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Intermolecular nitroso Diels–Alder cycloaddition of α-acetoxynitroso derivatives in aqueous medium

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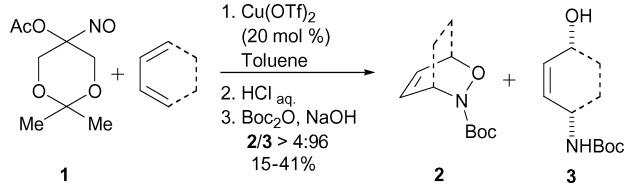
Received 21st September 2005, Accepted 14th October 2005
First published as an Advance Article on the web 15th November 2005

The Diels–Alder cycloadditions of the α-acetoxynitroso dienophile **1** in water are reported. The rapid and high yielding synthesis of structurally diverse 3,6-dihydro-1,2-oxazines complements the straightforward elaboration of aminoalcohols obtained from the α-acetoxynitroso derivative **1** in anhydrous medium. A rationale for this solvent-dependent product distribution is proposed.

Introduction

Since its first report in 1947,[1] the nitroso Diels–Alder cycloaddition has proved to be a useful synthetic tool to prepare 3,6-dihydro-1,2-oxazines, and asymmetric versions of this [4 + 2] cycloaddition have mainly relied on chiral nitroso derivatives.[2] In addition, the synthesis of enantiopure 3,6-dihydro-1,2-oxazines from achiral starting materials in a catalytic fashion has been an exciting field over the past few years.[3] Recent accomplishments include the use of organocatalysis[4] and chiral Lewis acid catalysis.[5] We recently reported the synthesis of the α-acetoxynitroso derivative **1** and its application as a useful dienophile in nitroso Diels–Alder cycloadditions.[6] During the course of our investigations, an unanticipated reaction involving N–O bond scission was observed, leading to synthetically valuable 1,4-aminoalcohol **3** in a one-pot operation (**2**/**3** <4 : 96, Scheme 1). Moreover, we found that a catalytic amount of Lewis acid such as $Cu(OTf)_2$ or $Zn(OTf)_2$ was necessary to ensure reproducible results.



Scheme 1 The [4 + 2] cycloaddition reaction of heterodienophile **1** in an anhydrous medium.

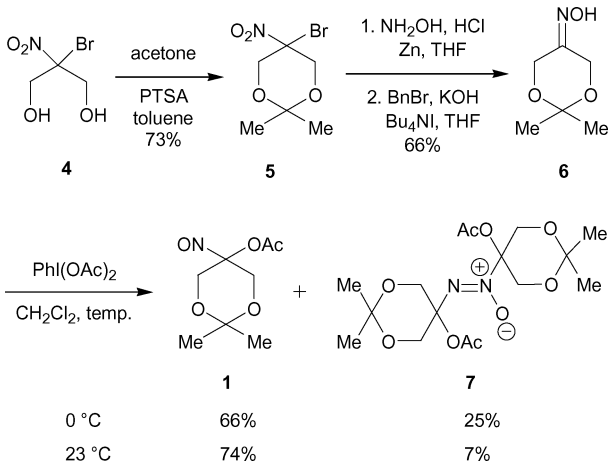
We recently observed that, quite surprisingly, traces of water led to a dramatic reversal of the product distribution. Since the pioneering studies of Breslow, reaction rates, and the regio- and stereochemistry of Diels–Alder [4 + 2] cycloadditions have been known to be influenced by aqueous media.[7] However, the impact of water on nitroso Diels–Alder reactions has been much less studied.[8] Kibayashi has elegantly shown that the addition of water increased the *cis*/*trans* selectivity of the intramolecular acylnitroso cycloaddition.[9] The corresponding intermolecular cycloaddition reaction has not been reported, which might be due to the limited lifetime of acylnitroso species in organic solution (~1 ms).[10] The addition of a small amount of water (0.5% v/v) to the reaction solvent (2-propanol–chloroform) was also found to increase the yield of the [4 + 2] cycloaddition product of α-chloronitroso derivatives.[11] Engberts also reported that water was able to stabilize the otherwise unstable cycloadduct of nitrosobenzene and cyclopentadiene.[12]

This article describes our results concerning the reactivity of an α-acetoxynitroso dienophile towards 1,3-cyclohexadiene in wet toluene and water. The scope of this cycloaddition with diversely substituted cyclic and acylic 1,3-dienes was also studied.

Results and discussion

Synthesis of the α-acetoxynitroso dienophile 1

The α-acetoxynitroso derivative **1** has been obtained by oxidation of the corresponding oxime **6**.[6] However, large-scale preparation of the latter by the literature procedure proved to be cumbersome due to the handling of large amounts of aluminum amalgam.[13] Therefore, a more scalable route had to be devised. Acetalization of 2-bromo-2-nitro-1,3-propanediol **4** afforded the corresponding nitro derivative **5** in 73% yield. Zinc-mediated debromination followed by *O*-benzylation initiated a Kornblum-like reaction, leading to the desired oxime **6** in 66% yield (Scheme 2).[14] Oxidation of **6** with diacetoxyiodobenzene in CH_2Cl_2 at room temperature led cleanly to the desired α-acetoxynitroso dienophile **1** in 74% yield. Lowering the temperature to 0 °C led to the concurrent formation of the corresponding azoxy derivative **7**[15] (25%), whose structure was determined by X-ray diffraction crystallography (Fig. 1).



Scheme 2 Synthesis of heterodienophile **1**.

† Corresponding author for the crystallographic data.

DOI:10.1039/b513397a

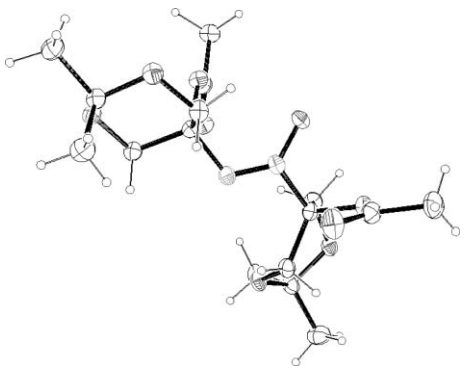


Fig. 1 X-Ray crystal structure of azoxy derivative **7**.

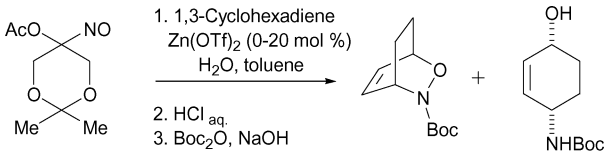
Reactivity of dienophile 1 with 1,3-cyclohexadiene in wet toluene

The reactivity of dienophile **1** towards 1,3-cyclohexadiene in various solvent systems was then evaluated (Table 1). Zinc triflate (20 mol%) was selected as a promoter since this Lewis acid proved to be more water-tolerant than copper triflate (*vide infra*). The $Zn(OTf)_2$-promoted cycloaddition reaction in anhydrous toluene led exclusively to the hydroxycarbamate **9** (Table 1, entry 1, **8/9** = 8 : 92).[6]

In the presence of only two equivalents of water, a totally different product distribution was observed, the protected cycloadduct **8** being the major product of the crude reaction mixture (Table 1, entry 2, **8/9** = 60 : 40). The nitroso Diels–Alder cycloaddition of **1** in the presence of 20 mol% of zinc triflate can even be conducted in pure water, in the absence of any organic solvent (Table 1, entry 4). The reaction was very clean and considerably faster than under anhydrous conditions (15 min *vs.* 4 h). Eventually, the optimal **8/9** ratio was found in pure water when zinc triflate was omitted (Table 1, entry 5, **8/9** >98 : 2). The characteristic blue color of dienophile **1** disappeared in 30 min, a slightly longer reaction time than in the presence of zinc triflate (Table 1, entries 4 *vs.* 5). The desired cycloadduct **8** was thus isolated in 74% yield for two steps.

The use of other Lewis acids (20 mol%) was investigated for the cycloaddition of dienophile **1** with 1,3-cyclohexadiene in water (Table 2). Copper triflate, the best promoter under anhydrous conditions, performed poorly, leading to 23% of a **8/9** = 90 : 10 mixture (entry 1). Scandium triflate,[16] ytterbium triflate[16] cerium trichloride and lithium chloride led to moderate-to-good yields (45, 50, 61 and 70% respectively). However, the **8/9** selectivity was not as high as previously obtained without any Lewis acid.[17] Therefore, Lewis acids were omitted when exploring the scope of this aqueous nitroso Diels–Alder cycloaddition.

Table 1 [4 + 2] Cycloaddition reaction of heterodienophile **1** with 1,3-cyclohexadiene in the presence of $Zn(OTf)_2$ and water

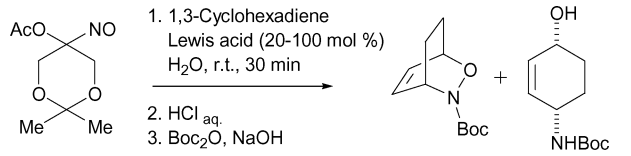


1 **8** **9**

Entry	$Zn(OTf)_2$	Water (equiv.)	Time[a]	Yield[b]	**8/9**[c]
1	20 mol%	—[d]	4 h	40%	8 : 92
2	20 mol%	2	4 h	39%	60 : 40
3	20 mol%	10	4 h	53%	85 : 15
4	20 mol%	H_2O only	15 min	78%	90 : 10
5	—	**H_2O only**	**30 min**	**74%**	**>98 : 2**

[a] For 100% conversion of **1**. [b] Isolated yield (two steps). [c] Ratio determined by integration of the crude ^{1}H NMR spectra and/or by GC. [d] Powdered 4 Å molecular sieves were used as a drying agent.

Table 2 Lewis acids screened for the aqueous [4 + 2] cycloaddition reaction of heterodienophile **1** with 1,3-cyclohexadiene



1 **8** **9**

Entry	Lewis acid	Yield[a]	**8/9**[b]
1	$Cu(OTf)_2$	23%	90 : 10
2	$Sc(OTf)_3$	45%	92 : 8
3	$Yb(OTf)_3$	50%	91 : 9
4	$CeCl_3 \cdot 7H_2O$	61%	94 : 6
5	LiCl[c]	70%	92 : 8

[a] Isolated yield (two steps). [b] Ratio determined by integration of the crude ^{1}H NMR spectra and/or by GC. [c] 100 mol%.

These preliminary experiments highlighted the synthetic potential of the α-acetoxynitroso dienophile **1**, since a simple switch of solvent, from anhydrous toluene to water, allowed the selective formation of either the protected aminoalcohol **9** or its parent cyclic system **8**, in high yield from the *same* nitroso species.

Scope of the aqueous cycloaddition of dienophile 1 with diversely substituted 1,3-dienes

The scope of the [4 + 2] cycloaddition of **1** under the optimal aqueous conditions with different dienes was studied next (Table 3). Two classes of 1,3-dienes were evaluated: cyclic and acyclic symmetric 1,3-dienes (**10a–b** and **12a–b**), and cyclic and acyclic dissymmetric 1,3-dienes (**14a–d** and **16**), dissymmetric dienes raising the issue of regiocontrol[18] during the cycloaddition. When the solubility of the diene was a problem, tetrahydrofuran was used as a miscible cosolvent.

Cyclic and acyclic symmetric 1,3-dienes

Cyclopentadiene and cycloheptadiene led to the corresponding cycloadducts **11a** and **11b** in 65 and 56% yield respectively (Table 3, entries 1 and 2). Improved yields of cycloadducts were obtained with symmetric acyclic 1,3-dienes **12a** and **12b** (69 and 100% yield, entries 3 and 4).

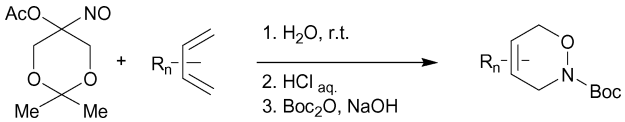
In all these experiments, the corresponding N–O bond cleaved products were not detected in the ^{1}H NMR spectrum of the crude reaction mixture.

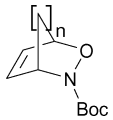
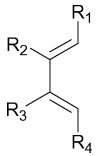
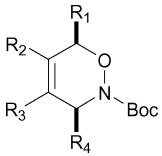
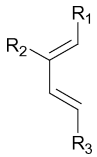
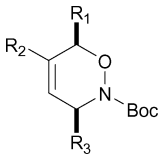
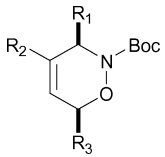
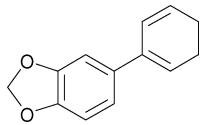
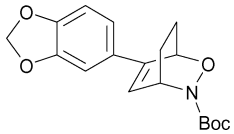
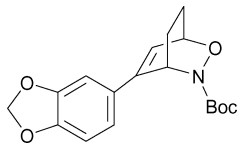
Cyclic and acyclic dissymmetric 1,3-dienes

Dissymmetric acyclic 1,3-dienes **14a–d** led to moderate-to-good yields (44–80%) of 3,6-dihydro-1,2-oxazines **15a–d**[19] (Table 3, entries 5–8). A drop in yield and regioisomeric ratio was observed when the cycloaddition reaction was carried out with 1,3-diene **14c** rather than 1,3-diene **14b** (entries 7 and 6, 63 : 37 *vs.* 80 : 20). Intermolecular H-bonding in the *endo* transition state between the primary alcohol function of **14b** and the oxygen atom of the nitroso moiety of **1** might help to reinforce the intrinsic preference[18] of the 1,3-diene **14b** for the proximal cycloadduct (Fig. 2). This hypothesis was supported by the lower regioselectivity in the cycloaddition of protected diene **14c**.

Actually, Wajer[20] had shown that the oxygen atom of a *C*-nitroso compound was a proton acceptor in hydrogen bonding. A closely related intramolecular H-bond between a hydroxyl function and the oxygen atom of a nitroso moiety

Table 3 [4 + 2] Cycloaddition of heterodienophile **1** with 1,3-dienes in water



Entry	1,3-Diene[a]	Proximal (pr) and distal (ds) 3,6-dihydro-1,2-oxazines					Yield (pr/ds ratio)[b]
1		**10a**, $n = 1$				**11a**[c]	65%
2		**10b**, $n = 3$				**11b**	56%
3		**12a**, $R_1 = R_4 = H$, $R_2 = R_3 = Me$				**13a**	69%
4		**12b**,[d] $R_1 = R_4 = Me$, $R_2 = R_3 = H$				**13b**[e]	100%
5		**14a**, $R_1 = R_3 = H$, $R_2 = Me$		**15a-pr**		**15a-ds**	48% (75 : 25)
6		**14b**, $R_1 = CH_2OH$, $R_2 = H$, $R_3 = Me$		**15b-pr**		**15b-ds**	80% (80 : 20)
7		**14c**, $R_1 = CH_2OTBS$, $R_2 = H$, $R_3 = Me$		**15c-pr**		**15c-ds**	44%[f] (63 : 37)
8		**14d**, $R_1 = CH_2OTBS$, $R_2 = H$, $R_3 = Ph$		**15d-pr**		**15d-ds**	69%[f,g] (2 : 98)
9		**16**		**17-pr**		**17-ds**	49%[f] (50 : 50)

[a] 3–5 equivalents. [b] Isolated yield, ratio determined by integration of the crude ^{1}H NMR spectra. [c] Acidic hydrolysis omitted (see text). [d] As a commercially available $(E,E)/(Z,E) = 70 : 30$ mixture. [e] Containing 20% of the *trans*-isomer. [f] 50% Aqueous THF. [g] Based on 84% conversion.

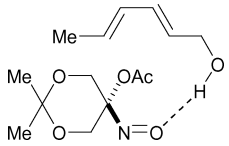


Fig. 2 Proposed H-bonding in the *endo* transition state for the cycloaddition of α-acetoxynitroso derivative **1** with 1,3-diene **14b**.

was also invoked by Kirby[21] and Procter[22] in their studies of α-hydroxyacylnitroso dienophiles.

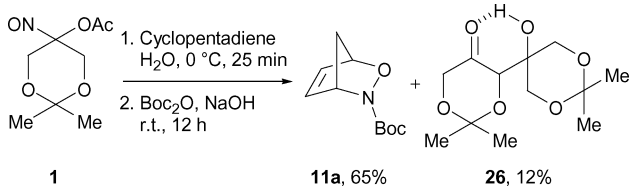
Use of the 1,3-diene **14d** rather than **14c** led to a complete reversal of proximal/distal regioisomeric ratio (Table 3, entries 8 and 7, 2 : 98 *vs.* 63 : 37), which confirmed that a phenyl substituent has a much stronger directing effect than a methyl group.

Finally, the sensitive[23] 2-aryl-1,3-cyclohexadiene **16** was evaluated, in relation to the ongoing total synthesis of a natural product (Table 3, entry 9). The nitroso Diels–Alder cycloaddition of dienophile **1** in aqueous THF afforded the proximal (pr) and distal (ds) regioisomers[18] **17** in a 1 : 1 ratio and a moderate 49% combined yield after protection.

Rationale for the solvent-dependent product distribution

Among the different strategies known for the elaboration of dihydrooxazines by nitroso Diels–Alder cyloadditions, this methodology has the advantage of being flexible, allowing straightforward access to the N–O bond cleaved product **21** in anhydrous solvent, or the corresponding 3,6-dihydro-1,2-oxazine **25** in aqueous medium (Scheme 3). The sequence leading to **21** can be explained by considering that the intermediate **18** undergoes iminium–enamine tautomerization, thereby generating **19**. The latter could then initiate a spontaneous and irreversible N–O bond cleavage, leading *via* the acidic hydrolysis of **20** to **21**.[24] In contrast, dihydrooxazine **25** was the only product obtained when water was used as a solvent. This mechanistic dichotomy can be understood by considering that water might act as a nucleophile, able to intercept the iminium species **18** before tautomerization to enamine **19**, thereby funneling the reaction pathway to **23**.

The presence of ketone **24** in the aqueous reaction medium was ascertained by TLC mobility in several solvent systems *vs.* an authentic sample of **24**.[25] Moreover, indirect proof of the presence of ketone **24** was obtained in the cycloaddition of α-acetoxynitroso **1** with cyclopentadiene (Scheme 4). After cycloaddition reaction, the usual acidic hydrolysis of the reaction mixture was omitted due to the reported instability of the corresponding bicylic 3,6-dihydro-1,2-oxazinium chloride.[26b] Protection of the amino moiety as a *tert*-butyl carbamate in basic aqueous THF led to the desired protected cycloadduct **11a** (65%) and to the hydroxyketone **26** (12%), arising from self-condensation of ketone **24**.



Scheme 4 Indirect proof of the presence of ketone **24**.

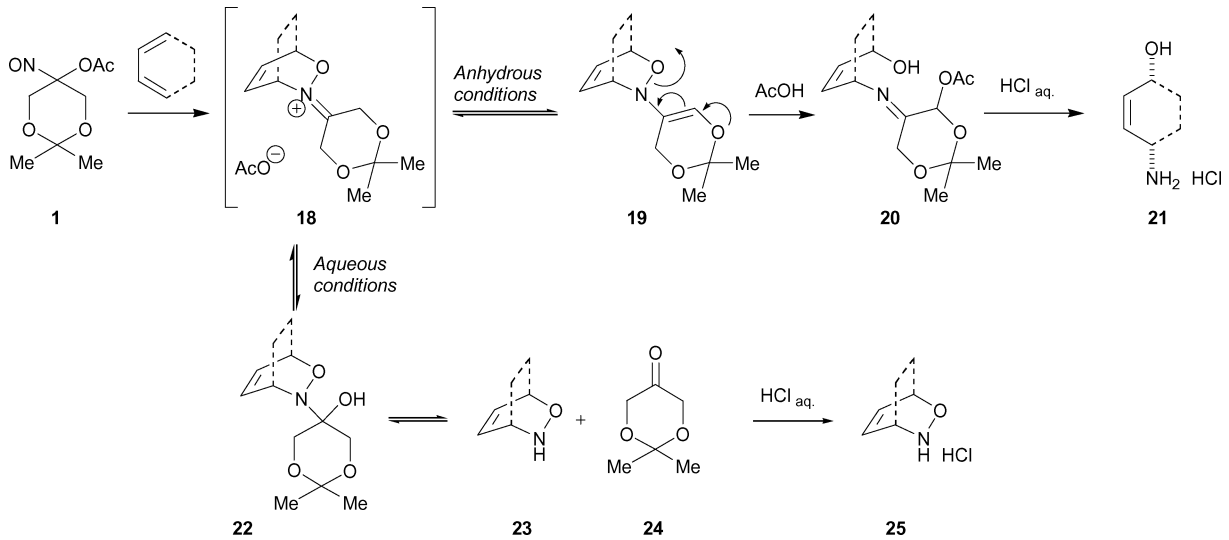
Conclusion

We have reported the Diels–Alder cycloaddition of the α-acetoxynitroso dienophile **1** in an aqueous medium. From the same nitroso derivative **1**, it is possible to selectively obtain 3,6-dihydro-1,2-oxazines in an aqueous medium, or the corresponding N–O bond cleaved products in an anhydrous medium. This aqueous version is convenient since no additives such as Lewis acids or surfactants are required to reach synthetically useful yields. The extension of this methodology to the synthesis of biologically active natural products is underway in our laboratories.

Experimental

Material and methods

All reactions were conducted in flame-dried or oven-dried glassware under an atmosphere of dry nitrogen. All solvents were purified before use unless otherwise indicated. Tetrahydrofuran, diethyl ether and toluene were distilled over sodium/benzophenone ketyl anion under argon. Dichloromethane was distilled over CaH_2 under argon. Analytical-grade water was obtained from a Millipore Elix 10 system. All other reagents were purchased and used without further purification. Molecular sieves (powdered, 4 Å) were heated at 560 °C for 14 h, cooled *in vacuo* and stored in a Schlenk flask under dry nitrogen. Solvent removal was performed at reduced pressure using a rotary evaporator with water aspiration. Analytical thin layer chromatography (TLC) was performed on glass plates precoated with a 0.25 mm thickness of Kieselgel 60 F_{254}. The TLC plates were visualized by



Scheme 3 Mechanistic dichotomy for the reaction of **1** in aqueous *vs.* anhydrous media.

shortwave UV light, potassium permanganate, *p*-anisaldehyde or ceric ammonium molybdate stain. Flash chromatography was performed according to the method of Still on Kieselgel 60 (230–400 mesh) silica gel. Infrared spectra were recorded as thin films on NaCl plates using a Perkin–Elmer Spectrum One FT-IR spectrophotometer. ^{1}H NMR spectra were measured at 400 MHz, 360 MHz, 250 MHz or 200 MHz on Bruker Advance 400, AC360, AC250 (or AM250) or AC200 spectrometers, using $CDCl_3$ as solvent. Chemical shifts are reported in δ units to 0.01 ppm precision, with coupling constants reported to 0.1 Hz precision using residual chloroform (δ 7.27 ppm) as an internal reference. Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, bs = broad singlet. ^{13}C NMR spectra were measured at 100 or 62.5 MHz using $CDCl_3$ (δ 77.0 ppm) as an internal reference. The GC device (9000 series, Fisons instruments, capillary column CP Sil 19 CB, 25 m length, 0.25 mm inside diameter, 0.20 µm film thickness, helium as carrier gas) was fitted with a hardware (NCI 9000 series interface) and software (Turbochrom) system developed by Perkin–Elmer. GC conditions were: 140 to 280 °C, 10 °C min^{-1}, p_{He} = 50 kPa. Retention times (t_R) are: **8**, 5.41 min; **9**, 6.32 min; internal standard (dibutylphthalate), 9.65 min. Mass spectra were measured on a MAT 95S Finnigan–Thermo spectrometer at the Institut de Chimie Moléculaire d'Orsay (ICMMO) Mass Spectrometry Laboratory. Elemental analyses were performed at ICSN, CNRS (Gif sur Yvette, France). Compounds **8**, **9**, **11a**, **13a–b**, **15a–d-pr**, **15a–d-ds**, have been described previously.[26]

Synthesis of 2,2-dimethyl-5-nitroso-1,3-dioxanyl acetate (1)

5-Bromo-2,2-dimethyl-5-nitro-1,3-dioxane (5). The following procedure was adapted from Lechevallier and co-workers.[27] 2-Bromo-2-nitropropan-1,3-diol **4** (25 g, 125 mmol) in acetone (46 mL) was stirred at room temperature until complete dissolution. Toluene (250 mL) and *p*-toluenesulfonic acid (0.24 g, 1.25 mmol) were added and the flask was equipped with a Soxhlet extractor filled with dry 4 Å molecular sieves. The reaction mixture was heated to 120 °C, and additional acetone (2 × 46 mL) was added until no starting material could be detected by TLC analysis (24 h). The solution was cooled to room temperature, saturated aqueous $NaHCO_3$ was added and the aqueous phase was extracted with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude solid was purified by flash chromatography on silica gel (heptane–acetone = 95 : 5 to 50 : 50) to give **5** (21.8 g, 73%) as a tan powder, mp 76–77 °C (lit.,[28,29] 81–83 °C, 77–78 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.78 (2H, d, *J* 13.0 Hz, 2 × OC*H*$_2$C), 4.27 (2H, d, *J* 13.0 Hz, 2 × OC*H*$_2$C), 1.54 (3H, s, C(2)Me), 1.38 (3H, s, C(2)Me). These spectroscopic data were in agreement with those previously reported.[29]

2,2-Dimethyl-5-nitro-1,3-dioxane. To a solution of 5-bromo-2,2-dimethyl-5-nitro-1,3-dioxane **5** (17.8 g, 74.2 mmol) in THF (285 mL) was added hydroxylamine hydrochloride (6.30 g, 90.7 mmol) in water (47 mL). The solution was cooled to 0 °C and zinc (7.6 g, 116 mmol) was added in portions over 20 min. After 2 h 30 min, the reaction mixture was concentrated to 60 mL. Saturated aqueous $NaHCO_3$ was added and the aqueous phase was extracted with EtOAc. The combined organic phases were dried over $MgSO_4$, filtered and concentrated. The crude solid was purified by flash chromatography on silica gel (heptane–CH_2Cl_2 = 80 : 20) to give 2,2-dimethyl-5-nitro-1,3-dioxane (10.16 g, 85%) as a white solid, mp 68 °C (lit.,[27,30] 59–60 °C, 60–61 °C); ν_{max}/cm^{-1} 1557, 1380, 1199, 1120, 1065, 820; ^{1}H NMR (200 MHz, C_6D_6) δ 4.11 (2H, dd, *J* 4.0 and 13.2 Hz, 2 × OC*H*$_2$CH), 3.42 (2H, dd, *J* 3.8 and 13.2 Hz, 2 × OC*H*$_2$CH), 3.26 (1H, q, *J* 4.0 Hz, CH$_2$C*H*CH$_2$), 1.28 (3H, s, C(2)Me), 1.12 (3H, s, C(2)Me); ^{13}C NMR (62.5 MHz, C_6D_6) 98.8, 77.3, 59.6, 27.0, 19.7.

2,2-Dimethyl-1,3-dioxan-5-one oxime (6). To a solution of 2,2-dimethyl-5-nitro-1,3-dioxane (1 g, 6.21 mmol) in THF (62 mL) was added benzyl bromide (0.82 mL, 6.83 mmol), powdered potassium hydroxide (366 mg, 6.52 mmol) and tetrabutylammonium iodide (115 mg, 0.31 mmol). The reaction mixture was stirred at room temperature for 1 h and quenched with saturated aqueous NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 and the combined organic phases were dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash chromatography on silica gel (toluene–EtOAc = 90 : 10) to give **6** (706 mg, 78%) as a white solid. Spectroscopic data were in agreement with those previously reported.[13]

2,2-Dimethyl-5-nitroso-1,3-dioxan-5-yl acetate (1) and acetic acid 5-(5-acetoxy-2,2-dimethyl-[1,3]dioxan-5-yl-ONN-azoxy)-2,2-dimethyl-[1,3]dioxan-5-yl ester (7). To a solution of 2,2-dimethyl-1,3-dioxan-5-one oxime **6** (502 mg, 3.46 mmol) in CH_2Cl_2 (35 mL) at 0 °C under argon was added (diacetoxyiodo)benzene (1.11 g, 3.46 mmol). After 3 h at room temperature, the reaction mixture was poured into saturated aqueous $NaHCO_3$ (25 mL). The aqueous layer was extracted with CH_2Cl_2, washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude blue oil was purified by flash chromatography on silica gel (pentane–diethyl ether = 95 : 5, 80 : 20, 50 : 50) to give **1** (522 mg, 74% from **6**) as a bright blue oil and **7** (48.6 mg, 7%) as a colorless solid. **1**: R_f (heptane–ethyl acetate = 80 : 20) = 0.46; Anal. calcd. for $C_8H_{13}NO_5$: C 47.29, H 6.45, N 6.89; found: C 47.26, H 6.51, N 6.81; λ_{max}($CHCl_3$)/nm 665 (ε/dm^3 mol^{-1} cm^{-1} 27); ν_{max}/cm^{-1} 1756, 1570, 1375, 1294, 1221, 1100; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.29 (2H, d, *J* 12.7 Hz, OC*H*$_2$C), 3.78 (2H, d, *J* 12.7 Hz, OC*H*$_2$C), 2.23 (3H, s, C(O)C*H*$_3$), 1.54 (3H, s, C(2)Me), 1.47 (3H, s, C(2)Me); ^{13}C NMR (62.5 MHz, $CDCl_3$) 166.8, 121.0, 100.3, 59.8, 23.6, 23.0, 20.5; *m*/*z* LRMS (ES) 775.3 [4(M − Me) + Na]$^+$, 399.1 [2(M − Me) + Na]$^+$. **7**: Anal. calcd for $C_{16}H_{26}N_2O_9$: C 49.23, H 6.71, N 7.18; found: C 49.45, H 6.65, N 7.33; ν_{max}/cm^{-1} 1760, 1223, 1158, 830; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.55 (1H, d, *J* 18.0 Hz, OC*H*$_2$C), 4.42 (1H, d, *J* 18.0 Hz, OC*H*$_2$C), 4.20–4.02 (6H, m, 6 × OC*H*$_2$C), 2.18 (3H, s, C(O)C*H*$_3$), 2.08 (3H, s, C(O)C*H*$_3$), 1.44 (6H, s, 2 × C(2)Me), 1.41 (6H, s, 2 × C(2)Me); ^{13}C NMR (90 MHz, $CDCl_3$) 168.7, 168.4, 100.2, 100.1, 99.3, 89.6, 64.1, 62.5, 24.1, 24.0, 23.4, 22.0, 21.7, 20.4, 20.1.

Crystal data. **7**: $C_{16}H_{26}N_2O_9$, M = 390.39, orthorhombic, a = 10.6750(4), b = 10.8521(5), c = 33.5940(12) Å, V = 3891.7(3) Å^3, T = 293 K, space group *Pbca* (no. 61), Z = 8, μ(Mo–Kα) = 0.109 mm^{-1}, 7851 reflections measured, 4347 unique (R_{int} = 0.0230), 2829 reflections used ($I > 2\sigma(I)$). The final R was 0.0452 (0.0788 for all data). CCDC reference number 274918. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b513397a.

Lewis acid promoted nitroso Diels–Alder cycloaddition of dienophile 1:

Procedure A: Anhydrous medium (Table 1, entry 1). A dry Schlenk flask, equipped with a septum and a magnetic stirring bar, was charged with 100 mg of dry molecular sieves (powdered, 4 Å) and 35.8 mg (20 mol%) of zinc triflate. The solids were dried under high vacuum at 125 °C overnight, with magnetic stirring. The Schlenk flask was cooled under vacuum and flushed with dried argon. A solution of the dienophile **1** (100 mg, 0.49 mmol) in dry toluene (1.2 mL) was added dropwise and the suspension was cooled to 0 °C. After 1 min, 1,3-cyclohexadiene (0.24 mL, 2.46 mmol) was added dropwise. The resulting suspension was stirred at 0 °C until complete disappearance of the characteristic blue color of **1**. The reaction mixture was hydrolyzed with aqueous HCl (1 N, 2 mL) and the biphasic solution was stirred for 45 min at room temperature. Aqueous NaOH (20 mol%) was added dropwise at 0 °C until the mixture reached pH ~10. A solution of Boc_2O (215 mg, 1 mmol) in THF (5 mL)

was added, and the resulting mixture was stirred at room temperature overnight. The aqueous layer was extracted with CH_2Cl_2, washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude oil was filtered through a plug of silica gel (Et_2O), and dibutylphthalate (internal standard) and acetone (2 mL) were added. The **8/9** ratio was determined to be 8 : 92 by GC as specified in 'Materials and methods'. The crude oil was purified by flash chromatography on silica gel (pentane–diethyl ether = 75 : 25 to 40 : 60) to give a mixture of **8** and **9** (41.6 mg, 40% from **1**) as a colorless oil.

Procedure B: Aqueous toluene (Table 1, entries 2 and 3). A dry Schlenk flask, equipped with a septum and a magnetic stirring bar, was charged with 35.8 mg (20 mol.%) of zinc triflate. The solids were dried under high vacuum at 125 °C overnight, with magnetic stirring. The Schlenk flask was cooled under vacuum and flushed with dried argon. A solution of α-acetoxynitroso dienophile **1** (100 mg, 0.49 mmol) in dry toluene (1.2 mL) was added dropwise and the suspension was cooled to 0 °C. The required volume of deionised water was then added *via* a microsyringe (2–10 equivalents). After 1 min, 1,3-cyclohexadiene (0.24 mL, 2.46 mmol) was added dropwise. Reaction time, work-up, **8/9** ratio determination and purification were performed as in Procedure A.

Procedure C: Water (Table 1, entries 4 and 5). In a 10 mL flask was charged with **1** (100 mg, 0.49 mmol). Water (1.2 mL) was added with rapid stirring to ensure efficient dispersion of the reactants. 1,3-Cyclohexadiene (0.24 mL, 2.46 mmol) was then added dropwise. Reaction time, work-up, **8/9** ratio determination and purification were performed as in Procedure A.

(1*R**,5*S**) *Tert*-butyl 7-oxa-6-aza-bicyclo[3.2.2]non-8-ene-6-carboxylate (11b)

White crystals, mp 75 °C (lit.,[11] 50–53 °C); ν_{max}/cm^{-1} 2977, 2933, 1736, 1686, 1366, 1247, 1167, 1084, 860, 826; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.34 (1H, ddd, *J* 1.3, 6.5 and 9.0 Hz, CH=C*H*), 6.14 (1H, ddd, *J* 1.8, 6.3 and 9.0 Hz, C*H*=CH), 4.75 (2H, m, C*H*O, C*H*N), 1.93–1.66 (4H, m, 2 × CH_2), 1.60–1.20 (2H, m, CH_2), 1.46 (9H, s, 3 × Me); ^{13}C NMR (90 MHz, $CDCl_3$) 156.1, 129.3, 127.5, 80.9, 74.8, 54.2, 30.5, 28.1, 27.4, 18.3. These spectroscopic data were in agreement with those previously reported.[11]

Synthesis of diene 16

1,3-Cyclohexadien-2-yl triflate. To a solution of diisopropylamine (1.89 mL, 14.4 mmol) in THF (20 mL) at 0 °C was added *n*-BuLi (9.0 mL, 14.4 mmol). After 30 min, the LDA solution was cooled to −78 °C, a solution of 2-cyclohexenone (1.27 mL, 13.1 mmol) in THF (20 mL) added *via* cannula, and stirring continued for 30 min. A solution of *N*-phenyltrifluoromethanesulfonimide (5.12 g, 14.3 mmol) in THF (20 mL) was then added and the reaction mixture allowed to warm slowly to 0 °C. After 2 h, the solution was concentrated. The residue was diluted with Et_2O, washed with water and the organic phase was dried over sodium sulfate, filtered and concentrated. The crude oil was purified by flash chromatography on silica gel (pentane) to give the dienyl triflate (1.63 g, 55%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.0 (1H, td, *J* 4.2 and 10.0 Hz, CC*H*CHCH$_2$), 5.8 (1H, qd, $J_{1H–19F}$ 2 Hz, $J_{1H–1H}$ 10.3 Hz, CH$_2$C*H*C), 5.7 (1H, dt, *J* 2.3 and 4.5 Hz, CH$_2$C*H*CHC), 2.4–2.3 (2H, 2 × CH_2CH$_2$), 2.3–2.2 (2H, 2 × CH_2CH$_2$); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 146.0, 131.5, 120.7, 118.6 (q, $J_{13C–19F}$ = 318.6 Hz), 114.7, 21.4, 21.3. Spectroscopic data were in agreement with those previously reported.[31]

5-(Cyclohexa-1,5-dienyl)benzo[1,3]dioxolane (16). To a suspension of magnesium turnings (0.18 g, 7.43 mmol) in THF (4 mL) at room temperature was added 1,2-methylenedioxy-4-bromobenzene (0.95 mL, 7.89 mmol) and stirring was continued for 2 h.[32] In a separate flask, CuI (9.4 mg, 0.005 mmol) was added to 1,3-cyclohexadien-2-yl triflate (1.13 g, 4.95 mmol) in THF (10 mL) at 0 °C. The Grignard reagent was then added slowly *via* cannula and the yellow suspension was stirred for 20 min before being hydrolyzed with saturated aqueous NH_4Cl. The aqueous phase was extracted with Et_2O, the combined organic phases dried over $MgSO_4$, filtered and concentrated. The crude oil was quickly filtered through neutral alumina (Et_2O) to give the title compound (1.3 g, quant.) as a colorless oil. This diene is known to undergo rapid decomposition upon standing at room temperature, and was therefore used rapidly without further purification or characterization.[23]

***Tert*-butyl (1*R**,4*S**)-5-benzo-1,3-dioxol-5-yl-2-oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate (17-pr) and *tert*-butyl (1*R**,4*S**)-6-Benzo-1,3-dioxol-5-yl-2-oxa-3-azabicyclo[2.2.2]oct-5-ene-3-carboxylate (17-ds).** To a dispersion of dienophile **1** (100 mg, 0.49 mmol) in water (1.25 mL) was added a solution of 5-(cyclohexa-1,5-dienyl)benzo[1,3]dioxolane **16** (197 mg, 0.98 mmol) in THF (1.25 mL). The reaction mixture was stirred at room temperature for 30 min, hydrolyzed with aqueous HCl (1 N, 2 mL) and the biphasic solution stirred for 45 min. Aqueous NaOH (20 mol%) was added dropwise at 0 °C so that the mixture was pH ~10. A solution of Boc_2O (220 mg, 1 mmol) in THF (5 mL) was added and the resulting mixture was stirred at room temperature overnight. The aqueous layer was extracted with CH_2Cl_2, washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The regioisomeric ratio (**17-pr/17-ds** = 50 : 50) was determined by ^{1}H NMR (C_6D_6). The crude oil was purified by flash chromatography on silica gel (heptane–EtOAc = 80 : 20 to 70 :30) to give a mixture of **17-pr** and **17-ds** (80.2 mg, 49%) as a waxy solid. An analytical sample was prepared by preparative TLC (heptane–EtOAc = 60 : 40). **17-pr**: White crystals, mp 98 °C; ν_{max}/cm^{-1} 3069, 2976, 2935, 1738, 1694, 1505, 1488, 1248, 1160, 1080, 1038, 939, 810; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03–7.00 (2H, 2 × *H*-Ar), 6.79 (1H, d, *J* 8.6 Hz, *H*-Ar), 6.55 (1H, dd, *J* 2.4 and 6.1 Hz, C(6)H), 5.95 (2H, 2 × OCH_2O), 5.14 (1H, m, C(4)H), 4.84 (1H, m, C(1)H), 2.25–2.15 (2H, C(7)H + C(8)H), 1.54 (1H, m, C(7)H), 1.41 (1H, m, C(8)H), 1.32 (9H, s, 3 × Me); ^{13}C NMR (100 MHz, $CDCl_3$) 157.3, 148.0, 147.6, 142.5, 129.7, 121.5, 119.1, 108.1, 105.3, 101.1, 81.6, 71.1, 52.3, 27.9, 20.9, 24.2; *m/z* HRMS (ESI, Na$^+$): calcd for [2M + Na$^+$] 685.2737, found 685.2732. **17-ds**: Waxy solid; ν_{max}/cm^{-1} 2977, 2937, 1699, 1505, 1489, 1251, 1234, 1159, 1038, 933, 810; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (2H, d, *J* 6.8 Hz, 2 × *H*-Ar), 6.81 (1H, m, *H*-Ar), 6.64 (1H, dd, *J* 1.8 and 5.6 Hz, C(5)H), 5.98 (2H, s, 2 × OCH_2O), 5.17 (1H, m, C(4)H), 4.87 (1H, dt, *J* 3.0 and 6.4 Hz, C(1)H), 2.38–2.13 (2H, C(7)H + C(8)H), 1.57–1.43 (11H, C(7)H + C(8)H), including 1.46 (9H, s, 3 × Me); ^{1}H NMR (400 MHz, C_6D_6) δ 6.51 (1H, s), 6.30 (2H), 6.08 (1H, dd, *J* 2.8 and 9.2 Hz), 5.04 (2H, s), 4.61 (2H, s), 1.74–1.69 (2H), 1.14 (9H, s), 0.85–0.62 (2H); ^{13}C NMR (100 MHz, $CDCl_3$) 157.5, 148.1, 147.6, 142.8, 129.9, 122.9, 118.7, 108.3, 105.4, 101.1, 81.5, 72.8, 50.4, 28.1, 23.8, 21.4; MS (ESI, Na$^+$): 354.1 (56, [M + Na$^+$]), 685.3 (100, [2M + Na$^+$]); *m/z* HRMS (ESI, Na$^+$): calcd for [M + Na$^+$] 354.1312, found 354.1321.

***Tert*-butyl (1*S**,4*R**)-2-oxa-3-azabicyclo[2.2.1]hept-5-ene-3-carboxylate (11) and 4-(5-hydroxy-2,2-dimethyl-1,3-dioxan-5-yl)-2,2-dimethyl-1,3-dioxan-5-one (26).** To a suspension of dienophile **1** (87 mg, 0.428 mmol) in deionised water (1.1 mL) at 0 °C was added freshly distilled cyclopentadiene (105 µL, 1.28 mmol). After 25 min the characteristic blue color of **1** disappeared and the solution turned yellow. A solution of sodium hydroxide (20% in water, 1 mL) was added dropwise, followed by di-*tert*-butyl dicarbonate (187 mg, 0.856 mmol) in THF (5 mL). The reaction mixture was stirred overnight. Brine was added and the aqueous phase was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$,

filtered and concentrated. The crude oil was purified by flash chromatography on silica gel (pentane–diethyl ether = 80 : 20) to give **11a**[26b] (55 mg, 65%) and **26** (6.8 mg, 12%) as colorless oils. **26**: R_f (heptane–ethyl acetate = 70 : 30) = 0.18; ν_{max}/cm^{-1} 3480, 1748, 1376, 1225, 1201, 1074, 832; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.48 (1H, d, *J* 1.3 Hz, OC*H*C(O)), 4.29 (1H, dd, *J* 1.3 and 17.0 Hz, OCH_2C), 4.13 (1H, dd, *J* 1.3 and 12.0 Hz, OCH_2C), 4.03 (1H, d, *J* 17.0 Hz, OCH_2C), 4.00 (1H, dd, *J* 1.3 and 10.7 Hz, OCH_2C), 3.86 (1H, d, *J* 12.0 Hz, OCH_2C), 3.67 (1H, d, *J* 10.7 Hz, OCH_2C), 2.82 (1H, s, O*H*), 1.50 (3H, s, C(2)Me), 1.49 (3H, s, C(2)Me), 1.47 (3H, s, C(2)Me), 1.43 (3H, s, C(2)Me); ^{13}C NMR (62.5 MHz, $CDCl_3$) 208.5, 101.3, 98.4, 73.9, 68.8, 67.4, 65.3, 64.6, 23.9, 23.5, 23.4, 23.3; MS (ESI, Na$^+$): 283.1 (100, [M + Na$^+$]), 252 (9), 196 (8); *m*/*z* HRMS (ESI, Na$^+$): calcd for [M + Na$^+$] 283.1152, found 283.1159.

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