Pergamon

Tetrahedron Letters 43 (2002) 9633–9636

TETRAHEDRON
LETTERS

Evidence for the non-concerted [4+2]-cycloaddition of *N*-aryl imines when acting as both dienophiles and dienes under Lewis acid-catalysed conditions

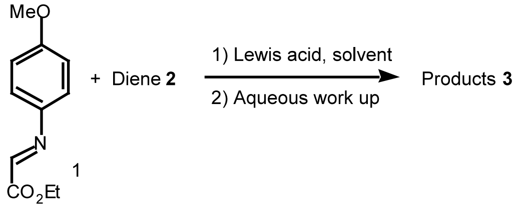
Stephen Hermitage,[a] David A. Jay[b] and Andrew Whiting[b,*]

[a] *GlaxoSmithKline Medicines Research Centre, Gunnels Wood Road, Stevenage, Herts SG1 2NY, UK*
[b] *Department of Chemistry, Science Laboratories, University of Durham, South Road, Durham DH1 3LE, UK*

Received 8 August 2002; revised 14 October 2002; accepted 24 October 2002

Abstract—The ytterbium(III) triflate-catalysed reaction of a *para*-methoxyaniline, ethyl glyoxalate-derived imine, with a series of different dienes has resulted in products which initially suggest the operation of two possible modes of aza-Diels–Alder reaction, however, a more likely explanation is that a common reaction mechanism is operating, involving a stepwise Lewis acid-catalysed process and a common type of zwitterionic ytterbium complex. © 2002 Elsevier Science Ltd. All rights reserved.

There have been several recent reports of the application of inverse electron-demand aza-Diels–Alder reactions involving *N*-aryl imino dienes.[1] However, many groups have also reported that such imines react readily as dienophiles with a range of dienes.[2] Our interest in this field and in particular the development of new asymmetric aza-Diels–Alder reactions[3] has led us to consider this apparent dichotomy using *para*-methoxyaniline imine **1** by studying its reactivity with a range of dienes under Lewis acid conditions (Eq. (1)), with a view to not only gaining a deeper understanding of the aza-Diels–Alder process, but potentially developing new catalytic asymmetric aza-Diels–Alder processes.[3] In order to achieve this and to enable rational planning of subsequent synthetic applications, it is necessary to understand the chemoselectivity and therefore mechanism operating in such processes. In this communication, we propose that a common, non-concerted mechanism can explain the apparently dichotomous behaviour of a single *N*-aryl imine with a range of relatively electron-rich dienes under Lewis acid-catalysed conditions.



(1)

Imine **1** and its methyl ester analogue have been reported[3a,4] to undergo facile asymmetric Lewis acid-catalysed ‘cycloaddition’ with Danishefksy’s diene.[5] The reaction of **1** was also examined with several dienes (see Table 1) under parallel reaction screening conditions with a range of different Lewis acids, different solvents and in both the presence and absence of air (and hence water, vide infra), in order to identify rapidly which reactions could be cleanly catalysed. It is noteworthy that imine **1** fails to react significantly with any of the listed dienes in the absence of a Lewis acid catalyst at ambient temperatures. Of the various catalysts and solvents screened, ytterbium(III) triflate proved to be the best general catalyst for all the reactions reported herein. However, it became immediately obvious that the reaction products were not all derived from imine **1** behaving solely as an imino dienophile. Indeed, one reaction which immediately attracted our attention was entry 2, Table 1, which required the presence of water to provide the product **3b** (under anhydrous reaction conditions, the reaction produced a highly complex mixture of products from which it was not possible to isolate clean reaction products). In contrast, the remaining dienes, i.e. 1-acetoxybutadiene, cyclopentadiene and 1-methoxycyclohexadiene (entries 3–5) only produced the corresponding tetrahydroquinolines **3c**–**e**, respectively, but it was noteworthy that the products in

---

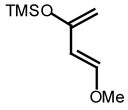
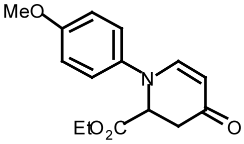
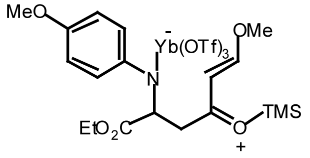
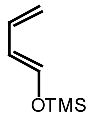
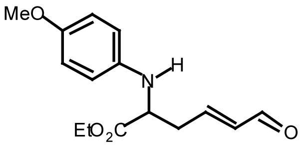
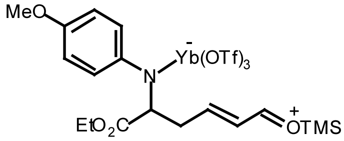
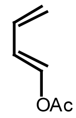
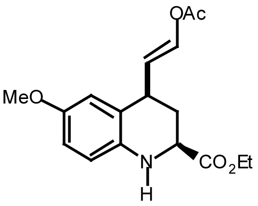
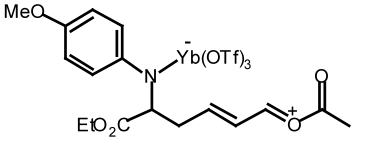
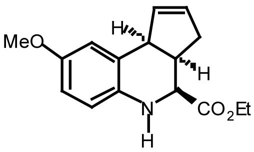
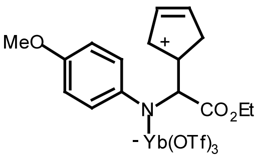
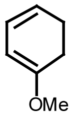
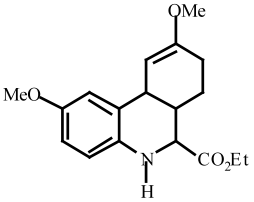
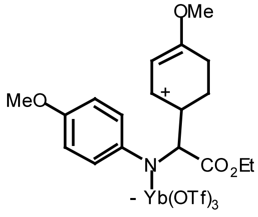
* Corresponding author.

0040-4039/02/$ - see front matter © 2002 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(02)02392-4

entries 3[†] and 5 (Table 1) were obtained as mixtures of diastereoisomers.

At first sight, it was tempting to infer that three different reaction mechanisms could be operating to explain the observed products in Table 1. These are: (1) normal electron-demand imino-dienophile–Danishefsky's diene Diels–Alder reaction (entry 1); (2) nucleophilic addition

Table 1.

Entry	Diene **2**	Product **3**	Isolated yield (%)[a]	Intermediate **4**
1		 **3a**[b]	65	 **4a**
2		 **3b**[c]	59	 **4b**
3		 **3c**[b, d]	61	 **4c**
4		 **3d**[b, e]	81	 **4d**
5		 **3e**[b, f]	57	 **4e**

[a] All yields are isolated after silica gel chromatography.

[b] Reaction conditions: dry MeCN, 5 mol% Yb(OTf)$_3$, Ar, 5 h.

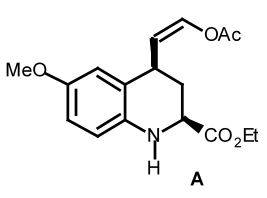
[c] Reaction conditions: MeCN, 100 mol% H$_2$O, 5 mol% Yb(OTf)$_3$, Ar, 5 h.

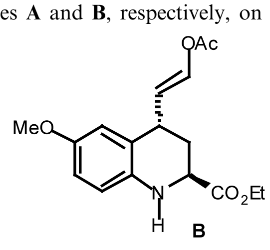
[d] **3c** is obtained as the major diastereoisomer, together with two other minor stereoisomers.[†] This compound is also unstable and aromatises to the corresponding quinoline on silica gel and in air in EtOAc solution (half-life ca. 3 days, rt).

[e] Obtained as a single diastereoisomer, stereochemistry assigned according to the ^{1}H NMR spectrum and literature precedent (see Ref. 8).

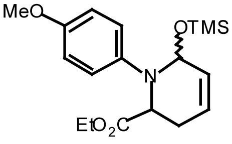
[f] Obtained as a mixture of two major diastereoisomers (2:1 ratio) according to the ^{1}H NMR spectrum.

[†] Compound **3c** was obtained together with small amounts (ca. 19 and 17%, respectively, with respect to **3c**) of the two further diastereoisomers, tentatively assigned structures **A** and **B**, respectively, on the basis of the ^{1}H NMR spectrum of the mixture.

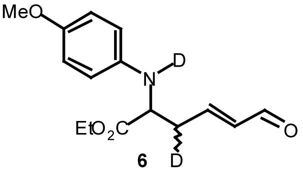

A


B

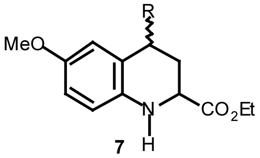
of 1-trimethylsilyloxybutadiene to an electron-deficient imine (Mannich-like reaction) (entry 2); and (3) inverse electron-demand aniline–imine–diene+alkene dienophile Diels–Alder reaction. However, a more reasonable explanation is that all the observed products are derived from the same initial imine activation mechanism, i.e. Lewis acid complexation of the imine **1**, followed by nucleophilic addition of the different dienes to form the corresponding intermediate zwitterionic ytterbium complexes (**4a**–**e**). The final products are then derived from two alternative regioselective cyclisation reactions or direct hydrolysis of the zwitterion. The fate of each of the zwitterions **4**, in terms of which mode of reaction occurs, i.e. cyclisation versus hydrolysis, can be readily explained by their different substituents and therefore relative stabilities. In the case of entry 1, the cationic part of zwitterion **4a** is particularly stabilised by resonance and presumably cyclises relatively slowly, subsequent hydrolysis then provides cycloadduct **3a**. In contrast, zwitterion **4b** is less stable and tends to produce several unidentified products in the absence of an external nucleophile. However, the presence of water in the reaction mixture allows rapid hydrolysis of the zwitterion **4b** to provide addition product **3b**. In the cases of entries 3–5, each of the zwitterions have intermediate stability and cyclise via an electrophilic aromatic substitution mechanism to provide each of the products **3c**–**e**.



5



6



7

a; R = *E*-CH=CHOTMS
b; R = CH_2CHO

It is possible to gain mechanistic insight into the processes operating in the reactions outlined in Table 1 by closely examining the origin of product **3b**. A normal electron-demand Diels–Alder reaction of imine **1** and 1-trimethylsiloxybutadiene would produce Diels–Alder adduct **5**, which after hydrolysis of the trimethylsilyloxy hemi-aminal function and *Z* to *E* isomerisation of the unsaturated aldehyde could result in the formation of the observed product **3b**. Hence, if the reaction were carried out in the presence of D_2O, hydrolysis of adduct **5** would be accompanied by deuteration to give the deuterated analogue of **3b**, i.e. *E*-unsaturated aldehyde **6**. The alternative reaction mechanism would involve an inverse electron-demand Diels–Alder reaction between the aryl imine **1** and the non-oxygenated terminal olefin of the 1-trimethylsilyloxybutadiene, which would initially produce **7a**, then **7b** after hydrolysis of the trimethylsilyl ether. Products resulting from either of these pathways were not identified in the crude reaction mixture. In addition, support for the fact that zwitterion **4b** is indeed involved in the formation of product **3b** is demonstrated by the fact that use of anhydrous $Yb(OTf)_3$, dry MeCN, but using D_2O in place of water to quench the intermediate in situ, produced no deuterium incorporation in the CH_2CH=CHCHO position of product **3b**, i.e. did not produce **6**.

In summary, it has long been considered that aza-Diels–Alder reactions can proceed through either an unsymmetric, yet concerted cycloaddition mechanism, or via stepwise processes.[6] However, it is very likely that in certain cases of Lewis acid-catalysed reactions of *N*-aryl imines which are seemingly acting as either dienes or dienophiles, that in fact the observed chemoselectivity is controlled by a metal-activated, acyclic reaction mechanism, i.e. an addition–cyclisation process. On occasion, the intermediate zwitterionic addition products can be intercepted, adding support to this hypothesis. This analysis may remove the necessity to invoke the intervention of independent mechanisms operating[7] in systems which appear to be remarkably similar.

Acknowledgements

We thank EPSRC and GlaxoSmithKline for an industrial CASE studentship (to DAJ) (Ref. no. 99314731X).

References

1. (a) Ishitani, H.; Kobayashi, S. *Tetrahedron Lett*. **1996**, *37*, 7357–7360; (b) Stevenson, P. J.; Nieuwenhuyzen, M.; Osborne, D. *Chem. Commun*. **2002**, 444–445.
2. (a) Kobayashi, S.; Komiyama, S.; Ishitani, H. *Angew. Chem., Int. Ed. Engl*. **1998**, *37*, 979–981; (b) Kobayashi, S.; Kusakabe, K.; Ishitani, I. *Org. Lett*. **2000**, *2*, 1225–1228; (c) Kobayashi, S.; Kusakabe, K.; Komiyama, S.; Ishitani, I. *J. Org. Chem*. **1999**, *64*, 4220–4221.
3. (a) Bromidge, S.; Wilson, P.; Whiting, A. *Tetrahedron Lett*. **1998**, *39*, 8905–8908; (b) McFarlane, A. K.; Thomas, G.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2803–2808; (c) McFarlane, A. K.; Thomas, G.; Whiting, A. *Tetrahedron Lett*. **1993**, *34*, 2379–2382.
4. Yao, S.; Saaby, S.; Hazell, R. G.; Jørgensen, K. A. *Chem. Eur. J*. **2000**, *6*, 2435–2448.
5. Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc*. **1974**, *96*, 7807–7808.
6. (a) Boger, D. L.; Weinreb, S. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987; (b) Jung, M. E.; Shishido, K.; Light, L.; Davis, L. *Tetrahedron Lett*. **1981**, *22*, 4607–4610; (c) Stanetty, P.;

Mihovilovic, M. D. *Chem. Lett.* **1997**, 849–850; (d) McCarrick, M. A.; Wu, Y.-D.; Houk, K. N. *J. Org. Chem.* **1993**, *58*, 3330–3345; (e) Whiting, A.; Windsor, C. M. *Tetrahedron* **1998**, *54*, 6035–6050.

7. Stanetty, P.; Mihovilovic, M. D.; Mereiter, K.; Völlenkle, H.; Renz, F. *Tetrahedron* **1998**, *54*, 875–894.
8. Bertilsson, S. K.; Ekegren, J. K.; Modin, S. A.; Andersson, P. G. *Tetrahedron* **2001**, *57*, 6399–6406.