Stereoselective *N*-Heterocyclic Carbene Catalyzed Formal [4+2] Cycloaddition: Access to Chiral Heterocyclic Cyclohexenones

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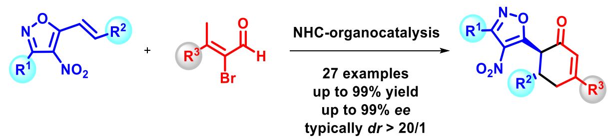
Supporting Information Placeholder



ABSTRACT: The present study reports an asymmetric NHC-catalyzed formal [4+2] cycloaddition of heterocyclic alkenes containing polarized double bond with azolium-dienolate intermediate generated from *α*-bromo-*α*,*β*-unsaturated aldehydes without external oxidation of Breslow intermediate. Heterocyclic cyclohexenones were produced in good isolated yields (typically about 90%) with good stereochemical outcomes (typically *dr* > 20/1, and 70-99% *ee*). The synthetic utility of the protocol was exemplified by the scope of heterocyclic alkenes.

The first isolation of *N*-heterocyclic carbene (NHC)[1] done by Arduengo,[2] and followed by the discovery of Enders´s triazolylidene carbenes[3] initiated the investigation made by Knight and Leeper on rigid chiral bicyclic scaffolds.[4] Since then, the evolution of carbenes in synthetic chemistry from unstable intermediates to versatile organocatalysts for an unprecedented array of asymmetric reactions began.[5] The underlying principle of the NHC catalyzed transformations is the umpolung activation of aldehydes through the Breslow intermediate,[6] leading to the functionalization of the aldehydic group (for example, benzoin,[7] Stetter reaction[8]). In the last years, considerable attention has been drawn on the development of NHC-bounded azolium-dienolate, which mirrors the nucleophilic nature of the Breslow intermediate. NHC-bounded azolium-dienolates are typically generated from substituted *α*,*β*-unsaturated aldehydes, and acid derivatives, alternatively from substituted cyclobutenones (Figure 1, A).[9] In 2011, Ye described the formation of azolium-dienolates via the addition of NHC to vinyl ketenes,[10] *in situ* generated from *α*,*β*-unsaturated acid chlorides. Soon after, Chi generated azolium-dienolate by oxidation/*γ*-deprotonation of homoenolate formed from *β*-methyl enals using quinone oxidant.[11] Later, Yao successfully realized the formation of azolium-dienolates either from *α*-brominated enals or 1-hydroxybenzotriazole *α*,*β*-unsaturated esters bearing *γ*-hydrogen atom.[12] Recently, Yang and Zhang described enantioselective spirocyclization using azolium-dienolate generated from *γ*-chloro enals.[13] Nowadays, oxidative generation of azolium-dienolate is probably the most popular, although a stoichiometric amount of an external oxidant is needed.[14]

Generally, NHC-bounded azolium-dienolates were used as key intermediates for *α*- or *γ*-carbon functionalization.[15] Most of the transformations realized with azolium-dienolates can be classified as [4+2] cycloadditions, where activated ketones, imines and azodicarboxylates were employed as reacting partners.[16] Interestingly, the reactivity of azolium-dienolates with other electron-deficient alkenes, such as substrates bearing polarized C=C bonds (X=Y is alkene, Figure 1, A) are significantly less explored. Despite that, methodology for [4+2] cycloaddition using external oxidation is known for alkenes derived from oxindole,[17] coumarine, chromone,[18] and fullerene-based alkenes,[19] 3-nitroindoles,[20] and alkenyl 4-nitroisoxazoles.[21] To our best knowledge, an asymmetric method for preparing chiral cyclohexenones through azolium-dienolate intermediate generated without an external oxidation step is almost unexplored.[13] Importance of developing novel enantioselective methodologies for the preparation of chiral cyclohexenones is demonstrated by biological acitivity[22,23] (Figure 1, B) and synthetic valuability of chiral cyclohexenones.[24]

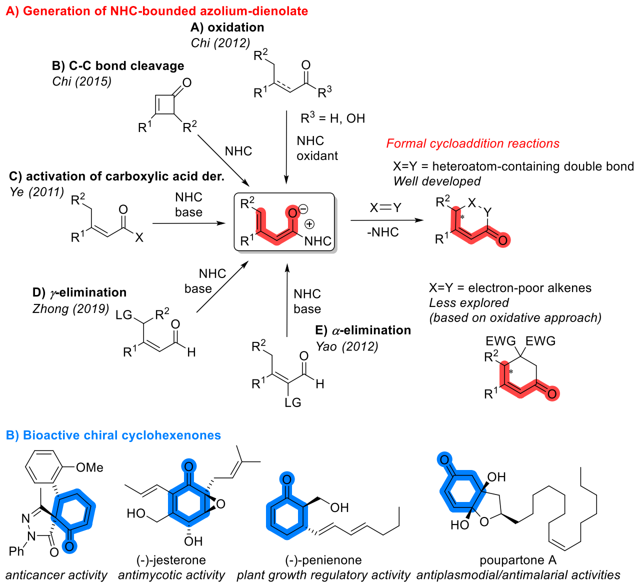
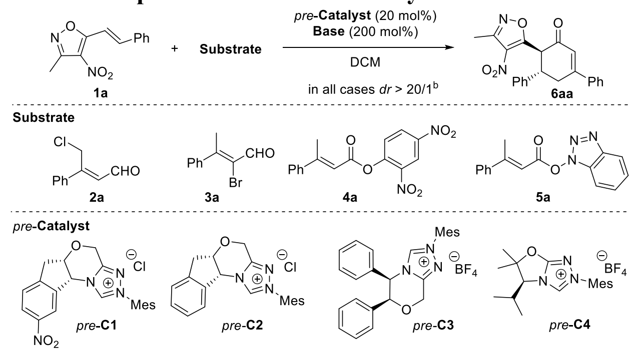


Figure 1. Generation of azolium-dienolate and its reactivity.

Drawing inspiration from previously reported approaches and considering our interest in asymmetric cyclization reactions,[25] we aimed to develop an atom-economical strategy for constructing chiral cyclohexenones from azolium-dienolates generated without the use of any oxidant with electron-deficient alkenes.

We began our investigation by optimizing of reaction partner for the formal [4+2] cycloaddition with alkenyl 4-nitroisoxazoles **(1)**, selected based on our previous works.[26] Simple mixing of easily accessible styryl derivative **1a** with *γ*-chloro-*α*,*β*-unsaturated aldehyde **(2a)** in the presence of chiral carbene precursor and excess of base (triethylamine) produced cyclohexenone **6aa** in high isolated yield and stereocontrol (Table 1, entry 1). Despite that result, the preparation of starting aldehyde **(2a)** was low yielding, and the starting material was significantly unstable in our hands, which did not allow good reproducibility of results (for details, please see the SI file). Good efficiency was shown in reactions with *α*-bromo-*α*,*β*-unsaturated aldehyde (**3a**, entry 2) or activated *α*,*β*-unsaturated esters (**4a**/**5a**, entries 3, 4). Worthmentioning, both substrates were bench-stable and easy to prepare, a better atom economy was represented using *α*-bromo-*α*,*β*-unsaturated aldehyde **(3a)**. After the selection of the proper substrate for the generation of azolium-dienolate, the efficiency and stereochemical effect of various chiral NHC catalysts was evaluated. The reaction produced the expected product **6aa** in the presence of various morpholinone or oxazolidine-based catalysts. For example, the reaction of **1a** and **3a** mediated by pre-**C3** provided **6aa** with slightly increased enantiocontrol but with a significantly lower reaction rate (entry 6). Apart from the highlighted catalyst precursors, we tested other NHC precatalyst (for details, please see the SI file). Unfortunately, none of the tested salts afforded cyclohexenone **6aa** in yield and enantiopurity comparable to the reaction performed with pre-**C1**. A lower reaction rate was observed when caesium carbonate was used instead of TEA (entry 8). Interestingly, the yield was increased in the reaction conducted with DIPEA (entry 9). Similarly, high yields of **6aa** were obtained from the reaction carried out in ethers, for example, in MTBE (entry 10). Further optimization of reaction conditions revealed high efficiency and stereocontrol of the model reaction using a lowered amount of precatalyst (10 mol%) in toluene and the presence of molecular sieves at 0 °C (entry 13). For complete optimization studies, please, see the SI file.

Table 1. Optimization studies of cycloaddition reaction.



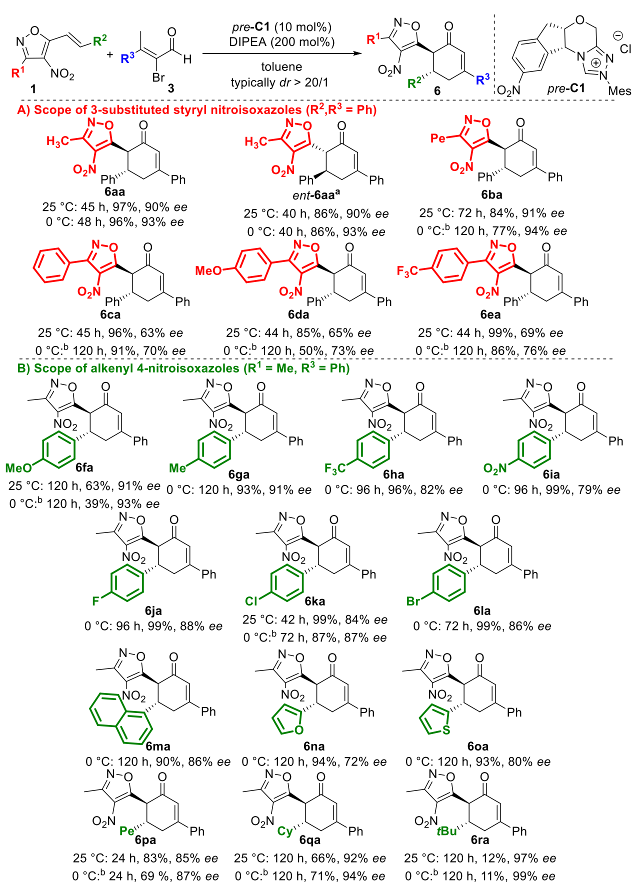
entry[a]	subs.	*pre*-catalyst	base	time (h)	yield[c] (%)	*ee*[d] (%)
1	**2a**	*pre*-**C1**	TEA	20	70	83
2	**3a**	*pre*-**C1**	TEA	16	62	81
3	**4a**	*pre*-**C1**	TEA	94	48	79
4	**5a**	*pre*-**C1**	TEA	16	68	82
5	**3a**	*pre*-**C2**	TEA	91	66	60
6[e]	**3a**	*pre*-**C3**	TEA	120	48	86
7[e]	**3a**	*pre*-**C4**	TEA	120	8	31
8	**3a**	*pre*-**C1**	Cs_2CO_3	112	67	83
9	**3a**	*pre*-**C1**	DIPEA	21	81	82
10[f]	**3a**	*pre*-**C1**	DIPEA	63	89	86
11[g]	**3a**	*pre*-**C1**	DIPEA	15	69	90
12[h]	**3a**	*pre*-**C1**	DIPEA	16	91	90
13[i]	**3a**	*pre*-**C1**	DIPEA	48	96	93

[a] Reactions were conducted with **1a** (0.10 mmol), corresponding substrate **2a**-**5a** (0.15 mmol), corresponding base (0.20 mmol), and *pre*-**catalyst** (20 mol%) in corresponding solvent (1.0 ml) at room temperature. [b] Determined by ^{1}H-NMR of the crude reaction mixture. [c] Isolated yield after column chromatography. [d] Determined by chiral HPLC analysis. [e] Full conversion of **1a** was not observed. [f] MTBE was used. [g] Toluene was used. [h] Reaction was conducted in toluene with molecular sieves (30 mg, 5 Å). [i] Reaction was conducted with **1a** (0.10 mmol), **3a** (0.15 mmol), *pre*-**C1** (10 mol%), and molecular sieves (30 mg, 5 Å) in toluene at 0 °C.

After optimizing the reaction conditions, we began exploring the scope of formal [4+2] cycloaddition by varying 4-nitroisoxazole derivative **1** (Scheme 1, A/B). First, we assessed the effect of the electronic properties of the substituents at position 5 of 4-nitroisoxazole on reactivity and the stereochemical outcome (Scheme 1, A). The reaction generally tolerates various alkyl or aryl substituents at this position affording the corresponding cyclohexenones **6aa-6ea** in high isolated yields (84-99% at room temperature). We observed a lower reaction rate for reactions of aryl-substituted 4-nitroisoxazoles at 0 °C. Thus, we conducted organocatalytic reactions at room temperature, prompting a higher reaction rate with a slightly deleterious effect on enantioselectivities. On the other hand, excellent enantiopurities for alkyl-substituted 4-nitroisoxazoles (**1a, b**) were reached (93-94% *ee*) at 0°C. Conversely, enantiopurities significantly dropped for reactions with 5-aryl-substituted derivatives **1** (around 70% *ee*). Subsequently, the scope of developed [4+2] cycloaddition was investigated by varying of alkenyl part of 4-nitroisoxazole (Scheme 1, B). High-to-excellent yields of cyclohexenones **6** with good enantioselectivities were obtained with (hetero)aromatic styryl derivatives bearing electron-donating groups and electron-withdrawing groups. Remarkably, reaction rates were significantly decreased when aliphatic alkenyl derivatives were used. Noteworthy, increasing sterical hindrance of **1** resulted in prolonged reaction times, but products were obtained with increased enantiopurity. For example, cyclohexenone **6ra** was isolated in very low yield as a nearly optical pure compound (99% *ee*). Next, the scope of the developed method was explored by various *α*-bromo-*α*,*β*-unsaturated aldehydes (**3**). Excellent efficiency of the developed method was shown in reactions of aromatic enals **3** bearing electron-donating as well as electron-withdrawing groups (exept nitro-substituted derivative) producing cyclohexenones **6ab**-**6ai** with excellent isolated yields (above 82%) and excellent enantioselectivities (typically around 90% *ee*). Besides aromatic, aliphatic enals were also tested. Reaction tolerated simple aliphatic enal (R^3 = Me), and cyclohexenone **6ai** was isolated in good yield and stereoselectivity. In spite of that, longer aliphatic enal (R^3 = Hex) decomposed without any conversion to cyclohexenone **6aj**.

Additionally, the absolute configuration of **6ag** was determined using X-ray diffraction analysis, and the configuration was assigned as 5*S*, 6*S* (for details, please see the SI file). The absolute configurations of the other cyclohexenones **6** were assigned by analogy.

Scheme 1. Scope of cycloaddition reaction.



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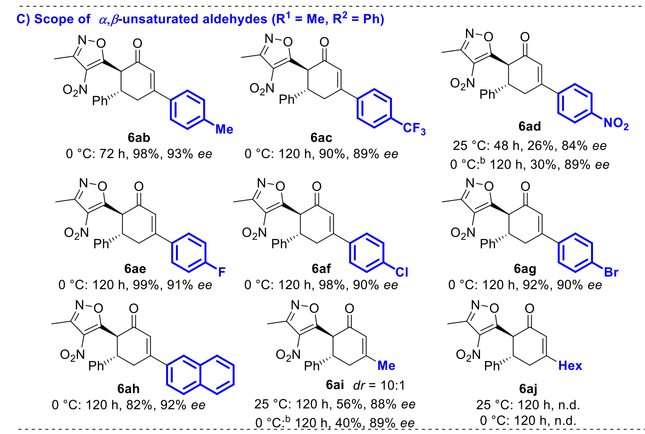
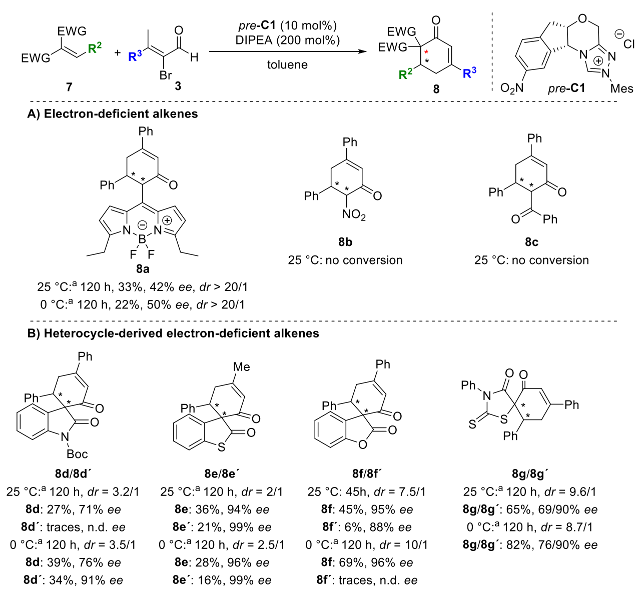


[a] *Ent-pre-***C1** was used. [b] Full conversion of **1** was not observed.

To expand the scope of the developed asymmetric [4+2] cycloaddition, other electron-deficient alkenes were examined (Scheme 2, A/B). In agreement with the previous report,[27] we identified BODIPY (BOron DIPYrromethene) as a strong electron-withdrawing group, which efficiently activates the double bond of styryl BODIPY derivatives. Under the developed reaction conditions, the cycloaddition of styryl BODIPY derivative **7a** produced corresponding cyclohexenone product **8a** in low yield and moderate enantiopurity. Unfortunately, reactions of **3** with other activated alkenes, including nitrostyrenes and chalcones, did not show any conversion of starting materials (Scheme 2, A). Despite that, heterocycle-derived alkenes showed higher reactivity, and various spirocycles containing N, O, and S atoms were formed under optimized reaction conditions (Scheme 2, B). For example, the reaction of benzofuranone-derived alkene produced the corresponding spirocycle **8f** in high yield with great stereochemical outcomes (96% *ee*, 10/1 *dr* at 0 °C).

Scheme 2. Scope of cycloaddition reaction using diverse alkenes.



[a] Full conversion of alkene was not observed.

To demonstrate the synthetic utility of the developed cycloaddition reaction, we performed a reaction between **1a** and **3a** in a gram-scale, giving the product **6a** in nearly quantitative yield (95% yield) with retained stereochemical outcome (93% *ee*, and dr >20/1). Moreover, examples of late-stage transformations of **6a** were carried out, including isoxazole and cyclohexanone cleavage, and 1,2-reduction of cyclohexanone under Luche conditions. For complete results, please, see the SI file.

In summary, we have developed a NHC-catalyzed formal [4+2] cycloaddition of α-bromo-α,β-unsaturated aldehyde with activated alkenes. This operationally simple strategy provides robust access to a variety of chiral cyclohexenones in good-to-excellent yields and excellent stereochemical outcomes under mild reaction conditions. The utility of the developed methodology is demonstrated by using readily available and benchstable substrates, including heterocyclic alkenes affording novel spirocyclic compounds. A study dealing with the preparation of spirocyclic compounds is ongoing in our laboratory.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its online Supporting Information.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Reactions conditions optimization, crystallographic data, copies of ^{1}H NMR, ^{13}C NMR, ^{19}F NMR, and copies of chiral HPLC (PDF)

CIF file for compound **6ag** (CIF)

FAIR data, including the primary NMR FID files for all compounds (ZIP)

Accession Codes

CCDC 2217286 contains the supplementary crystallographic data of this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

L.L., and V.D. performed the synthesis of all compounds. I. C. performed X-ray analysis. V.D., and J.V. wrote the manuscript. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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