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Lewis Acid-Promoted Hetero Diels–Alder Cycloaddition of α-Acetoxynitroso Dienophiles

Géraldine Calvet, Marion Dussaussois, Nicolas Blanchard, and Cyrille Kouklovsky*

Laboratoire de Synthèse des Substances Naturelles, Institut de Chimie Moléculaire et des Matériaux d'Orsay, Batiment 410, Université Paris Sud, 91400 Orsay-France

cykouklo@icmo.u-psud.fr

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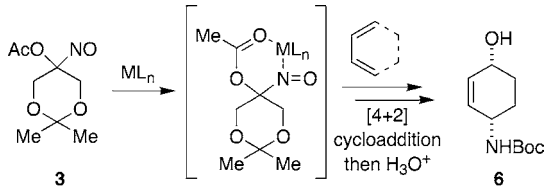
ABSTRACT



α-Acetoxynitroso compound 3 has been prepared as a new stable, isolable, and reactive dienophile in nitroso Diels–Alder reactions. The yield of the [4 + 2] cycloaddition of α-acetoxynitroso dienophile with 1,3-dienes could be enhanced in the presence of 20 mol % Lewis acid. An unexpected retro hetero-Michael reaction from 26 was observed, leading to the cleavage of the N–O bond of the cycloadduct. This tandem nitroso Diels–Alder/retro hetero-Michael sequence has been used with cyclic and acyclic 1,3-dienes.

The hetero Diels−Alder reaction is a powerful transformation, allowing rapid and stereoselective access to complex heterocyclic structures. This particular class of nitroso Diels−Alder cycloadditions[1] affords the corresponding 3,6-dihydro-1,2-oxazine **1**, a valuable building block in the context of total synthesis of natural or biologically active products. Until very recently, this class of cycloadditions was resistant to asymmetric catalysis despite an increasing number of reports adressing this problem.[2] In the case of acylnitroso dienophiles **2** (Scheme 1), these efforts have been hampered by the very high reactivity of the nitroso moiety, as recently demonstrated by time-resolved IR spectroscopy.[3] Acylnitroso derivatives **2** are mostly obtained from hydroxamic acids by oxidation with periodates,[1j,4] Dess−Martin periodinane,[5] or under Swern conditions[6] (Scheme 1, A). Ruthenium-,[2e,g,h] iridium-,[2f] and copper-catalyzed[2c] hydrogen peroxide oxidations of hydroxamic acids emerged recently as alternatives (Scheme

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(2) (a) Yamamoto, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 4128−4129. (b) Ding, X.; Ukaji, Y.; Fujinami, S.; Inomata, K. *Chem. Lett.* **2003**, *32*, 582−583. (c) Pulacchini, S.; Sibbons, K. F.; Shastri, K.; Motevalli, M.; Watkinson, M.; Wan, H.; Whiting, A.; Lightfoot, A. P. *Dalton Trans.* **2003**, 2043−2052. (d) Lightfoot, A. P.; Pritchard, R. G.; Wan, H.; Warren, J. E.; Whiting, A. *Chem. Commun.* **2002**, 2072−2073. (e) Flower, K. R.; Lightfoot, A. P.; Wan, H.; Whiting, A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2058−2064. (f) Iwasa, S.; Fakhruddin A.; Tsukamoto, Y.; Kameyama, M.; Nishiyama, H. *Tetrahedron Lett.* **2002**, *43*, 6159−6161. (g) Iwasa, S.; Tajima, K.; Tsushima, S.; Nishiyama, H. *Tetrahedron Lett.* **2001**, *42*, 5897−5899. (h) Flower, K. R.; Lightfoot A. P.; Wan, H.; Whiting, A. *Chem. Commun.* **2001**, 1812−1813. (i) Nakash, M.; Clyde-Watson, Z.; Feeder, N.; Davies, J. E.; Teat, S. J.; Sanders, J. K. M. *J. Am. Chem. Soc.* **2000**, *122*, 5286−5293. (j) Zhang, D.; Süling, C.; Miller, M. J. *J. Org. Chem.* **1998**, *63*, 885−888. (k) Meekel, A. A. P.; Resmini, M.; Pandit, U. K. *Bioorg. Med. Chem.* **1996**, *4*, 1051−1057.

(3) Lifetime of **2** in organic solutions was estimated on the order of 1 ms before being trapped by 1,3-cyclohexadiene: Cohen, A. D.; Zeng, B.-B.; King, S. B.; Toscano, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 1444−1445.

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(5) Jenkins, N. E.; Ware, R. W., Jr.; Atkinson, R. N.; King, S. B. *Synth. Commun.* **2000**, *30*, 947−953. See also ref 1a.

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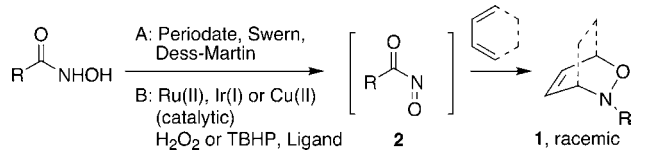
Scheme 1. Literature Precedent Addressing the (Asymmetric) Catalytic Nitroso Diels−Alder [4 + 2] Cycloaddition[2a−c,h]

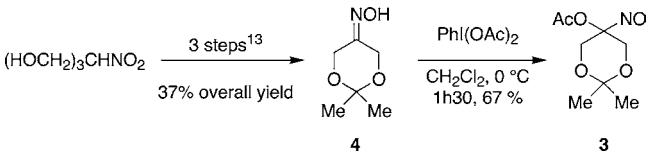


1, B). In the presence of a conjugated diene, the intermediate acylnitroso **2** is efficiently trapped to afford the corresponding hetero Diels−Alder adduct **1**. However, the use of enantiopure metal complexes as oxidizing agents did not induce asymmetry, which tends to indicate that dissociation of the acylnitroso **2** from the chiral metal complex occurs before the [4 + 2] cycloaddition.[2c,e]

Less reactive nitroso dienophiles such as arylnitroso derivatives could be better suited for a Lewis acid-mediated catalysis in the nitroso Diels−Alder cycloaddition as pointed out by Streith.[1c] Moreover, several complexes of arylnitroso with metals have been reported in the literature.[7] Disappointingly, Lewis acids in general failed to affect the rate of the arylnitroso cycloaddition with 1,3-cyclohexadiene, as elegantly demonstrated by Whiting.[2c] Very recently, Yamamoto[2a] described the catalytic asymmetric nitroso Diels−Alder reaction of 2-nitrosopyridine derivative in the presence of 10 mol % of a chiral copper(I) complex. Excellent yields and enantioselectivities up to 92% ee were observed. These results prompted us to report our own studies in this field.

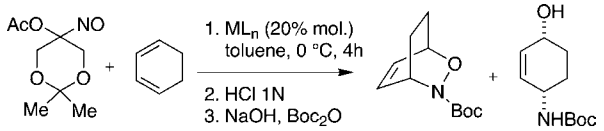
We decided to address the catalytic version of the nitroso Diels−Alder [4 + 2] cycloaddition using α-acyloxynitroso dienophiles[8] (Scheme 2). The latter have elicited theoretical[9]

Scheme 2. Synthesis of the α-Acetoxynitroso Dienophile **3**



and pharmacological studies,[10] but, to the best of our knowledge, have never been used as dienophiles in [4 + 2] cycloadditions. Conveniently, α-acyloxynitroso could be synthesized by the reaction between hypervalent iodine reagents and an oxime.[11] Since a large variety of (diacyloxyiodo)benzenes are easily available,[12] this procedure constitutes an efficient synthesis of sterically and electronically tunable α-acyloxynitroso compounds.

Table 1. [4 + 2] Cycloaddition of Heterodienophile **3** with 1,3-Cyclohexadiene in the Presence of Various Lewis Acids



entry	Lewis acid	**5**/**6**[a]	yield (three steps, %)[b]
1	none	2/98	14
2	$Mg(OTf)_2$	2/98	41
3	$CrCl_3$	2/98	41
4	$Cu(OTf)_2$	2/98	41

[a] Ratio determined by integration of the crude ^{1}H NMR spectra and/or by GC calibrated toward an internal standard (butylphthalate). [b] Isolated yield.

For these preliminary studies, we focused our attention on the α-acetoxynitroso dienophile **3** (Scheme 2). Following literature precedent,[13] oxime **4** was prepared in three steps from commercially available trishydroxy-methylnitromethane. When treated with (diacetoxyiodo)-benzene in CH_2Cl_2 at 0 °C, oxime **4** was smoothly transformed into the desired dienophile **3** in 67% yield after chromatographic purification.[14]

With a suitable preparation of **3** in hand, we next examined the cycloaddition reaction of this dienophile with 1,3-cyclohexadiene. The background reaction was investigated first, in the absence of any Lewis acid promoter (Table 1, entry 1). The crude reaction mixture was very clean, consisting of only two products, the expected bicyclic oxazine **5**[2j] and the hydroxycarbamate **6**,[15] after acidic hydrolysis, neutralization, and treatment with Boc_2O. To our surprise, **5** was only a minor component of the crude reaction mixture (**5**/**6** > 2:98). This uncatalyzed reaction proved to be unreproducible, as **6** was isolated in 0−19% yields in five different runs. Screening of various achiral Lewis acids revealed that $Mg(OTf)_2$, $Cu(OTf)_2$, and $CrCl_3$ were able to increase the yield of this sequence, allowing access to **6** in 41% isolated yield over three steps (74% average per step, Table 1, entries 2−4).[16,17]

The unexpected N−O bond cleavage leading to the hydroxycarbamate **6** is very interesting from a synthetic point

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(11) This synthesis of α-acetoxynitroso derivatives capitalizes on a fortuitous observation reported by Moriarty: Moriarty, R. M.; Prakash, O.; Vavilikolanu, P. R. *Synth. Commun.* **1986**, *16*, 1247−1254.

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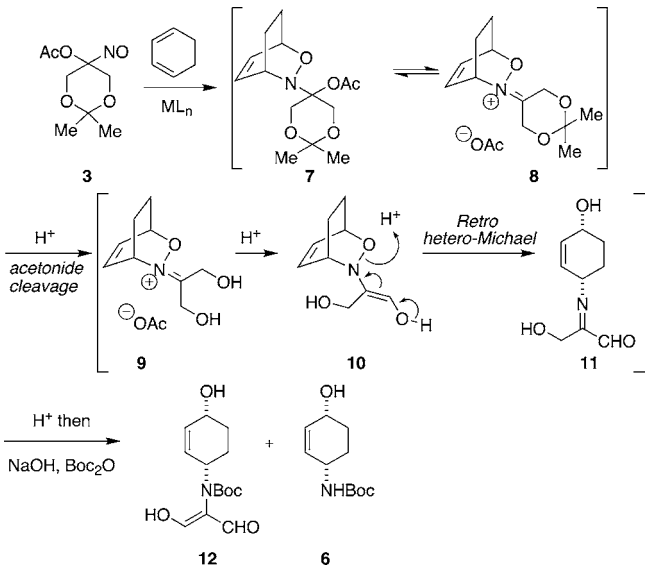
(13) Majewski, M.; Gleave, D. M.; Nowak, P. *Can. J. Chem.* **1995**, *73*, 1616−1626.

(14) This bright blue compound is stable at room temperature and can be stored for several months without dimerization to the corresponding colorless azodioxide derivative.

(15) Hall, A.; Bailey, P. D.; Rees, D. C.; Rosair, G. M.; Whightman, R. H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 329−343.

(16) Other Lewis acids screened are $TiCl_4$, $Ti(Oi\text{-}Pr)_4$, $FeCl_3$, $AgBF_4$, AgOAc, LiBr, $BF_3{\cdot}OEt_2$, $MgCl_2$, ZnF_2, $ZnBr_2$, $ZrCl_4$, $SnCl_4$, $Sn(OTf)_2$, $PdCl_2$, $Sc(OTf)_3$, $CeCl_3$, $Yb(OTf)_3$, and $Zn(OTf)_2$. All proved to be inferior to the Lewis acids listed in Table 1: see Supporting Information.

Scheme 3. Postulated Mechanism for the Formation of Compound **6**



of view since it avoids the use of toxic and expensive reagents such as $Mo(CO)_6$[18] or Na(Hg) amalgam,[19] which are tradionally used to achieve the N−O bond scission of the cycloadducts. The formation of **6** could be tentatively explained (Scheme 3). Compounds **7** and **8** arise from the [4 + 2] cycloaddition of α-acetoxynitroso **3** and 1,3-cyclohexadiene and are thought to be in equilibrium. Acidic hydrolysis of the acetonide moiety could lead to the 1,3-diol **9**, which could equilibrate to the corresponding enaminol **10**. Retro hetero-Michael reaction of **10** followed by hydrolysis of the resulting imine and protection of the amino moiety as a *tert*-butylcarbamate could then lead to the observed product **6**. Support for this mechanism comes from the isolation of traces of compound **12**, a byproduct of the reaction. The stereochemistry of **12** has been determined by extensive multinuclear two-dimensional NMR experiments.[20] Furthermore, when the hydrolysis of the reaction mixture (**7**/**8**) was conducted with 20% aqueous NaOH solution, hydroxycarbamate **6** was isolated in less than 3% yield, which supported the fact that the N−O bond cleavage is initiated by deprotection of the acetonide moiety of **7**/**8**.

This nitroso Diels−Alder/retro hetero-Michael sequence has been applied to cyclic and acyclic 1,3-dienes (**13**, **15**, **17**, and **19**, Scheme 4). Clean conversion to the corresponding hydroxycarbamates (**14**, **16**, **18**, and **20**) was observed in moderate yield over three steps.

α-Acetoxynitroso is expected to be less reactive than acylnitroso **2**.[1] On the basis of the coordination chemistry of *C*-nitroso compounds,[7] we anticipate that the presence of

(17) The solvent effect was also briefly investigated, and toluene turned out to be superior to trifluorotoluene, nitromethane, acetonitrile, THF, and CH_2Cl_2. DMF led only to decomposition products.

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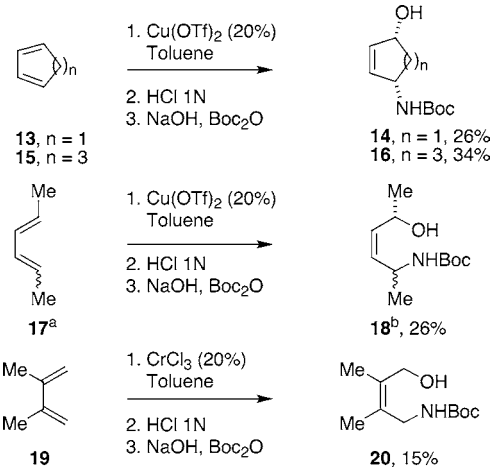
(20) See Supporting Information.

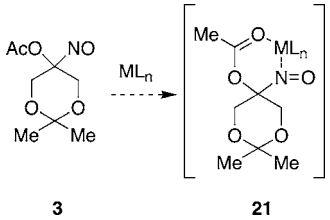
Scheme 4. Cycloaddition of **3** with Cyclic and Acyclic Dienes



[a] (*E*,*E*)/(*E*,*Z*) = 65:35. [b]Isolated as a 60:40 mixture.

a Lewis acid would lead to the more common N-binding mode. Moreover, the presence of an ester moiety in the α-position should favor the formation of a six-membered chelate **21** (Scheme 5). Studies to clarifiy the role of the

Scheme 5. Postulated Lewis Acid Activation of α-Acetoxynitroso Dienophile **3** in [4 + 2] Cycloaddition



Lewis acid in this nitroso Diels−Alder/retro hetero-Michael sequence are in progress.

In conclusion, we have disclosed the use of α-acetoxynitroso as a new class of heterodienophile for the nitroso Diels−Alder reaction. The yield of this [4 + 2] cycloaddition with electron-rich 1,3-dienes could be enhanced in the presence of a catalytic amount of Lewis acid. An unexpected N−O bond cleveage was observed during this study, leading to synthetically useful amino alcohol derivatives. Extension of this preliminary work to an asymmetric catalytic version of the nitroso Diels−Alder is in progress in our laboratory.

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Supporting Information Available: Experimental procedures and characterization data for compounds **3**, **5**, **6**, **12**, **14**, **16**, **18**, and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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