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Diastereomeric control of photoinduced Diels–Alder reactions of 1-anthracen-9-yl-ethanol by hydrogen-bonding effects

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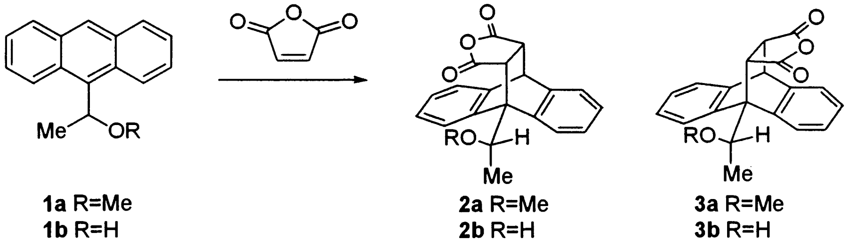
Abstract—Photoinduced Diels–Alder reactions of 1-anthracen-9-yl-ethanol with maleic anhydride proceed with high diastereoselection but with complete reversal of the sense of selectivity compared to analogous *O*-methyl compound. Hydrogen-bonding effects have been established as the predominant factors in determining this selectivity. © 2001 Elsevier Science Ltd. All rights reserved.

Many asymmetric transformations using currently employed chiral auxiliaries are dominated by acyl chemistry (e.g. enolate and conjugate addition reactions). This is a direct consequence of the addition process that usually occurs by reaction of the auxiliary with a suitably functionalised acyl fragment. Use of a different addition/cleavage strategy would facilitate access to a range of transformations not available to a majority of chiral auxiliaries currently employed. We have been working towards the development of a novel photoactivated chiral auxiliary based on functionalised 9-anthracyl derivatives. These auxiliaries differ from others commonly employed by making use of a highly diastereoselective Diels–Alder reaction of an alkene with a chiral anthracene derivative to achieve the attachment process. Subsequent diastereoselective reactions of these compounds may then be carried out, followed by cleavage using flash-vapour pyrolysis or ultra-violet irradiation.

We have recently disclosed our studies of the photoinduced Diels–Alder additions of maleic anhydride and a chiral 9-anthracyl derivative **1a** to give addition product **3a** with excellent diastereoselectivity (>95% d.e.) and with a significant enhancement in rate compared to the corresponding thermal reactions (Scheme 1).[1] We now wish to report preliminary results of the photoinduced additions of maleic anhydride with 1-anthracen-9-yl-ethanol **1b**.

The carbinol **1b** used in this study was prepared in racemic form as previously described[1] and used in all subsequent reactions. Photoinduced cycloaddition was performed by illumination of this compound at 254 nm with maleic anhydride in the respective solvent for 3 h and the results summarised in Table 1. Control reactions were also performed for each solvent in the dark at 30°C and these results are shown in Table 2.[2]

It was immediately apparent that the rate of reaction had significantly increased in all cases compared to our previous studies, particularly in the case of reactions performed using dichloromethane as solvent. Under photochemical conditions, dichloromethane was found



1a R=Me
1b R=H

2a R=Me
2b R=H

3a R=Me
3b R=H

Scheme 1.

Keywords: anthracene; auxiliary; diastereocontrol; Diels–Alder; hydrogen bonding; photochemistry.

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Table 1. Diels–Alder additions under photochemical conditions[a]

Solvent	Conversion (%)[b]	D.e. (of **2b**) (%)
Dichloromethane	100	62
Diethyl ether	85	80
Toluene	76	64
Acetonitrile	47	78
Heptane	47	72
Tetrahydrofuran	38	86

[a] Illuminated at 254 nm in a quartz reaction vessel under nitrogen in a degassed solvent using a semi-micro photochemical reactor (Applied Photophysics).

[b] Calculated from the ratio of the integrals in the 500 MHz ^{1}H NMR spectrum.

Table 2. Diels–Alder additions in the dark at 30°C[a]

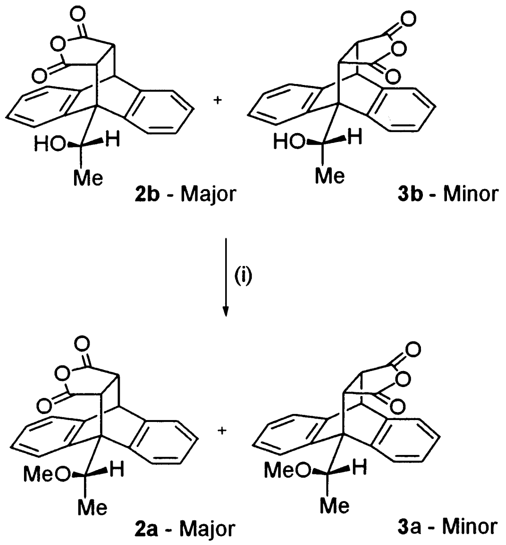
Solvent	Conversion (%)[b]	D.e. (of **2b**) (%)
Dichloromethane	90	64
Diethyl ether	43	84
Toluene	65	68
Acetonitrile	30	80
Heptane	39	64
Tetrahydrofuran	16	90

[a] Stirred at 30°C in the dark under nitrogen in a degassed solvent.

[b] Conversion calculated from the integration of signals of the individual diastereomers in the 500 MHz ^{1}H NMR spectrum.

to give the highest conversion to product, but diethyl ether was found to give the best combination of high conversion and good selectivity. In all cases expect heptane, the diastereoselectivities were comparable for those reactions conducted in the dark and with illumination. However in each case the conversion to product was significantly higher when illuminated, especially when using ethers (i.e. Et_2O and THF) as solvents where the conversion doubled. Attempts to correlate the rate enhancements with solvent effects due to electric dipole polarizability, dielectric constant, electric dipole moment or UV absorption cut-off wavelength were unsuccessful, although more intricate but complex solvent parameters that are available have not been explored at this time.[3]

The identity of the major diastereomer obtained in these reactions was determined by conversion to the known *O*-methyl ether. Thus, the alcohol addition product **2b** was treated with *t*-BuOK and methyl iodide followed by purification by silica gel chromatography (Scheme 2). The product obtained **2a** from this reaction was found to be the opposite diastereomer to the methyl ether **3a** obtained in our previous study. This means that the major diastereomer obtained from the cycloaddition reaction was somewhat unexpectedly the adduct **2b**. Thus with the carbinol substrate **1b**, cycloaddition must occur with the opposite sense of diastereoselection to that obtained when the Diels–Alder addition reaction is carried out with the *O*-methyl carbinol derivative **1a**.



Scheme 2. *Reagents and conditions*: (i) *t*-BuOK, THF, MeI (excess), rt, 24 h.

The reversal of the diastereoselectivity of the carbinol **1b** coupled with the increase in rate observed can be explained by considering hydrogen bonding between the alcohol group of the auxiliary and the carbonyl oxygen of maleic anhydride. This effectively tethers the approach of the dienophile as shown in Fig. 1, and overrides the inherent preference of these systems to undergo cycloaddition with the carbonyl group orientated away from the alkoxy substituent to avoid electrostatic repulsion.[4]

This proposed model for the reaction was further investigated using molecular modelling and the calculated transition state leading to the major diastereomer is shown in Fig. 2.[5] As can be seen from Fig. 2, the approach of maleic anhydride occurs from the same side as the hydroxyl group, causing deformation of the anthracene and maleic anhydride ring systems. The oxygen–oxygen distance of the hydrogen bond was found to be 2.785 Å and the O–H···O=C distance 1.842 Å which are both well within the limits observed from X-ray crystallographic studies of alcohols and carboxylic acids where hydrogen bonds are found.[6] In an attempt to disrupt the hydrogen-bonding effects the photoreaction was repeated using DMF as solvent. However, this led to the exclusive formation of the same single diastereomer **2b** but in reduced conversion (22%). Studies are currently underway to further inves-

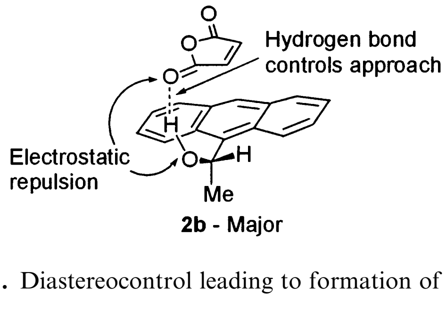


Figure 1. Diastereocontrol leading to formation of adduct **2b**.

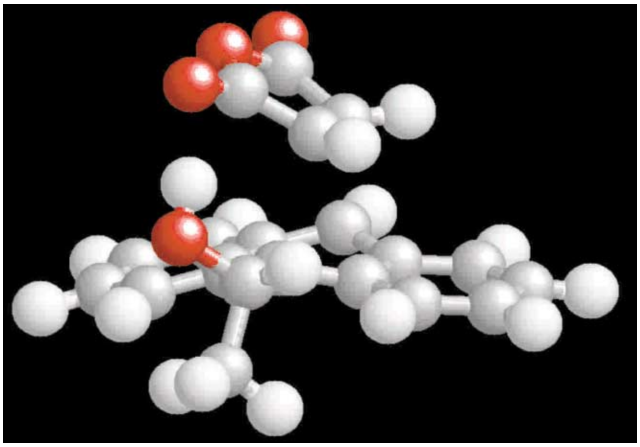


Figure 2. PM3-Modelled transition state for the addition of the carbinol **1b** to maleic anhydride.

tigate the role that hydrogen bonding plays in this reaction.

Similar results of hydrogen bonding exerting kinetic and diastereo-enhancements have been observed with chiral dienes based upon 2,4,6-trimethyl mandelic acid.[7] These have been shown to react with a series of dienophiles in the absence of a Lewis acid with excellent selectivity. However when the hydroxyl group was silylated the reaction rate was reduced and poor diastereoselectivity was observed. Other related examples include Diels–Alder additions[8] and 1,3-dipolar cycloadditions.[9]

The cycloadditions described have provided us with a method to effectively select the diastereoselectivity of the products by careful choice of the anthracene substrate. We are now evaluating the use of this diastereoselective addition process in the further development of our anthracyl auxiliaries.

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