahydrofuran unit in **10** and **12** was established by means of X-ray crystallography (Figure 1) and NOESY measurements, respectively. The percentages given in the schemes are the actual isolated yields.

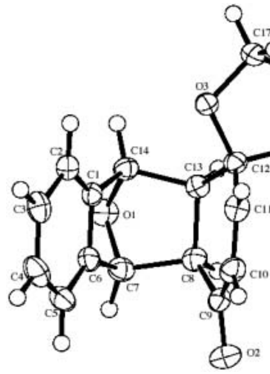
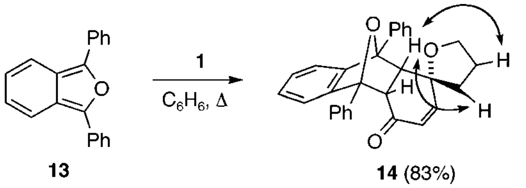


Figure 1. ORTEP diagram for **10**.

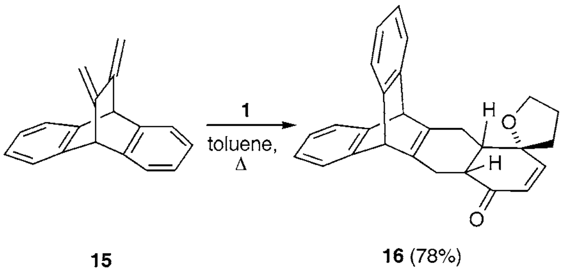
When the more sterically demanding diphenylisobenzofuran **13**[18] was heated in benzene with **1**, **14** was formed as the exclusive cycloaddition product (Scheme 3). The spectroscopic data for **14**, most particularly the features of its NOESY spectra, identify it as the result of endo addition from the direction syn to the tetrahyrofuranyl oxygen.

Scheme 3



The conformational inflexibility of **15**,[19] which enforces a reactive s-cis geometry, is likewise conducive to Diels–Alder cycloaddition with **1**. The sole product observed after heating in toluene for 48 h was **16** (78% yield) (Scheme 4).

Scheme 4



The structural assignment to **16** was validated by a three-dimensional crystallographic analysis (Figure 2), which clearly defines the fact that capture syn to oxygen is again kinetically dominant.

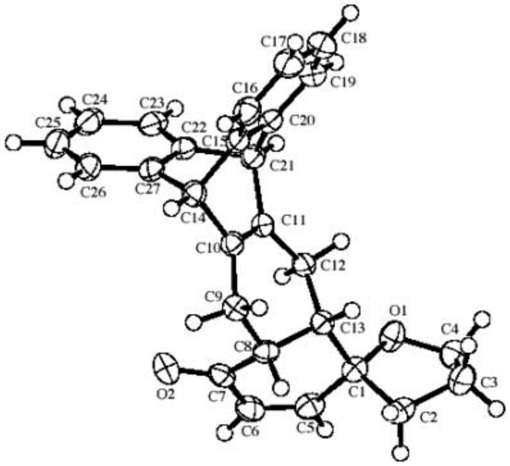


Figure 2. ORTEP diagram for **16**.

The next candidate reactions involved cyclopentadiene and spiro[2,4]hepta-4,6-diene.[20] When these cycloadditions were found to proceed very slowly in benzene and dichloromethane at room temperature as well as toluene at 90 °C, a switch in solvent to trifluoroethanol was made. Under these conditions, warming at 36 °C for 6 h was required to consume **1** and cyclopentadiene completely (Scheme 5). The product composition consisted of a chromatographically separable mixture of the endo adducts **17** (83%) (J = 4.3, 3.5 Hz) and **18** (7%) (J = 4.4, 3.4 Hz). The strong NOE interactions indicated on the formulas confirmed the preference for utilization of the π surface syn to the tetrahydropyranyl oxygen. As concerns the less reactive spiro diene, overnight heating at 55 °C resulted in 40% recovery of **1**. The key point is that the formation of **19** (66%) (J = 4.4, 3.3 Hz) dominates over the formation of **20** (20%) (J = 4.5, 3.5 Hz), but with an accompanying dropoff in syn selectivity from >10:1 to about 3:1.

The striking consistency of the stereoselectivity pattern exhibited by **1**, which exceeds in magnitude that found to be operational with acyclic dienes carrying a heteroatom substituent at C5,[21] is intriguing. Unlike the open-chain examples, rotation about single bonds with possible control

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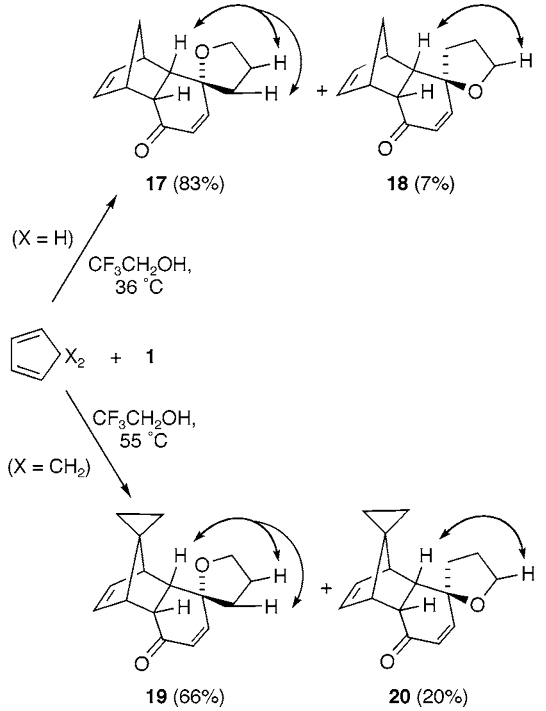
Scheme 5



arising from nonbonded steric factors cannot intervene in **1**. Wipf has calculated the dipole moment of **1** to be 2.1 D, with the vector components being oriented orthogonal to the plane of the π-system and elecrostatically directed outward from the ether oxygen.[9] Kahn and Hehre have suggested on theoretical grounds that electron-rich dienes should exhibit a preference for attack onto the face of the dienophile that is syn to the directing allylic substituent.[22] FMO and PM3 calculations involving related compounds have been reported by Winterfeldt, Houk, and co-workers.[4a,23] Our results are in concert with these deductions and reveal further that solvent changes do not seem to alter this kinetic bias significantly.

We conclude that elecrostatic control can be relied upon for reaction planning in asymmetric synthesis, at least where tetrahydrofuran controlling elements are concerned. The natural progression from methoxy to oxirane and then to oxetane and tetrahydrofuran is well recognized to be accompanied by changes in basicity.[24] For example, oxetane is a stronger base than methyl ethyl ether. In light of these issues, it would seem worthwhile to examine ring-size effects on π-facial stereoselectivity. Studies of this nature are in progress.

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Supporting Information Available: Experimental procedures and complete ^{1}H NMR, ^{13}C NMR, IR, and HRMS data for all compounds, as well as the crystallographic details for **10** and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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