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A newly designed heterodiene and its application to construct six-membered heterocycles containing an N–O bond†

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A new type of zwitterionic nitrosoalkene generated *in situ* from dehydrohalogenation of α-halo-*N*-alkylhydroxamic acids was designed. [4+2] cycloadditions of this heterodiene to olefins provide a facile route to construct six-membered heterocycles containing an N–O bond and a new protocol for 1,2-*syn* carbohydroxylate alkenes with a hydroxyl and acetamide group. DFT calculations support a concerted cycloaddition pathway and the solvent HFIP can stabilize the transition state through H-bonding interaction.

Hetero-Diels–Alder (HDA) reactions are among the most powerful transformations for the synthesis of functionalized heterocyclic rings with high regio-, diastereoselectivity and bond-forming economy.[1] This efficient method has found tremendous applications in the synthesis of natural products and biologically relevant compounds.[2] During the past decades, numerous heterodienes have been discovered and significantly expanded the application of this transformation.[1] However, HDA cycloadditions are often slow and require either thermal activation or the use of chemical promoters (such as Lewis acids) for the *in situ* generation of reactive heterodienes.[1] Thus, it remains challenging to design novel versatile heterodienes and develop robust HDA reactions which can be conducted under mild and environment-friendly conditions.

Heterocycles, such as the derivatives of tetrahydro-1,2-oxazines and 1,2-oxazinane-3-ones, are present in many natural products and pharmacologically active compounds (Fig. 1).[3] To date, common strategies for the construction of six-membered heterocycles containing N–O bonds include: [4+2] cycloadditions of dienes to nitroso compounds,[4] Lewis acid catalyzed [3+3] cycloaddition of nitrones to donor–acceptor (DA) cyclopropanes or allenes,[5] and hetero Diels–Alder (HDA) cycloadditions of olefins to conjugated nitrosoalkenes or nitroalkenes (Fig. 2a).[6] Nitrosoalkenes **1** are useful heterodienes which are usually generated *in situ* from dehydrohalogenation of the corresponding α-haloxoimes or Ag^+ induced dehalogenation of α-halonitrones.[6,7] Due to the lability of nitrosoalkenes **1** and their tendency toward polymerization, the cycloadditions of nitrosoalkenes to olefins often require a great excess of olefins, long reaction times, high dilution and afford cyclic oxime ethers in moderate yield.[8] In addition, the specific structures further limit the scope and application of these reactions.[9] Recently, azaoxyallyl cations have emerged as versatile intermediates in cycloaddition reactions.[10] Our group has also explored the azaoxyallyl cations as synthons for the total synthesis of (±)-minfiensine and developed a transition-metal-free synthesis of *N*-hydroxy oxindoles based on azaoxyallyl cations.[11] Inspired by these studies, we postulated that disconnection of the alkoyl group in azaoxyallyl cations into a hydroxyl group and alkyl group will make the oxygen a new nucleophilic site, and generate a novel zwitterionic intermediate **2** with the retention

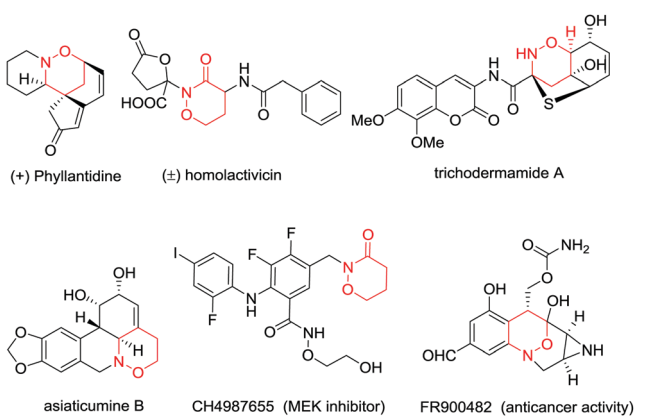

Fig. 1 Examples of natural products and pharmacologically active compounds featuring heterocycles containing an N–O bond.

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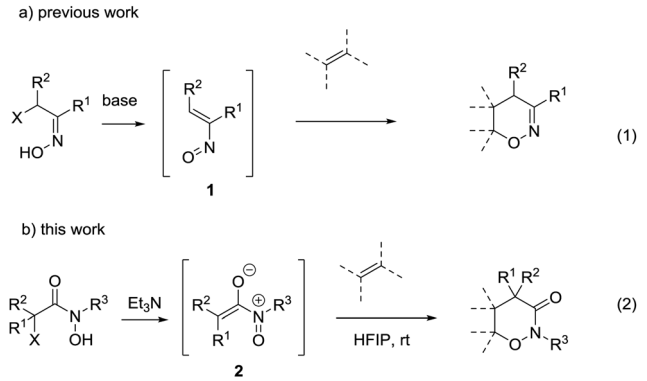
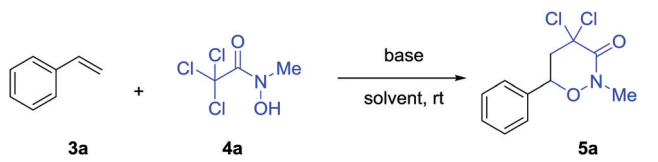


Fig. 2 (a) Hetero Diels–Alder reaction of olefins to nitrosoalkenes. (b) Newly designed heterodiene **2** and its applications.

of the fascinating characteristics of azaoxyallyl cations. Herein, we describe our newly designed heterodiene **2** generated *in situ* from α-halo-*N*-alkylhydroxamic acids and its applications to construct six-membered heterocycles containing an N–O bond and other related scaffolds.

To initiate our investigation, we chose styrene **3a** and 2,2,2-trichloro-*N*-hydroxy-*N*-methylacetamide **4a** as model substrates (Table 1). The desired product was obtained in 51% yield under our previous reaction conditions in HFIP.[11c] Further screenings of bases showed that Et_3N is an optimal base for the reaction, generating the annulation product **5a** in 85% yield (entry 5). The solvent was crucial to the reaction, and conducting the reaction in non-fluorinated solvents led to a trace amount of (<5%, LC-MS) or no desired product detected (entries 7–11). Interestingly, performing the reaction under the conditions of the classical HDA cycloaddition of nitrosoalkenes only resulted in a trace amount of the desired product (entries 12 and 13).[8]

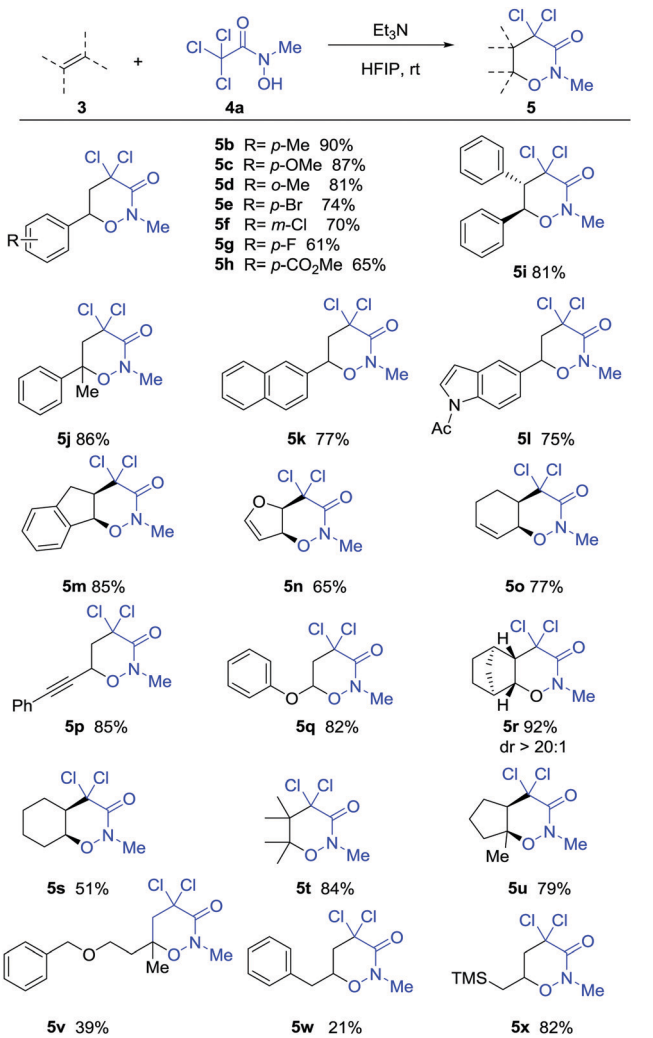
Table 1 Optimization of the reaction conditions



Entry	Base	Solvent	Yield[a] (%)
1	$KHCO_3$	HFIP	51
2	K_2CO_3	HFIP	63
3	DMAP	HFIP	77
4	DBU	HFIP	83
5	Et_3N	HFIP	85
6	Et_3N	CF_3CH_2OH	24
7	Et_3N	MeOH	Trace
8	Et_3N	CH_2Cl_2	Trace
9	Et_3N	THF	n.d.
10	Et_3N	MeCN	n.d.
11	Et_3N	Toluene	n.d.
12	Na_2CO_3	DCM	Trace
13	Na_2CO_3	Et_2O	Trace

Reaction conditions: **3a** (0.30 mmol, 1.0 equiv.), **4a** (2.0 equiv.), base (2.0 equiv.) in solvent (1.5 mL) at rt. [a] Yield was that of the isolated product, n.d. = not detected.

Using the optimized reaction conditions, we explored the scope of alkenes. A variety of alkenes were subjected to the reaction and the collected data are shown in Scheme 1. Functional groups such as methoxyl, halogens, and esters were all well-tolerated under standard conditions. The reactions with styrenes bearing electron-donating groups resulted in the desired products in excellent yields (**5b–d**). The reactions with styrenes substituted by electron-withdrawing groups provided the desired product in moderate yields (**5f–h**). Reactions with 1,2-disubstituted or 1,1-disubstituted styrenes were conducted under the optimized conditions and generated the cycloadduct **5i** or **5j** in 81% or 86% yield, respectively. Furthermore, reactions with other aromatic olefins, such as 2-vinylnaphthalene and 5-vinylindole, proceeded smoothly to give **5k** and **5l** in good yields. Notably, cycloaddition occurred with the C–C double bond in indene (**5m**) or furan (**5n**). Conjugated alkenes preferred to react with good yields. 1,3-Cyclohexadiene gave **5o** in 77% yield, while previous nitrosoalkenes tend to serve as 2π-components.[12] Note that if the molecule contained both

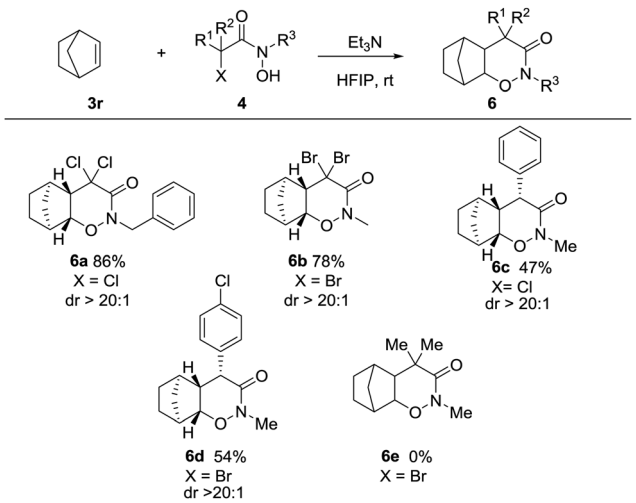


Scheme 1 Scope of the alkenes. Yield was that of the isolated product. Reaction conditions: **3** (0.30 mmol, 1.0 equiv.) **4a** (0.60 mmol, 2.0 equiv.) and Et_3N (2.0 equiv.) in HFIP (1.5 mL) at room temperature.

a C–C triple bond and a C–C double bond, cycloaddition took place with the double bond exclusively (**5p**). The reaction also worked very well with phenyl vinyl ether (**5q**) or strained olefins such as norbornene (**5r**), generating the desired product in 82% and 92% yields, respectively. Aliphatic olefins such as cyclohexene or tetramethylethylene performed well under the optimized conditions. When trisubstituted olefin (1-methylcyclopentene) was subjected to the reaction, **5u** was obtained as the sole product in 79% yield. The reactivities of other noncyclic simple aliphatic olefins (**5v** and **5w**) decreased dramatically, and the cyclized products were obtained in low yields. However, cycloaddition with allyltrimethylsilane resulted in a higher yield of 82% for **5x**. The enhanced reactivity was probably ascribed to the silicon effect.[13]

Next, the scope of α-halo-*N*-alkylhydroxamic acids was explored, and the results are shown in Scheme 2. Cycloaddition of norbornene **3r** with *N*-benzyl-2,2,2-trichloro-acetohydroxamic acid under standard conditions resulted in the cycloadduct **6a** in 86% yield. 2,2,2-Tribromo-*N*-methylacetohydroxamic acid is another alternative reagent for 1,4-dipolar cycloaddition (**6b**). Slightly diminished reactivity was observed when α-phenyl-α-halo-*N*-methylacetohydroxamic acids were subjected to the reaction, generating the corresponding products **6c** and **6d** in 47% and 54% yields, respectively. The reaction was carried out with simple α-alkyl substituted substrates such as 2-bromo-2-dimethylacetohydroxamic acid **6e**, and failed to provide any desired product. To demonstrate the versatility of the cycloaddition products, the compound **5a** was rapidly converted into different products (see the ESI,† Scheme S1, S-pg10).

Then, DFT calculations at the B3LYP/6-311+G(d,p)//B3LYP/6-31+G(d)[14] level were carried out (see the ESI† for details) to understand the reaction mechanism and regiochemistry (Fig. 3a). Calculations indicate that the reactant binding with two HFIP molecules can generate the heterodiene through the deprotonation by the amine with the assistance of the third HFIP molecule for removing a chloride anion. This is a multi-component reaction with an estimated activation energy of 17.0 kcal mol^{-1} (see the ESI†).



Scheme 2 Scope of the α-halo-*N*-alkylhydroxamic acids. Yield was that of the isolated product. Reaction conditions: **3r** (0.30 mmol, 1.0 equiv.) **4** (0.60 mmol, 2.0 equiv.) and Et_3N (2.0 equiv.) in HFIP (1.5 mL) at room temperature.

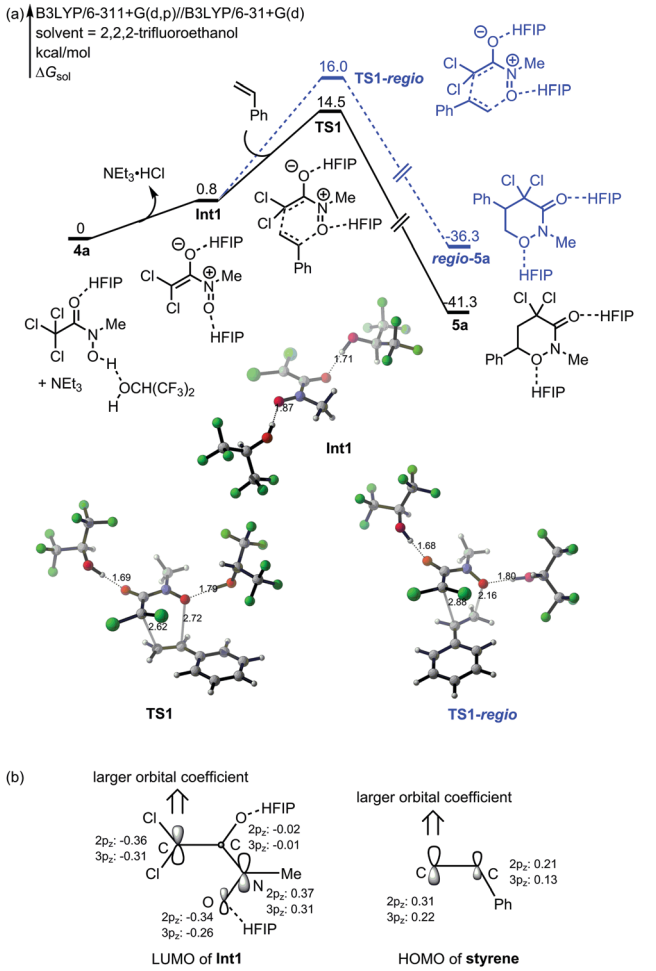


Fig. 3 (a) DFT calculations on the reaction of **4a** and styrene. (b) LUMO of **Int1**, and HOMO of styrene and their orbital coefficients.

The following [4+2] cycloaddition is a concerted process with a calculated activation free energy of 13.7 kcal mol^{-1}. From Fig. 3a, we can find that the product **5a** formation *via* **TS1** is the favorable pathway, while the product ***regio*-5a** formation pathway *via* **TS1-*regio*** is disfavored by 1.5 kcal mol^{-1} compared to **TS1**. The rate-determining step is the generation of zwitterionic heterodiene if considering that the [4+2] process is easy. The [4+2] process is an inverse electron demand process,[15] where alkene provides its HOMO to interact with the LUMO of the heterodiene. The HFLP molecules could lower the LUMO of the heterodiene and facilitate the cycloaddition (see this discussion in the ESI†). We can also understand the regiochemistry from Frontier Molecular Orbitals (FMOs).[16,17] The dichloride attached carbon atom of the heterodiene (**Int1**), which has a larger orbital coefficient in its LUMO than the terminal oxygen atom, prefers to react with the terminal vinyl carbon of styrene, which has a bigger orbital coefficient than that of the internal vinyl carbon in the HOMO of styrene (see Fig. 3b).

In conclusion, a novel type of zwitterionic nitrosoalkene generated *in situ* from dehydrohalogenation of α-halo-*N*-alkylhydroxamic acids was designed. The [4+2] cycloadditions of this heterodiene to alkenes offer a facile route to construct

1,2-oxazinane-3-ones and a new protocol for 1,2-*syn* carbohydroxylate alkenes with a hydroxyl and acetamide group. Computational studies support a concerted pathway and the solvent HFIP plays a crucial role in the stabilization of intermediates and help of the *in situ* generation of heterodienes. We anticipate that this new heterodiene synthon could be widely applied in other related reactions. Further studies on the application of this new intermediate are underway in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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