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N-Heterocyclic Carbene Catalyzed Switchable Reactions of Enals with Azoalkenes: Formal [4 + 3] and [4 + 1] Annulations for the Synthesis of 1,2-Diazepines and Pyrazoles

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Supporting Information

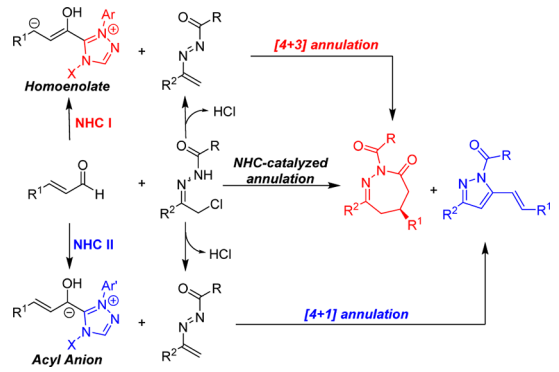
ABSTRACT: A regio- and enantioselective formal [4 + 3] annulation reaction between enals and in situ formed azoalkenes has been achieved. A diverse set of 1,2-diazepine derivatives were synthesized in good yields with excellent enantioselectivities (often 99% *ee*). Alternatively, modifying the standard NHC catalyst switched the reactivity toward a formal [4 + 1] annulation to afford functionalized pyrazoles. The electronic and steric properties of the N-heterocyclic carbene organocatalyst play a vital role in controlling the reaction pathway (homoenolate vs acyl-anion reactivity of enal), allowing selective access to diverse 1,2-diazepine and pyrazole derivatives from identical substrates.

In the past decade, N-heterocyclic carbene (NHC) catalyzed annulation reactions have emerged as powerful methods for the synthesis of various heterocycles.[1] In 2004, the Bode[2] and Glorius[3] groups independently reported the NHC-catalyzed [3 + 2] annulation of enals with aldehydes to give γ-butyrolactones, in which the enal β-carbon behaved as a reactive nucleophilic carbon. Consequently, the use of NHCs has introduced a variety of powerful and unconventional bond forming processes including reactions involving an acyl anion,[4] a homoenolate,[5−8] and enolate equivalents.[9] However, there are several challenges associated with the development of NHC catalyzed reactions, the most critical being the ability to control the reactivity modes of NHC (homoenolate vs acyl-anion reactivity). As documented in Bode's study and indicated by reactions from others, an NHC catalyst with different electronics and steric demands could control the reactive NHC-intermediate to generate different products.[4h,6f,10] We hypothesized that it might be possible to tune the desired selectivities through careful choice of NHC precursor.

Diazepines[11] and styryl pyrazoles[12] are important heterocycles, which are present in a wide range of natural products and bioactive compounds such as ACE inhibitors, analgesic agents, platelet aggregation inhibitors, and nonsteroidal anti-inflammatory agents. Moreover, the 1,2-diazepine motif is also an important scaffold in asymmetric synthesis.[13] A limited number of methods have been developed to address this longstanding problem, but they involve multistep synthetic sequences. Moreover, intermolecular reactions for the asymmetric synthesis of 1,2-diazepines have rarely been reported. Therefore, the development of more general strategies for the construction of enantioenriched 1,2-diazepine derivatives with functional diversity is still highly desirable. *Furthermore, it remains a challenge to selectively generate different products from identical substrates, utilizing catalyst rather than substrate control.*

Azoalkenes,[14] which are readily generated in situ from α-halogeno hydrazones, have been commonly employed as key intermediates for the synthesis of various N-containing heterocyclic compounds. The Bolm group developed an elegant chiral Cu-complex-catalyzed enantioselective formal [4 + 1] annulation of azoalkenes with sulfur ylides affording five-membered dihydropyrazole derivatives.[15] Very recently, the Wang group reported the asymmetric aza-Diels−Alder reaction of indoles with azoalkenes to generate fused indoline heterocycles.[16] The Scheidt[17] and Ye[18] groups independently reported annulation reactions of α,β-unsaturated aldehydes and *ortho*-quinone methides for the synthesis of benzoxopinones. Distinct from their findings, we envisioned that azoalkenes could be utilized as electrophiles with Breslow intermediates generated from enals for the construction of diverse 1,2-deazepines and pyrazoles derivatives. However, several challenges had to be overcome, such as (1) tolerance of the in situ generated azoalkenes under the reaction conditions of NHC catalysis; (2) chemoselectivity, i.e. selectivity, for 1,2-diazepines over pyrazoles; and (3) finding reaction conditions which afford high *ee*'s. Herein, we reported a successful introduction of NHC catalyzed formal [4 + 3] and [4 + 1] annulation reactions, providing 1,2-diazepines and pyrazoles with good chemo- and regioselectivity (Scheme 1).

Scheme 1. NHC-Catalyzed Regioselective Strategy



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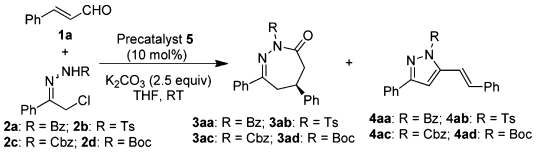
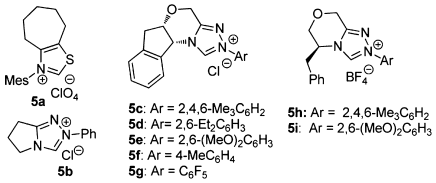
Based on our previous work,[19] we initiated the study by investigating the reaction between enal **1a** and hydrazone **2a** in the presence of the NHC precatalyst **5a** (Table 1, entry 1).

Table 1. Optimization of the Reaction Conditions[a]



entry	2	NHC	yield (%)[b]	3/4[c]	*ee* (%)[d]
1	**2a**	**5a**	trace	–	–
2	**2a**	**5b**	trace	–	–
3	**2a**	**5c**	52	2:3	91
4	**2b**	**5c**	50	>20:1	21
5	**2c**	**5c**	37	4:1	98
6	**2d**	**5c**	77	**9:1**	**99**
7	**2d**	**5d**	42	8:1	99
8	**2d**	**5e**	75	1:2	99
9	**2d**	**5f**	12	6:1	99
10	**2d**	**5g**	trace	–	–
11	**2d**	**5h**	52	6:1	99
12[e]	**2d**	**5i**	**64**	**<1:20**	–

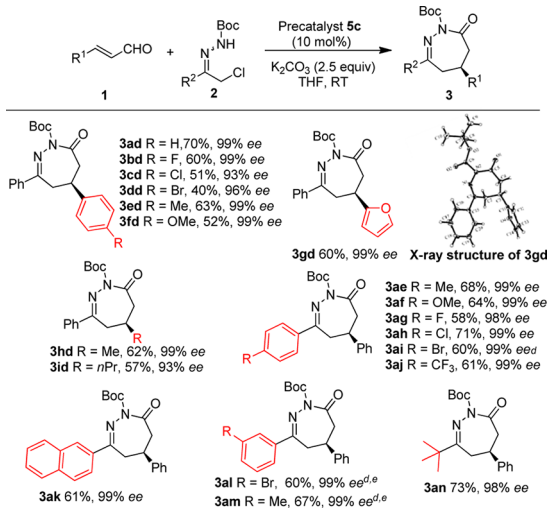
[a]Reactions were conducted with 2.0 equiv of **1a** and 1.0 equiv of **2**, for 16 h. [b]Isolated yields after chromatography are shown. [c]Determined by ^{1}H NMR spectroscopy. [d]Determined by HPLC analysis. [e]After 16 h, 6.0 equiv of TsOH were added.



However, the precatalysts **5a** and **5b** did not work for this reaction (Table 1, entries 1–2). Gratifyingly, the use of chiral triazolium precatalyst **5c** afforded 1,2-diazepine **3aa** and pyrazole **4aa** as a mixture in a ratio of 2:3 with a 52% combined yield, with **3aa** being obtained with excellent enantioselectivity (91% *ee*). With the goal of improving the regio- and enantioselectivity, the R substituent of the hydrazone was varied (entries 3–6). Notably, the *ee* of **3aa** increased to 99% with good regioselectivity when **2d** was employed (entry 6). However, no improvement in yield and regioselectivity was observed for the reaction by screening different bases and solvents (see Supporting Information (SI)). With this substrate, further attempts to switch the regioselectivity to afford pyrazole **4ad** were carried out using various other NHC precatalysts. We rationalized that the formation of the regioisomeric [4 + 1] cycloadduct was most likely to occur via an acyl-anion intermediate, which undergoes a Stetter reaction, followed by cyclization to **4ad**. Further studies focused on the effect of the *N*-substituent of the precatalyst on the regioselective annulation reaction (entries 7–10). Interestingly, when the reaction was repeated using **5g** as the precatalyst, which has been reported to favor the generation of acyl-anion intermediates, neither **3ad** nor **4ad** could be obtained (entry 10).[10] However, *N*-2,6-$(OMe)_2$ precatalyst **5e** afforded the desired pyrazole **4ad** as the major product (entry 8). Further optimization studies revealed that the morpholine backbone was also sensitive to the reaction intermediate (entries 11–12; for additional NHCs, see SI). Using **5i** as the precatalyst, we achieved a switch in the regioselectivity to the [4 + 1] cycloaddition, thus leading to the formation of the pyrazole **4ad** in 64% yield. Based on these experiments, the change of annulation mechanism is believed to be due to the electronic and steric differences of the NHC catalysts (entries 6–12).

With reaction conditions for the regioisomeric formal [4 + 3] annulation in hand, we explored the generality of this reaction (Table 2). A broad range of differently substituted enals, bearing

Table 2. Substrate Scope[a,b,c]



[a]Reactions were conducted with 2.0 equiv of **1a** and 1.0 equiv of **2**, for 16 h. [b]Yield of the isolated product after column chromatograpy. [c]Determined by ^{1}H NMR spectroscopy. [d]THF (2 mL). [e]**1** (4 equiv).

electron-neutral (**3ad**) or electron-deficient (**3bd**-**3dd**) substituents on the aromatic ring, reacted with *N*-Boc hydrazone **2d** to form a series of 1,2-diazepine molecules with excellent enantioselectivity, whereas the enal with a *p*-bromo substituent resulted in a decreased yield (**3dd**). Electron-rich substrates were suitable for the reaction with no apparent change in enantioselectivity (**3ed** and **3fd**). *β*-2-Furyl enal also worked well to give the 1,2-diazepine **3gd** in 60% yield and 99% *ee*. Remarkably, this method was compatible with *β*-alkyl enals, giving the desired products in good yields and excellent enantioselectivities (**3hd** and **3id**). The absolute configuration of the 1,2-diazepine **3gd** was assigned by its single-crystal X-ray diffraction analysis. Encouraged by the excellent results with various enals, we then investigated the formal [4 + 3] annulation reaction with a range of hydrazones. A variety of *α*-chloro *N*-Boc hydrazones proved to be excellent azoalkene precursors in this cycloaddition reaction, affording the expected heterocycles in high yields and excellent enantioselectivities (**3ae**–**3an**). Notably, alkyl substituted hydrazone **2n** also worked well, leading to a good yield (73%) of adduct **3an** with 98% *ee* (**3an**).

Further exploration revealed that cyclic hydrazones **2o** and **2p** were also suitable substrates (Scheme 2), giving the interesting polycyclic products **3ao** and **3ap** in good yields and enantioselectivities (87% and 85% *ee*). In contrast to the unsubstituted *α*-chloro *N*-Boc hydrazones, the enantioselectivities decreased markedly (Table 2 and Scheme 2). Based on our proposed stereochemical model, the modest enantioselectivity is likely caused by an interaction of the cyclic ring of the azoalkene with the *N*-substituted aromatic ring of the NHC catalyst. Consistent with this hypothesis, using less bulky precatalyst **5f**,

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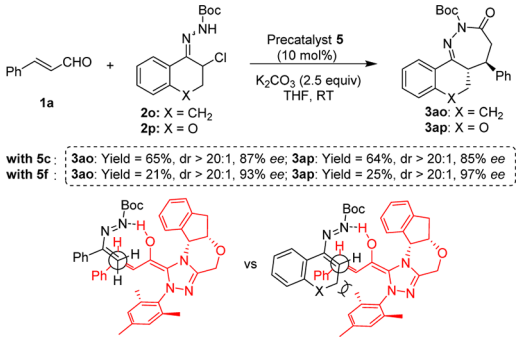
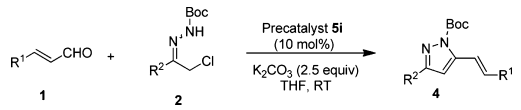
Scheme 2. Annulation of the Cyclic *N*-Boc Hydrazones



the enantioselectivities increased to 93% and 97%, albeit with reduced yields.

In contrast to the prevalence of reactions involving homoenolate reactivity, processes where the enal carbonyl carbon acts as a reactive nucleophilic carbon (acyl anion intermediate) for C−C bond formation are much less studied. Elegant reactions using enals as acyl anion precursors have only been achieved with nitroalkenes,[4d] modified chalcones,[4e] and activated ketimines.[4g,h] Using NHC catalyst **5i**, we were able to suppress the homoenolate reactivity of enals with azoalkenes and selectively access pyrazole products. Under the optimized reaction conditions, a broad range of enals and α-chloro *N*-Boc hydrazones were investigated (Table 3). Various substitution

Table 3. NHC-Catalyzed Formal [4 + 1] Reaction[a]



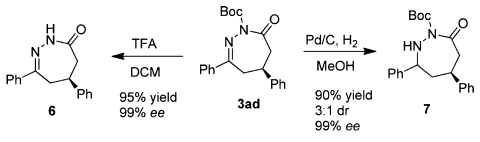
entry	R^1	R^2	4	yield (%)
1	Ph	Ph	**4ad**	64
2	4-FC_6H_4	Ph	**4bd**	57
3	4-MeC_6H_4	Ph	**4ed**	52
4	2-furyl	Ph	**4gd**	72
5	Ph	4-MeC_6H_4	**4ae**	68
6	Ph	4-FC_6H_4	**4ag**	62
7	Ph	4-ClC_6H_4	**4ah**	61
8	Ph	4-BrC_6H_4	**4ai**	55
9	Ph	2-naphthyl	**4ak**	58
10	Ph	3-MeC_6H_4	**4am**	67

[a]See the Supporting Information for details.

patterns on enals at the aromatic ring had little impact on the reaction (entries 1−4). α-chloro *N*-Boc hydrazones with different substituents on the aromatic ring also afforded good results (entries 5−10).

The optically active 1,2-diazepine heterocycle **3ad** can be readily elaborated, as shown in Scheme 3. Under the acidic conditions, the *N*-Boc group of **3ad** could be easily removed to afford **6** without loss of enantioselectivity. Direct hydrogenation

Scheme 3. Transformation of 1,2-Diazepine 3ad



of **3ad** in the presence of a catalytic amount of Pd/C led to the reduction of the C=N bond, providing compound **7** in good yield.

A reasonable mechanism for the regioselective umpolung annulations is illustrated in Figure 1.[1,4−9] The proposed catalytic

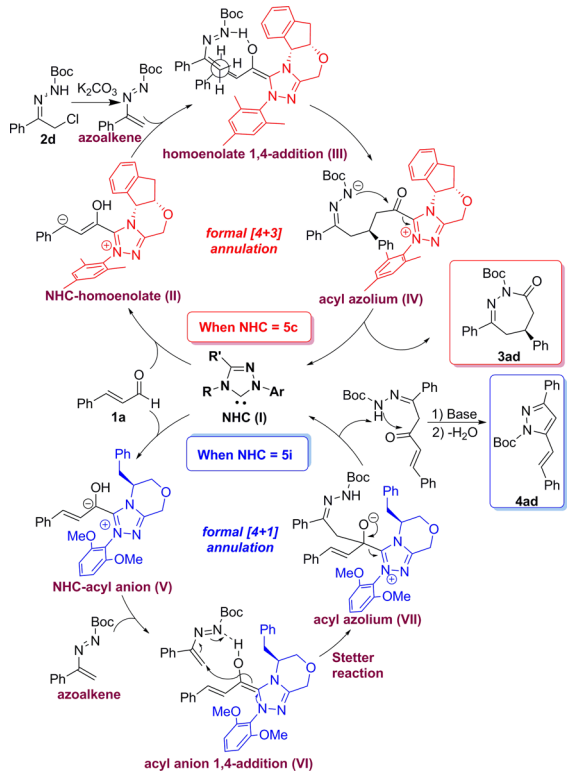


Figure 1. Proposed catalytic cycle.

cycles for both the 1,2-diazepine and the pyrazole derivatives begin with addition of the NHC (**I**) to cinnamaldehyde to generate the extended Breslow intermediate (**II** and **V**). The protecting group of the hydrazones had a high impact on the selectivity and yield; Boc protection was found to be ideal (Table 1). The competing homoenolate/acyl anion pathways were found to be controlled by the structure of the NHC catalysts. *N*-Mes containing NHC **5c** was used to realize selective homoenolate reactivity and preferentially afford 1,2-diazepine **3ad**, while seemingly less electron-rich[20] *N*-2,6-$(OMe)_2$ containing NHC **5i** was preferred for the enal acyl anion reaction pathway to give pyrazole **4ad**. At this point, the NHC **5c**-bound homoenolate **II** can undergo conjugate addition to the in situ formed azoalkene assisted by a H-bonding interaction (intermediate **III**, Figure 1, top cycle). In this case, following C−C bond formation, azolium **IV** undergoes *N*-acylation to release the NHC catalyst **5c** and furnish the 1,2-diazepine **3ad**. Alternatively, the regioisomeric [4 + 1] cycloaddition involves initial generation of acyl anion intermediate **V**, which reacts with the azoalkene in a Stetter reaction to give the adduct **VII** and regenerate the NHC **5i** (below cycle). Intramolecular cyclization and dehydration of **VII** furnishes the final [4 + 1] annulation product **4ad**.

In conclusion, we have successfully developed the first NHC-catalytic asymmetric formal [4 + 3] reaction of enals with in situ formed azoalkenes to generate a diverse set of 1,2-diazepine heterocycles in good yields and excellent enantioselectivities. Furthermore, a switch in NHC catalyst also allowed a controlled

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formal [4 + 1] reaction pathway, generating synthetically useful pyrazoles.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data. 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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