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Stereoselective Diels–Alder Reactions of Chiral Anthracenes

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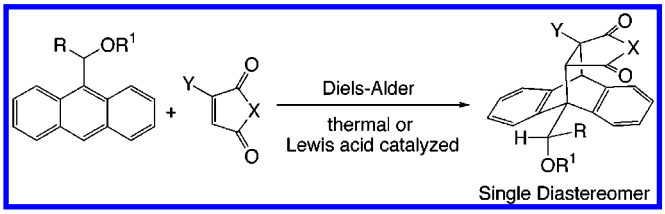
ABSTRACT



Various chiral (9-anthryl)carbinol templates undergo Diels–Alder cycloadditions with a variety of symmetric and nonsymmetric dienophiles with excellent π-facial selectivity and regioselectivity, under both thermal and Lewis acid catalyzed conditions.

Chiral anthracene derivatives and chiral anthracene cycloadducts have found numerous applications in organic chemstry. For example, 2,2,2-trifluoro-1-(9-anthryl)ethan-ol (Pirkle's alcohol) has been widely used as a chiral solvating agent[1] and more recently as a chiral auxiliary,[2] while chiral cycloadducts of anthracene have been employed as ligands in enantioselective transition metal catalyzed reactions.[3] The well-known biological activities of the butenolide pharmacophore stimulated our research into the enantioselective synthesis of γ-substituted butenolides through a Diels−Alder/retro Diels−Alder route[4] (Scheme 1) using a chiral, recyclable anthracene template. Other diene systems suitable for a Diels−Alder/retro Diels−Alder sequence are those based on furan and cyclopentadiene. While chiral analogues of these basic diene systems are known to participate in diastereoselective cycloadditions,[5] to the best of our knowledge, there is only a single series of reports of a chiral diene system employed as a stereocontrolling element in a Diels−Alder/retro Diels−Alder scheme.[6] In this work Winterfeldt prepared several chiral hydrindane cyclopentadiene-based templates which undergo diastereoselective cycloadditions with maleic anhydride and maleimides under high pressure. The use of a chiral anthracene template has advantages, however. These include elimination of the *endo/exo* issue in the cycloaddition, as well as the large, rigid anthracene skeleton that can be exploited for stereocontrol in further transformations of the adduct. The rich topology of the anthracene nucleus may also enable incorporation of functional groups to assist such transformations.

In the past, enantioenriched or enantiopure cycloadducts of anthracene have been derived by diastereoselective Diels−Alder reactions of achiral anthracenes with chiral dienophiles[7]

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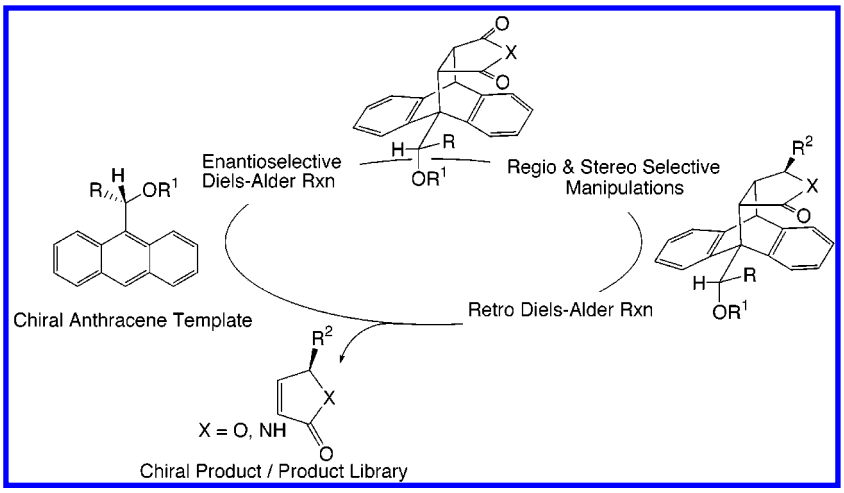
Scheme 1. General Strategy for Using Anthracene as a Diels–Alder/Retro Diels–Alder Template for the Asymmetric Synthesis of Butenolides and Related Derivatives



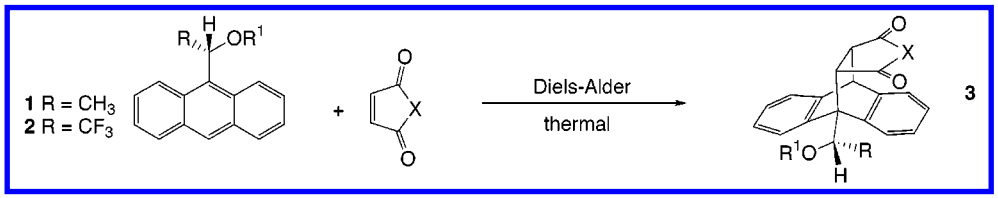
and enantioselective desymmetrization of *meso* adducts.[8] However, there are no prior studies of the use of chiral anthracenes in Diels–Alder reactions. This necessitated the development of chiral anthracenes as templates for cycloadditions with maleate derivatives.

Several reports of diastereoselective intermolecular Diels–Alder reactions of allylically chiral butadienes[9] prompted us to investigate the behavior of analogous anthracene carbinols and their derivatives as diene systems in Diels–Alder reactions. To this end, racemic 9-(1-hydroxyethyl)anthracene (**1a**) and enantiopure Pirkle's alcohol **2a** were chosen as candidates since both parent alcohols are readily available in enantiopure forms.[10]

Initially, the behavior of **1a**–**e** and **2b** in thermal cycloadditions with maleic anhydride and maleimides was surveyed (Table 1). All reactions required thermal promotion, with a competition experiment establishing that methyl ether **1b** was four times more reactive than anthracene toward maleic anhydride.[11] It was gratifying to find that all ether derivatives **1b**–**d** and **2b** reacted with maleic anhydride and the maleimides with complete diastereoselectivity and in good yields. In contrast, acetate **1e** produced an 83:17 mixture of diastereomers in refluxing benzene (Table 1, entry 8), while **1a** showed poor diastereoselection (Table 1, entry 1). Hence, to further the scope of the reaction, Lewis acid catalysis was also examined (Table 2).

The mild catalyst system generated by complexing Cu(OTf)$_2$ and the bisbenzyliminoethane (L*)[12] enabled the cycloaddition of **1e** with maleic anhydride to proceed at a lower temperature, thereby enhancing the diastereoselectivity

Table 1. Thermal Diels–Alder Cycloadditions with C_{2v}-Symmetrical Dienophiles



entry	1/2	R	R^1	X	conditions	adduct	% yield[a]	dr[b]
1	**1a**	CH_3	H	NMe	benzene, 80 °C, 9 h	**3a**	66	1:1.7
2	**1b**	CH_3	CH_3	O	benzene, 80 °C, 9 h	**3b**	89	>99:1
3	**1b**	CH_3	CH_3	NH	benzene, 80 °C, 9 h	**3c**	88	>99:1
4	**1b**	CH_3	CH_3	NMe	benzene, 80 °C, 9 h	**3d**	92	>99:1
5	**1c**	CH_3	*n*-Butyl	O	benzene, 80 °C, 9 h	**3e**	69	>99:1
6	**1d**	CH_3	Bn	O	benzene, 80 °C, 9 h	**3f**	70	>99:1
7	**1d**	CH_3	Bn	NMe	benzene, 80 °C, 9 h	**3g**	78	>99:1
8	**1e**	CH_3	Ac	O	benzene, 80 °C, 9 h	**3h**	74	83:17
9	**2b**	CF_3	CH_3	O	toluene, 110 °C, 18 h	**3i**	75	>99:1
10	**2b**	CF_3	CH_3	NMe	toluene, 110 °C, 18 h	**3j**	76	>99:1

[a] Isolated yields; [b] Determined by 400 MHz NMR.

Table 2. Lewis Acid Catalyzed Diels−Alder Cycloadditions[a]

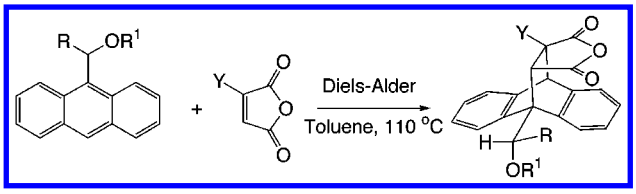
item	sub	X	Lewis acid[b]	3	% yield	dr
1	**1b**	O	L*Cu(OTf)$_2$	**3b**	83	>99:1
2	**1e**	O	L*Cu(OTf)$_2$	**3h**	52	>97:3
3	**2b**	NMe	MeAlCl$_2$	**3j**	50[c]	>99:1
4	**2b**	NMe	AlCl$_3$	**3j**	72	>99:1

[a] 1.1 equiv of Lewis acid. [b] L*: *N,N′*-dibenzylideneethylenediamine. [c] NMR conversion. [d] All reactions were carried out in CH_2Cl_2 at room temperature, using 1 equiv of catalyst and 1 0.2 equiv of dienophile.

to ca. 97:3 (Table 2, entry 2). The less reactive anthracene **2b** also underwent cycloadditions in good yield and complete diastereoselectivity at rt upon using $AlCl_3$, though no reaction resulted in the presence of the Cu(II) catalyst, while a milder aluminum catalyst such as $MeAlCl_2$ led to a much lower extent of reaction.

Reactions of **1b** and **1d** with the unsymmetrical dienophiles bromomaleic anhydride and citraconic anhydride were both highly diastereoselective and regioselective (Table 3).

Table 3. Diels−Alder Reaction with Unsymmetrical Maleate-Type Dienophiles



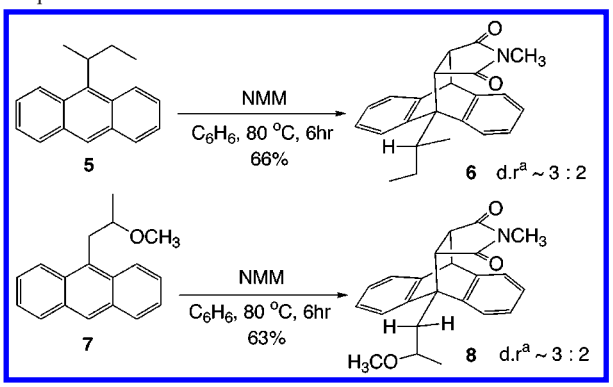
entry	sub	Y	adduct	dr[c]	% yield
1	**1b**	Br[a]	**4a**	>99:1	82
2	**1b**	CH$_3$[b]	**4b**	>99:1	84
3	**1d**	Br[a]	**4c**	>99:1	80
4	**1d**	CH$_3$[b]	**4d**	>99:1	86

[a] Reactions were performed with 1.1 equiv of dienophile. [b] Reactions were performed with 4 equiv of dienophile. [c] dr reported based on ^{1}H NMR (400 MHz). Regioselectivity by ^{1}H NMR (>15:1).

In all cases, the regioisomer with the dienophile substituent located away from the C9 substituent of anthracene, which minimizes crowding in the transition state, was formed as the major product (>15:1). Similar reactions with **2b** gave only trace amounts of products. As expected the sense of diastereoselection remains the same for both symmetric and nonsymmetric dienophiles, which was confirmed upon subjecting the cycloadduct **4c** to debromination using Pd/C, Et_3N, and H_2 to obtain the diastereomer **3f**.

To probe the origin of the diastereoselection, **5** and **7** were subjected to cycloadditions with NMM under the same conditions that furnished a single diastereomer in the reaction of **1b** with NMM (Table 1, entry 4). The observed diastereoselectivity with both **5** and **7** was ca. 3:2 (Scheme 2). From

Scheme 2. Model Anthracenes To Ascertain Minimal Requirements for Diastereoselection in Diels−Alder Reaction

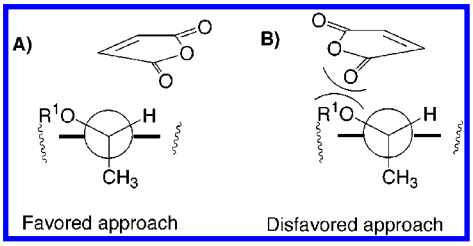


[a] dr determined by ^{1}H NMR (400 MHz).

these studies it was evident that an oxygen functionality on a chiral center adjacent to the anthracene greatly enhanced the diastereoselectivity.

The facial selectivity in the reactions of **1b**−**e** may be controlled by electrostatic repulsion between the maleic anhydride carbonyl oxygens and the alkoxy oxygen on the C9 substituent, with the methyl group oriented away from the approaching dienophile to minimize steric interactions and maximize σ-donation (Scheme 3). This model, which is

Scheme 3. Proposed Model for Observed Facial Selectivity



analogous to the "inside alkoxide model",[13] predicts the observed diastereoselectivity.

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(11) Equimolar amounts of anthracene and **1b** were reacted with 1 equiv of maleic anydride in C_6H_6 at 80 °C under Ar for 6 h. Product distribution was analyzed by integration of 400 MHz ^{1}H NMR. Refluxing the individual cycloadducts in the presence of the other anthracene in C_6H_6 did not show any scrambling.

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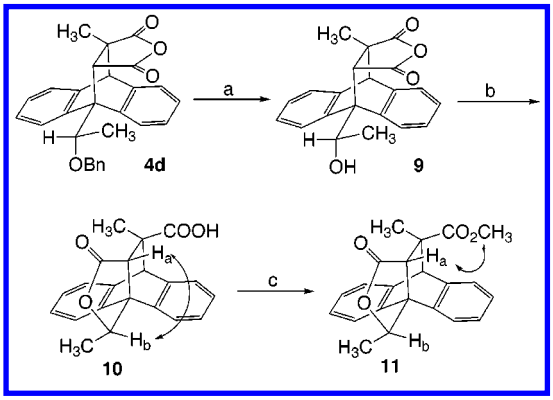
Scheme 4. Assignment of the Stereochemistry of **4d**[a]

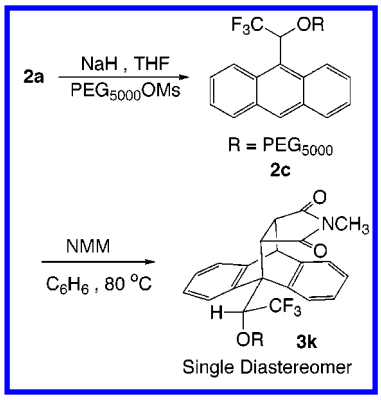


[a] Reaction conditions: (a) DDQ, CH_2Cl_2, 70%; (b) NaOMe, CH_3OH, 65%; (c) CH_2N_2, Et_2O, 99%.

To confirm that this was the case, cycloadduct **4d** was transformed into lactone **10**, where the *syn* relation of H_a to H_b was established by NOE's (Scheme 4). Subsequent NOE studies on the methyl ester **11** revealed that epimerization had occurred during lactonization to produce **10**. Reversal in diastereoselection was found for the alcohol **1a**,[14] which may be due to "hydrogen bonding" between the hydroxy group on the anthracene and the carbonyl of the approaching dienophile.[9b]

Current interest in parallel solid and solution phase chemistry prompted a preliminary effort to attach these chiral anthracenes to a polymer support. Incorporation onto a polyethylene glycol polymer support (PEG5000), which allows liquid phase homogeneity under reaction conditions with subsequent solid phase purification, was undertaken. Anthracene **2a** was bonded to PEG5000 by a mesylate displacement to give **2c** (Scheme 5).[15] The Diels−Alder reaction of **2c** gave with NMM a single diastereomer as shown by NMR (yield 68%).

Scheme 5. Diels−Alder Reaction of PEG-Supported Chiral Anthracene



In conclusion, chiral C9-substituted anthracenes undergo highly selective cycloadditions with various symmetric and nonsymmetric dienophiles under both thermal and Lewis acid catalyzed conditions, which makes them potential candidates as chiral templates for a Diels−Alder/retro Diels−Alder sequence. Adaptation to the polymer support without deterioration of the diastereoselectivity provides a handle for the application in parallel synthesis.

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Supporting Information Available: Experimental procedures and characterization data for compounds **1a**−**e**, **2a**−**c**, **3a**−**k**, **4a**−**d**, and **6**−**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Debenzylation of **3g** with DDQ gave the diastereomer corresponding to the minor one obtained in reaction of **1a** with NMM.

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