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Aerobic Tetrazine-Catalyzed Oxidative Nitroso-Diels-Alder Reaction of *N*-Arylhydroxylamines with Dienecarbamates: Access to Functionalized 1,6-Dihydro-1,2-oxazines

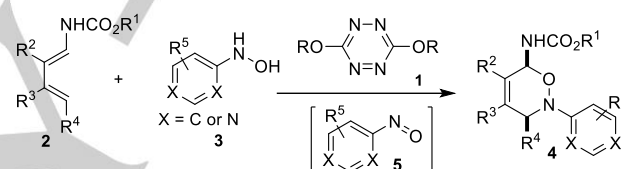
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Abstract: A new organocatalytic and environmentally friendly aerobic oxidative-catalyzed nitroso-Diels-Alder (NDA) reaction of *N*-arylhydroxylamines with dienecarbamates has been developed. 3,6-Bis(2,2,2-trifluoroethoxy)-*s*-tetrazine was found to be an effective catalyst to selectively oxidize various *N*-arylhydroxylamines in the presence of molecular oxygen, but in the absence of photostimulation, as a terminal oxidant. In addition, active catalytic species can be generated *in situ* from commercially available 3,6-dichlorotetrazine.

Oxidation reactions are fundamental chemical processes as witnessed by their heavy use in organic synthesis^[1]. Conceptually, molecular oxygen is considered as an ideal oxidant owing to low cost, abundance and non-toxicity^[2]. However, this last advantage goes hand in hand with a poor oxidizing ability for kinetics reasons. The use of molecular oxygen as sole oxidant to achieve the direct oxidation of organic molecules, therefore, involves high energy activation barriers and has seldom been reported.^[3] As a result, aerobic oxidations mostly require the presence of metal catalysts to activate molecular oxygen.^[2d,4] While metal-free protocols using organic compounds such as aminoxyl radical,^[5] quinone derivatives^[6], flavin^[7] and others^[8] can be preferred to overcome the metal contamination, their relatively moderate oxidation potentials can limit their applications. Consequently, the development of new organic oxidants which can be used in catalytic amounts, alongside with oxygen as the terminal oxidant, is still highly desirable.

In recent years, the generation of strong organic oxidants by visible-light photoexcitation of photosensitizers has attracted much attention.^[9] Many efficient photocatalytic systems have been developed using organic dyes such as eosin Y, cyanoarenes (4CzIPN) and acridinium salts.^[10] In this context, the work of Biswas on tetrazines^[11] caught our attention, since some

of us brought to light over the past 15 years that 3,6-disubstituted *s*-tetrazines constitute a new class of organic fluorophores that display reversible reduction processes.^[12] In addition, their photophysical and redox properties are easily modulated by changing the electronic influence from the 3,6-substituents.^[12,13] With the idea of expanding further the synthetic potential of tetrazine catalysis, we herein report a mild and effective aerobic oxidative nitroso-Diels-Alder reaction (Scheme 1),^[14] which in particular does not require an additional visible light stimulus.



Scheme 1. Tetrazine-catalyzed oxidative NDA reaction.

In the last decades, our group^[15] and others^[16] have reported several efficient oxidative NDA reactions in which the nitroso dienophile intermediate **5** was generated *in situ* from hydroxylamines. As a matter of fact, we recently set up an oxidative Ru(bpy)₃Cl₂-catalyzed NDA reaction between transient nitrosoaryl derivatives and dienecarbamates.^[15a] Although effective, a large excess of *N*-arylhydroxylamines was required due to a competing reaction between *N*-arylhydroxylamines **3** and nitrosobenzene intermediates **5**.^[17] Additionally, examples of oxidative NDA involving an organocatalyst and molecular oxygen as a terminal oxidant are elusive. Driven by facing these two challenges, we assumed that 3,6-oxy-*s*-tetrazines could constitute competitive photocatalysts to promote such a tricky transformation. To that extent, we began our study by evaluating the potential of 3,6-bis(3-chlorophenoxy)-1,2,4,5-tetrazine **1a** to promote the model oxidative NDA reaction between *N*-[(4-methoxycarbonyl)phenyl]hydroxylamine (**3a**) and benzyl-(penta-1,3-dien-1-yl)carbamate (**2a**). It was found that irradiation with green LEDs of **1a** (20 mol%) under O₂ atmosphere in CH₂Cl₂ in the presence of 2,6-lutidine led to the formation of cycloadduct **4a** as a single *cis*-diastereomer with 38% yield after 20 h. (Table 1, entry 1). Additionally, as expected, and consistently with our previous DFT calculations,^[15c] a complete *O*-regioselectivity was observed.^[18] Encouraged by this observation, other dyes **1b-e** (entries 2-5) were tested and compounds **1b** and **1e** were found to give the best results (49% yield, entry 4). A screening of solvents revealed that fluorinated alcohols, 2,2,2-trifluoroethanol (TFE, entry 8) and hexafluoro-2-propanol (HFIP, entry 9) resulted

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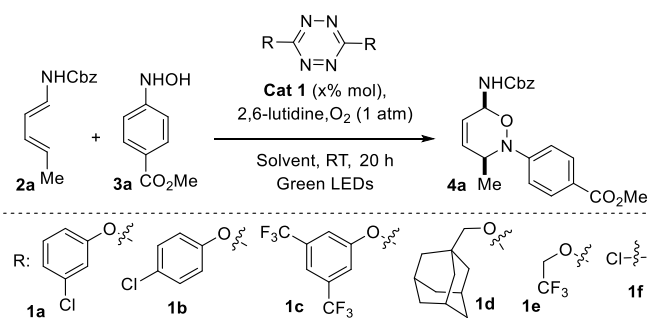
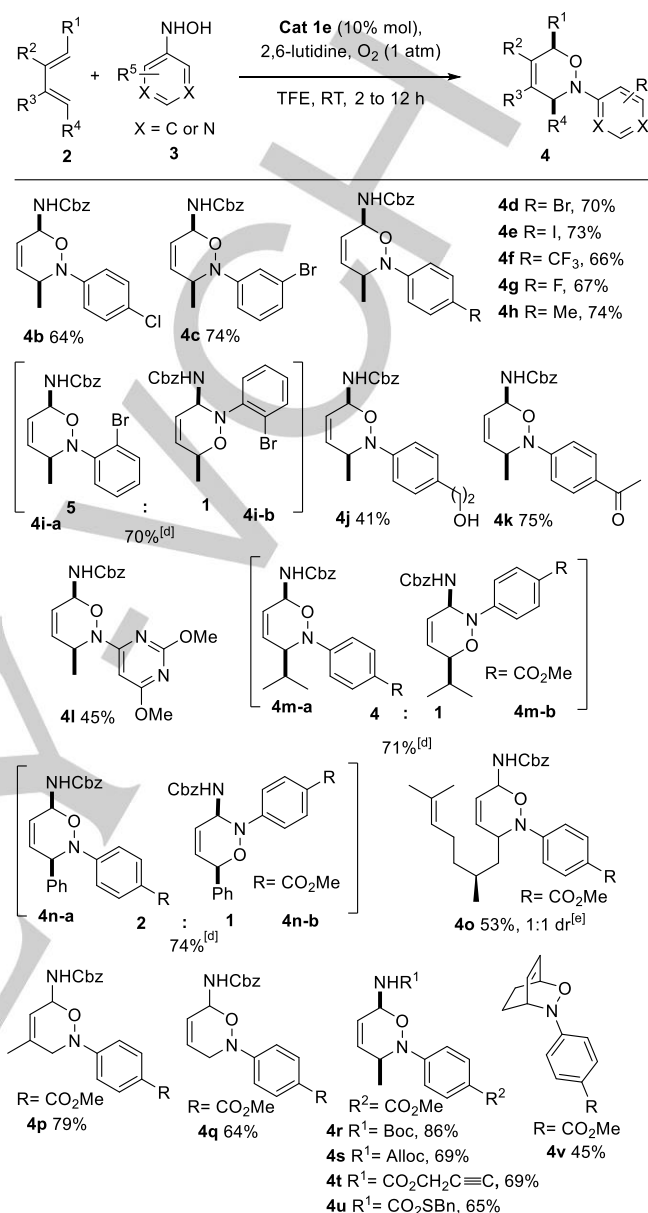


Table 1. Synthesis of 3,6-dihydro-1,2-oxazines: a survey of reaction conditions.^[a]

Entry	Pcat 1	X% mol	Solvent	Yield [%] ^[b]
1	1a	20	CH ₂ Cl ₂	38
2	1b	20	CH ₂ Cl ₂	49
3	1c	20	CH ₂ Cl ₂	31
4	1d	20	CH ₂ Cl ₂	28
5	1e	20	CH ₂ Cl ₂	49
6	1f	20	CH ₂ Cl ₂	22
7 ^[c]	1e	20	TFE	65
8 ^[c]	1e	20	HFIP	67
10	1e	20	EtOH	42
11	1e	10	TFE	65
12 ^[d]	1e	10	TFE	74
13 ^[d]	-	10	TFE	0
14 ^[d,e]	1e	10	TFE	25
15 ^[d,f]	1e	10	TFE	27
16 ^[c,g]	1e	10	TFE	74
17 ^[c,g]	1e	10	CH ₂ Cl ₂	48
18 ^[c,h]	1e	10	TFE	80

[a] General conditions: **2a** (0.10 mmol, 1 equiv.), **3a** (0.10 mmol), **1** (0.020 equiv.), in CH₂Cl₂ (1 mL) irradiated with 5 W green LEDs at RT for 20 h [b] Yields refer to chromatographically pure products. [c] For 2 h. Irradiated with 5 W green LEDs. [d] With 1.2 equiv of **2a**. [e] Reaction conducted under argon atmosphere. [f] Reaction conducted without base [g] Reaction performed in the dark [h] Reaction performed on a 1 mmol scale (of **3a**).

Table 2. Substrates scope of the organocatalytic oxidative NDA reaction.^[a,b,c]



[a] General conditions: **3** (0.1 mmol, 1 equiv.), **2** (0.12 mmol, 1.2 equiv.), **1e** (0.01 equiv.) 2,6-lutidine (0.21 mmol) in TFE (1 mL) at RT for 2 to 12h [b] Yields refer to chromatographically pure products. [c] dr>95:5 determined by ¹H NMR spectroscopy of the crude reaction mixture. [d] r.r. determined by ¹H NMR spectroscopy of the crude reaction mixture. [e] d.r. determined by ¹H NMR spectroscopy of the crude reaction mixture.

in a dramatic rate reaction acceleration (65% and 67% yield in only 2 h). while less acidic alcohols (EtOH, entry 10) did not improve the reaction efficiency. In light of these results and a recent work,^[19] we hypothesize that stronger acidic protic solvents can activate nitrosobenzene via H-bonding with more electronegative O-atom.^[19] To our delight, the catalyst loading can be reduced down to 10 mol% without significant loss of performance (entry 11). Ultimately, the yield was improved when

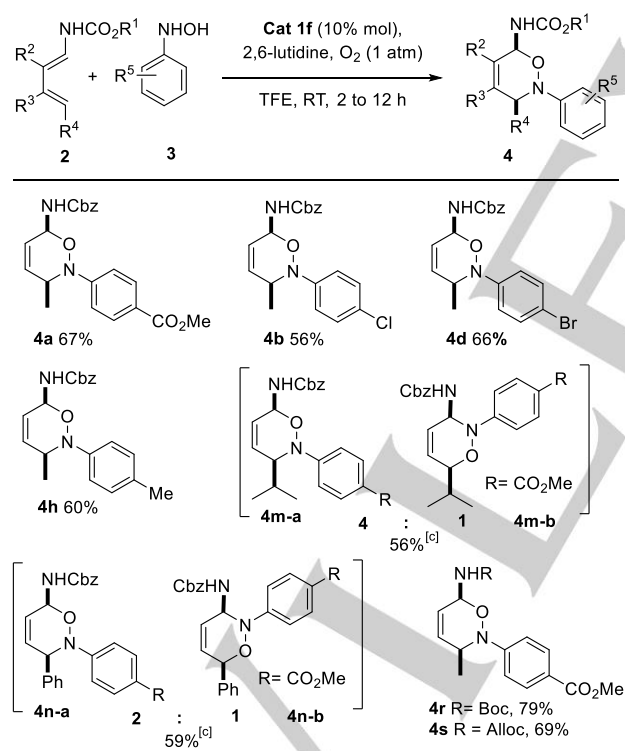
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diene **3a** was used in slight excess (entry 12). This last observation revealed that those reaction conditions are uniquely efficient to prevent undesired condensation between the nitroso intermediate and the unreacted hydroxylamine. Control experiments showed that the cycloaddition failed in the absence of tetrazines (entry 13).

Moreover, the combined action of oxygen and 2,6-lutidine was crucial to regenerate the catalyst. Indeed, the yield of **4a** did not exceed the catalyst loading (entries 14 and 15) when one of these reaction partners is missing. However, the use of light irradiation was still a limitation in view to scale up the process. Fortunately, we were pleased to find that similar yield in cycloadduct **4a** was obtained when the oxidative NDA reaction was carried out in the dark, regardless the nature of the solvent (entry 16 and 17). This striking observation suggested that the ground state of **1e** is able to oxidize **3a**. To our knowledge, only one example has been previously reported using tetrazine as light-free oxidant.^[20]

With the optimized reaction conditions in hand, the reaction scope was next investigated. As shown in Table 2, various *N*-arylhydroxylamines **3** substituted at the *para* or *meta* position with electron-rich or electron-poor substituents on aromatic rings were compatible with this oxidative catalytic process, affording

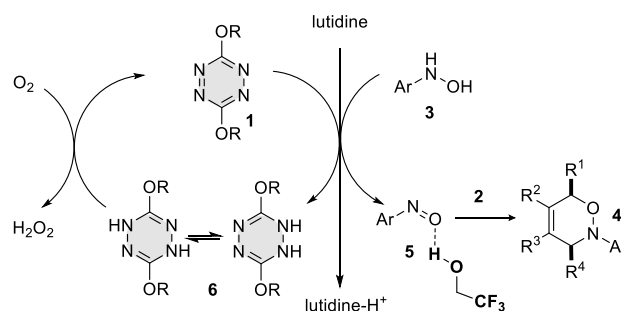
Table 3. Substrates scope of the oxidative NDA reaction with in situ formation of active catalytic oxidant^[a,b,c]



[a] Reaction conditions: **3** (0.1 mmol, 1 equiv.), **2** (0.12 mmol, 1.2 equiv.), **1e** (0.01 equiv.), 2,6-lutidine (0.21 mmol) in TFE (1 mL) at RT for 2 to 12h [b] Yields, 2,6-lutidine (0.21 mmol) in TFE (1 mL) at RT for 2 h. [c] Isolated yields. [d] dr>95:5 determined by ¹H NMR spectroscopy of the crude reaction mixture. [e] r.r. determined by ¹H NMR spectroscopy of the crude reaction mixture.

expected 3,6-dihydro-1,2-oxazines **4b-h** in moderate to good yields and excellent diastereoselectivity. When *N*-(*ortho*-bromophenyl)hydroxylamine was used, two regioisomers **4i-a** and **4i-b** were isolated in a 5:1 ratio. A wide range of functional groups such as ester (**4a**), halides (**4b-4e** and **4g**), unprotected alcohol (**4j**), and ketone (**4k**) were demonstrated to be well tolerated. *N*-containing heteroaromatic groups as 2,4-dimethoxypyrimidine, can also be used as substrates (**4l**). In addition, dienecarbamates displaying various δ -substituents reacted smoothly to deliver cycloadducts **4m-o** in moderate to good yields (41-79%) Changing the steric profile or the electronic affinity of the substituents at the δ position of **2** did affect the regioselectivity of the NDA reaction **4m** and **4n** were isolated as a mixture of two regioisomers.^[18a] To our delight, the dienecarbamate derived from (*S*)-citronellol behaved likewise very well in this process to deliver **4o** in 53% yield. The oxidative NDA reaction was also successful on γ -substituted and unsubstituted dienes affording molecules **4p** and **4q**, respectively. A variety of protecting groups bonded to the nitrogen atom of **2**, including benzylthiocarbamate, propyn-1-yl carbamate, Alloc and Boc, were well tolerated. Finally, 1,3-cyclohexadiene could be used to give desired bicyclic product **4v** with a moderate yield of 45%. The model reaction could also be scaled-up to 1 mmol scale giving a better yield of desired compound (80%) **4a** showing that tetrazine catalysis (Table 1, entry 18) could be a very inexpensive way to perform aerobic oxidation reaction on a reasonable scale.

In order to set up a highly practical methodology and inspired by our previous work,^[15a] we reasoned that active s-tetrazine oxidant **1e** might be generated *in situ* from commercially available 3,6-dichlorotetrazine **1f**. The ability of **1f** to be used as a pre-catalyst was evaluated by running the cycloaddition using 10 mol% of **1f** and 2 equiv of 2,6-lutidine. To our delight, this protocol provides the same levels of efficiency than the procedure harnessing the preformed catalyst **1e**. This new set of conditions was applied to the synthesis of various 3,6-dihydro-1,2-oxazines **4** (Table 3). We observed that *N*-arylhydroxylamines bearing slightly electron-donating or electron-withdrawing substituents successfully afforded the corresponding cycloadducts. Finally, we were pleased to observe that this method was also applicable to various dienecarbamates (**4n**, **4r** and **4s**).



Scheme 2. Suggested reaction mechanism

To gain some insight into the reaction mechanism, control experiments were conducted. First of all, the nature of the solvents (TFE or DCM) does not impact the reduction and oxidation potentials of **1a** and **3a**, respectively. In contrast, the

oxidation potential of **3a** was dramatically decreased when the measure was carried out in the presence of 2,6-lutidine (from 0.93 V to 0.32 V vs SCE, see supporting information). This result confirms that electron transfers between **3a** and **1e** at ground state are thermodynamically feasible. Based on literature data^[19] and according to the results of control experiments (Table 1, entries 13-17) a plausible mechanism for this aerobic oxidative NDA reaction is depicted in Scheme 2. Tetrazine **1** with the assistance of 2,6-lutidine may directly oxidize the *N*-arylhydroxylamine **3** to produce intermediate **5** through a PCET process.^[21] Subsequent NDA reaction between diene-carbamate **2** and the resulting nitroso compound activated through hydrogen bonding with TFE afforded the NDA cycloadduct **4**^[7,13] On the other hand, as previously mentioned by Pinner,^[22] oxidation of the dihydrotetrazine by molecular oxygen could regenerate the organocatalytic tetrazine oxidant **1**. The formation of H₂O₂ was demonstrated by a potassium iodide–starch indicator test (see Supporting Information).^[23]

In conclusion, we have demonstrated that 3,6-dioxy *s*-tetrazine, which can be prepared in situ from commercially available dichlorotetrazine, efficiently catalyzes the aerobic oxidative NDA reaction. Various *N*-arylhydroxylamines underwent aerobic oxidation and NDA reaction to produce oxazines with excellent diastereoselectivities. Most importantly, the ease of experimental conditions coupled with the use of molecular oxygen as a terminal oxidant make this process in line with the global challenge of designing environmentally friendly catalytic processes. We believe that such a process could find useful applications in view of the scope of NDA reaction and that the concept could be extended to other transformations involving nitrosoaryl compounds.

Experimental Section

Additional data supporting the conclusions are available in the Supporting Information

General procedure

In a flame-dried tube ($\varnothing = 10$ mm) were placed diene **2** (0.12 mmol, 1.2 equiv.), *N*-arylhydroxylamine **3** (0.10 mmol, 1 equiv.) and tetrazine **1e** (0.01 equiv.). Then 2,6-lutidine (25 μ L, 2.1 equiv) and TFE (1 mL) were added and the solution was sparged with O₂ for 1 min. The balloon was left on the top of the tube to maintain the O₂ atmosphere and the solution was stirred at rt for 2 hours. The reaction was quenched by careful addition of a solution 1M of HCl. The solution was extracted with DCM (3 times) and the combined organic phases were dried with MgSO₄, filtered and concentrated under vacuum. The residue was purified by silica gel flash chromatography (P.E/EtOAc gradient).

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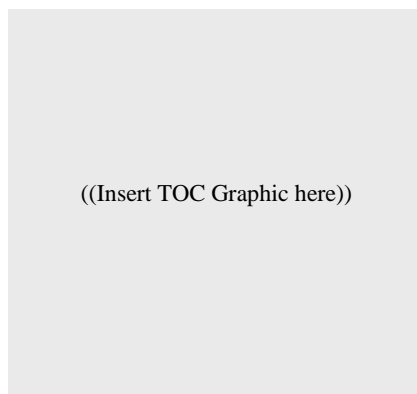
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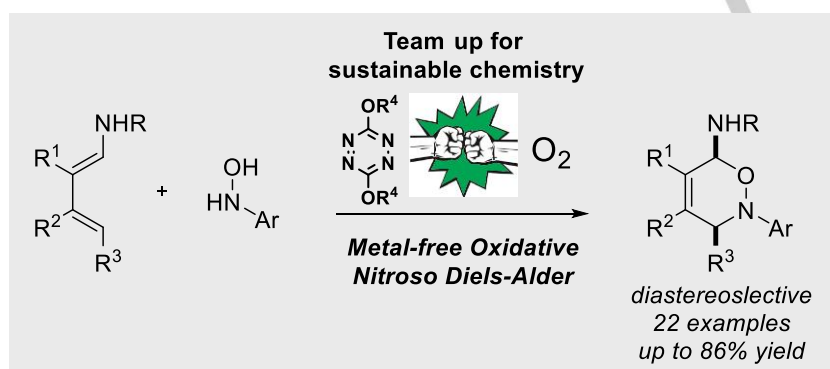
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Page No. – Page No.
Aerobic tetrazine-catalyzed oxidative nitroso-Diels-Alder reaction of N-arylhydroxylamines with dienecarbamates: access to functionalized 1,6-dihydro-1,2-oxazines

New s-tetrazine derivatives were revealed to be effective organocatalytic for the oxidative nitroso-Diels-Alder (NDA) reaction of N-arylhydroxylamines with dienecarbamates. Using molecular oxygen as a terminal oxidant, a series of functionalized 1,6-dihydro-1,2-oxazines were prepared in moderate to good yields with excellent diastereoselectivity. This mild and eco-friendly oxidation method is applicable to a broad substrate range.