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α-Acyloxynitroso dienophiles in [4+2] hetero Diels–Alder cycloadditions: mechanistic insights

Géraldine Calvet [a], Susannah C. Coote [a], Nicolas Blanchard [b,*], Cyrille Kouklovsky [a,*]

[a] Laboratoire de Chimie des Procédés et Substances Naturelles, ICMMO, CNRS UMR 8182, Bâtiment 410, Université Paris-Sud, F-91405 Orsay, France
[b] Laboratoire de Chimie Organique, Bioorganique et Macromoléculaire, CNRS FRE 3253, Université de Haute-Alsace, ENSCMU, 3 rue A. Werner, F-68093 Mulhouse cedex, France

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ABSTRACT

α-Acyloxynitroso derivatives are a class of heterodienophiles leading to valuable 3,6-dihydro-1,2-oxazines or the corresponding aminoalcohols in good yields. The discovery that a β-oxygenated moiety led to a domino [4+2] cycloaddition/σ_{N-O} bond cleavage in the presence of a catalytic amount of Lewis acid was investigated in detail, through kinetic profiling of the reaction both in the absence and presence of a promoter. These studies showed that the role of the Lewis acid was to accelerate the σ_{N-O} bond cleavage thereby promoting a highly reproducible sequence. In addition, our preliminary results on an asymmetric version of this domino sequence are reported.

1. Introduction

Building molecular complexity from simple starting materials in a stereocontrolled manner is definitely an exciting challenge for synthetic chemists. Among the various strategies developed over the past decades, the Diels–Alder cycloaddition reaction occupies a prominent position, allowing the stereoselective elaboration of mono- or polycyclic compounds in a single step. The nitroso Diels–Alder reaction is a subclass of this venerable [4+2] cycloaddition that uses nitroso dienophiles, leading to 3,6-dihydro-1,2-oxazines **1** (Fig. 1).[1] The latter are valuable scaffolds since they can be directly incorporated into natural product-based drug design, as in the field of non-immunosuppressant neuroprotective derivatives.[2] Alternatively, the nitroso Diels–Alder cycloadducts can undergo oxidation reactions to the corresponding polyols **2**[3] or carboxylic acid esters **3**,[4] ring-opening reactions with nucleophiles[5] or organometallic reagents (**1**→**4**),[6] ring contraction to the corresponding pyrroles **5**,[7] ring-rearrangement metathesis to isoxazolo[2,3-*a*]pyridin-7-ones **6**[8] or σ_{N-O} bond scissions (**1**→**7**).[9] For the synthesis of biologically relevant compounds, reduction of the N–O bond is by far the most popular transformation of 3,6-dihydro-1,2-oxazines **1**. The corresponding 1,4-*cis*-aminoalcohols **7** are obtained stereospecifically and have been further transformed into numerous aminocyclitols,[10] carbapenem[11] or alkaloids such as (−)-epibatidine[12], (±)-fasicularin[13] or (±)-lepadiformine.[1,13]

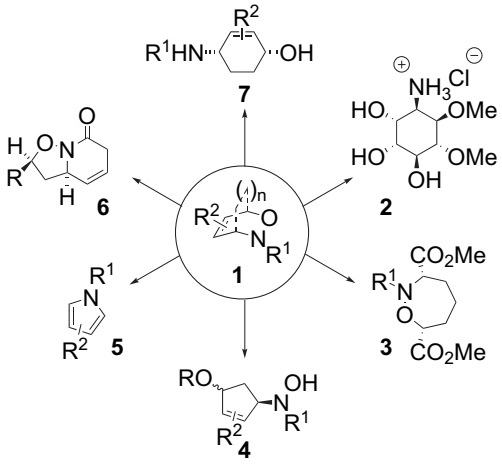

Figure 1. Nitroso Diels–Alder cycloadducts as valuable scaffolds.

The development of a catalytic version of the nitroso Diels–Alder cycloaddition has elicited a great deal of interest, as an efficient Lewis acid catalysis would pave the way for a catalytic and asymmetric cycloaddition, a long-standing goal in this research field. Until recently, since the first use of a chiral α-chloronitroso derivative in 1976,[14] only the chiral auxiliary-based strategy was known for the synthesis of non-racemic 3,6-dihydro-1,2-oxazines.[12,15] Two conceptually different approaches for the catalysis of the nitroso Diels–Alder cycloaddition have lately been reported:

(a) In situ generation and trapping of an intermediate acylnitroso dienophile **11** (Scheme 1, a). Ruthenium-,[16,17] iridium-,[18]

* Corresponding authors; e-mail addresses: nicolas.blanchard@uha.fr (N. Blanchard), cykouklo@icmo.u-psud.fr (C. Kouklovsky).

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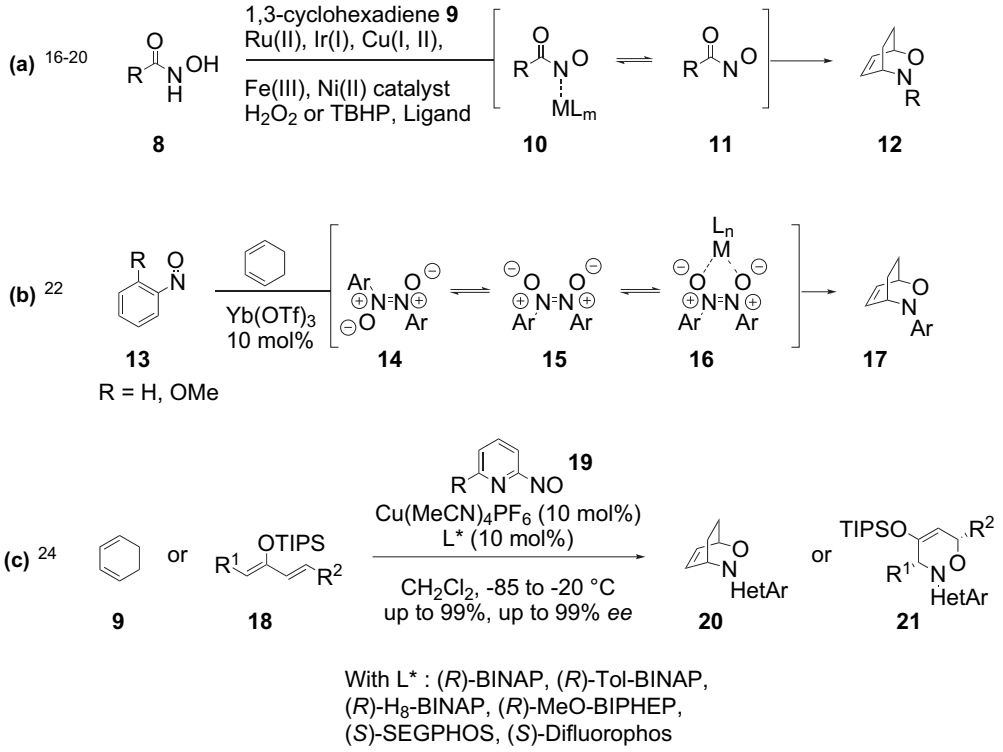
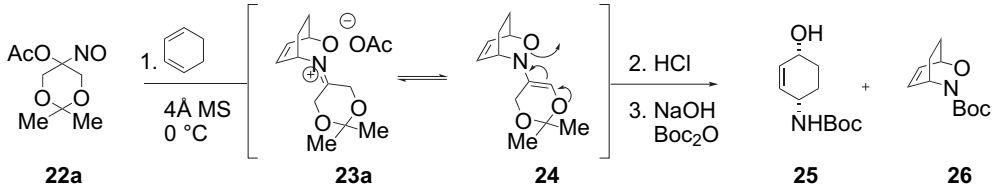


Scheme 1.

copper-,[19,17] nickel-,[17] iron-,[16d,17] and chromium[16d]-catalyzed hydrogen peroxide oxidation of hydroxamic acids emerged as a powerful strategy for the synthesis of 3,6-dihydro-1,2-oxazines under mild conditions. Catalyst loadings as low as 0.1 mol % could be used. Elegant and detailed mechanistic studies of this reaction were reported by Whiting in 2008 using time-resolved NMR and IR spectroscopy as well as cyclic voltammetry.[20] Disappointingly, the use of enantiopure metal complexes[16,17,20] to oxidize hydroxamic acids **8** induced only a low enantioselectivity in the intermolecular version (10% ee with the [$RuCl_2$(*R*)-PROPHOS(PPh_3)]) catalyzed cycloaddition at −60 °C.[16a] These experimental results support a rapid dissociation of the highly reactive acylnitroso **11** from the chiral metal complex **10** before the bimolecular [4+2] cycloaddition reaction. On the other hand, Shea reported in 2005 that Whiting's ruthenium–salen catalytic system was successful in the intramolecular version (type II IMDA, up to 75% ee).[21]

(b) Activation of a moderately reactive arylnitroso dienophile **13** by a Lewis acid (Scheme 1, b).[22] This second strategy was particularly attractive since several complexes of arylnitroso derivatives with metals are reported in the literature.[23] Disappointingly, Lewis acids in general failed to affect the rate of the arylnitroso cycloaddition with 1,3-cyclohexadiene, as elegantly demonstrated by Whiting et al.[16] The catalytically inactive **16**, the structure of which has been determined by X-ray crystallography, appears to sequester the Lewis acid; cycloadduct **17** then arises from the [4+2] cycloaddition reaction of **13** with 1,3-cyclohexadiene. A low enantiomeric excess (15%) was observed in the presence of chiral ligand.[22] Recently, Yamamoto reported a catalytic and highly enantioselective nitroso Diels–Alder cycloaddition reaction using 2-nitrosopyridines **19** as dienophiles (Scheme 1, c).[24] Excellent yields and enantiomeric excesses (up to 99%) were obtained with cyclic 1,3-dienes and electron-rich acyclic dienes **18**. Several steps are then required to excise the 2-pyridyl moiety. Yamamoto's historical breakthrough relies on the clever use of a bidentate coordination of Cu(I) to **19**, thus creating an efficient asymmetric environment for the cycloaddition reaction.[25]

In parallel to Yamamoto's seminal report, we showed in a preliminary communication[26] that a new type of heterodienophile, α-acetoxynitroso derivatives, such as **22a**, are reactive partners in [4+2] cycloaddition reactions with electron-rich 1,3-dienes (Scheme 2). Surprisingly, the major product of the reaction was aminoalcohol **25** instead of the expected bicyclic 3,6-dihydro-1,2-oxazine **26** (**25**/**26**>96:4). The discovery of this one-pot transformation is of synthetic importance since it avoids



Without Lewis acid: non-reproducible
With 20 mol% $Cu(OTf)_2$ or $Cu(MeCN)_4PF_6$:
53-54% (3 steps), 25/26 > 96:4

Scheme 2.

the use of toxic and expensive reagents, such as Zn/AcOH, $Mo(CO)_6$ or Na(Hg), which are traditionally used to achieve the N–O bond scission of the cycloadducts in a separate step.[9] This domino [4+2] cycloaddition/σ_{N-O} bond cleavage sequence was proposed to proceed through iminium ion **23**, which is in equilibrium with β-aminoenol ether **24**.[27] We also discovered that the yield and reproducibility of these cycloaddition reactions were greatly improved in the presence of 20 mol% of a Lewis acid, preferentially zinc(II) or copper(I or II) salts (53–54% over three steps, 81% per step, **25**/**26**>96:4).[28]

We now report that several α-acyloxynitroso derivatives undergo this domino [4+2] cycloaddition/σ_{N-O} bond cleavage in the presence of a sub-stoichiometric amount of Lewis acid. In addition, we present new insights regarding the unexpected role of the Lewis acid, through kinetic profiling of the cycloaddition reactions both in the presence and absence of Lewis acid. The crucial electronic nature of the α-acyloxy group on the equilibrium between iminium **23** and β-aminoenol ether **24**, and thus on the product distribution, is also discussed. Finally, our preliminary results concerning the asymmetric version of the Diels–Alder cycloaddition of several α-acyloxynitroso derivatives are reported.

2. Results and discussion

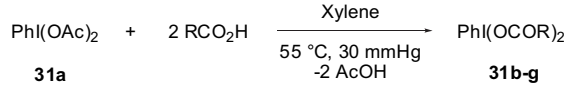
2.1. α-Acyloxynitrosos as potential dienophiles

Although α-acyloxynitroso derivatives **28** (Scheme 3) were reported as early as 1956 by Iffland and Criner,[29] to the best of our knowledge these compounds have never been used as dienophiles in [4+2] cycloaddition reactions but have only elicited theoretical[30] and pharmacological studies.[31–34] We recognized several attractive features in α-acyloxynitroso derivatives. First of all, they present an extended shelf life and a much reduced toxicity compared to *N*-nitrosamines[31,32] or *N*-nitrosamides,[31] Rehse and Herpel showed that these compounds only inhibit platelet aggregation and thrombus formation.[33] In 2006, King demonstrated that these α-acyloxynitroso derivatives are actually a new class of HNO donors,[34] the nitroxyl being of high interest in nitric oxide chemistry and biochemistry.[35] Besides these pharmacological considerations, we anticipated that the coordination of the nitroso moiety to a Lewis acid via the most common *N*-binding mode[23] would constitute an activation of the dienophile toward the [4+2] cycloaddition with an electron-rich 1,3-diene. The presence of several Lewis basic atoms in the vicinity of the coordinated nitroso could potentially lead to chelates, such as **29**. From this perspective, a straightforward synthesis of sterically and electronically tunable α-acyloxynitroso **28** from oximes **27** should be extremely valuable (Scheme 3). After the cycloaddition reaction the α-acyloxy group would be easily hydrolyzed, leading to the corresponding dihydrooxazinium salt **30**, which could be directly derivatized.

2.2. Synthesis of α-acyloxynitroso derivatives

α-Acetoxynitroso derivatives have been historically prepared from the reaction of an oxime with lead tetraacetate.[29,36] Although the latter reagent is relatively inexpensive, the yields of the desired α-acetoxynitroso compounds were quite low in our hands.[37] Capitalizing on a fortuitous observation of Moriarty,[38] we developed a high yielding and more general method for the synthesis of α-acyloxynitroso derivatives under mild and neutral conditions using (diacyloxy)iodobenzene. Following the procedure of Merkushev,[39] a range of (diacyloxy)iodobenzenes was easily prepared from commercially available carboxylic acids and (diacetoxy)iodobenzene, a stable and non-hazardous reactant compared to lead tetraacetate.[40] Seven different iodinanes **31a–g** were selected based on their different electronic character (R=*p*-MeOPh—entry 2, *p*-ClPh—entry 4, Cl_2CH—entry 6) or the crystallogenicity that they should confer on the corresponding α-acyloxynitroso derivatives (R=Ph—entry 1, R=*p*-Ph-Ph—entry 5, Table 1).

Table 1
Synthesis of (diacyloxy)iodobenzenes **31b–g** from **31a**

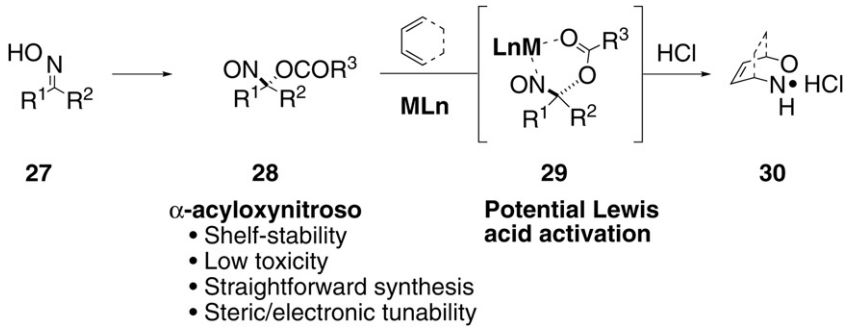


Entry	R	$PhI(OCOR)_2$	Yield[a]
1	Ph	**31b**	91
2	*p*-MeOPh	**31c**	94
3	*o*-MeOPh	**31d**	92
4	*p*-Cl-Ph	**31e**	99
5	*p*-Ph-Ph	**31f**	95
6	Cl_2CH	**31g**	73

[a] Isolated yield.

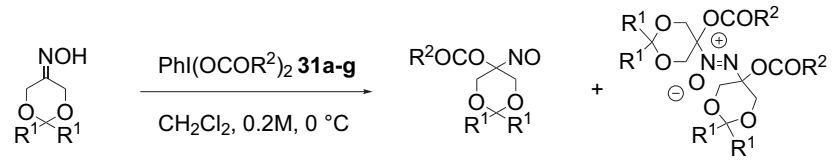
These stable white powders were then reacted with two oximes, **32**[41] and **34**[42] (Table 2). The latter was chosen on the basis of their anticipated higher reactivity compared to the corresponding all-carbon analog **37** (vide infra). Formation of the desired α-acyloxynitroso **22a–g** and **35a,b** was accompanied in some cases by the corresponding disproportionation derivatives **33a–f** as crystalline materials (5–15%).[20,43] The structure of azoxy compound **33a** was determined by X-ray diffraction.[27] The structures of azoxy compounds **33b–f** were assigned by analogy.

With the exception of α-acetoxynitroso derivatives **22a**, **22g**, and **35a**, these α-acyloxynitrosos were crystalline. Thus, we undertook a detailed crystallographic study of the conformational preference of these compounds.[44] We have shown that the 1,3-dioxanyl ring of α-benzoyloxynitroso **22b** and **22e** crystallizes in the 2,5-twist conformation with the N=O and the benzoyloxy substituents occupying the isoclinal positions.[45] When the isopropylidene ketal unit of derivative **22b** is replaced by a methylene



Scheme 3.

Table 2
Synthesis of α-acyloxynitroso derivatives



32, R^1 = Me
34, R^1 = H

22a-g, R^1 = Me
35a,b, R^1 = H

33a-f, R^1 = Me

Entry	R^1	R^2	Nitroso	Azoxy	Nitroso/Azoxy ratio[a]	Yield[b]
1	Me	Me	**22a**	**33a**	83:17	83
2	Me	Ph	**22b**	**33b**	84:16	86
3	Me	*p*-MeOPh	**22c**	**33c**	86:14	84
4	Me	*o*-MeOPh	**22d**	—	—	86
5	Me	*p*-Cl-Ph	**22e**	—	—	57
6	Me	*p*-Ph-Ph	**22f**	**33f**	81:19	42
7	Me	Cl_2CH	**22g**	—	—	52
8	H	Me	**35a**	—	—	47[c]
9	H	Ph	**35b**	—	—	23[c]

[a] ^{1}H NMR analysis of the crude reaction mixture.
[b] Isolated combined yield.
[c] Conditions: 0.1 M in CH_2Cl_2 at 20 °C.

ketal group as in dienophile **35b**, the conformation changes dramatically to a chair. The nitroso unit then occupies an equatorial position and the benzoyloxy substituent an axial position. King recently reported a very similar X-ray structure for the α-(*p*-nitrobenzoyloxy)nitroso derived from cyclohexanone oxime.[34] Worthy of note is the fact that the blue oily α-acetoxynitroso derivative **22a** crystallizes upon standing at −20 °C into colorless crystals of the corresponding azodioxy (***E***)-**36**, the structure of which has been determined by X-ray crystallography (Fig. 2). Upon dissolution of (***E***)-**36** into dichloromethane, immediate dissociation to α-acetoxynitroso **22a** occurs, as expected.[1] We hypothesized that these structural insights would be useful for the development of more reactive and/or selective α-acyloxynitroso dienophiles (vide infra).

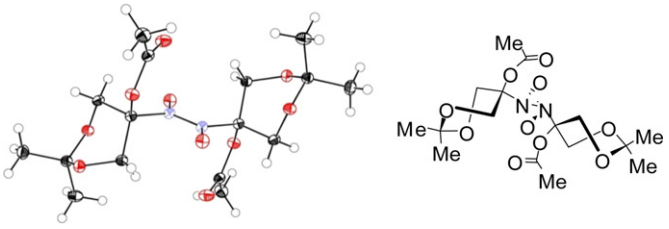


Figure 2. X-ray Structure of azodioxy derivative (*E*)-36 with displacement ellipsoids depicted at the 50% probability level. H atoms are shown as small spheres of arbitrary radii.

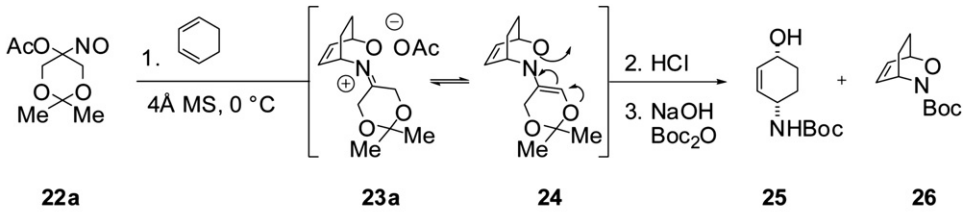
2.3. Relative amounts of 25 and 26 versus time in the absence of Lewis acid

As mentioned above, the domino [4+2] cycloaddition/σ_{N-O} bond cleavage of heterodienophile **22a** is not reproducible in the absence of a sub-stoichiometric amount of Lewis acid (Scheme 2).[26] To gain insights into this phenomenon, we studied the yield and distribution of the products of the reaction of **22a** with 1,3-cyclohexadiene in toluene over four hours (Fig. 3). The reaction mixture was quenched at different times with 1 N aqueous HCl then treated with 3 M aqueous NaOH and with Boc_2O. The crude mixture was then analyzed by GC. Each run was repeated at least three times and the observed variability in yield is reported. In the absence of Lewis acid, the cycloaddition reaction is quite rapid, since a 76±9% yield is attained after only 15 min. Worthy of note is the fact that both cycloadduct **26** and hydroxycarbamate **25** are present to the same extent. At 30 min, the total GC yield is constant (70±10%) and at 60 min, a sharp decrease in the amount of cycloadduct **26** is observed (43±14%, **25**/**26**=85:15). After 90 min, the yield of **25** is at a maximum (57±4%) and continuously decreases until 14% yield at 240 min. It should be noted that the yields vary considerably during this cycloaddition (±14% at 60 min, for example).[46]

Some decomposition of reaction intermediates clearly occurred since a dramatic drop in yield is observed between 90 min (57±4%) and 240 min (14%). We suspected that the sensitive oxygenated functions of intermediate **24** might be responsible for the observed decomposition. Control experiments were thus performed with dienophile **37**, which lacks the intracyclic oxygen atoms of derivative **22a** (Fig. 4). Only bicyclic 3,6-dihydro-1,2-oxazine **26** was observed with a variability maximum of 2.9% over duplicate experiments, thus confirming that the lack of reproducibility of the cycloaddition reaction in the absence of Lewis acid is ascribable to the sensitive β-aminoenol ether moiety. In addition, these control experiments unambiguously showed that the presence of the α-oxygenated function is critical for a productive σ_{N-O} bond cleavage, thus confirming the proposed mechanism (Scheme 2).

2.4. Relative amounts of 25 and 26 versus time in the presence of Lewis acid

The [4+2] cycloaddition reaction of α-acetoxynitroso **22a** with 1,3-cyclohexadiene in the presence of 20 mol % of a Lewis acid was then studied over time (Fig. 5). As in Figure 3, the crude reaction mixture was analyzed by GC. Each run was repeated at least three times and the observed variability in yield is reported. It is immediately apparent that the two profiles in Figure 3 and Figure 5 are totally different. In the Lewis acid-promoted cycloaddition reaction, yields are highly reproducible throughout the 4 h of reaction (maximum variability ±2.5% over 3–5



22a 23a 24 25 26

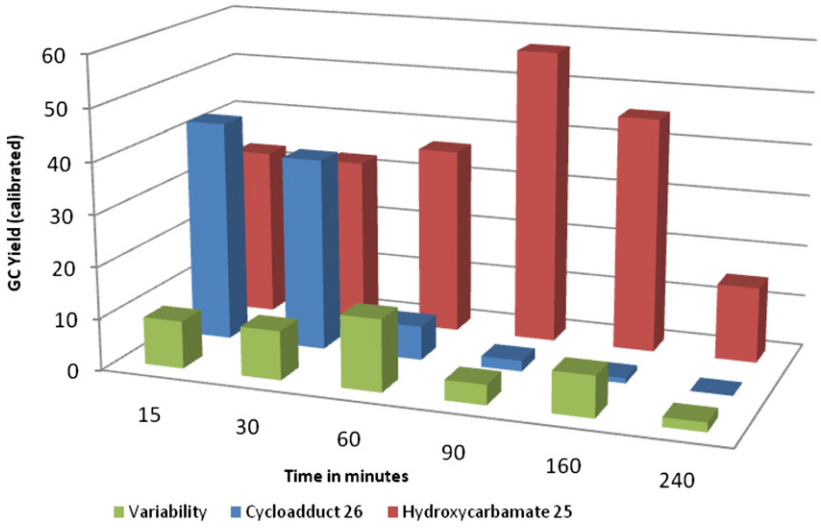
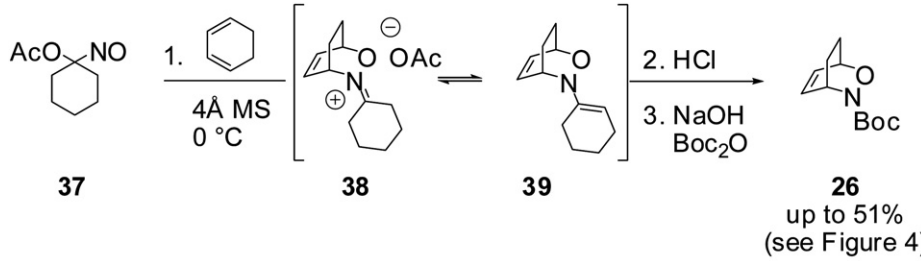


Figure 3. Plot of yield versus time for the cycloaddition reaction of **22a** with 1,3-cyclohexadiene without Lewis acid.

reactions run in parallel). In addition, the **25**/**26** ratio is almost constant, **26** being detected only as traces after 160 min. The maximum yield is obtained at 160 min and then slightly decreases (from 63±2% at 160 min to 53% at 240 min) but not to the extent observed in the non-promoted reaction (Fig. 3, from 57±4% at 90 min to 14% at 240 min).

Several conclusions can be drawn from this study. The reaction in the absence of Lewis acid is faster than in its presence,



37 38 39 **26**
up to 51%
(see Figure 4)

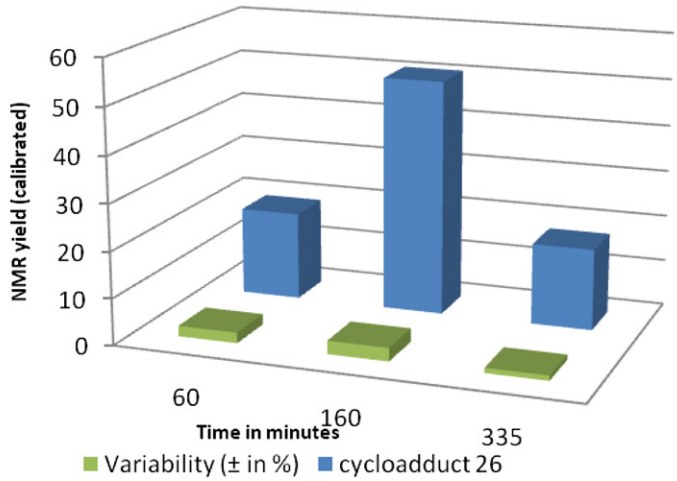
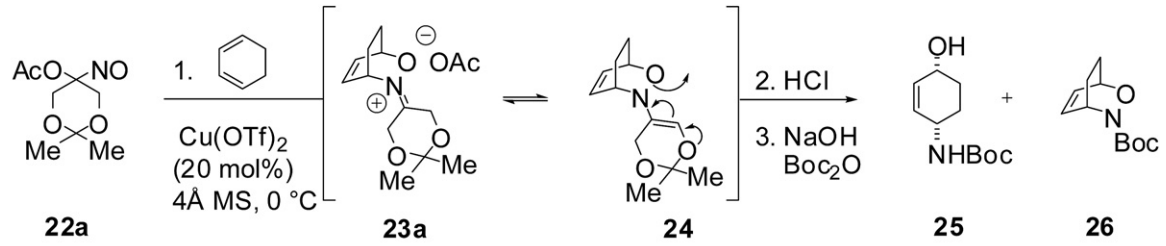


Figure 4. Plot of yield versus time for the cycloaddition reaction of **37** with 1,3-cyclohexadiene.



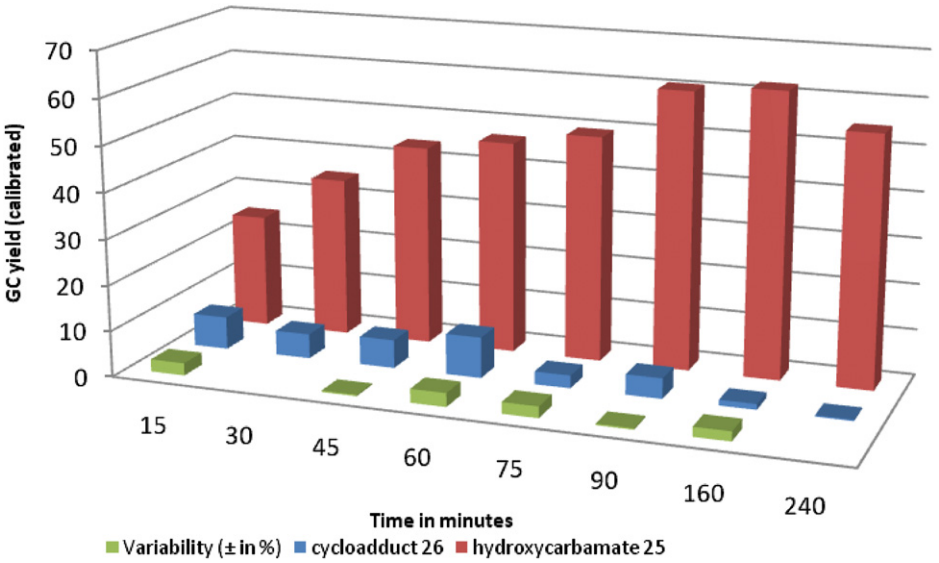
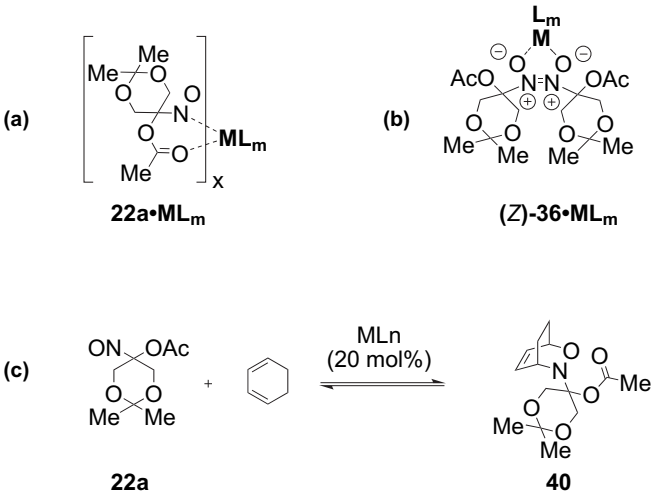


Figure 5. Plot of yield versus time for the cycloaddition reaction of **22a** with 1,3-cyclohexadiene with 20 mol % of $Cu(OTf)_2$.

since a 76±9% yield is obtained after 15 min in the former case as opposed to 30±2.5% for the same time in the latter case. The role of the copper(II) salt (20 mol %) is therefore not to accelerate the reaction. Several hypotheses could be put forward to rationalize this overall copper(II)-induced deceleration (Scheme 4): (a) complexation of the metal to several α-acetoxynitroso molecules simultaneously thereby limiting their availability for the cycloaddition (**22a**·$\mathbf{ML_m}$, a); (b) formation of the inactive (*Z*)-azodioxy **36**/Lewis acid complex as previously suggested by Whiting[22] ((***Z***)-**36**·$\mathbf{ML_m}$, b); (c) intervention of a copper(II)-mediated reversible cycloaddition (Eq. c). In order to corroborate the presence of the proposed α-acetoxynitroso/Lewis acid complexes **22a**·$\mathbf{ML_m}$ and (***Z***)-**36**·$\mathbf{ML_m}$, variable temperature ^1H and ^{13}C solution NMR as well as infrared studies were conducted with dienophiles **22a** and **36** and $Zn(OTf)_2$ (100 mol %). However, in spite of extensive efforts detailed in the Supplementary data, only marginal chemical shift or wave number differences were observed.[47]



Scheme 4.

In addition, the sub-stoichiometric quantity of copper(II) salt accelerates the N–O bond cleavage pathway since the bicyclic 3,6-dihydro-1,2-oxazine **26** is always a minor component of the reaction mixture (Fig. 5). Such an acceleration was also noticed in our previously reported aqueous cycloaddition reaction (20 mol % of $Zn(OTf)_2$ in H_2O, 78% yield, **25**/**26**=10:90; without zinc triflate 74% yield, **25**/**26**=2:98).[27] This faster σ_{N-O} bond scission could be explained by the coordination of the Lewis acid to the oxygen atom of the N–O motif of compound **24** (Scheme 2). The reproducible yields observed in Figure 5 are therefore a direct consequence of this faster σ_{N-O} bond cleavage. As detailed earlier, intermediate **24** is prone to decomposition, a pathway that is limited by the rapid conversion of **24** in the Lewis acid-promoted conditions.

Thus, it appears that the cycloaddition of α-acetoxynitroso **22a** with 1,3-dienes is reproducible and high yielding (53% over three steps, i.e., an average of 81% per step) when the reaction is conducted in the presence of 20 mol % of a Lewis acid, Cu(I) and Cu(II) salts leading to the best results in terms of yield and product ratio. With Cu(II), an unexpected rate deceleration was observed that could originate in chelation of the Lewis acid to the dienophile thereby sequestering part of the reactant.

2.5. Reactivity of α-acyloxynitroso dienophiles 22b–g and 35a

At this stage of our investigations, it was of interest to evaluate the reactivity of the α-acyloxynitroso derivatives **22b–g** and **35a** bearing

a variable acyloxy moiety. The background reaction of α-benzoyloxynitroso **22b** led to a very poor yield (8%, Table 3, entry 1) as for the reactions promoted by 20 mol % of $CeCl_3$ or $Yb(OTf)_3$ (Table 3, entries 2 and 3). 19–23% yields were observed for cycloadditions promoted by $Ti(O^iPr)_4$, $CrCl_3$ and $Cu(OTf)_2$ whereas $FeCl_3$ allowed the yield to get above 30% (Table 3, entry 7). In all these cycloaddition reactions, bicyclic dihydrooxazine **26** was obtained only in trace amounts. Considering our previous results and for the sake of consistency with [4+2] reactions of α-acetoxynitroso **22a**, we selected $Cu(OTf)_2$ as the Lewis acid for the rest of our studies. α-Acyloxynitroso derivatives **22c–f** were then reacted under similar conditions (Table 3, entries 8–11). Hydroxycarbamate **25** was the sole compound detected in the crude reaction mixture by GC and/or ^1H NMR analysis. Electron-rich α-benzoyloxynitrosos **22c**,**d**, and **22f** led to 22–26% yields, similar to that obtained with α-benzoyloxynitroso **22b** (23%, entry 6). On the other hand, electron-poor α-(*p*-chlorobenzoyloxy)nitroso derivative **22e** led to a synthetically useful yield (55%, Table 3, entry 10) similar to the one obtained with α-acetoxynitroso **22a** (53%, Scheme 2). In addition, this 55% yield was obtained after 105 min of reaction, thus emphasizing the similar reactivity of α-(*p*-chlorobenzoyloxy)nitroso **22e** and α-acetoxynitroso **22a** (cf. Fig. 5). Next, the cycloaddition reaction of the less stable dienophile **35a** was investigated.[48] Disappointingly, a poor yield of hydroxycarbamate **25** was obtained (26%, Table 3, entry 13) highlighting the fact that subtle differences in the dienophile can have a dramatic impact on the reaction outcome. Thus, although none of these α-acyloxynitroso derivatives proved superior to the α-acetoxynitroso **22a**, useful information relative to their conformational behavior in the solid state was obtained, which we hoped would facilitate the development of an asymmetric version of this reaction.

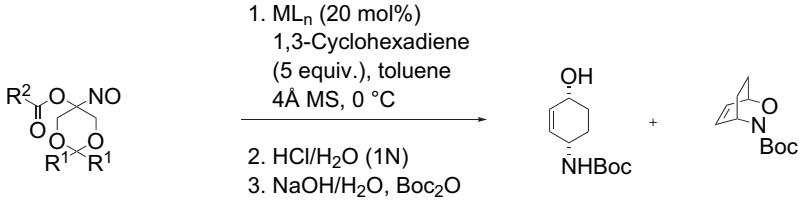
However, a very interesting observation was made during the cycloaddition reaction of dienophile **22g**, bearing an α-dichloroacetate substituent (Table 3, entry 12). In the presence of 20 mol % of zinc triflate, cycloadduct **26** was obtained as the sole product in 44% yield (for two steps). This result indicates that the equilibrium between iminium **23g** and β-aminoenol ether **24** is totally shifted toward **23g** in this case (Scheme 5).

Dichloroacetate is too weak a base to promote abstraction of a proton α to the iminium function of intermediate **23g**, thus leading to a long-lived iminium ion. In fact, the crucial importance of the counter anion or additives, such as salts on the enamine/iminium equilibrium is a well-documented phenomenon[49] that found recently widespread application in asymmetric organocatalysis.[50] Our results thus indicate that in the cycloaddition reactions of α-acyloxynitroso dienophiles, the electronic nature of the acyloxy moieties is also able to control the product distribution through the iminium/β-aminoenol ether equilibrium.

2.6. Cycloaddition reactions in the presence of Lewis acid and a chiral ligand

Finally, the influence of a chirally ligated Lewis acid on the enantioselectivity of the tandem [4+2] cycloaddition/NO bond cleavage of α-acetoxynitroso **22a** was evaluated. Based on our previous results, $Cu(OTf)_2$ and $Cu(MeCN)_4PF_6$ were chosen as the most promising Lewis acids and BINOL, Box and Synphos-type ligands were screened (Scheme 6). Disappointingly, only racemic hydroxycarbamate **25** was obtained. In addition, a dramatic decrease in yield was commonly observed (10–37%) compared to the non-asymmetric version (53–54%, Scheme 2). $AgSbF_6$ (20 mol %) was also used as an additive to increase the electrophilicity of the metallic center, without success.[51] This (common) rate deceleration in the presence of chiral ligand could originate in the extra steric hindrance around the binding site of the copper(II) salt, as noted by

Table 3
[4+2] Cycloaddition reactions of α-acyloxynitroso derivatives **22b–g** and **35a**

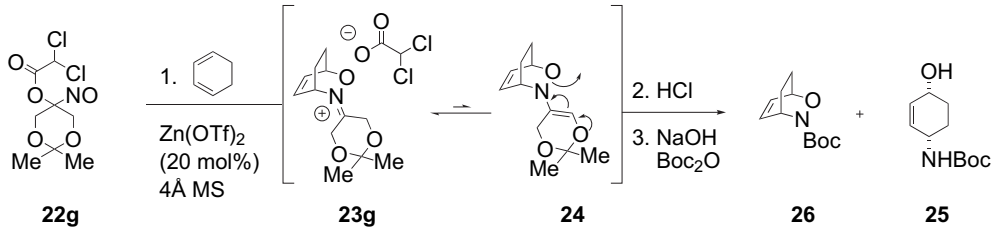


22b, R^1 = Me, R^2 = Ph
22c, R^1 = Me, R^2 = *p*-MeO-Ph
22d, R^1 = Me, R^2 = *o*-MeO-Ph
22e, R^1 = Me, R^2 = *p*-Cl-Ph
22f, R^1 = Me, R^2 = *p*-Ph-Ph
22g, R^1 = Me, R^2 = Cl_2CH
35a, R^1 = H, R^2 = Me

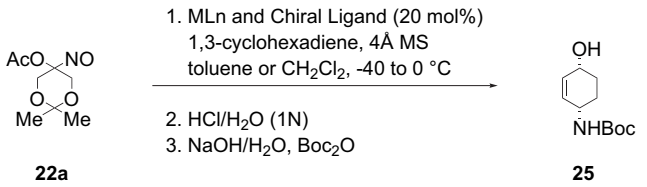
25 **26**

Entry	Dienophile	Lewis acid	Time (h)	**25**/**26** ratio[a]	Yield[b]
1	**22b**	—	4	>99:1	8
2	**22b**	$CeCl_3$	4	>99:1	8
3	**22b**	$Yb(OTf)_3$	4	90:10	9
4	**22b**	$CrCl_3$	4	97:3	20
5	**22b**	$Ti(O^iPr)_4$	4	93:7	19
6	**22b**	**$Cu(OTf)_2$**	**4**	**90:10**	**23**
7	**22b**	$FeCl_3$	4	>96:4	32
8	**22c**	$Cu(OTf)_2$	1.5	>96:4	26
9	**22d**	$Cu(OTf)_2$	1.5	>96:4	23
10	**22e**	**$Cu(OTf)_2$**	**1.75**	**>96:4**	**55**
11	**22f**	$Cu(OTf)_2$	3	>96:4	22
12	**22g**	**$Zn(OTf)_2$**	**1**	**1:99**	**44**
13	**35a**	$Cu(OTf)_2$	3	>96:4	26

[a] ^1H NMR and/or GC analysis of the crude reaction mixture.
[b] Isolated yield.



Scheme 5.



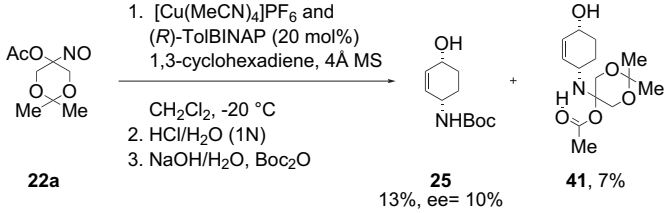
With $Cu(OTf)_2$ or $[Cu(MeCN)_4]PF_6$ And (*R*)-BINOL, (*R,R*)-tBuBox, (*R,R*)-PhBox, (*R,R*)-PhPyBox, (*R*)-SYNPHOS: **10-37%, ee < 3%**

With $Zn(OTf)_2$ And (*R*)-BINOL, (*R,R*)-tBuBox, (+)-DET: **25-38%, ee < 3%**

Scheme 6.

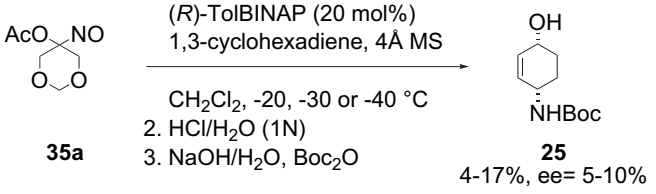
Sharpless in his landmark review on ligand-accelerated catalysis.[52] Catalytic systems based on zinc-Lewis acids were also evaluated (Scheme 6). In the absence of chiral ligand, the zinc triflate-mediated cycloaddition led to a 38% yield of protected amino-alcohol **25**.[26] In the presence of (*R,R*)-^{t}Bu-Box (20 mol %), the yield of **25** was identical but no enantioselectivity was observed, as in the case of zinc alkoxides ($ZnEt_2$/(+)-DET or (*R*)-BINOL).[53]

The best result in term of enantiomeric excess was obtained with $Cu(MeCN)_4PF_6$/(*R*)-Tol-BINAP (20 mol %) in dichloromethane at −20 °C (Scheme 7). The desired hydroxycarbamate **25** was isolated with 10% ee. Although this enantioselectivity is low, this result lends experimental support, for the first time, to a complexation between the enantiopure Lewis acid complex and the α-acetoxynitroso **22a** in the stereodetermining step of the cycloaddition.[54] As mentioned above, reactivity is strikingly eroded (13% isolated yield) and 7% of the *O*-acyl heminal **41** was also isolated. The latter is stable under the acidic conditions used for the hydrolysis of the cycloaddition. Actually, the hydrolysis of *O*-acyl heminals has been occasionally reported to occur upon prolonged exposure to acid at elevated temperature.[55]



Scheme 7.

Further efforts to increase the reactivity and enantioselectivity of the cycloaddition reaction focused on the X-ray diffraction studies conducted previously. We have shown that α-benzoyloxynitroso derivatives **22b** and **22e** adopt a 2,5-twist conformation.[44] A reasonable hypothesis is that α-acetoxynitroso **22a**, a blue mobile oil, follows the same tendency. Theoretical studies have shown that the 1,4-twist structure of 1,3-dioxane is only 1.36±0.12 kcal mol^{-1} (HF) and 1.0 kcal mol^{-1} (DFT) higher in energy than the 2,5-twist conformer.[56] The accessibility of different conformers with a low energetic cost could be responsible for the low enantiomeric excesses observed in the previous [4+2] reactions. The cycloaddition reaction of a dienophile adopting the more stable chair conformation would be of interest in this context, the chair conformer of 1,3-dioxane being 4.67±0.31 kcal mol^{-1} (HF) and 5.19±0.8 kcal mol^{-1} (DFT) more stable than the 2,5-twist conformer.[56] We have shown previously that α-benzoyloxynitroso **35b** crystallizes in the chair conformation.[44] By analogy, it is reasonable to assume that α-acetoxynitroso **35a**, a blue mobile oil, follows the same trend. The cycloaddition reactions of dienophile **35a** with 1,3-cyclohexadiene in the presence of 20 mol % of $Cu(MeCN)_4PF_6$/(*R*)-Tol-BINAP in dichloromethane were then studied at temperatures ranging from 0 to −40 °C (Scheme 8). Experimental results were disappointing since the reactivity of the catalytic system and the enantiomeric excess were still low (4–17%, 5–10% ee).

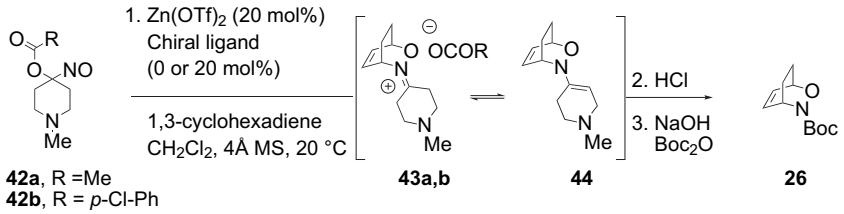


Scheme 8.

The lack of reactivity and/or enantioselectivity in the cycloaddition reactions of α-acetoxynitroso dienophiles **22a** and **35a** led us to consider a new type of nitroso derivative, based on the *N*-methyl piperidone scaffold. The presence of a tertiary amine could be beneficial for the interaction with the (chirally ligated) Lewis acid. A brief optimization showed that α-acyloxynitroso compounds **42a** and **42b** (prepared in two steps from commercially available *N*-methyl piperidone) are reactive dienophiles in the presence of 20 mol % of zinc triflate in methylene chloride at room temperature. Cycloadduct **26** was obtained as the sole product in 50–52% yield for two steps. Other Lewis acids ($Mg(OTf)_2$, $CrCl_3$, $AlEt_2Cl$, $Cu(OTf)_2$, $Cu(MeCN)_4PF_6$) led to inferior results. Disappointingly, all attempts to run the reaction in the presence of a chiral ligand ((−)-sparteine, (*R,R*)-^{t}Bu-Box) or chiral zinc alkoxide[53] ($ZnEt_2$/L-DIPT, BINOL or TADDOL) led to low yields (5–22%) of racemic cycloadducts (Scheme 9).

3. Conclusions

We have reported that α-acyloxynitroso derivatives are useful dienophiles in [4+2] cycloaddition reactions with electron-rich



Scheme 9.

1,3-dienes in anhydrous conditions. Products resulting from a formal *syn*-1,4-hydroxyamination of the diene were obtained stereoselectively via a tandem cycloaddition/σ_{N-O} bond cleavage. Detailed investigations have revealed that a sub-stoichiometric amount of Lewis acid slows down the reaction but more importantly allows a reproducible reaction (20 mol % of Cu(I) or Cu(II) salts leading to the best results). Kinetic profiling of the cycloaddition reaction both in the presence and absence of a Lewis acid suggested that the role of the copper(II) salt was to accelerate the σ_{N-O} bond cleavage thereby leading to more stable reaction intermediates and consequently to a reproducible yield. In addition, control experiments have been carried out to confirm the proposed mechanism of the tandem cycloaddition/σ_{N-O} bond cleavage. Comparison of several dienophiles, conformationally different in the solid state, has shown that subtle differences in the dienophiles can have a dramatic impact on stability, reactivity, and reaction outcome. Finally, the asymmetric version of this domino [4+2] cycloaddition/σ_{N-O} bond cleavage has been investigated. Low yields and enantiomeric excesses up to 10% have been observed. Further studies directed toward a more efficient asymmetric version of the copper-mediated [4+2] cycloaddition reaction are underway and will be reported in due course.

4. Experimental section[57]

4.1. General procedure A

*4.1.1. Synthesis of acetic acid 2,2-dimethyl-5-nitroso-[1,3]dioxan-5-yl ester (**22a**) and acetic acid (5-acetoxy-2,2-dimethyl-[1,3]dioxan-5-yl-ONN-azoxy)-2,2-dimethyl-[1,3]dioxan-5-yl ester (**33a**).* To a solution of 2,2-dimethyl-1,3-dioxan-5-one oxime **32**[41] (306 mg, 3.46 mmol) in CH_2Cl_2 (0.2 M) at rt was added (diacetoxy)iodobenzene (1.11 g, 3.46 mmol) portionwise over 45 min. The reaction mixture was then stirred 2 h at rt and quenched with a saturated aqueous solution of $NaHCO_3$ (25 mL). The aqueous phase was extracted with CH_2Cl_2 and the combined organic phases were dried over sodium sulfate, filtered, and concentrated. The blue residue was purified by flash chromatography on silica gel (pentane/diethyl ether=95:5 to 50:50) to give 522 mg (74%) of the desired α-acetoxynitroso **22a** as a blue oil and 48.6 mg (7%) of azoxy **33a** as a colorless oil. α-Acetoxynitroso **22a**: ^{1}H NMR (200 MHz, $CDCl_3$), δ (ppm): 4.29 (d, J=12.7 Hz, 2H), 3.78 (d, J=12.7 Hz, 2H), 2.23 (s, 3H), 1.54 (s, 3H), 1.47 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$), δ (ppm): 166.8, 121.0, 100.3, 59.8, 23.6, 23.0, 20.5. IR (neat), ν (cm^{-1}): 1756, 1570, 1375, 1294, 1221, 1100. LRMS (ESI) m/z 775.3 [4(M−Me)+Na]$^+$, 399.1 [2(MMe)+Na]$^+$. 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} ($CHCl_3$)=665 nm (ε=27 dm^3 mol^{-1} cm^{-1}). Azoxy **33a**: ^{1}H NMR (250 MHz, $CDCl_3$), δ (ppm): 4.55 (d, J=18.0 Hz, 1H), 4.42 (d, J=18.0 Hz, 1H), 4.20–4.02 (6H), 2.18 (s, 3H), 2.08 (s, 3H), 1.44 (s, 6H), 1.41 (s, 6H). ^{13}C NMR (90 MHz, $CDCl_3$), δ (ppm): 168.7, 168.4, 100.2, 100.1, 99.3, 89.6, 64.1, 62.5, 24.1, 24.0, 22.0, 21.7, 20.4, 20.1. IR (neat), ν (cm^{-1}): 1760, 1223, 1158, 830. 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.

*4.1.2. Benzoic acid 2,2-dimethyl-5-nitroso-[1,3]dioxan-5-yl ester (**22b**) and benzoic acid (5-benzoyl-2,2-dimethyl-[1,3]dioxan-5-yl-ONN-azoxy)-2,2-dimethyl-[1,3]dioxan-5-yl ester (**33b**).* Following general procedure A, oxime **32** (303 mg, 2.1 mmol) was treated with bis-[(benzoyloxy)iodanyl]benzene **31b** (933 mg, 2.1 mmol). Purification of the crude reaction mixture by flash chromatography on silica gel (heptane/ethyl acetate=90:10 to 70:30) gave 396 mg (72%) of the desired α-benzoyloxynitroso **22b** as a blue solid and 55 mg (10%) of azoxy **33b** as a colorless solid. α-Benzoyloxynitroso **22b**: ^{1}H NMR (250 MHz, $CDCl_3$), δ (ppm): 8.09 (d, J=8.3 Hz, 2H), 7.65 (br m, 1H), 7.50 (br m, 2H), 4.39 (d, J=12.7 Hz, 2H), 3.95 (d, J=12.7 Hz, 2H), 1.56 (s, 3H), 1.48 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$), δ (ppm): 164.3, 133.9, 130.1, 128.5, 121.2, 100.4, 60.0, 23.7, 23.1. Mp= +64 °C. IR (neat), ν (cm^{-1}): 2993, 1732, 1568, 1276, 1227, 1101, 710. Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.86; H, 5.70; N, 5.28: Found: C, 58.79; H, 5.73; N, 5.13. Azoxy **33b**: In spite of extensive efforts, the proton NMR spectrum of **33b** is not well resolved. ^{1}H NMR (250 MHz, $CDCl_3$), δ (ppm): 8.15–8.05 (4H), 7.62–7.42 (6H), 4.70–4.65 (2H), 4.39–4.23 (6H), 1.47 (br s, 12H). ^{13}C NMR (62.5 MHz, $CDCl_3$), δ (ppm): 172.2, 164.5, 164.3, 133.9, 133.7, 133.2, 130.2, 129.3, 129.2, 128.4, 100.6, 99.7, 90.4, 64.6, 62.9, 24.7, 24.5, 22.2, 21.8. Mp= +90 °C. IR (neat), ν (cm^{-1}): 2993, 1732, 1694, 1454, 1294. LRMS (ESI) m/z 537.3 ([M+Na]$^+$, 100), 538.3 (30). HRMS (ESI, Na^+): calculated for $C_{26}H_{30}N_2O_9Na$ [M+Na]$^+$: 537.1844, found: 537.1849.

*4.1.3. 4-Methoxy-benzoic acid 2,2-dimethyl-5-nitroso-[1,3]dioxan-5-yl ester (**22c**) and 4-methoxy-benzoic acid (5-(4-methoxy)-benzoyl-2,2-dimethyl-[1,3]dioxan-5-yl-ONN-azoxy)-2,2-dimethyl-[1,3]dioxan-5-yl ester (**33c**).* Following general procedure A, oxime **32** (318 mg, 2.2 mmol) was treated with [bis-(*p*-methoxybenzoyloxy)iodanyl]benzene **31c** (1.1 g, 2.2 mmol). Purification of the crude reaction mixture by flash chromatography on silica gel (heptane/ethyl acetate=90:10 to 70:30) gave 446 mg (69%) of the desired α-benzoyloxynitroso **22c** as a blue waxy solid and 56 mg (9%) of azoxy **33c** as a colorless oil. α-Benzoyloxynitroso **22c**: ^{1}H NMR (360 MHz, $CDCl_3$), δ (ppm): 8.02 (d, J=8.6 Hz, 2H), 6.93 (d, J=8.6 Hz, 2H), 4.33 (d, J=12.6 Hz, 2H), 3.93 (d, J=12.6 Hz, 2H), 3.84 (s, 3H), 1.53 (s, 3H), 1.45 (s, 3H). ^{13}C NMR (90 MHz, $CDCl_3$), δ (ppm): 164.0, 163.9, 132.1, 120.7, 120.5, 113.7, 100.2, 59.9, 55.3, 23.5, 23.1. Mp= +42–43 °C. IR (neat), ν (cm^{-1}): 2992, 1723, 1717, 1607, 1514, 1260, 1097, 848, 769. Anal. Calcd for $C_{14}H_{17}NO_6$: C, 56.94; H, 5.80; N, 4.74. Found: C, 56.83; H, 5.91; N, 4.72. Azoxy **33c**: ^{1}H NMR (360 MHz, $CDCl_3$), δ (ppm): 8.04–7.97 (4H), 6.93–6.87 (4H), 4.64 (d, J=6.5 Hz, 2H), 4.33–4.15 (6H), 3.84 (s, 6H), 1.41 (br s, 12H). ^{13}C NMR (90 MHz, $CDCl_3$), δ (ppm): 164.1, 164.0, 163.6, 132.4, 132.1, 121.6, 120.8, 113.7, 113.6, 100.5, 99.6, 90.2, 64.6, 63.0, 55.4, 24.7, 24.5, 22.2, 21.9. IR (neat), ν (cm^{-1}): 2990, 1729, 1606, 1511, 1259, 1093, 830, 767. LRMS (ESI, Na^+) m/z 597.1 ([M+Na]$^+$, 100), 598.1 (33), 505.1 (25). HRMS

(ESI, Na^+): calculated for $C_{28}H_{34}N_2O_{11}Na$ $[M+Na]^+$: 597.2055, found: 597.2070.

*4.1.4. 2-Methoxy-benzoic acid 2,2-dimethyl-5-nitroso-[1,3]dioxan-5-yl ester (**22d**).* Following general procedure A, oxime **32** (312 mg, 2.1 mmol) was treated with [bis-(*o*-methoxybenzoyloxy)iodanyl]-benzene **31d** (1.1 g, 2.2 mmol). Purification of the crude reaction mixture by flash chromatography on silica gel (heptane/ethyl acetate=90:10 to 70:30) gave 543 mg (86%) of the desired α-benzoyloxynitroso **22d** as a blue oil. ^1H NMR (360 MHz, $CDCl_3$), δ (ppm): 7.98 (d, *J*=7.9 Hz, 1H), 7.52 (t, *J*=7.2 Hz, 1H), 7.02–6.97 (2H), 4.32 (d, *J*=13.0 Hz, 2H), 3.92 (d, *J*=13.0 Hz, 2H), 3.86 (s, 3H), 1.51 (s, 3H), 1.45 (s, 3H). ^{13}C NMR (90 MHz, $CDCl_3$), δ (ppm): 163.0, 160.0, 134.7, 132.1, 120.6, 119.9, 117.1, 112.0, 100.1, 59.8, 55.7, 23.3, 23.2. IR (neat), ν (cm^{-1}): 2991, 1738, 1601, 1567, 1492, 1247, 1226, 1100, 757. Anal. Calcd for $C_{14}H_{17}NO_6$: C, 56.94; H, 5.80; N, 4.74. Found: C, 56.77; H, 5.99; N, 4.61.

*4.1.5. 4-Chloro-benzoic acid 2,2-dimethyl-5-nitroso-[1,3]dioxan-5-yl ester (**22e**).* Following general procedure A, oxime **32** (290 mg, 2.0 mmol) was treated with [bis-(*p*-chlorobenzoyloxy)iodanyl]benzene **31e** (1.0 g, 2.0 mmol) at 0 °C. Purification of the crude reaction mixture by flash chromatography on silica gel (heptane/ethyl acetate=90:10) gave 307 mg (57%) of the desired α-benzoyloxynitroso **22e** as a blue solid. ^1H NMR (250 MHz, $CDCl_3$), δ (ppm): 8.02 (d, *J*=9.0 Hz, 2H), 7.47 (d, *J*=9.0 Hz, 2H), 4.40 (d, *J*=13.1 Hz, 2H), 3.93 (d, *J*=13.1 Hz, 2H), 1.57 (s, 3H), 1.48 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$), δ (ppm): 163.5, 140.5, 131.5, 129.0, 126.9, 121.6, 100.5, 60.0, 23.9, 23.0. Mp= +84 °C. IR (neat), ν (cm^{-1}): 2993, 1732, 1595, 1568, 1273, 1227, 1095, 848, 758. Anal. Calcd for $C_{13}H_{14}ClNO_5$: C, 52.10; H, 4.71; N, 4.67. Found: C, 52.31; H, 4.93; N, 4.49.

*4.1.6. Biphenyl-4 carboxylic acid 2,2-dimethyl-5-nitroso-[1,3]dioxan-5-yl ester (**22f**) and biphenyl-4 carboxylic acid (5-(4-phenyl)-benzoyl-2,2-dimethyl-[1,3]dioxan-5-yl-ONN-azoxy)-2,2-dimethyl-[1,3]dioxan-5-yl ester (**33f**).* Following general procedure A, oxime **32** (322 mg, 2.2 mmol) was treated with [bis-(*p*-phenylbenzoyloxy)iodanyl]benzene **31f** (1.3 g, 2.2 mmol). Purification of the crude reaction mixture by flash chromatography on silica gel (heptane/ethyl acetate=90:10 to 70:30) gave 333 mg (44%) of the desired α-benzoyloxynitroso **22f** as a blue solid and 84 mg (11%) of azoxy **33f** as a colorless oil. α-Benzoyloxynitroso **22f**: ^1H NMR (250 MHz, $CDCl_3$), δ (ppm): 8.18 (d, *J*=8.4 Hz, 2H), 7.73 (d, *J*=8.4 Hz, 2H), 7.66 (d, *J*=7.0 Hz, 2H), 7.53–7.43 (3H), 4.44 (d, *J*=12.8 Hz, 2H), 4.00 (d, *J*=12.8 Hz, 2H), 1.59 (s, 3H), 1.51 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$), δ (ppm): 164.2, 146.6, 139.6, 130.7, 128.9, 128.3, 127.3, 121.2, 100.4, 60.0, 23.7, 23.1, 23.1. Mp= +146 °C. IR (neat), ν (cm^{-1}): 2987, 1724, 1227, 1098, 745, 698. Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.64; H, 5.56; N, 3.95. Azoxy **33f**: ^1H NMR (250 MHz, $CDCl_3$), δ (ppm): 8.14 (d, *J*=6.3 Hz, 2H), 8.11 (d, *J*=6.0 Hz, 2H), 7.68–7.59 (8H), 7.49–7.39 (6H), 4.66 (d, *J*=13.3 Hz, 2H), 4.34–4.25 (6H), 1.55 (s, 3H), 1.43 (s, 3H), 1.42 (s, 3H), 1.41 (s, 3H). ^{13}C NMR (90 MHz, $CDCl_3$), δ (ppm): 164.4, 164.2, 147.0, 146.0, 139.7, 130.8, 130.6, 128.9, 128.3, 128.2, 128.0, 127.3, 127.2, 100.6, 99.7, 90.5, 64.7, 63.0, 24.8, 24.6, 22.2, 21.9. IR (neat), ν (cm^{-1}): 2991, 1732, 1608, 1511, 1375, 1275, 1227, 1094, 746, 698. LRMS (ESI, Na^+) *m*/*z* 689.1 ($[M+Na]^+$, 100), 319.0 (54), 538.1 (49). HRMS (ESI, Na^+): calculated for $C_{38}H_{38}N_2O_9Na$ $[M+Na]^+$: 689.2470, found: 689.2467.

*4.1.7. Dichloroacetic acid 2,2-dimethyl-5-nitroso-[1,3]dioxan-5-yl ester (**22g**).* Following general procedure A, oxime **32** (42 mg, 0.3 mmol) was treated with [bis-(2,2-dichloroacetyloxy)-iodanyl]benzene **31g** (133 mg, 0.3 mmol). Purification of the crude reaction mixture by flash chromatography on silica gel (heptane/ethyl acetate=90:10) gave 41 mg (52%) of the desired α-dichloroacetyloxynitroso **22g** as a blue oil. ^1H NMR (300 MHz, $CDCl_3$), δ (ppm): 6.10 (s, 1H), 4.46 (d, *J*=13.2 Hz, 2H), 3.83 (d, *J*=13.2 Hz, 2H), 1.59 (s, 3H), 1.50 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 162.4, 123.3, 100.6, 63.4, 59.5, 24.0, 22.7. IR (neat), ν (cm^{-1}): 2995, 2943, 1777, 1571, 1451, 1378, 1228, 1159, 1099, 1046, 829.

*4.1.8. 5-[(4-Hydroxy-2-cyclohexen-1-yl)amino]-2,2-dimethyl-1,3-dioxan-5-yl acetate (**41**).* $Cu(MeCN)_4PF_6$ (18 mg, 50 μmol), (*R*)-Tol-BINAP (33 mg, 50 μmol), and powdered 4 Å molecular sieves (12 mg) were stirred slowly for 2.5 h in a Schlenk tube under vacuum. The reaction mixture was placed under argon and CH_2Cl_2 (0.3 mL) was added. The resulting mixture was stirred at rt for 3 h, then was cooled to −20 °C. A solution of acetoxynitroso **22a** (50 mg, 0.2 mmol) in CH_2Cl_2 (0.3 mL), then cyclohexadiene (117 μL, 1.2 mmol) were added sequentially dropwise at −20 °C, and the resulting mixture was stirred at −20 °C for 4 h. After this time, 0.5 mL of a 1.0 M solution of $HCl_{(aq)}$ was added, and the resulting mixture was stirred at rt for 45 min. The pH of the mixture was adjusted to pH10 with 5% w/v $NaOH_{(aq)}$, then Boc_2O (107 mg) and THF (0.5 mL) was added and the resulting mixture was stirred at rt for 16 h. CH_2Cl_2 (3 mL) and water (3 mL) were added and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3×3 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude product. Purification by flash column chromatography on silica with heptane–EtOAc (1:1) as eluent gave hydroxycarbamate **25**[26] (6.7 mg, 13%) and *N*,*O*-acetal **41** (5.0 mg, 7%) as a pale yellow oil. ^1H NMR (360 MHz, $CDCl_3$) δ 5.98 (ddd, *J*=10.0, 3.0, 0.5 Hz, 1H), 5.78 (ddd, *J*=10.0, 3.0, 0.5 Hz, 1H), 4.53 (dd, *J*=12.5, 7.0 Hz, 2H), 4.55–4.48 (m, 1H), 4.25–4.18 (m, 1H), 4.09 (d, *J*=12.5 Hz, 2H), 2.19 (s, 3H), 1.96–1.78 (m, 4H), 1.62 (br s, 2H, NH and OH), 1.45 (s, 3H), 1.44 (s, 3H). ^{13}C NMR (90 MHz, $CDCl_3$) δ 169.0, 133.6, 126.5, 100.6, 99.4, 65.1, 64.6, 55.5, 29.0, 24.3, 22.7, 22.4, 21.0.

*4.1.9. Acetic acid 5-nitroso-[1,3]dioxan-5-yl ester (**35a**).* Following general procedure A, oxime **34**[42] (1.53 g, 13.1 mmol) was treated with (diacetoxy)iodobenzene (4.22 g, 13.1 mmol) at 0 °C. Purification of the crude reaction mixture by flash chromatography on silica gel (pentane/diethyl ether=90:10) gave 1.08 g (47%) of the desired α-acetoxynitroso **35a** as a blue oil. ^1H NMR (300 MHz, $CDCl_3$), δ (ppm): 4.99 (d, *J*=14.1 Hz, 2H), 4.42 (d, *J*=12.3 Hz, 2H), 3.95 (d, *J*=12.3 Hz, 2H), 2.17 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 168.3, 115.6, 93.2, 66.4, 20.5. IR (neat), ν (cm^{-1}): 2870, 1778, 1568, 1196, 1094, 1051, 926. Anal. Calcd for $C_6H_9NO_5$: C, 41.15; H, 5.18; N, 8.00. Found: C, 41.13; H, 5.01; N, 8.13.

*4.1.10. Benzoic acid 5-nitroso-[1,3]dioxan-5-yl ester (**35b**).* Following general procedure A, oxime **34** (502 mg, 4.3 mmol) was treated with bis-[(benzoyloxy)iodanyl]benzene **31b** (1.91 g, 4.3 mmol) at 0 °C. Purification of the crude reaction mixture by flash chromatography on silica gel (pentane/diethyl ether=90:10) gave 235 mg (23%) of the desired α-benzoyloxynitroso **35b** as a blue solid. ^1H NMR (250 MHz, $CDCl_3$), δ (ppm): 8.08 (d, *J*=7.5 Hz, 2H), 7.64 (t, *J*=7.5 Hz, 1H), 7.49 (t, *J*=7.5 Hz, 2H), 5.11 (d, *J*=6.0 Hz, 1H), 5.06 (d, *J*=6.0 Hz, 1H), 4.58 (d, *J*=12.5 Hz, 2H), 4.16 (d, *J*=12.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 164.0, 134.0, 130.2, 128.6, 115.9, 93.6, 66.8. IR (neat), ν (cm^{-1}): 2868, 1740, 1687, 1566, 1293, 1270, 707. Anal. Calcd for $C_{11}H_{11}NO_5$: C, 55.70; H, 4.67; N, 5.90. Found: C, 55.65; H, 4.68; N, 5.7.

*4.1.11. 1-Methyl-4-nitroso-4-piperidinyl acetate (**42a**).* $PhI(OAc)_2$ (1.38 g, 4.29 mmol) was added in one portion to a stirred solution of 1-methyl-4-piperidinone oxime[58] (500 mg, 3.90 mmol) in CH_2Cl_2 (20 mL) at 0 °C under argon. After stirring at 0 °C for 0.5 h, the resulting solution was allowed to warm to rt and stirred at rt for a further 6 h. Then, the reaction mixture was poured into a saturated aqueous solution of $NaHCO_3$ (5 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2, and the

combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure to give the crude product. Purification by preparative thin-layer chromatography (EtOAc/MeOH=9:1) as eluent gave α-acetoxynitroso **42a** (506 mg, 70%) as a blue-green oil that slowly crystallises to a green solid. IR (neat), ν (cm^{-1}): 2943, 2851, 2800, 1751, 1563, 1447, 1370, 1280, 1221, 1160, 1100, 1021. ^1H NMR (300 MHz, $CDCl_3$) δ 2.90–2.85 (m, 2H), 2.35 (s, 3H), 2.29–2.24 (m, 4H), 2.20 (s, 3H), 1.89–1.83 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 120.8, 50.9, 45.6, 29.3, 21.2. Mp= 46–47 °C. MS (CI, NH_3) *m*/*z* 187 [$(M+H)^+$, 100]. HRMS (ESI): calculated for $C_8H_{15}N_2O_3$ $[M+H]^+$: 187.1077, found: 187.1077.

*4.1.12. 1-Methyl-4-nitroso-4-piperidinyl 4-chlorobenzoate (**42b**).* [Bis-(*p*-chlorobenzoyloxy)iodanyl]benzene **31e** (2.00 g, 3.90 mmol) was added in one portion to a stirred solution of 1-methyl-4-piperidinone oxime[58] (500 mg, 3.90 mmol) in CH_2Cl_2 (20 mL) at 0 °C under argon. After stirring at 0 °C for 0.5 h, the resulting solution was allowed to warm to rt and stirred at rt for a further 6 h. Then, the reaction mixture was poured into a saturated aqueous solution of $NaHCO_3$ and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give the crude product. Purification by flash chromatography on silica (EtOAc/MeOH=9:1) as eluent gave α-acyloxynitroso **42b** (535 mg, 48%) as a bright blue solid. IR (neat), ν (cm^{-1}): 3429, 2942, 1723, 1594, 1564, 1457, 1443, 1401, 1284, 1162, 1090. ^1H NMR (360 MHz, $CDCl_3$) δ 8.03 (d, *J*=8.8 Hz, 2H), 7.48 (d, *J*=8.8 Hz, 2H), 3.05–2.95 (2H), 2.49–2.35 (7H including 2.41 (s 3H)), 2.10–2.02 (2H). ^{13}C NMR (90 MHz, $CDCl_3$) δ 163.2, 140.1, 131.3, 128.9, 127.9, 121.1, 51.1, 45.6, 29.3. Mp= 90–92 °C. MS (CI, NH_3) *m*/*z* 285 [$(M(^{37}Cl)+H)^+$, 33], 283 [$(M(^{35}Cl)+H)^+$, 100]. HRMS (ESI): calculated for $C_{13}H_{16}ClN_2O_3$ $[M+H]^+$: 283.0844, found: 283.0849.

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Supplementary data

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