Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 111–114

TETRAHEDRON LETTERS

A simple and versatile method to determine the enantiomeric purity of Diels–Alder adducts

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Received 26 September 2002; revised 15 October 2002; accepted 1 November 2002

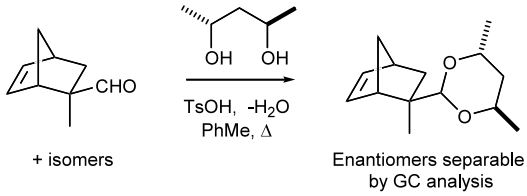
Abstract—The determination of the enantiomeric purity of Diels–Alder adducts derived from cyclopentadiene and a series of electron-deficient dienophiles is conveniently achieved by HPLC analysis on their 2,4-dinitrophenylhydrazine derivatives formed in one-pot directly from the cycloaddition reaction.

The chemistry and reactivity of Lewis acids has intrigued and stretched the imagination of scientists over many years.[1] Significant advances have now been made in the field of catalytic asymmetric versions of the numerous transformations that Lewis acids can catalyse, to the extent that many methods now exist to carry out these reactions in high chemical yield with excellent stereo- and enantiocontrol.[2] This is a great tribute to the skill and ingenuity of the synthetic community, and developments are continually being made.[3]

We have recently initiated a programme directed towards the rational design of a novel family of Lewis acids with the hope of probing the nature and subtleties involved in the frequently inferred yet little understood face–face π–π interaction.[4] As a starting point for our catalytic studies we chose the Diels–Alder reaction in order to compare our catalysts to those already reported in the literature and to ascertain any rationale in the nature of the proposed π–π interactions.

In order to monitor the enantiomeric excesses in our reactions we sought a simple, cheap, rapid and versatile method for the evaluation of selectivity observed. There are several methods available for the determination of the enantiomeric excess of both the *endo*- and *exo*-isomers of the Diels–Alder adducts between, for example, methacrolein and cyclopentadiene. These methods include direct determination of the ee using ^{1}H NMR techniques in the presence of the chiral shift reagent $Eu(hfc)_3$[5] or the indirect ee determination via the formation of diastereomeric acetals followed by GC or HPLC analysis (Scheme 1).[6]

Both of these methods require a stoichiometric amount of either the external chiral ligand or chiral reagent, which was proving to be rather expensive and time and labour intensive, requiring both aqueous work-up and column chromatography. We considered the formation of the corresponding aminals with (*R*,*R*)-1,2-diphenylethylene diamine followed by ^{13}C NMR analysis as reported by Alexakis as another possible method for ee determination, but once again decided against this due to the cost of the diamine and the amount of NMR machine time that would be required.[7] We therefore sought an alternative derivatisation method for the Diels–Alder adducts that would both shorten the time taken for our analyses and reduce the costs associated with the ee determination. Herein we report a simple method for the determination of the enantiomeric purity of Diels–Alder adducts derived from cyclopentadiene and a series of electron deficient dienophiles by HPLC analysis of their 2,4-dinitrophenylhydrazones.



Scheme 1.

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0040-4039/03/$ - see front matter
PII: S0040-4039(02)02454-1

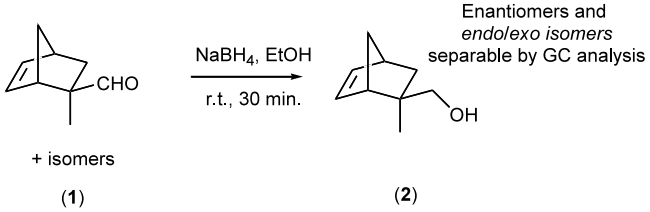
Prior to the development of this new method we examined a number of alternative protocols to determine the ee of our Diels–Alder adducts. Initially we looked at directly reducing the adducts **1**, derived from methacrolein and cyclopentadiene with sodium borohydride to afford the corresponding mixture of *exo*- and *endo*-alcohols **2** as a simple indirect method for ee determination. Analysis of these alcohols by GC using a chiral stationary phase gave a clean separation of all four possible stereoisomeric products, which allowed for the determination of both the *endo*/*exo* ratio and the enantiomeric excess for the reaction. The results and conditions for this method of analysis are outlined in Table 1. Although this satisfied our original criteria of providing a simple, cheap and rapid way of establishing the stereo- and enantioselectivity of the reaction, the method did not prove to be general and the use of acrolein, bromoacrolein, crotonaldehyde and methyl vinyl ketone as the dienophiles within the cycloaddition reaction did not lead to similar separations being observed by GC.

We then turned our attention to alternative methods for derivatisation of the products. Eventually we found success with the 2,4-dinitrophenylhydrazine derivatives of the Diels–Alder adducts. For example, with bromoacrolein as the dienophile it was possible to determine both the *endo*/*exo* selectivity of the reaction as well as separate both the (+)- and (−)-enantiomers of the adducts using a Chiracel OD HPLC column. A typical HPLC trace of the 2,4-dinitrophenylhydrazine derivative **3** of the bromoacrolein adduct is shown in Figure 1.

We found that optimal reaction conditions involved addition of 2,4-dinitrophenylhydrazine to a stirred ethanolic solution of the Diels–Alder adduct followed by aqueous work-up. Direct analysis of the reaction mixture then provided both the *endo*/*exo* ratios and the enantiomeric excesses for the original Diels–Alder reaction.

In order to use this as a high throughput method to scan a number of potential Lewis acid catalysts and reaction conditions it was then necessary to ascertain if

Table 1. GC analysis of reduced methacrolein adduct



Dienophile	*endo*-Isomers		*exo*-Isomers	
Methacrolein	62.4	64.9	70.0 (*S*)	72.0 (*R*)

Performed on a 50 m WCOT fused silica capillary column coated with CP cyclodextrin-B-2,3,6-M-19. Retention time in minutes, absolute configuration of *exo*-isomers shown in parentheses.

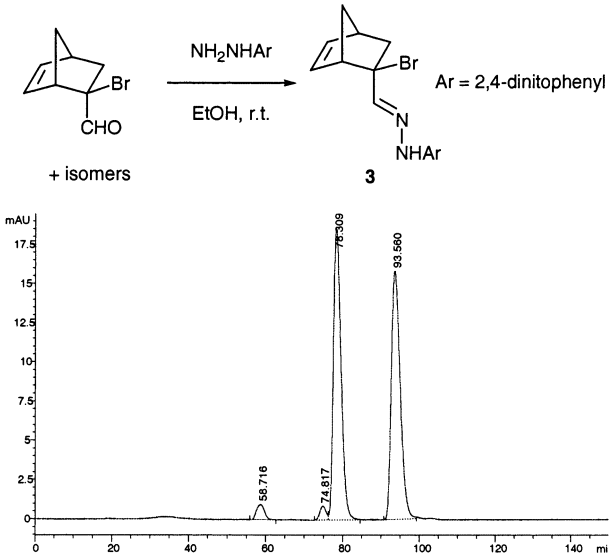
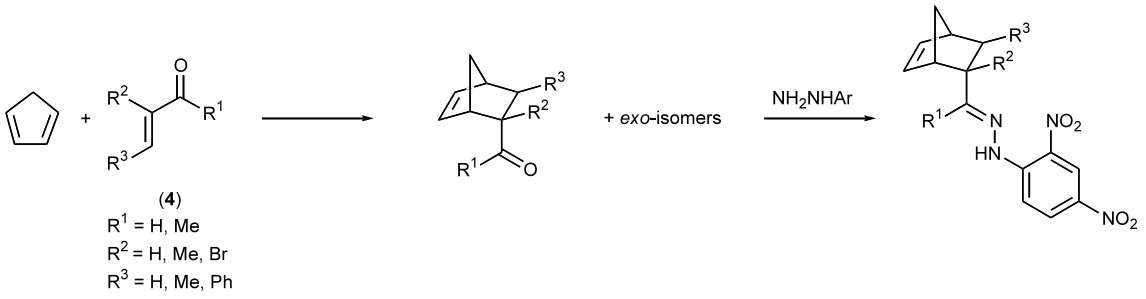


Figure 1.

this method was general and applicable to the Diels–Alder reaction of a variety of electron deficient dienophiles with cyclopentadiene. We therefore sought to investigate if substitution at any position on the dienophiles (i.e. R^1, R^2 and R^3 in **4**) would allow us to carry out similar analysis of the adducts. To this end we selected acrolein, methyl vinyl ketone (R^1), methacrolein and bromoacrolein (R^2), and cinamaldehyde and crotonaldehyde (R^3) as representative examples of substitution in each of these positions. There have been a plethora of examples of chiral Lewis acids in the literature that have been designed, synthesised and tested for use as catalysts in the asymmetric Diels–Alder reaction. Most of these have exemplified their use by the reaction of this small, yet informative group of dienophiles. We therefore prepared the 2,4-dinitrophenylhydrazine derivatives from the reaction of this set of dienophiles with cyclopentadiene and were delighted to discover that in each case we were able to separate the isomers using chiral HPLC methods. The retention times for each adduct together with the optimal HPLC conditions are shown in Table 2. This has allowed us to develop a cheap, reliable, high-throughput method for the determination of enantiomeric excess for the Diels–Alder reaction that has proved considerably more cost effective than the alternative methods reported previously in the literature.

Once we had established the general applicability of our method with a variety of dienophiles we then needed to correate the peaks of the 2,4-dinitrophenylhydrazines with the known absolute configurations of the methacrolein/cyclopentadiene adducts in order to confirm that no racemisation was occurring upon formation of the hydrazone. This was achieved by preparing the tartaric acid derivative **5**[8] and the styrene derivative **6**[9] reported previously by Yamamoto and Jones respectively (Fig. 2). These ligands were then utilised in the catalytic conditions reported in the corresponding papers for the Diels–Alder cycloaddition of cyclopentadiene and methacrolein followed by the

Table 2. HPLC analysis of 2,4-dinitrophenylhydrazine derivatives



Dienophile	*endo*-Isomers		*exo*-Isomers	
Acrolein	42.0	53.4	68.1	75.6
Methacrolein	47.0	58.5	60.9	71.9
Bromoacrolein	58.7	74.8	78.3	93.6
Crotonaldehyde	71.1	79.6	92.4	97.8
Methyl vinyl ketone	78.3	93.6	58.7	74.8

Performed on a Chiracel OD column, eluting with 1% isopropanol in hexanes: flow rate 1 mL/min. Retention times in minutes.

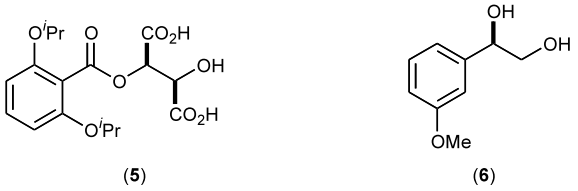


Figure 2.

direct addition of 2,4-dinitrophenylhydrazine to the reaction mixture. In each case we established that the peak at 60.9 min corresponded to the (*R*)-adduct and the peak at 71.9 min corresponded to the (*S*)-adduct in the Diels–Alder reaction. Each of these reactions was run in duplicate and gave identical selectivities to those reported. This serves to show that during the formation of the 2,4-dinitrophenylhydrazine derivatives there is no compromise in the stereoselectivities of the original Diels–Alder adduct upon derivatisation and the ratios observed are an accurate reflection of the stereochemical course of the reaction under investigation with both boron and aluminium as the Lewis acidic metal.

In summary, we have developed an efficient method for the determination of the enantiomeric excess for the Diels–Alder reaction between cyclopentadiene and a variety of conjugated carbonyl compounds. The experimental procedure for this transformation is trivial and can be performed directly on the reaction mixture on completion of the cycloaddition. Isolation of the product by aqueous work-up followed by HPLC analysis of the crude reaction mixture gives an accurate method by which to determine both the *endo*/*exo* ratio of the reaction as well as the enantiomeric ratio of each of the adducts. The reactions proceed readily at room temperature in ethanolic solution without loss of optical purity of the original Diels–Alder adduct. This provides a convenient method by which to determine the enantiomeric excess of this much studied and pivotal reaction of Lewis acid catalysis, without the need for difficult chemical manipulation or the use of costly reagents and may well prove applicable to a number of other asymmetric transformations that rely on the use of carbonyl group chemistry.

Experimental[10]

GC method for the determination of *endo*/*exo* ratio and enantiomeric excess of the Diels–Alder adduct between cyclopentadiene and methacrolein

The purified Diels–Alder adduct (100 mg, 0.73 mmol) was dissolved in ethanol (5 mL) and treated with sodium borohydride (27 mg, 0.77 mmol) in one portion. After stirring at room temperature for 30 min the reaction mixture was evaporated to dryness and saturated aqueous ammonium chloride (10 mL) was added to the residue. After extraction with dichloromethane (3×20 mL) the organics were dried over magnesium sulfate and reduced to give a mixture of the *endo*- and *exo*-alcohols **2** which were analysed directly by GC.

General HPLC method for determination of enantiomeric excess of Diels–Alder adducts

To a stirred solution of the Diels–Alder adduct derived from acrolein and cyclopentadiene (100 mg, 0.82 mmol) in ethanol (4 mL) at room temperature was added 2,4-dinitrophenylhydrazine (162 mg, 0.82 mmol) and the resulting orange solution was stirred at room temperature for 30 min. The crude reaction mixture was

poured into water (10 mL) and the aqueous phase was extracted with ether (4×10 mL). The organic solution was washed with brine (20 mL), dried over magnesium sulfate and concentrated to give the 2,4-DNP adduct that could be analysed directly by HPLC. Crystallisation from ether/light petroleum gave the 2,4-DNP *endo*-adduct: mp 125–127°C; IR (Nujol mull) 3307, 1618 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.87 (s, 1H, NH), 9.05 (d, 1H, $J=2.5$ Hz, CH=N), 8.22 (dd, 1H, $J=6.7$ and 2.4 Hz, ArH), 7.84 (s, 1H, ArH), 7.08 (d, 1H, $J=6.7$ Hz, ArH), 6.22 (m, 1H, vinylic), 5.96 (m, 1H, vinylic), 3.04 (m, HC=CHCH), 2.95 (m, 1H, HC=CHCH), 2.03–1.14 (m, 5H, ring protons); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.9, 140.5, 137.6, 134.0, 125.5, 118.5, 51.7, 49.0, 44.7, 44.1, 32.9; HRMS (found 302.1006; $C_{14}H_{14}N_4O_4$ requires 302.1015).

In situ formation of 2,4-dinitrophenylhydazine adducts from asymmetric Lewis acid-catalysed reactions

The Diels–Alder reaction was performed on a 1 mmol scale as described. After stirring for the stated time at −78°C, the reaction was quenched by the drop-wise addition of ethanol (2 mL). After stirring at −78°C for 15 min a solution of 2,4-dinitrophenylhydrazine (198 mg, 1 mmol) in ethanol (2 mL) was added and the reaction mixture was allowed to warm to room temperature over 1 h. Work-up of the crude reaction mixture as described above allowed for the determination of both *endo*/*exo* ratios and ee of the adducts by HPLC.

Acknowledgements

The authors wish to express their extreme gratitude to the EPSRC for a studentship GR/R41750/01 (L.D.H.), GlaxoSmithKline for CASE support (C.L.J.), the Royal Society and the Nuffield Foundation for equipment grants, and the EPSRC HRMS service at Swansea for analyses.

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