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Versatile Scope of a Masked Aldehyde Nitrone in 1,3-Dipolar Cycloadditions

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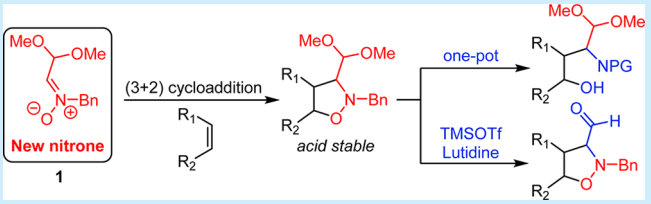
Supporting Information

ABSTRACT: A new masked aldehyde-containing nitrone **1** that is easily available through a facile one-step procedure has been developed. It undergoes a [3 + 2]-thermal cycloaddition with a wide range of dipolarophiles, affording isoxazolidine cycloadducts that are suitable for versatile postcycloaddition modifications. The acetal cycloadducts are acid-stable, but allow for acetal hydrolysis under mildly basic conditions. The isoxazolidine ring can be opened via an efficient one-pot procedure to give amine-protected γ-alcohols that can be further converted to furanose derivatives.



The nitrone−olefin [3 + 2] cycloaddition reaction is a powerful tool in organic chemistry for the stepwise construction of the backbone of a wide range of complex molecules.[1] A key feature of this reaction is that it allows for the introduction of three new stereogenic centers in a single step. For example, several classes of alkaloid derivatives[2] and non-natural amino acids[3] that contain multiple neighboring stereogenic centers have been synthesized using a [3 + 2] cycloaddition as a key step. Most examples of regio- and enantioselective cycloadditions that use structurally small and easily accessible nitrones, however, involve *C*- and/or *N*-aryl-substituted nitrones. This limits the options for subsequent synthetic modification of the cycloaddition product.[4] One of the few examples of easily accessible and simple nitrones that are more suitable for post-cycloaddition modification are α-amino ester-derived nitrones, possessing a masked carboxylic acid and a deprotectable *N*-substituent.[5] In our ongoing synthetic investigations toward novel glycomimetics for studying phenomena in glycobiology,[6] we required a small (masked) aldehyde-containing nitrone. However, to the best of our knowledge no precedent existed for such a compound, so we set out to develop one. We here present a new and readily accessible nitrone **1** (Figure 1) for the facile synthesis of synthetically versatile, masked aldehyde-containing cycloadducts.

This nitrone displays selective reactivity with a wide range of 1,3-dipolarophiles combined with mild subsequent deprotection and derivatization of the resulting cycloadducts to allow further modification.

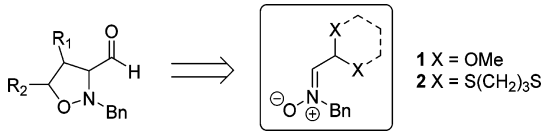
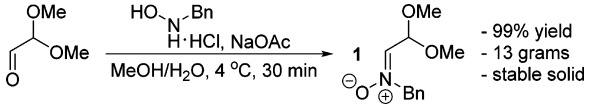


Figure 1. Nitrones possessing a masked aldehyde for the synthesis of versatile cycloadducts.

Initial efforts focused on the synthesis of nitrone **2**, containing a thioacetal, starting from 1,3-dithiane. We were able to obtain **2** via a two-step procedure in moderate yield. However, nitrone **2** proved to be ineffective for use in nitrone−olefin [3 + 2] cycloaddition reactions, as the nitrone was not reactive at low temperatures and quickly degraded upon heating (see Supporting Information (SI) for details).

The thermal instability of nitrone **2** in this reaction led us to focus on the synthesis of acetal **1** from readily available *N*-benzylhydroxylamine and dimethoxyacetaldehyde. These compounds reacted readily to give **1** in excellent yield on a multigram scale (Scheme 1). In addition, this reaction does not require a purification step, whereas similar nitrones that are synthesized in this fashion usually require purification through chromatography or crystallization.[5a,7] The purification step could be avoided by performing the reaction at 0 °C and performing a basic workup.

Scheme 1. Synthesis of Nitrone 1



An initial scope study of nitrone **1** in the 1,3-dipolar cycloaddition reaction with a variety of achiral olefins and other dipolarophiles was performed using a general reaction protocol (Scheme 2). The *syn*/*anti* stereoselectivity of the resulting cycloadducts was assigned using NOESY experiments.

We observed that cycloadditions involving both electron-deficient (providing **3**−**4**) and electron-rich olefins (providing

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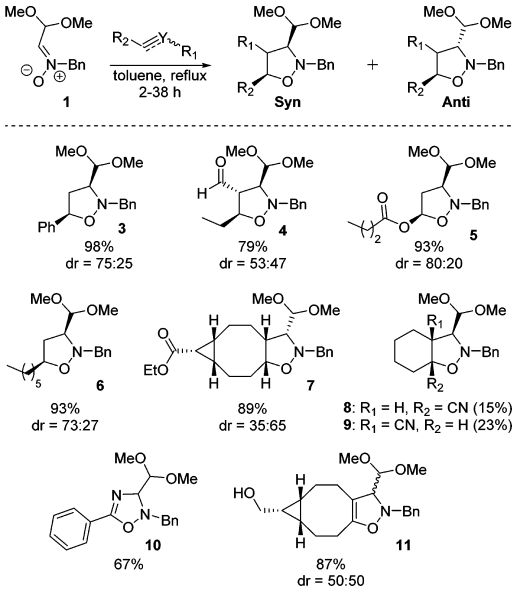
Scheme 2. Substrate Scope of Nitrone 1 with Different 1,3-Dipolarophiles in [3 + 2] Cycloaddition Reactions[a,b]



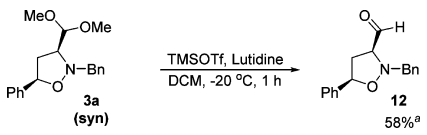
[a]Isolated yield after column chromatography. [b]*Syn*/*anti* ratio determined by ^{1}H NMR and assigned by NOESY.

5–**6**) proceeded rapidly, leading to complete conversion within 2 h at 110 °C in toluene. For a sterically bulky, disubstituted alkene a longer reaction time (38 h) was required to obtain cycloadduct **7** in good yield. A trisubstituted olefin also showed lower reactivity, but still gave complete conversion to products **8** and **9** after 2 days. The occurrence of two regioisomers (**8** and **9**), instead of the two *syn*- and *anti*-diastereomers observed in most cases, is common for cycloadditions with α-alkyl trisubstituted olefins.[8]

After these encouraging results for nitrone **1** with olefins, we evaluated several different dipolarophiles such as nitriles and alkynes. First, **1** was reacted with benzonitrile and selectively gave one major isomer (**10**) in good yield. Next, a cycloaddition with a cyclooctyne yielded cycloaddition product **11** within 5 min at rt. Cyclooctynes have recently been reported to react with nitrones in so-called SPANC click reactions.[9] The nitrones reported in literature for this click reaction with strained alkynes were either cyclic nitrones[9a] or produced cycloadducts possessing *N*-methyl groups,[9b,c] complicating further modification compared to **11**. The cycloadditions described in Scheme 2 overall show that nitrone **1** allows for the synthesis of a variety of cycloadducts in reasonable to excellent yield, while tolerating a variety of functional groups, including esters, alcohols, and aldehydes.

Encouraged by these results, we next attempted to liberate the aldehyde by selectively deprotecting the dimethyl acetal (Scheme 3). Surprisingly, when using typical acidic hydrolysis conditions no conversion was observed even after testing a variety of acidic conditions (e.g., TFA, HCOOH, $HClO_4$). We hypothesize that

Scheme 3. Hydrolysis of Isoxazolidine Acetal 3a



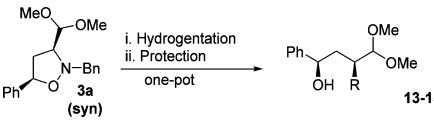
[a]Crude yield determined by ^{1}H NMR; isolated yield: 40%.

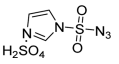
protonation of the nitrogen atom in the isoxazolidine ring in close proximity to the acetal might be suppressing methoxy protonation and thus the acidic hydrolysis.

To validate this hypothesis, several neutral and basic conditions were tested for liberation of the aldehyde.[10] Neutral conditions using iodine, however, led to degradation, and TMS-I gave only minute amounts of product. In contrast, the use of TMSOTf under basic conditions gave the desired product in reasonable yield (Scheme 3). Even though many examples of similar acetal/ketal-substituted isoxazolidines exist in literature,[11] this is the first successful example of acetal hydrolysis on such a substrate.

We also wanted to identify conditions to selectively modify the N–O ring through hydrogenation, followed by an *in situ* protection of the liberated amine with a versatile set of protecting groups (Table 1). An initial hydrogenolysis attempt of substrate

Table 1. Mild One-Pot Hydrogenation/Protection Optimization



entry	conditions[a]	reagent	R/protecting group	yield (%)[b]
1	A	Fmoc-OSu	N–Fmoc (**13**)	degr.
2	B	Fmoc-OSu	**13**	24
3	C	Fmoc-OSu	**13**	80
4	C	Boc_2O	N–Boc (**14**)	80
5	C		N_3 (**15**)	52

[a]Conditions: (A) 10% Pd/C, H_2 (1 bar), MeOH, rt, 3 d; (B) (i) Raney-Ni, H_2 (1 bar), THF, rt, 30 min; (ii) 10% Pd/C, C_6H_{10}, THF, reflux, 3 h; (iii) Fmoc-OSu, $NaHCO_3$, THF, H_2O, 0–20 °C, o/n; (C) (i) Raney-Ni, H_2 (1 bar), THF, rt, 1.5 h; (ii) Pd/C, H_2 (5 bar), rt, 5 h; (iii) for entries 3 and 4: Fmoc-OSu or Boc_2O, $NaHCO_3$, THF, H_2O, 0–20 °C, o/n; for entry 5: Diazotransfer reagent, K_2CO_3, $CuSO_4 \cdot 5H_2O$. [b]Isolated yield after purification by column chromatography.

3a with Pd/C in MeOH under atmospheric pressure (entry 1) resulted in very slow conversion. Complete hydrogenation of **3a** was only observed after 3 days at rt, at which point significant degradation had occurred. Degradation of **3a** might be caused by partial unwanted hydrogenation of the benzylic C–O bond in the isoxazolidine ring before desired cleavage of the N–O. This side reaction has been reported for similar compounds.[12] We therefore investigated whether the known ability of Raney-Ni to selectively cleave N–O bonds would prevent C–O hydrogenation. Hydrogenolysis with Raney-Ni indeed quantitatively cleaved the N–O bond of substrate **3a** within 1 h and left the C–O and N–Bn bonds intact. However, subsequent *N*-benzyl removal using transfer hydrogenation with refluxing cyclohexene, followed by *in situ* protection with Fmoc-OSu, gave **13** in only 21% yield (entry 2), probably due to thermal degradation of the starting material or intermediate during reflux. It was therefore decided to perform the second hydrogenation step under pressure in a Parr apparatus at rt. This allowed for the removal of the benzyl group in 5 h, and the resulting primary amine could be converted *in situ* to Fmoc-protected amine **13** in 80% yield (entry 3).

The advantage of this approach is that the whole sequence can be carried out in one pot, since Raney-Nickel can be conveniently

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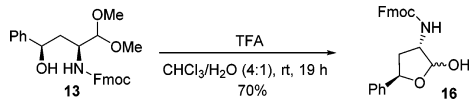
removed using a magnet, before adding 10% Pd/C to liberate the primary amine.[13] The optimized conditions of this staged hydrogenation could also be used to install a Boc protecting group (entry 4; **14**) or an azide (entry 5; **15**).

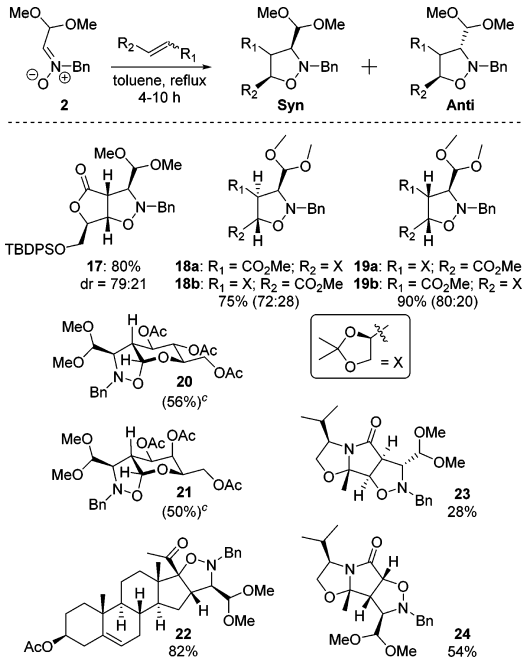
The acetal-masked aldehyde in this ring-opened substrate (**13**) could now be liberated under standard acid hydrolysis conditions to furanose **16** (Scheme 4), indicating that earlier attempts to hydrolyze substrate **3** were indeed hampered by the vicinity of the basic isoxazolidine ring.

Scheme 4. Acid-Catalyzed Hydrolysis of Acetal 13



Encouraged by the synthetic versatility of the racemic isoxazolidine substrates, we searched for an asymmetric approach toward these building blocks, since these compounds could represent a promising point for the enantioselective synthesis of functionalized carbohydrate derivatives. The first approach toward chiral isoxazolidine derivatives employed chiral olefins in [3 + 2] cycloaddition reactions with achiral nitrone **1** (Scheme 5); in a second approach (vide infra) chiral derivatives of nitrone **1** were reacted with achiral alkenes (Table 2).

Scheme 5. Scope of 1 in cycloadditions with chiral olefins[a,b]



[a]Isolated yield after column chromatography. [b]*Syn*/*anti* ratio determined by ^{1}H NMR and assigned by NOESY. [c]Reaction performed at 165 °C in mesitylene with 5 equiv of **1**.

The reaction of **1** with a chiral furanone gave bicyclic compound **17**, which is a useful precursor to polyhydroxylated piperidine derivatives.[14] Compound **17** was obtained in good yield with excellent regioselectivity and good stereochemistry. Cycloaddition reaction of **1** with two D-mannitol-derived olefins also proved to be stereoselective, providing cycloadducts **18**–**19**. Interestingly, while the *E*-olefin provided regioisomer **18b** as a minor cycloadduct, the Z-olefin provided the analogous regioisomer **19a** as the major isomer, owing to the attack of the oxygen atom on the nitrone at the α-position of the α,β-unsaturated alkene.[15] Asymmetric cycloadditions were then carried out with the enol ether in carbohydrate derivatives to obtain cycloadducts **20** and **21**. These cycloaddition reactions with D-glucal- and D-galactal derivatives, which are known for their low reactivity,[16] resulted in only limited conversion of the dipolarophiles after 2 days. We were unable to increase the conversion significantly beyond ∼33% by using a high excess of **1** or by increasing the duration of the reaction, since **1** slowly degrades over the course of several days, probably via dimerization as indicated by MS and NMR analysis. As the degradation of **1** by dimerization was thought to be the limiting step we opted to add **1** portionwise at 165 °C in mesitylene to limit this. Consequently we were able to reach 56% conversion for D-glucal derived **20**, which is good considering there is only one other reported successful cycloaddition of an acyclic nitrone on a glycal.[16a] The D-glucal and D-galactal derived cycloadducts were obtained as a single product, illustrating the high regio- and stereoselectivity of these reactions. Furthermore, the unconverted D-glucal and D-galactal derivatives could be recovered through column chromatography. The reaction of nitrone **1** with a trisubstituted steroid also proved to be very regio- and stereoselective, providing **22** as a single product in good yield. However, the regioselectivity of this reaction was reversed compared to other electron-poor dipolarophiles. There is precedent in literature[8a,17] for similar reversed nitrone cycloaddition results, and this indicates that steric factors may change the dominant frontier molecular orbital interactions between a nitrone and a dipolarophile, thus changing the regiochemical outcome.

Finally, the olefin in an enantiopure lactam was reacted with **1**, providing regioisomers **23** and **24** in a total yield of 82%. Surprisingly, although two regioisomers were formed, none of the other six possible stereoisomers were observed. We hypothesize that the two isolated cycloadducts represent the most stable isomers, resulting from the least steric hindrance during the cycloaddition. To validate this hypothesis, the geometries of all eight possible stereo- and regioisomers of the nitrone reaction on the unsaturated lactam were sequentially optimized by molecular mechanics MMFF94 calculations and density functional theory M11-L/6-311+G(d,p) calculations. This indeed yielded the lowest energies for compounds **23** and **24**. All other isomers were less stable, largely due to (significantly) increased steric hindrance (see SI for more information).

Finally, for the second approach, an asymmetric cycloaddition with achiral dipolarophiles was achieved using nitrone **25** as a chiral derivative of nitrone **1**. Nitrone **25** was easily obtained in excellent yield in the same manner as **1**, using (*S*)-*N*-(α-methylbenzyl)hydroxylamine as a chiral precursor, and subsequently employed in several nitrone−olefin [3 + 2] cycloaddition reactions with achiral olefins. These cycloadditions proved to be quite effective, affording the different substrates in very good to excellent yield (Table 2). While the facial selectivity appeared to be moderate, the different major cycloadducts could be isolated in very good yields.

In summary, a novel nitrone **1** containing a masked aldehyde was prepared via a simple and scalable procedure in excellent yield. Using this nitrone in [3 + 2] cycloaddition reactions with a variety of olefins and other dipolarophiles afforded a set of original isoxazolidines in reasonable to excellent overall yields. These cycloadducts can be considered as a masked form of amino

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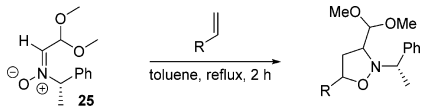
Table 2. Scope of Chiral Nitrone 25 in Asymmetric Cycloadditions Reactions with Achiral Olefins



entry	olefin	diastereomeric ratio[a] *syn*1:*syn*2:*anti*1:*anti*2	yield (%)[b]
1	Ph	52 : 29 : 12 : 7	100
2	$(\!)_5$	51 : 27 : 13 : 9	93
3	tBuO	47 : 41 : 5 : 7	100

[a]*Syn*/*anti* ratio determined by ^{1}H NMR and assigned by NOESY. [b]Isolated yield after column chromatography.

aldehydes, making them interesting from a synthetic point of view. The synthetic versatility of these substrates was shown by liberating the masked aldehyde under basic conditions, while the amine could be liberated and immediately protected via an efficient staged one-pot hydrogenolysis procedure. The stability of the masked aldehyde toward acid hydrolysis before ring opening enables facile acid-catalyzed modification of different groups, while still allowing facile acid hydrolysis of the acetal after N−O ring opening. Finally, a diverse set of chiral olefins led to cycloadducts with high diastereopurity. We are currently pursuing the application of nitrones **1** and **25** in cycloadditions toward several complex glycomimetics,[6] which will be duly reported.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02662.

Experimental procedures, characterization data and copies of ^{1}H and ^{13}C NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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