Exo selective Diels–Alder reaction of nitroolefins with Danishefsky's diene

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Diels–Alder reaction of nitroolefins with Danishefsky's diene exhibit abnormal *exo* selectivity based on electrostatic repulsion between the nitro group and the silyloxy group of diene.

The Diels–Alder reaction is a powerful tool for the construction of six-membered rings with high regio- and stereo-selectivities. The *endo* selectivity (Alder's rule) has been widely recognized in the reactions of an electron-rich diene and an electron-deficient dienophile. However, *exo* selective Diels–Alder reactions have been reported in special cases, such as α-methylenelactones,[1] α-substituted dienophiles[2] and metal complexes.[3] For the Diels–Alder reaction[4] of nitroolefins with *trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene **2** (Danishefsky's diene),[5] *endo* selectivity has been reported but there was no documentation of the stereochemical assignment on the selectivity of the products.[4a,b] Here we report the abnormal *exo* selectivity of the Diels–Alder reaction of nitroolefins with Danishefsky's diene.

The results of Diels–Alder reactions of various nitroolefins are compiled in Table 1. All the reactions carried out showed *exo* selectivity, regardless of the kind of aliphatic and aromatic nitroolefins as well as the bulkiness of the substituent on β-carbon of nitroolefins. The ratio of *exo*:*endo* was observed in the range of 10:1 to 2:1. The aromatic nitroolefins showed higher exo selectivity than the aliphatic nitroolefins.

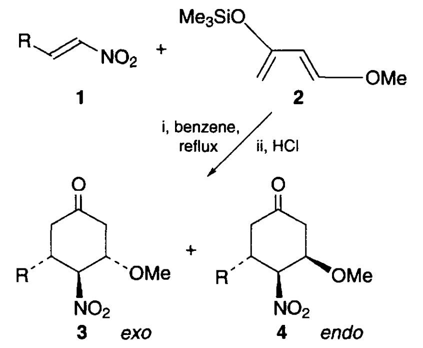
The relative configuration of the contiguous three carbons on the cyclohexanone ring of the product was determined by ^{1}H NMR and NOE experiments,[6] and the stereochemical relationship between lactone ring and cyclohexanone ring of **3a** was elucidated by an X-ray crystallographic analysis, Fig. 1.‡

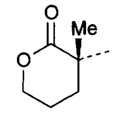
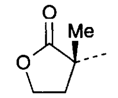
Diels–Alder reactions of (*E*)-nitrostyrene with other dienes such as 1-methoxybutadiene, cyclopentadiene gave the normal *endo* adducts preferentially [*exo*:*endo* = 36:64 (13%) and 24:76 (73 %), respectively]. Therefore, the *exo* selectivity of the Diels–Alder reactions of nitroolefins is characteristic of Danishefsky's diene. Furthermore, the reverse selectivity [**3g** (*exo*) : **4g** (*endo*) = 15:85 (54%)] to the selectivity in entry 7, was observed by the reaction of (*E*)-nitrostyrene by the addition of 10 mol% Eu(fod)$_3$.

The transition state giving the major *exo* adduct in the usual concerted mechanism has a large steric repulsion between a substituent on the β-carbon of the nitroolefin and the TMS group of the diene (Fig. 2, **A**). The steric repulsion would be particularly large due to the substituents having quaternary carbons on the β-carbons of nitroolefins **1** (entries 1, 2 and 4, Table 1). In order to explain this abnormal *exo* selectivity, thermodynamic isomerization of the adducts might be possible during the Diels–Alder cycloaddition.[7] If isomerization of the kinetically preferred *endo* adduct to thermodynamically stable *exo* adduct occurs during the reaction, the *endo* adduct should be obtained exclusively at an early reaction time when starting material still remains. The ratios of the *exo* and *endo* adducts were, however, almost constant (*ca.* 86:14) throughout the reaction (measured at 1, 2, 4, 24 and 48 h). Therefore, no *endo* to *exo* isomerizations involved. The attempted stepwise double Michael addition did not proceed by the addition of fluoride anion, so that the stepwise mechanism would be negligible. Furthermore, this *exo* selectivity could not be explained even by Houk's model based on an asynchronous transition structure.[8]

The explanation of this selectivity might be the electrostatic repulsion between the strong negative charge of the nitro group and the other negative charge on the oxygen of the OTMS group[9] in Danishefsky's diene. Although this Diels–Alder reaction of a nitroolefin with Danishefsky's diene is a special case, the secondary orbital effect and the steric repulsion might be overcome by the electrostatic repulsion (Fig. 2). If this electrostatic effect acts as the major factor controlling the selectivity, the *exo* selectivity can be reasonably explained, and higher *exo* selectivity of aromatic nitroolefins compared with aliphatic ones can also be explained by the steric repulsion as a

Table 1 *Exo* selective Diels–Alder reaction of nitroolefins with Danishefsky's diene[a]



Entry	Compd.	R	*t* (d)	Yield (%)[b]	**3**:**4**[c]
1[d]	**1a**		2	95	63:37
2	**1b**		4	74	70:30[e]
3	**1c**	cyclohexyl	2	42	75:25
4	**1d**	Bu^t	2	34	71:29
5	**1e**	hexyl	2	36	79:21
6	**1f**	pentyl	2	71	66:34
7	**1g**	Ph	2	60	87:13
8	**1h**	3-methoxyphenyl	2	83	91:9
9	**1i**	4-methoxyphenyl	2	79	87:13
10	**1j**	3,4,5-trimethoxyphenyl	2	55	84:16

[a] The reactions were performed with nitroolefin (1.3 mmol) and Danishefsky's diene (2.7 mmol), followed by hydrolysis with 1 mol dm^{-3} HCl–THF (1:1, 16 ml) for 1 h at 0 °C. [b] Isolated yields. [c] The ratios were determined by ^{1}H NMR (300 MHz). [d] Cited from ref. 6(*a*). [e] Including unseparable two diastereoisomers (7%, 1% calculated by ^{1}H NMR).

minor factor, because the steric bulkiness of an aromatic substituent keeping co-planar to the nitroolefin plane is smaller than that of the aliphatic substituent in the transition state. The ratios of *exo*:*endo* adduct changed from 87:13 in benzene to 67:33 in acetonitrile. This observed solvent effect partially supports the above electrostatic effect in the Diels–Alder reaction. The change of selectivity from *exo* to *endo* by the addition of Eu(fod)$_3$ could also uphold the electrostatic effect in the reaction, in which two negative oxygens of the nitro group and the OTMS group were directed to the same side by the chelation with europium.

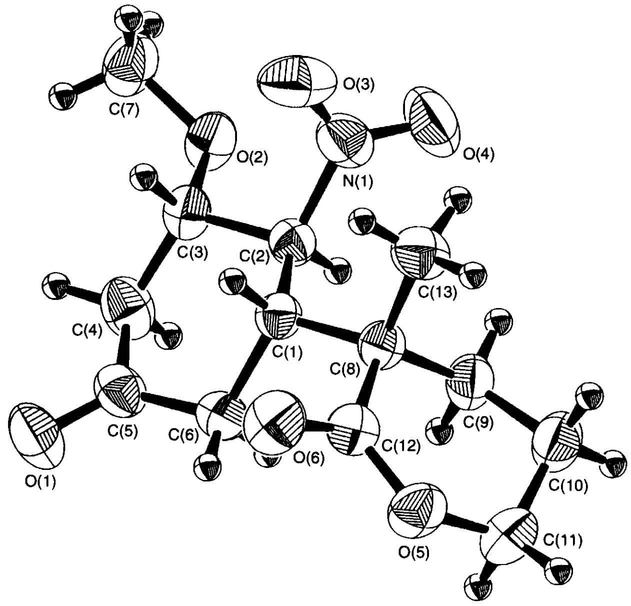


Fig. 1 X-ray structure of **3a**

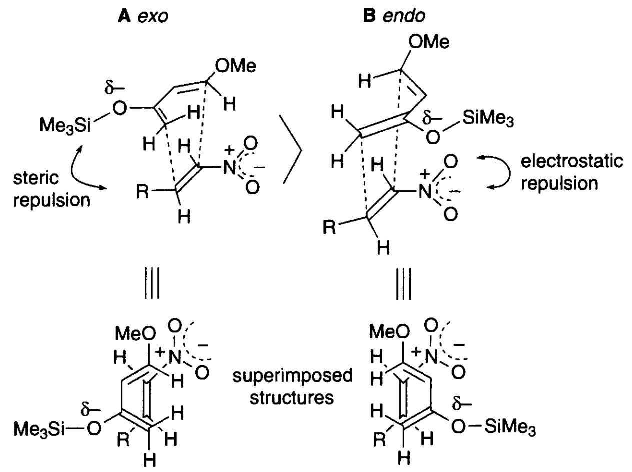


Fig. 2 Transition states

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Footnotes

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‡ *Crystal data* for **3a**: $C_{13}H_{19}NO_6$, M = 285.30, monoclinic, space group $P2_1/c$(#14), a = 9.270(3), b = 9.681(2), c = 15.248(2) Å, β = 94.34(2), V = 1364.4(5) Å^3, Z = 4, D_c = 1.389 g cm^{-3}, μ = 9.35 cm^{-1}, T = 293 K, 2321 measured reflections, 2172 unique reflections, 1562 reflections with $I > 3\sigma(I)$ used in refinement, direct methods and Fourier techniques, R = 0.029, R_w = 0.034. The data were collected using a Rigaku AFC7R diffractometer with graphite-monochromated Cu-Kα radiation (λ = 1.54178 Å) by the ω-2θ scan technique in the range $36.4 < \theta < 39.9°$. The structure was solved by direct methods and Fourier techniques and refined anisotropically for non-hydrogen atoms with H-atoms isotopic. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/255.

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