Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 1117–1119

TETRAHEDRON:
ASYMMETRY

Highly diastereoselective photochemical Diels–Alder reactions: towards the development of a photoactivated chiral auxiliary

Simon Jones* and J. C. Christian Atherton

Department of Chemistry, University of Newcastle upon Tyne, Bedson Building, Newcastle upon Tyne NE1 7RU, UK

Received 11 April 2001; accepted 3 May 2001

Abstract—Photochemical Diels–Alder additions of maleic anhydride to a homochiral anthracene derivative occur with excellent diastereoselectivity (>95:5) and faster than the corresponding thermal reactions. © 2001 Elsevier Science Ltd. All rights reserved.

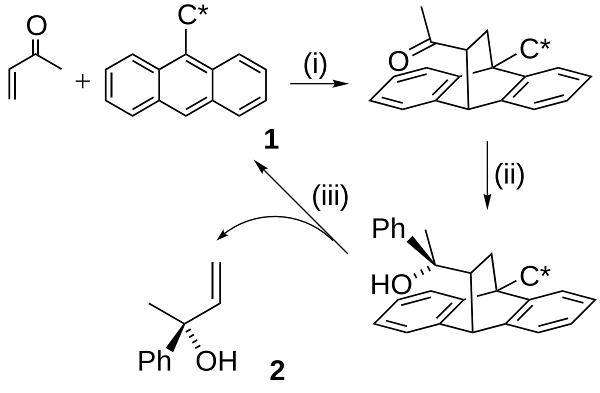
1. Introduction

Many complex total syntheses rely on the use of chiral auxiliaries, the most successful of which being the oxazolidinone and sultam auxiliaries developed by Evans and Oppolzer, respectively.[1] These auxiliaries are highly versatile and undergo many asymmetric transformations on attached acyl fragments such as enolate alkylation and aldol reactions. The types of transformations that may be carried out are primarily influenced by the acyl carbonyl group, which is a direct consequence of the nature of the attachment/cleavage step. Development of a new class of chiral auxiliary that makes use of a different attachment/cleavage strategy would facilitate the use of a number of other asymmetric transformations that would be impracticable with most commonly used auxiliaries.

Anthracene undergoes a well known thermal and photochemical Diels–Alder reaction with alkenes to give stable adducts that can easily be reverted to the original anthracene and alkene by flash vapour pyrolysis (FVP).[2,3] The latter reaction has been used extensively to prepare unusually substituted alkenes, such as allenes and ketene acetals that are normally difficult to isolate.[4] The anthryl ring system has also been shown to act as a powerful stereodirecting group[5] and these features together lend anthracene to being a useful framework for the development of a novel class of photoactivated chiral auxiliary. Helmchen et al. have capitalised upon these properties, demonstrating that chiral acrylates add to anthracene with excellent levels of diastereoselectivity.[6] The cycloadducts formed underwent a series of transformations prior to cleavage by subjecting the adduct to FVP, which afforded an allylic alcohol with excellent enantioselectivity. The main drawback of this approach is that the stereodirecting group originally present in the acrylate must be removed before transformation into a substrate for subsequent synthetic manipulation. A far better solution would be to install the stereodirecting group into the anthracene moiety, e.g. **1** (Scheme 1). This group would control the diastereoselectivity of the addition step, while the anthryl group would govern the stereochemistry of any subsequent asymmetric transformations. Cleavage would then afford the desired product **2** and the original auxiliary **1** for recycling.

2. Results

Our target auxiliary was based upon a mono-substituted anthryl carbinol derivative **3** that could easily be accessed in non-racemic form by asymmetric reduction



Scheme 1. *Reagents*: (i) *hv*; (ii) PhMgBr, THF; (iii) FVP or *hv*.

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* Corresponding author. Tel.: 0191 222 7128; fax: 0191 222 6929; e-mail: s.jones@ncl.ac.uk

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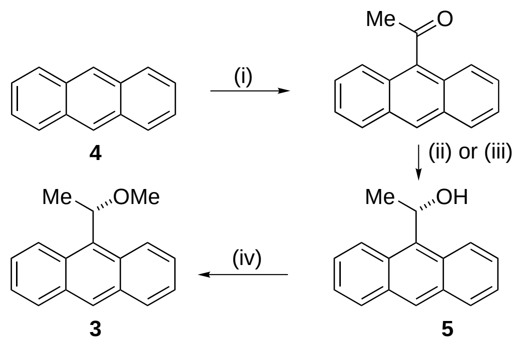
PII: S0957-4166(01)00203-8



Scheme 2. *Reagents and conditions*: (i) AcCl, $AlCl_3$, CH_2Cl_2, 0°C; (ii) $NaBH_4$, EtOH; (iii) *cis*-(1*R*)-(2*S*)-1-amino-2-indanol, $(MeO)_3B$, BH_3, THF; (iv) MeI, NaH, THF.

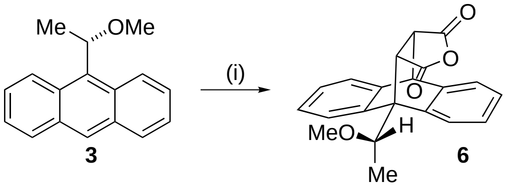
Table 1. Diels–Alder additions under photochemical conditions[a]

Conditions[a]	Time (h)	Conversion[b] (%)
THF	3	9
CH_3CN	3	23
Et_2O	3	26
$PhCH_3$	3	30
C_7H_{16}	3	33
CH_2Cl_2	3	54
CH_2Cl_2[c]	3	51
CH_2Cl_2	7	94

[a] Irradiated at 254 nm.

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

[c] Irradiated at 350 nm.



Scheme 3. *Reagents and conditions*: (i) maleic anhydride, solvent, *hv* as text.

Table 2. Diels–Alder additions under thermal conditions

Conditions	Time (h)	Conversion[a] (%)
30°C, CH_3CN	3	34
30°C, CH_3CN	24	55
30°C, CH_2Cl_2	3	42
30°C, CH_2Cl_2	3	39[b]
1 equiv. $Cu(OTf)_2$; 1.1 equiv. BEN; 15°C, CH_2Cl_2	20	42
1 equiv. $Cu(OTf)_2$; 1.1 equiv. BEN; 15°C, CH_2Cl_2	42	56
1 equiv. $Cu(OTf)_2$; 1.1 equiv. BEN; 30°C, CH_2Cl_2	23	69

[a] Calculated from the ratio of the integrals in the ^1H NMR spectrum.

[b] Reaction performed in the dark.

of a ketone precursor. The synthesis was accomplished by Friedel–Crafts acetylation of anthracene **4**,[7] followed by sodium borohydride reduction and methylation (Scheme 2). The enantiomerically enriched version of this auxiliary was prepared in 87% e.e. by asymmetric reduction in the presence of catalytic (1*R*)-amino-(2*S*)-indanol[8] and the absolute configuration determined by comparison of the specific rotation of the alcohol **5** with the literature value.[†]

The desired substrate **3** was then subjected to photoinduced Diels–Alder addition with maleic anhydride under a variety of conditions. The results are summarised in Table 1 (Scheme 3).[‡] For most reactions a duration of 3 h was used as a standard by which to compare all further reactions. In all cases no side products formed and only a single diastereomer **6** was obtained, the identity of which was confirmed by X-ray crystallography.[§] Lower conversions were observed when the experiment was carried out in solvents other than CH_2Cl_2, and essentially no difference in the product was observed when light of 350 nm wavelength was used instead of 254 nm. Pure samples of cycloadduct could be obtained by photoinduced reaction for 7 h in dichloromethane followed by recrystallisation.

Control experiments were also carried out under thermal conditions and are summarised in Table 2. Once again in each case a single diastereomer **6** was formed and no side products were observed. Of particular note was that no background reactions appeared to take place in the presence of laboratory lighting, additionally, a significant increase in the yield of product was observed when the reaction was conducted in the presence of UV light. This latter point confirms that the addition is indeed photoinduced. During the progress of this work, Sanyal and Snyder reported an identical Diels–Alder addition with >99:1 diastereomeric excess at room temperature in the presence of a stoichiometric amount of copper catalyst.[10] In our hands, reaction of the auxiliary **3** and maleic anhydride with copper(II) triflate and *N*,*N*′-ethylenebis(benzaldimine) (BEN) gave the desired cycloadduct **6** as a single diastereomer but in reduced yield (56% conversion after 42 h) compared to that previously reported (83% after 48 h). We also found that the catalyst for this reaction was unnecessary and that comparable conversions could be obtained without added catalyst and at much lower temperatures.

Preliminary Diels–Alder additions of less reactive unsymmetrical alkenes were not as successful. Attempted photoinduced addition of both cyclopentenone and methyl vinyl ketone under the reaction

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[†] $[\alpha]_D^{20} = -19.6$ (*c* 1, $CHCl_3$), lit.[9] $[\alpha]_D^{20}$ for the (*S*)-enantiomer $= -18.8$ (*c* 1.1, $CHCl_3$).

[‡] A semi-micro photochemical reactor (Applied Photophysics, obtained from Photochemical Reactors Ltd, Reading, UK) was used. Irradiation was carried out in a quartz reaction vessel under nitrogen in a degassed solvent.

[§] Details will be published separately.

conditions noted above returned unreacted starting material. Identical results were obtained under thermal or catalytic conditions.

3. Conclusions

We have demonstrated that the photoinduced Diels–Alder reactions of a chiral anthracene derivative occur in excellent yield and with very high diastereoselectivity. These reactions are considerably more efficient than the corresponding thermal or copper catalysed conditions. It is also notable that the thermal reactions proceeded with or without added catalyst to give the adduct in similar yields and diastereoselectivities. Sanyal and Snyder have proposed a model for the origin of the level of diastereoselectivity that accounts for the observations that we have made at this time.

We are currently in the process of developing structural variants of the above auxiliary and comparing their relative reactivity. We are also further investigating the Diels–Alder reaction of less reactive and unsymmetrical dienophiles, in addition to a more detailed study of the photochemistry of the addition adducts. This is of key importance in elucidating a simple and mild cleavage process to complete the development of this auxiliary.

Acknowledgements

The authors would like to thank EPSRC and Thomas Swan and Co. Ltd for a CASE studentship (J.C.C.A.) and Rhodia-Chirex for the generous donation of (1*R*)-amino-(2*S*)-indanol.

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