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Diels-Alder Cycloadditions of Rigid Dienophiles: A Probe for Allylic Axial Substituent Control of the pi-Facial Selectivity in the Diels-Alder Reaction.

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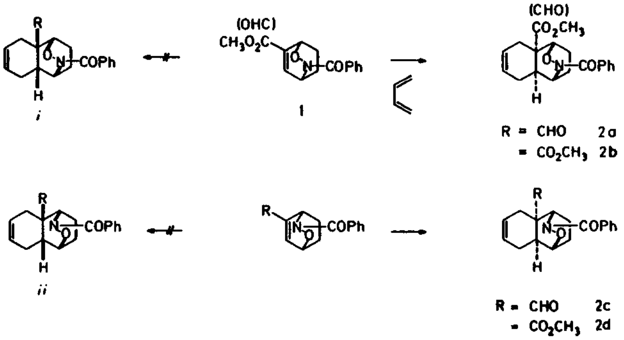
Summary: A study of the pi-facial selectivity of the Diels-Alder reaction of N-benzoyl 5-methoxycarbonyl-2-aza-oxabicyclo[2.2.2]oct-4-ene, a rigid electron deficient dienophile bearing two allylic axial heteroatom substituents, with 1-methoxy-3-trimethylsilyloxybutadiene, a representative electron rich diene, is detailed.

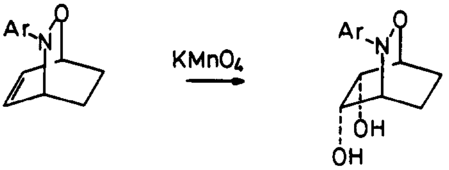
Recent interest in the application of the Diels-Alder reaction to the stereo- and enantiocontrolled synthesis of functionalized aliphatic substrates has focused attention on the potential ability of allylic substituents to effectively control or direct the pi-facial selectivity observed in the [4 + 2] cycloaddition.[2] A guiding pretext for the expectant observation of such control is derived from the detailed observations on nucleophilic attack on pi systems and analogies which might be drawn between the two reaction types. Thus, it has been advanced that in the absence of complexation or chelation control and in the absence of overriding steric considerations, the pi-facial selectivity of the normal Diels-Alder ($HOMO_{diene}$ controlled) reaction may be subject to the same allylic substituent control as nucleophilic attack at an electron deficient pi system.[3] In the case of nucleophilic addition to a pi system, theoretical support[4] has been provided for the observed pi-facial approach of the incoming nucleophile which occurs antiperiplanar to a large or electronegative allylic substituent. These observations, which are based on the initial empirical generalizations of Cram[5] and which have been further refined in the recent studies of Felkin[6] and Houk,[7] have been advanced to explain the observed [4 + 2] cycloaddition products in Diels-Alder reactions subject to such secondary orbital control.[3]

In recent efforts,[8] we disclosed the results of a study of the Diels-Alder reaction of butadiene with a series of electron deficient N-benzoyl 2-aza-oxabicyclo[2.2.2]oct-4-enes (eqn. 1), rigid dienophiles possessing two allylic axial heteroatom substituents. Expectant efforts to obtain the [4 + 2] cycloadducts **i** - **ii** (eqn. 1), which would arise from an antiperiplanar pi-facial approach of butadiene to the two allylic axial heteroatom substituents were not successful and exclusive approach of butadiene syn to the heteroatom bridge was observed. Thus, the observed results contrast the predictions based on the currently proposed secondary orbital control.[3] These



eqn (1)

results were particularly surprising in light of the reported behavior of *N*-(*p*-chlorophenyl)-2-aza-oxabicyclo[2.2.2]oct-4-ene (i) in which antiperiplanar attack of potassium permanganate provides the diol ii, eqn. 2.[9] Thus, predictions based on conventional evidence would seem to substantiate the expected, but not observed, approach of butadiene antiperiplanar to the allylic heteroatom substituents.



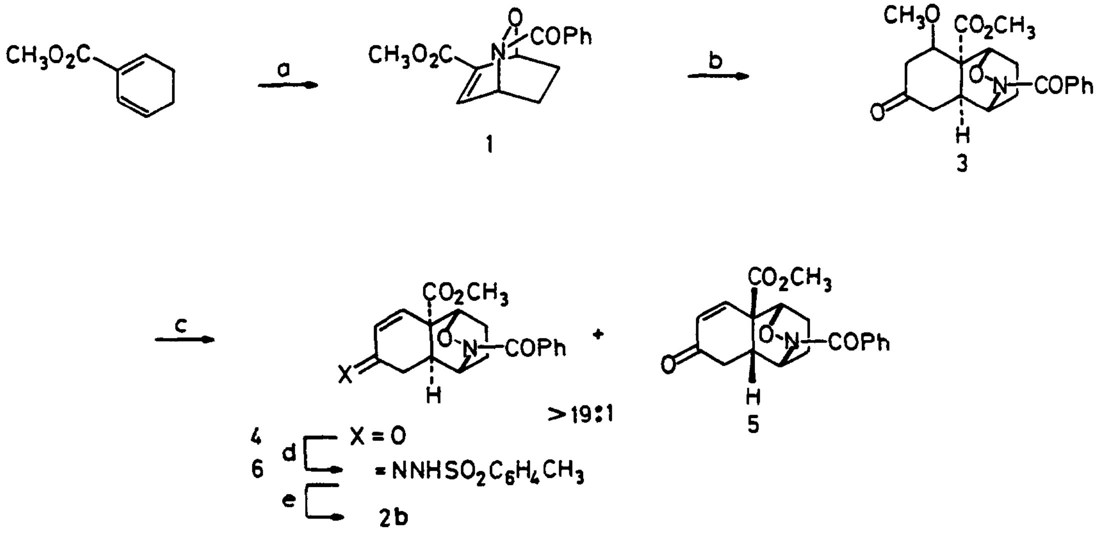
i ii

eqn (2)

In order to determine whether the observed behavior of butadiene with **1** represented the general pi-facial selectivity capable of extrapolation to conventional $HOMO_{diene}$ controlled Diels-Alder reaction of electron-rich dienes with **1** and perhaps related electron deficient dienophiles, a similar study of the stereochemical, pi-facial selectivity of **1** with 1-methoxy-3-trimethylsilyloxybutadiene, a commonly employed nucleophilic diene was investigated, scheme I. Treatment of **1** with 1-methoxy-3-trimethylsilyloxybutadiene (2.0 equiv, 120 °C, 48h) afforded **3** (75%) which upon acid catalyzed elimination of methanol provided the near exclusive formation of **4** (4:5, 96:4, 80%).[10] Confirmation of the stereochemistry of the major adduct **4** rested on its subsequent conversion to **2b**, via catecholborane reduction of the corresponding *p*-toluenesulfonylhydrazone.[11] Adduct **2b**,[10] derived from the thermal reaction of butadiene with **1** and whose structure was firmly established by X-ray analysis,[8] proved identical in all respects to **2b** derived from **4**. Thus the pi-facial approach of the electron rich diene, 1-methoxy-3-trimethylsilyloxybutadiene, preferentially occurs syn to the heteroatom bridge of the bicyclo[2.2.2]oct-3-ene system **1** and not antiperiplanar to the allylic axial heteroatom substituents, figure 1.

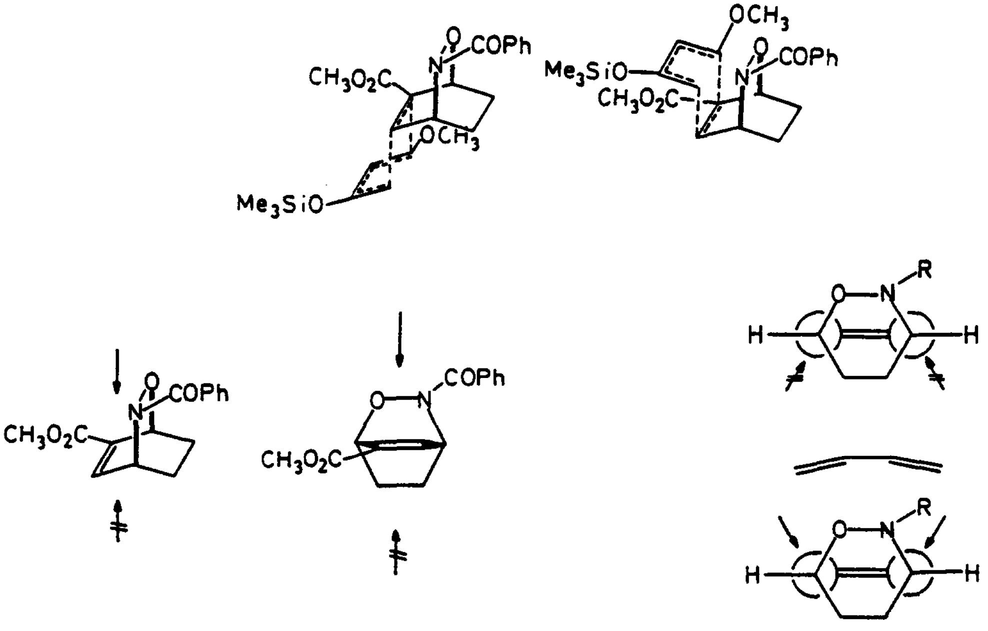
The observed Diels-Alder pi-facial selectivity of **1** with dienes suggests an "inside alkoxy (heteroatom)"[12] controlling effect of the allylic heteroatom substituents and it does not appear to be under the currently advanced secondary orbital control predicting diene pi-facial approach antiperiplanar to the allylic axial heteroatom substituents. The results further suggest that the interpretation of the control of related Diels-Alder pi-facial selectivities by electronegative (heteroatom) allylic axial substituents in freely rotating systems should be regarded as tentative.[3]

Scheme I



(a) 2.2 Equiv PhCONHOH, 2.3 equiv ($\underline{n}$-Bu)$_4$NIO$_4$, CH$_2$Cl$_2$, 25 °C, 47%. (b) 2 Equiv 1-methoxy-3-trimethylsilyloxybutadiene, mesitylene, 120 °C, 48h, 75%. (c) 0.1 Equiv $\underline{p}$-TsOH, C$_6$H$_6$, 80 °C, 3 - 4 h, 80% (4:5, 96:4). (d) 1.0 Equiv CH$_3$C$_6$H$_4$SO$_2$NHNH$_2$, CH$_3$OH, 100%. (e) 1.1 Equiv catecholborane, CHCl$_3$, 0 - 25 °C (1 h) and 50 °C (12 h), 86%.

Figure I



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10. **2b**: ^{1}H NMR (CDCl$_3$, ppm) 7.75-7.25 (m, 5H), 5.95 (m, 2H), 4.6 (br m, 1H), 4.15 (br m, 1H), 3.65 (s, 3H), 2.85-1.5 (br m, 9H); IR (film) ν_{max} 3044, 2951, 2872, 1734, 1633, 1452, 1323, 1300, 1205, 1196, 1082, 981 cm^{-1}; EIMS *m/e* 327 (M$^+$), 131, 105 (base), 91, 77, 68; HRMS *m/e* 327.1477 ($C_{19}H_{21}NO_4$ requires 327.1469). **4**: ^{1}H NMR (CDCl$_3$, ppm) 7.65-7.3 (m, 5H), 6.70 (d, J = 11 Hz, 1H), 6.15 (d, J = 11 Hz, 1H), 4.55 (br m, 2H), 3.80 (s, 3H), 3.5-1.8 (m, 7H); IR (film) ν_{max} 2953, 2916, 2882, 1732, 1689, 1628, 1578, 1450, 1435, 1417, 1390, 1290, 1255, 1070, 997, 708 cm^{-1}; EIMS *m/e* 341 (M$^+$), 257, 103 (base), 77, 51; HRMS *m/e* 341.1266 ($C_{19}H_{19}NO_5$ requires 341.1262). **5**: ^{1}H NMR (CDCl$_3$, ppm) 7.75-7.3 (m, 5H), 6.60 (d, J = 11 Hz, 1H), 6.15 (d, J = 11 Hz, 1H), 4.7 (m, 1H), 4.4 (m, 1H), 3.8 (s, 3H), 3.03 (dd, J = 17, 9 Hz, 1H), 2.40 (dd, J = 17, 2 Hz, 1H), 2.25 (m, 5H).

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