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Asymmetric NHC-Catalyzed Aza-Diels–Alder Reactions: Highly Enantioselective Route to α-Amino Acid Derivatives and DFT Calculations

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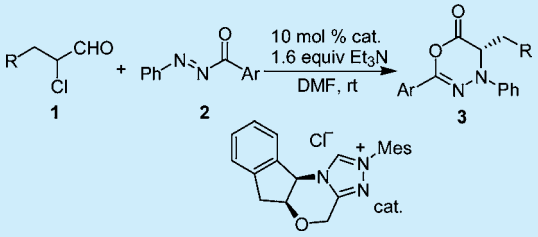
Supporting Information

ABSTRACT: A facile *N*-heterocyclic carbene catalytic enantioselective aza-Diels–Alder reaction of oxodiazenes with α-chloroaldehydes as dienophile precursors is reported, with excellent enantioselectivity (ee > 99%) and excellent yield (up to 93%). DFT study showed that *cis*-**TSa**, formed from a top face approach of oxodiazene to *cis*-**IIa**, is the most favorable transition state and is consistent with the experimental observations.

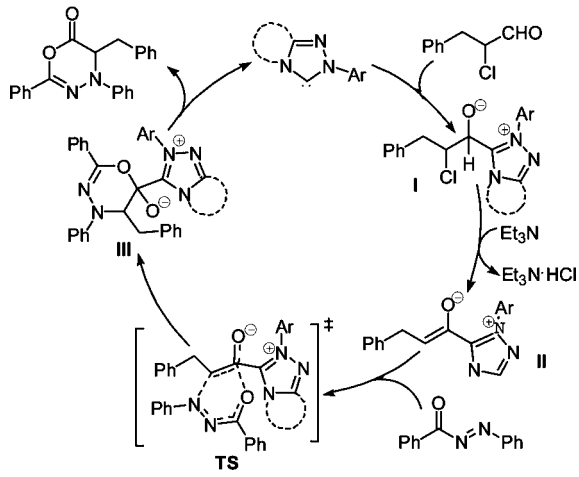


As a result of their special electronic characteristics, *N*-heterocyclic carbenes (NHCs) have led to the rapid development of many organocatalysis reactions[1] in addition to organometallic catalysis reactions[2] in the past decade. Making use of the intriguing organocatalytic activation of NHC for new bond formation opens up a new avenue for the synthesis of target molecules. The traditional a^1-d^1 umpolung (benzoin condensation[3] and Stetter reaction[4]) and a^3-d^3 umpolung (homoenolate cycloaddition[5]) approaches have been extensively investigated. We have also reported the trapping of the homoenolate intermediate by 4-nitrosotoluene to afford unexpected seven-membered β-amino ester derivatives via 1,2-Bamberger rearrangement,[6] while NHC-catalyzed Diels–Alder reaction,[7] an important development in the NHC organocatalysis in that enol or enolate species are formed during the process, still remains challenging. Recently, we disclosed a chiral NHC-catalyzed oxo-Diels–Alder reaction of α,β-unsaturated amide with *in situ* generated enolate species to afford dihydropyranone moieties, which are important building blocks in the synthesis of natural products.[8] Our ongoing interest in NHC-catalyzed hetero-Diels–Alder reaction of *in situ* generated enolate species prompted us to study the NHC-catalyzed aza-Diels–Alder (aza-DA)[9] reaction of oxodiazene with racemic α-chloroaldehydes as dienophile precursors, providing a facile enantioselective route to α-amino acid derivatives.[10] Relevant DFT calculations were also carried out to elucidate the observed enantioselectivity.

The chemistry described in this communication builds on the investigation of Rovis and Bode in exploring the NHC-catalyzed reactions of α-haloaldehydes with a variety of electrophiles. In the earlier studies, these two groups independently discovered that enols or enolates could be generated from the reaction of α-haloaldehydes and the NHC catalysts under appropriate conditions.[7b,11] In our report, the enolate generated from an α-haloaldehyde with NHC catalyst can be engaged in an enantiocontrolled Diels–Alder reaction with oxadiazene, which facilitates the formation of a new C–N bond. The importance of this method is due to its great potential for accessing α-amino acid derivatives from the 1,3,4-oxadiazin-6-one products.

Our proposed pathway for this aza-DA reaction (Scheme 1) first involves the nuclephilic addition of the NHC organocatalyst

Scheme 1. Proposed Catalytic Pathway



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to the α-chloroaldehyde to afford adducts **I**. This is followed by elimination of hydrogen chloride to provide enolate species **II**. The enolate species then participates in the $LUMO_{oxodiazene}$-controlled inverse electron demand Diels–Alder cycloaddition with *N*-benzoyldiazene to afford the cycloaddition adducts **III**. Subsequent acylation completes the catalytic cycle and releases the enantioenriched 1,3,4-oxadiazin-6-ones and regenerates the NHC catalyst.

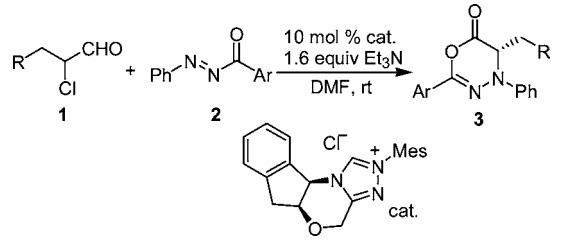
One of the challenges of this reaction lies in the reactivity of oxodiazenes, which are more inert than α,β-unsaturated imines and oxodiene counterparts. Furthermore, α-chloroaldehydes, which are readily accessible substrates, can undergo unwanted elimination of hydrogen chloride to give α,β-unsaturated aldehydes. This can in turn lead to the generation of pyrazolidinone by [3 + 2] cycloaddition of the enal with diazene via a homoenolate intermediate[12] and/or direct amination of aldehyde via Stetter reaction.

To investigate this unprecedented oxodiazene aza-DA cycloaddition, we first surveyed the readily prepared α-chlorohydrocinnamaldehyde (**1a**) and *N*-phenyl-*N*′-benzoyl-diazene (**2a**) with different chiral triazolium salts, bases, solvents, and reaction stoichiometries for optimization studies (see Supporting Information). *N*-Mesityl-substituted triazolium salt (refer to as cat.) was determined as the optimal catalyst.[4d,7b,13] The desired product was afforded in excellent enantioselectivity, albeit low conversion. Intensive investigations of the reaction conditions revealed that the consumption of oxodiazene was increased when polar, nonprotic solvents were used. The use of DMF as solvent and Et_3N as base led to complete consumption of oxodiazene within several hours. We also noticed that decreasing the catalyst loading to 10 mol % under the above-mentioned conditions caused no loss in yield and enantioselectivity of the product. Reactions typically took 0.5–12 h to reach completion.

Experiments that probed the scope of this [4 + 2] cycloaddition under optimized condition are summarized in Table 1. The generality of [4 + 2] cycloaddition was investigated by using various oxodiazene. The reaction proceeded smoothly for oxodiazenes bearing electron-withdrawing groups on the aryl ring (Table 1, entries 2–6, 10, 11). 4-Nitrophenyl oxodiazene afforded the best enantioselectivity (>99% ee) with good yield (Table 1, entry 11). Similarly, electron-donating groups (Table 1, entry 12) and heteroaryloxodiazenes (Table 1, entries 8 and 9) were also well-tolerated, with 4-methoxyphenyl oxodiazene giving high enantioselectivity (97% ee), despite a relatively lower yield and longer reaction time (12 h) (Table 1, entry 13). 2-Naphthyl oxodiazene provided the highest yield and almost complete enantioselectivity (Table 1, entries 7 and 19). The position of the substituent on the phenyl ring seemed to have little influence on the reaction outcome (Table 1, entries 4–6). We then varied the α-chloroaldehyde component of this reaction. Excellent yields and high enantioselectivities were obtained in most cases. The α-chloroaldehyde derived from ether and silyl ether were well-tolerated, with the latter affording the highest yield and excellent enantioselectivity (Table 1, entry 20). When a straight linear aliphatic substitute was employed, the reaction processed smoothly regardless of the length of the alkyl chain (Table 1, entries 14–16). Benzyloxy ether substituted substrates provided a slight decrease of enantioselectivities with reasonable yield (Table 1, entries 17 and 18). The presence of an electron-withdrawing group on the phenyl ring of α-chlorohydrocinnamaldehyde provided a better result (Table 1, entry 19).

To determine the stereochemistry of the 1,3,4-oxadiazin-6-ones formed via the asymmetric NHC-catalyzed aza-Diels–Alder reactions, the absolute configuration of the product **3s** was determined by X-ray carystallographic analysis (Figure 1). The (1*R*,2*S*)-(+)-*cis*-*N*-mesityl-substituted triazolium salt prepared from (1*R*,2*S*)-(+)-*cis*-1-aminoindan-2-ol exclusively provided (*S*)-1,3,4-oxadiazin-6-one **3s**.

Table 1. Substrate Scope of NHC-Catalyzed aza-DA Reaction[a]



entry	R	Ar	yield (%)[b]	ee (%)[c]
1	C_6H_5 (**1a**)	C_6H_5 (**2a**)	75 (**3a**)	98
2	C_6H_5 (**1a**)	4-FC_6H_4 (**2b**)	81 (**3b**)	98
3	C_6H_5 (**1a**)	4-ClC_6H_4 (**2c**)	84 (**3c**)	98
4	C_6H_5 (**1a**)	4-BrC_6H_4 (**2d**)	82 (**3d**)	97
5	C_6H_5 (**1a**)	3-BrC_6H_4 (**2e**)	80 (**3e**)	97
6	C_6H_5 (**1a**)	2-BrC_6H_4 (**2f**)	76 (**3f**)	97
7	C_6H_5 (**1a**)	2-naphthyl (**2g**)	87 (**3g**)	>99
8	C_6H_5 (**1a**)	2-furyl (**2h**)	73 (**3h**)	98
9	C_6H_5 (**1a**)	2-thienyl (**2i**)	75 (**3i**)	98
10	C_6H_5 (**1a**)	4-$CF_3C_6H_4$ (**2j**)	76 (**3j**)	98
11	C_6H_5 (**1a**)	4-$O_2NC_6H_4$ (**2k**)	78 (**3k**)	>99
12	C_6H_5 (**1a**)	4-$CH_3C_6H_4$ (**2l**)	67 (**3l**)	98
13	C_6H_5 (**1a**)	4-$MeOC_6H_4$ (**2m**)	60 (**3m**)	97
14	CH_3 (**1b**)	2-naphthyl (**2n**)	83 (**3n**)	96
15	C_3H_7 (**1c**)	2-naphthyl (**2n**)	91 (**3o**)	94
16	C_6H_{13} (**1d**)	2-naphthyl (**2n**)	89 (**3p**)	96
17	$BnOC_2H_4$ (**1e**)	2-naphthyl (**2n**)	89 (**3q**)	94
18	4-$BrBnOC_2H_4$ (**1f**)	2-naphthyl (**2n**)	87 (**3r**)	94
19	4-BrC_6H_4 (**1g**)	2-naphthyl (**2n**)	90 (**3s**)	>99
20	$TBSOC_2H_4$ (**1h**)	2-naphthyl (**2n**)	93 (**3t**)	97

[a]Reaction conditions: α-chloroaldehyde **1** (0.3 mmol) and oxadiazene **2** (0.2 mmol) and cat. (0.02 mmol), Et_3N (0.32 mmol) in DMF (1 mL). The mixture was stirred for 0.5–12 h at rt. [b]Yields of isolated product. [c]ee values determined by HPLC analysis on Chiralpak AS-H and OD-H column.

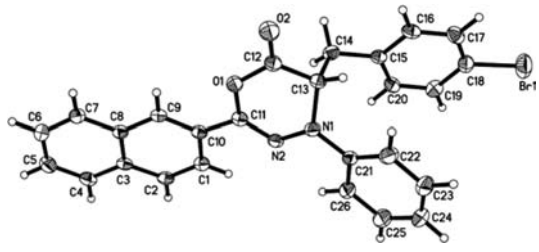


Figure 1. X-ray crystal structure of **3s**. Thermal ellipsoids are shown at 50% probality.

In order to fully appreciate the generation of the preferred stereochemistry for this cycloaddition process, density functional theory (DFT) calculations were carried out to elucidate the observed enantioselectivity.[14] In principle, both *cis* and *trans* enolate **II** could be formed after the elimination of 1 equiv of **HCl** from intermediate **I** in the presence of Et_3N, and each form also has two rotamers, namely, *cis*-**IIa**, *cis*-**IIb**, *trans*-**IIa**, and *trans*-**IIb**

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(see Supporting Information, Figure S1). These four structures were located, and the comparison of their energies revealed that the *cis* forms are thermodynamically more stable than the *trans* forms by approximately 3.9−6.5 kcal/mol.

The participation of *cis*-enolate **II** in the cycloaddition process leads to four kinds of *cis*-transition state (**TS**) (see Supporting Information, Figure S2), and all of the structures suggest that one face of the enolate intermediate **II** is blocked by the indane moiety, thus leaving the unblocked face more accessible for the [4 + 2] cycloaddition with the oxodiazene substrate. It was found that the cycloaddition process of oxodiazene to *cis*-enolate **II** on the unblocked face, corresponding to the *cis*-**TSa** and *cis*-**TSb** transition states, is 3.7−9.5 kcal/mol thermodynamically more stable than that on the blocked face, which refers to *cis*-**TSc** and *cis*-**TSd** transition states. As a result, the stereochemistry of the final products is determined by the relative transition state energy barriers for the *re* face and *si* face (unblocked face) addition of the oxodiazene onto two rotamers, *cis*-**IIa** and *cis*-**IIb**, respectively (as depicted in Figure 2). It was found that *cis*-**TSa**, which was formed by the cycloaddition process of the oxodiazene to *cis*-**IIa** on the *re* face and leads to the formation of the *S*-enantiomer, is both kinetically (by 2.0 kcal/mol) and thermodynamically (by 3.5 kcal/mol) more favorable than *cis*-**TSb**, formed by the cycloaddition process to *cis*-**IIb** on the *si* face. These observations are all consistent with the experimental observations.

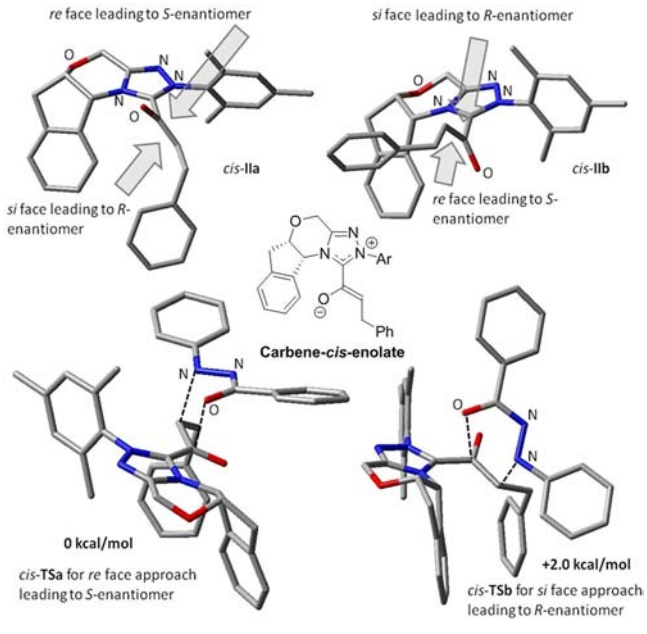


Figure 2. (Top) Possibilities for approaches by the oxodiazene. (Bottom) Transition state (TS) structures of the *re* and *si* face approach for the formation of *S*- and *R*-enantiomers, respectively. Dotted lines show the bonds formed during the [4 + 2] process. Hydrogen atoms are omitted for carity.

To further exclude intermediate **III** in the cycloaddition process, *cis*-**IIIa**, derived from *cis*-**TSa**, was found to be more stable than *cis*-**IIIb**, which was derived from *cis*-**TSb**, by 3.5 kcal/mol (see Supporting Information, Figure S3).

In order to rule out the participation of *trans*-enolate **II** in the cycloaddition process, *trans*-**TS**, the rotamers leading to the transition state were located and were found to be 13.0−16.6 kcal/mol higher in energy than *cis*-**TSa** (see Supporting Information, Figure S4).

The essence of inverse demand electron aza-DA can be exactly illuminated by the electrophilicity, ω, of the substates (diene and dienophile), which determines the direction in which charge transfers from one to another. This is in accordance to the theoretical basis that the transfer occurs from higher to lower electronic chemical potential, μ.[15] Thus, calculating the electrophilicity of the reactants, where $\omega = -\mu^2/2\eta$,[16] will enable us to determine the relation in the movement of electrons. The chemical potential μ is the average of the HOMO and LUMO energies, while the chemical hardness η is the difference of HOMO and LUMO energies. The enolate has ω = 1.01 eV and the oxodiazene ω = 2.63 eV, which is characteristic of an inverse demand Diels−Alder as charge transfer occurs from the dienophile to diene.[17] It is also evidenced from the orbital analysis of transition state during the cycloaddition that the HOMO from enolate interacts with the LUMO of the oxodiazene (Figure 3).

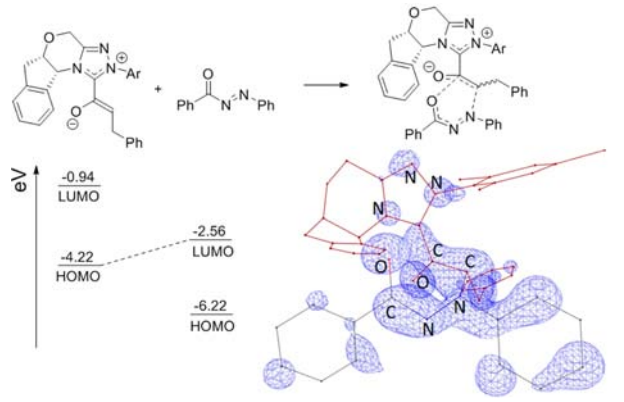
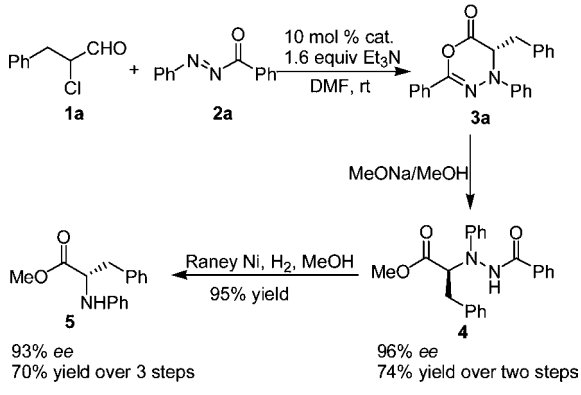


Figure 3. (Top) Blown-up orbital interactions of diene and dienophile in the inverse demand Diels−Alder. (Bottom) HOMO−LUMO interaction diagram of the reactants.

In view of the above achievements, we decided to explore the synthetic utility of the product 1,3,4-oxadiazin-6-ones (**3**, Scheme 2). Upon the completion of the cycloaddition reaction between 2-chloro-3-phenylpropanal (**1a**) and phenyl benzohydrazide (**2a**), MeONa/MeOH solution was added into the reaction mixture, and (*S*)-methyl 2-(2-benzoyl-1-phenylhydrazinyl)-3-phenylpropanoate (**4**) was formed rapidly in good yield with excellent optical activity (96% ee). Hydrogenation in the presence of Raney Ni in methanol promotes N−N bond cleavage

Scheme 2. Transformation of (*S*)-1,3,4-Oxadiazin-6-ones into (*S*)-α-Amino Acid Ester



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to provide (*S*)-*N*-phenyl-α-amino ester **5**, which is an important building block in the synthesis of natural product and biologically active compounds,[18] in high yield, albeit with slight loss of optical purity (93% ee).

In summary, we have described a facile asymmetric NHC-catalyzed aza-Diels–Alder reaction of oxodiazenes with α-chloroaldehydes as dienophile precursors providing 1,3,4-oxadiazin-6-ones in good to excellent yields (up to 93%) with excellent enantioselectivities (94% to >99% ee). The cycloaddition product was efficiently transformed into the α-amino ester derivative in good yield with excellent enantioselectivity, thereby demonstrating that the NHC-catalyzed reaction is a powerful approach for organic synthesis. DFT studies showed that the most favorable transition state, *cis*-**TSa**, is formed by the approach of oxodiazene at the *re* face of *cis*-**IIa** and are consistent with experimental observations. The calculation of electrophilicity ω and orbital analysis of the transition state revealed the inverse electron demand essence of the aza-DA reaction.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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